Initial Cross-Over Test of A Positive Allosteric Modulator of Alpha-7 Nicotinic Receptors to Aid Cessation in Smokers With Or Without Schizophrenia

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Preclinical research shows that compounds acting at $\alpha 7$ nicotinic receptors (nAChRs) can reduce nicotine self-administration, suggesting that a positive allosteric modulator (PAM) of $\alpha 7$ receptors, JNJ-39393406, may aid smoking cessation. Moreover, individuals with schizophrenia, who have very high rates of smoking, have reduced expression of $\alpha 7$ nAChRs and may particularly benefit from this compound. In two parallel studies using a within-subject cross-over design, 36 healthy smokers (Study 1) and 62 smokers with schizophrenia (Study 2), both groups high in quit interest, attempted to initiate quitting temporarily during each of two 3-week phases. Treatments were the $\alpha 7$ nicotinic receptor PAM JNJ-39393406 (100 mg b.i.d.) or placebo (double-blind, counter-balanced). In each phase, all smoked *ad lib* with no drug on week 1 or during dose run-up on week 2, and then tried to quit every day during week 3. Abstinence (confirmed by CO <5 p.p.m.) and smoking reduction (CO <8), as well as cigarettes/day (in Study 1), were assessed daily (Monday–Friday) each quit week and compared between conditions. Secondary outcomes included abstinence symptoms (withdrawal and craving) and cognitive test responding (N-back; continuous performance task). In both studies, compared with placebo, active JNJ-39393406 did not increase the number of abstinent days nor reduce total smoking exposure. We also found no significant improvements in craving, withdrawal, or cognitive function. With this dose and study duration, our findings do not support further testing of this $\alpha 7$ nAChR PAM compound for possible efficacy in smoking cessation, in smokers with or without schizophrenia.

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INTRODUCTION

Despite most smokers wanting to quit, the vast majority who try ultimately do not succeed, even with the best available therapeutics (Babb *et al*, 2017). Without more effective cessation medications, very low quit rates are likely to continue (eg, Hughes (2011)). Of dozens tested for potential efficacy in the past 30 years, only three first-line drugs have been approved by the FDA (nicotine replacement, bupropion, and varenicline), highlighting a need for more efficient screening of novel compounds that may warrant further development efforts (Lerman *et al*, 2007).

Acute intake of nicotine is critical for onset and maintenance of smoking (US Dept of Health and Human Services (USDHHS), 2010), and its actions at nicotinic acetylcholine receptors (nAChRs) in the brain are responsible for the reinforcing effects of cigarette smoking

(DeNoble and Mele, 2006). Thus, in addition to the efficacious partial agonist varenicline (Mihalak *et al*, 2006), compounds acting at $\alpha 4$ and $\alpha 7$ nAChRs offer promise for aiding cessation. In particular, the orthosteric sites of nAChRs are the direct molecular targets of nicotine and the endogenous neurotransmitter ACh, as nAChRs are cation channels that modulate neuron activity in brain areas that regulate mood, cognition, and reward (Brunzell, 2008). Preclinical studies show that activation of $\alpha 7$ nAChRs with a selective agonist significantly attenuates motivation to self-administer nicotine (Brunzell and McIntosh, 2012), evidence supported by a study showing that galantamine, an $\alpha 7$ nAChR positive allosteric modulator (PAM), can also decrease nicotine intake in rats (Hopkins *et al*, 2012).

Consequently, selective stimulation of $\alpha 7$ nAChRs could prove effective for smoking cessation. The JNJ-39393406 compound, developed by Janssen Research and Development LLC, selectively potentiates nicotine and ACh activity at $\alpha 7$ nAChRs via binding to a separate, allosteric site and, therefore, is considered a PAM of $\alpha 7$ nAChRs. JNJ-39393406 PAM does not activate $\alpha 7$ nAChRs on its own but, in binding to an allosteric site (different from nicotine/ACh-binding site), enhances nicotine and ACh activity at $\alpha 7$ nAChRs (Winterer *et al*, 2013). So,

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JNJ-39393406 could decrease motivation to persist in smoking when trying to quit.

Moreover, preclinical findings may suggest possible efficacy of this compound for cessation in a specific and vulnerable subpopulation of highly dependent smokers, those with schizophrenia. Compared to the current 15% smoking prevalence in the general population, prevalence is nearly 70% in patients with schizophrenia, who tend to be very heavy smokers (De Leon and Diaz, 2005; Dickerson *et al*, 2013). Post mortem studies show that individuals with schizophrenia have reduced expression of $\alpha 7$ nAChRs (Freedman *et al*, 1995; Leonard *et al*, 2000; Mexal *et al*, 2010). Preclinical studies suggest JNJ-39393406 could aid cessation in smokers with schizophrenia by overcoming their likely deficit of $\alpha 7$ nAChR function (Adler *et al*, 1998). For these reasons, we hypothesized that JNJ-39393406-associated stimulation of $\alpha 7$ nAChRs would promote tobacco cessation, especially in smokers with schizophrenia.

In two parallel studies, we tested active JNJ-39393406 *vs* placebo for efficacy in cessation with separate samples of smokers already planning to quit soon: healthy smokers (Study 1) and smokers with schizophrenia (Study 2). To increase statistical power (Cohen, 1988), both studies used an efficient 'early Phase 2' cross-over procedure that we have validated for initial evaluation of a novel medication's potential efficacy for cessation (Perkins and Lerman, 2014). This procedure's specific objective is to quickly determine whether a novel medication does, or does not, show sufficient promise of efficacy to justify the substantial effort of a larger randomized Phase 2 clinical trial of that medication. The cross-over design enhances efficiency and statistical power because all participants receive both medication conditions, eliminating individual variability between conditions and allowing smaller sample sizes to test differences between conditions (Cleophas, 1993). Importantly, a key to the procedure's sensitivity and specificity is to conduct evaluations among smokers recruited for being high in quit interest (ie, already planning to permanently quit soon; Perkins, 2014).

In both studies, the primary outcome was number of days abstinent during each separate week-long 'practice' quit attempt under the two drug conditions manipulated in the cross-over design, active JNJ-39393406 *vs* placebo. Each drug condition was administered for 2 weeks following a baseline week, in counter-balanced order and double-blind. We also examined reductions in daily smoking exposure short of complete abstinence. In secondary outcomes to explore possible mechanisms of action, we assessed medication effects on abstinence-induced withdrawal and craving, and on cognitive function when abstinent.

MATERIALS AND METHODS

Nearly all procedures were common to both studies and so will be described once below. Those few procedures specific to one study or the other are noted as such.

Recruitment

As in sample sizes of comparisons for active drug *vs* placebo in our prior studies using this procedure (Perkins and

Lerman, 2014), both studies aimed to recruit 60 smokers already intending to quit permanently in the next 2 months (ie, high in quit interest). Prospective participants in Study 1 were those from the Pittsburgh PA community responding to online or print ads, and in Study 2 were smokers with schizophrenia receiving outpatient treatment at the ambulatory clinics associated with Western Psychiatric Institute and Clinic (WPIC). All were recruited in November 2014 through March 2017, with follow-up ending May 2017. In both studies, after obtaining informed written consent, screening assessments included participants' smoking and health history, as well as their response to an open-ended question on when they hoped to make a permanent quit attempt (with study eligibility requiring next 2 months). Eligible subjects were required to be aged 18–65, smoke for ≥ 1 year, and meet DSM-V criteria for nicotine dependence (American Psychiatric Association (APA), 2013), provide a mid-day screening CO reading ≥ 10 p.p.m. (SRNT Subcommittee on Biochemical Verification, 2002), and to not currently be taking cessation medication to help quit and no use of smokeless tobacco or electronic cigarettes in past month. (Other requirements specific to Study 2 are described below.) Screening also included assessment of alcohol use via the AUDIT (Saunders *et al*, 1993), as those with scores indicating dependence were excluded. Self-report of no more than 15 drinks per week and 3 drinks on any day in the past week was required.

Those not ineligible at screening received a physical exam by study physician, including EKG, bloodwork to check liver and kidney function (CBC, and so on), illicit drug screen (other than THC), urine pregnancy test (women), and interview to assess history of psychiatric disorders, suicidal ideation, current major health problems (eg, heart disease, diabetes) or contraindicated medications (eg, fentanyl, cyclosporine, pimozide, and quinidine). Smokers in Study 2 also had to have a total PANSS score of ≤ 70 (Positive and Negative Syndrome Scale Score; Kay *et al*, 1987), which indicates severity of psychiatric symptoms. Those in Study 1 (only) were excluded if taking medications to treat serious psychological problems (eg, psychosis, anxiety disorders, and major depression). All confirmed as eligible were randomized to the two orders, either JNJ-39393406 ('JNJ') first or placebo first, with the other condition second in this cross-over design.

Although Study 1 and Study 2 were each described as 'not a treatment study,' all prospective participants were told that one benefit included free open-label treatment with FDA-approved medication (bupropion in Study 1; their choice in Study 2) and brief counseling to make a permanent quit attempt after completing the study. No further participant payment would be provided, just assistance to quit smoking. This benefit was offered specifically to attract participation by smokers high in quit interest (Perkins and Lerman, 2014), as those not wanting to quit soon would be disinterested in such a study benefit lacking payment.

Medication

Active JNJ-39393406 (50 mg tablets), abbreviated here 'JNJ' and studied under IND #122957, and matching placebo were supplied by Janssen Research and Development LLC

(Titusville, NJ) and encapsulated by the WPIC Investigational Drug Service (IDS) research pharmacy. Study research staff and participants were blind to medication assignment by IDS (ie, double blind). To start the dose run-up, participants took one capsule of JNJ-39393406 (50 mg), or identically appearing placebo, once on day 1, incrementing by 50 mg daily to reach 200 mg by day 4. The full dose involved two capsules, each twice per day (100 mg b.i.d. for JNJ), in the a.m. and evening, over the remaining 7 days of that medication condition, including the 5-day practice quit period (Monday–Friday). One week of *ad lib* smoking followed the first quit attempt phase prior to the dose run-up week with the other condition, to allow separate tests of each in aiding smoking abstinence. This active JNJ medication reaches peak blood levels after 3 h, and the half-life is ~6 h (Winterer *et al*, 2013), allowing for complete washout over the week, if administered as the first condition before starting the placebo condition. The dose of 200 mg (100 mg b.i.d.) was chosen because it was the largest dose previously tested in patients with schizophrenia, shows dose-dependent exposure in pharmacokinetic data and evidence of brain penetrance, and is well-tolerated in patients also being treated with psychoactive medications (Winterer *et al*, 2013).

Compliance was >97% for each medication condition in both studies, assessed by observation of a.m. dosing at each study visit (two visits in dose run-up week and five visits during the quit week), along with pill counts (Study 1) or blister packs (Study 2) at the end of each week. Across the total of 40 given per participant during each condition, means (SD) were just 1.2 (1.8) active JNJ and 0.9 (1.6) placebo missed for those in Study 1, and 0.6 (1.4) for active JNJ and 0.1 (1.1) for placebo missed among those in Study 2.

Measures

Smoking outcomes. During the ‘quit week’ (week 3) of each condition, the primary outcome of 24-h abstinence was assessed daily on Monday–Friday by expired-air carbon monoxide (CO) <5 p.p.m., using a BreathCO CO monitor (Vitalograph; Lenexa KS). Depending on the type of CO monitor (Karelitz *et al*, 2017), this stringent biochemical criterion for validating cessation is more sensitive and specific than the traditional (higher) CO <8 cutoff (Perkins *et al*, 2013a). Yet, to gauge potential for smoking reduction short of complete abstinence, amount of daily smoking exposure was assessed in weeks 3 and 6 via CO <8 p.p.m., CO <10 p.p.m. (Study 2 only), and cigarettes per day (Study 1 only) by a validated prospective self-monitoring ‘tally’ form (Perkins *et al*, 2013).

Secondary outcomes. Also examined were abstinence symptoms of craving via Questionnaire of Smoking Urges-brief (QSU) (Cox *et al*, 2001) and the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes *et al*, 1991), with each item scored on a 0–100 VAS. In Study 2 only, severity of psychiatric symptoms was also examined using the PANSS.

In addition, because the original purpose for developing this compound was to attenuate cognitive deficits in schizophrenia (Winterer *et al*, 2013), which can also occur upon smoking abstinence (Patterson *et al*, 2009, 2010), we assessed two measures of cognitive performance, the

Letter-N-back task of working memory (Ragland *et al*, 2002), and the Penn Continuous Performance Task (CPT) assessing sustained attention (Kurtz *et al*, 2001; Gur *et al*, 2010). Other details on assessing the tasks during smoking abstinence are presented elsewhere (Perkins *et al*, 2013b).

Procedure

In both studies, participation for each subject was 6 weeks after randomization, involving two 3-week phases, one for each drug condition in this double-blind, cross-over procedure (see 3-week timeline in Supplementary Table S1). For each phase, visits occurred on Monday and on Thursday of the first 2 weeks and Monday–Friday of the third week. CO was assessed upon arrival to each session, along with QSU craving and MNWS withdrawal. Each phase began with a week of *ad libitum* smoking (baseline, week 1), with drug regimen started on Monday a.m. of week 2 while continuing to smoke (dose run-up). On week 3, they were instructed to try to abstain as of Sunday a.m. through the mid-day Friday visit, with CO assessments of quit status on Monday–Friday of week 3. On Monday of week 3, all completed testing of cognitive function (N-back, CPT). Also, those in Study 1 reported number of cigarettes over the past 24 h on every day (Monday–Friday) of week 3, via the daily tallies. After Friday of week 3, all then *ad lib* smoked for at least a week to repeat this 3-week phase for the other condition: smoking without drug (ie, washout; week 4), next dose run-up (week 5), and trying to quit during Monday–Friday (week 6).

Also assessed daily (Monday–Friday) of the two ‘quit’ weeks (weeks 3 and 6) were medication blinding and side effects. Effects were rated on a 0–3 scale (none, mild, moderate, severe) and included nausea, agitation, nervousness, constipation, dry mouth, fatigue, insomnia, headache, increased appetite, decreased appetite, and so on. When reported by participants, adverse events were also noted and addressed by study physician. EKG and bloodwork from the physical exam (above) were repeated at the end of weeks 2 and 5, and post study, to further evaluate safety. Finally, after study completion on Friday of week 6, all were offered the free regimen of medication and brief counseling (see the Recruitment section) for up to 8 weeks to help them make a permanent quit attempt. Both studies were approved by the University of Pittsburgh Institutional Review Board.

Data Analysis

Analyses were conducted using IBM SPSS 24.0. Preliminary analyses of variance (ANOVAs) examined effects of sex and of medication order between phases, finding no significant main or interaction effects. The primary outcome, number of days abstinent per assessment week (range of 0–5 days), was analyzed using paired *t*-tests (separately for CO <5 and CO <8 p.p.m. criteria). Medication condition (active JNJ, placebo) was the within-subjects factor. Generalized estimating equations (GEEs) assessed differences between conditions for smoking reduction and for the secondary outcomes of craving and withdrawal, which were limited to only responses from days in which smoking abstinence was confirmed, separately by CO <5 and then by CO <8. In this way, recent exposure to nicotine via smoking would not

confound symptom responses to medication condition. Results of cognitive testing were examined using paired *t*-tests for the CPT and RM ANOVA for the N-back. Medication condition was a within-subjects factor for both sets of analyses, with an additional within-subjects factor of memory load (0-, 1-, 2-, 3-back) for the N-back. Similar to analyses of craving and withdrawal, to detect potential efficacy of conditions on cognitive testing unconfounded by recent smoking, cognitive responses were analyzed only when CO < 10 on both the JNJ and placebo testing sessions, as in prior research (eg, Perkins *et al*, 2013b).

RESULTS

STUDY 1—Healthy Smokers

Participant characteristics. Due to greater than expected recruitment difficulty, only 36 healthy smokers (17 M, 19 F) were enrolled in Study 1. Mean (SD) characteristics were 37.6 (11.3) years of age, 16.2 (4.9) cigarettes per day, Fagerstrom test of nicotine dependence (FTND; Heatherton *et al*, 1991) score of 5.1 (1.6), and 2.1 (1.3) prior attempts to quit smoking. They mostly self-identified as Caucasian (72.2%), with 19.4% as African-American, and 8.3% as more than one race. Five (3 M, 2 F) dropped out before finishing, two during week 1 (prior to any medication), two during week 2 (prior to the first quit period), and one during week 6, leaving 31 completing study participation. See Consort diagram for Study 1 in Figure 1.

Smoking outcomes. Mean (SE) abstinent days out of five (Monday–Friday) when attempting to quit on JNJ vs placebo are shown in Figure 2, separately for the CO < 5 and CO < 8 cutoff criteria. In the primary analysis of paired *t*-tests in this within-subjects design, no significant effects on days abstinent were seen for medication condition, whether the criterion was CO < 5, $t(30) = 1.06$, $p = 0.30$, or CO < 8, $t(30) = 0.00$, NS. In Study 1, GEE analysis showed that cigarettes per day for all participants was significantly more (although of modest absolute difference) during the quit attempt week for the JNJ vs placebo condition, with means (SEM) of 5.69 (0.76) vs 5.05 (0.61) per day, respectively, Wald $X^2(1) = 4.64$, $p < 0.05$. Thus, no efficacy was found for the JNJ drug vs placebo in aiding smoking cessation or reduction.

Secondary outcomes. Craving and withdrawal. Self-reported craving and withdrawal were analyzed using GEE analyses. Compared to placebo, active JNJ actually increased QSU craving when CO < 5, Wald $X^2(1 \text{ df})$'s of 3.99, $p < 0.05$, and when CO < 8, 10.35, $p < 0.005$, as also shown in Figure 2. For MNWS withdrawal, no significant differences were seen between placebo and active JNJ, when CO < 5, Wald $X^2(1 \text{ df}) = 0.50$, NS, although JNJ marginally increased withdrawal over placebo when CO < 8, Wald $X^2(1 \text{ df})$ of 3.11, $p = 0.08$ (Figure 2).

Cognitive testing. As noted, analyses of cognitive results due to drug conditions during smoking deprivation was limited to the 12 subjects achieving CO < 10 on both the JNJ and placebo sessions. For the N-back (working memory), correct responses exceeded 75%, demonstrating validity of comparing reaction time (RT) on correct responses by drug condition. Repeated measures ANOVA showed that median RT was significantly influenced by memory load

Figure 1 Consort diagram for Study 1 (with healthy smokers).

(0-, 1-, 2-, 3-back), $F(3,33) = 4.65$, $p < 0.01$, as expected, but only marginally by drug condition, $F(1,33) = 3.23$, $p = 0.10$, and not by the load $\times$ drug interaction, $F(3,33) < 1$. As shown in Figure 3, median RT was non-significantly faster (better) for active JNJ vs placebo across memory loads. Correct responses on the CPT (sustained attention) was nearly 100%. However, no significant effects of JNJ vs placebo were found on median RT (SE) in ms for responses to numbers using paired-samples *t*-tests, 429 ± 15 vs 418 ± 8 , or letters, 460 ± 16 vs 458 ± 12 , $t(11)$'s of 1.30, $p = 0.22$, and of 0.12, $p = 0.91$, respectively.

Medication blinding, side effects, adverse events. During week 3 ('quit week') of each study phase, the percent of days that participants correctly identified the JNJ medication as 'active JNJ' was 14.2%, compared to 9.7% as 'placebo (no medication)' and 75.5% as 'don't know.' For the placebo condition, very similarly, they correctly identified placebo on 11.6% of days, compared to 14.2% as 'active JNJ' and 74.2% as 'don't know.' None of these values differed by condition, indicating successful blinding. Side effects were mild, as most participants responded '0' (none) on the 0–3 scale for each effect during both drug phases, and no effect mean was above 0.6, with overall means (SD) of 0.20 (0.29) vs 0.23 (0.27) for active JNJ vs placebo, respectively, $t(30) = 1.07$, $p = 0.30$. Finally, few adverse events were reported, none serious or treatment-limiting. Most occurred with similar frequency during both drug conditions, although gastrointestinal discomfort (mostly nausea) appeared more likely for active JNJ vs placebo (n 's of 7 vs 2), while dermatological

Figure 2 Study 1 means (SEM) for days quit (range 0–5), MNWS withdrawal, and QSU craving (both 0–100), by JNJ vs placebo, when abstinence was biochemically verified by CO < 5 p.p.m., or CO < 8 p.p.m. * $p < 0.05$, ** $p < 0.005$ for differences between JNJ vs placebo.

(skin rash, and so on; 0 vs 3), body aches (1 vs 4), and psychological (sadness, and so on; 1 vs 5) events appeared less likely for active JNJ vs placebo.

STUDY 2—Smokers with Schizophrenia

Participant characteristics. For the 62 smokers with schizophrenia (37 M, 25 F; 30.6% Caucasian, 69.4% African-American) randomized in Study 2, mean (SD) characteristics were 46.2 (11.1) years of age, 16.0 (7.1) cigarettes per day, FTND score of 6.0 (1.7), and 4.6 (13.8) prior attempts to quit smoking. Six (2 M, 4 F) dropped out (4) or were withdrawn (2) before finishing the study, leaving 56 completing study participation. See Consort diagram for Study 2 in Figure 4. All were being concurrently treated with antipsychotic medications (80% on atypicals and 27% on typicals,

Figure 3 Study 1 means (SEM) for N-back reaction time across memory loads (0–3), by JNJ vs placebo, when smoking reduction was biochemically verified by CO < 10 p.p.m.

Figure 4 Consort diagram for Study 2 (smokers with schizophrenia).

including those on more than one). Details include 39% on anti-depressants, 29% on mood stabilizers, 38% on anxiolytics/hypnotics, and 14% on anti-cholinergics.

Smoking outcomes. Mean (SE) abstinent days when attempting to quit on JNJ vs placebo are shown in Figure 5, by the CO <5 and CO <8 cutoff criteria, as in Study 1. In paired *t*-tests, days abstinent did not differ by drug condition, whether CO <5, $t(55)=0.78$, $p=0.44$, or CO <8, $t(55)=0.85$, $p=0.40$. To more closely relate our results with many quit trials in psychiatric patients (eg, Chengappa *et al*, 2013; Tsoi *et al*, 2013), we also examined reduced smoking exposure using CO <10 as a cutoff (SRNT Subcommittee on Biochemical Verification, 2002). Again, we found no differences due to drug condition, 0.93 (0.21) vs 1.00 (0.23) days for JNJ vs placebo, respectively, $t(55)=0.54$, $p=0.59$.

Secondary outcomes. Craving, withdrawal, and psychiatric symptom severity. As in Study 1, GEE analyses of craving and withdrawal were limited to days in which recent abstinence was confirmed by CO <5 or CO <8. No significant differences between active JNJ and placebo were found for QSU, MNWS, or in positive or negative psychiatric symptom severity, as well as total PANSS score (Figure 5).

Cognitive testing. In Study 2, comparisons between drug conditions on cognitive effects during smoking deprivation were limited to the seven subjects achieving CO <10 on both sessions. However, compared to Study 1 (above), N-back correct responding out of 15 items per load was much lower, <50% for loads above 0-back, questioning the validity of comparing median RT for correct responding between conditions. Because of these low percentages of correct responses, we determined median RT for N-back responding would not provide meaningful results, consistent with other studies of N-back testing in patients with schizophrenia (Jansma *et al*, 2004; Frydecka *et al*, 2014). Yet, CPT correct responding was over 75% for both letters and numbers, indicating valid data, when one subject with 0 correct during placebo was excluded (ie, n of 6). Using paired-samples *t*-tests, no significant differences were found during JNJ vs placebo, respectively, on median (SEM) RT for numbers, 519 ± 37 vs 505 ± 29 , or letters, 545 ± 31 vs 539 ± 35 , $t(5)$'s of 0.98, $p=0.37$, and 0.44, $p=0.68$.

Medication blinding, adverse events. During week 3 of each study phase, the percent of days that Study 2 participants correctly identified the JNJ medication as 'active JNJ' was 39.3%, compared to 39.3% as 'placebo (no medication)' and 21.4% as 'don't know.' For the placebo condition, they correctly identified placebo on 37.5% of days, compared to 46.4% as 'active JNJ' and 16.1% as 'don't know.' These results by condition indicated successful blinding. Most subjects, 80.3%, reported at least one adverse event, with some events appearing more common for active JNJ vs placebo, respectively (somnolence, 5 vs 1, and fever, 4 vs 1), while others appeared less common for active JNJ vs placebo (diarrhea, 4 vs 8; nausea, 4 vs 7; headache, 3 vs 5; muscle pain/soreness, 2 vs 5; and cold/nasal congestion, 2 vs 4). Cough was reported equally (3 vs 3). Three subjects experienced four total serious adverse events requiring hospitalization: pneumonia, acute diastolic congestive heart failure, persistent vomiting, and abdominal pain/vaginal

Figure 5 Study 2 means (SEM) for days quit (range 0–5), MNWS withdrawal, and QSU craving (both 0–100), and PANSS psychiatric symptom severity (pos and neg ranges are both 7–49; total score range is 30–210), by JNJ vs placebo, when abstinence was biochemically verified by CO <5 p.p.m., or CO <8 p.p.m.

bleeding. All four serious adverse events were reported during the washout or placebo conditions.

DISCUSSION

Compared with placebo, the highly selective $\alpha 7$ nAChR PAM, JNJ-39393406, did not increase days quit during

a brief practice quit period in dependent smokers high in current quit interest, whether otherwise healthy (Study 1) or with a diagnosis of schizophrenia (Study 2). In prior validity testing with healthy smokers, this cross-over procedure has demonstrated sensitivity in detecting clinical efficacy for each of the three first-line FDA-approved medications of nicotine patch, varenicline, and bupropion (Perkins and Lerman, 2014). It has also shown specificity in confirming lack of efficacy for modafinil (Perkins *et al*, 2013), a drug approved to help wakefulness but previously found ineffective for smoking cessation (Schnoll *et al*, 2008). Our procedure also recently found no evidence of efficacy for cessation with fenofibrate (Perkins *et al*, 2016), FDA-approved for lipid control and similar to fibrate drugs shown in preclinical research to reduce self-administration of nicotine in rodent and primate models (Panlilio *et al*, 2012) and of alcohol in rodents (Haile and Kosten, 2017). Therefore, despite the potential promise of preclinical findings that suggest that stimulation of $\alpha 7$ nAChR reduces nicotine reinforcement and reward (Brunzell and McIntosh, 2012; Brunzell *et al*, 2014; Harenza *et al*, 2014), results of the current clinical studies indicate this Janssen $\alpha 7$ nAChR PAM, at the dose and duration tested, lacks clinical efficacy in aiding ability of dependent smokers to quit smoking. Yet, even with this validated cross-over design, the optimum dosing and treatment regimen for detecting efficacy may prove challenging with novel compounds.

Although Study 1 tested just 31 healthy smokers completing both phases, Study 2 in 56 smokers with schizophrenia found virtually identical lack of efficacy for cessation (stringently verified by $CO < 5$) in this JNJ drug *vs* placebo, demonstrating replication of the Study 1 findings. That N of 56 is comparable or larger than our prior studies demonstrating sensitivity of this cross-over procedure (Perkins and Lerman, 2014). Both current studies also found no evidence of better outcomes with JNJ *vs* placebo on the other smoking behavior measures (cigarettes per day in Study 1, $CO < 8$ in both studies, and so on), or on secondary measures of craving or withdrawal during abstinence, consistent with lack of cessation efficacy for this $\alpha 7$ nAChR PAM. Surprisingly, the dose of JNJ compound used in these studies led to increased craving compared to placebo in Study 1 participants able to reduce smoking as measured by $CO < 5$ and $CO < 8$ p.p.m. (Figure 2). However, our findings could be specific to the brief duration, procedures used, and single dose tested. Longer duration and a broader dose range of this or perhaps other $\alpha 7$ nAChR PAMs may show efficacy for smoking cessation (eg, Marcus *et al*, 2016; Gee *et al*, 2017).

We also found no evidence of the JNJ drug's efficacy in improving responding on cognitive tests of working memory and sustained attention during smoking reduction ($CO < 10$). This null finding should be tempered by the small samples of smokers able to meet the $CO < 10$ criterion, as well as the inability of the smokers with schizophrenia in Study 2 to respond correctly on the N-back task. Yet, finding no beneficial effects of the JNJ compound on cognitive performance may be similar to a recent study showing no effects of JNJ-39393406 on reversing deficits in event-related potential (ERP) P50 sensory gating via EEG in non-abstinent male smokers with schizophrenia (Winterer *et al*, 2013). On

the other hand, Study 2 constitutes the first use in smokers with serious mental illness of our early Phase 2 cross-over procedure to evaluate cessation efficacy in novel compounds *vs* placebo, showing some feasibility despite the difficulty achieving abstinence here with either drug condition. Finally, this JNJ compound was safe and well-tolerated in both studies, and it may be worth noting that psychiatric symptoms of smokers with schizophrenia in Study 2 were not worsened by either condition, including in those able to abstain from smoking during the brief practice quit periods.

To conclude, results of the current studies do not provide support for proceeding with this $\alpha 7$ nAChR PAM, at the dose and duration tested, to a larger clinical trial randomizing treatment-seeking smokers, with or without schizophrenia, to permanently quit smoking.

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Supplementary Information accompanies the paper on the *Neuropsychopharmacology* website (<http://www.nature.com/npp>)