Long Title: Long-Term Effectiveness of a Digital Therapeutic Intervention for Smoking Cessation: A Randomized Controlled Trial

Short Title: Effect of a Digital Intervention for Smoking Cessation

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Abstract

Background: Smoking is the leading cause of preventable mortality worldwide. Digital therapeutic interventions offer a novel approach to smoking cessation and overcome many barriers to accessibility of traditional methods. Yet, the long-term efficacy of these interventions is largely unknown. Based on a chronic disease model of smoking, the present study evaluated the effects of Quit Genius, a novel, long-term digital therapeutic intervention for smoking cessation.

Methods and Findings: Using a single-blind, two-arm parallel-group, randomized controlled trial design, adult smokers of 5 or more cigarettes per day (N=556) were recruited between January and November of 2019 via social media advertisements and referrals from primary care practices in the UK. Participants were offered nicotine replacement therapy for a 12-week period and randomly assigned to one of two interventions.The Quit Genius group received a digital therapeutic intervention for smoking cessation comprising a clinician supported smartphone application delivering cognitive behavioral therapy (CBT). The CBT component included self-directed coping skills training and individually tailored therapeutic content, coupled with personalized clinician-delivered counselling via instant messaging. The control intervention was Very Brief Advice, a face-to-face, single session intervention based upon the Ask, Advise, Act model. Half of each group received a carbon monoxide (CO) device for biochemical verification of smoking abstinence. The primary outcome, by intention to treat (ITT), was sustained abstinence at 4, 26, and 52 weeks post-quit date. Secondary outcomes included self-reported 7-day point prevalence abstinence at 26 and 52 weeks post-quit date, and self-reported quit attempts and putative mechanisms of action of CBT for smoking cessation, including self-efficacy and psychological well-being. Participants (N=556) were randomly assigned to Quit Genius (n=277) or the Very Brief Advice control condition (n=279).

The final sample included 530 participants, comprising roughly equivalent proportions of men (n=291; 54%) and women, averaging 41 years of age (SD=12), who smoked an average of 15 cigarettes per day (SD=7). Using an Intention-to-treat (ITT) analysis, seven-day point prevalence abstinence from weeks 4 through 52 ranged from approximately 27% to nearly 45% among those who received the Quit Genius intervention, and from 13% to 29% for those in the control condition. Continuous smoking abstinence at 26 and 52 weeks occurred in 27.2% and 22.6% of Quit Genius participants, respectively, relative to 16.6% and 13.2% of those assigned to the control group; Quit Genius participants were more likely to remain abstinent than those in the control group Relative Risk [RR]= 1.71, 95% CI 1.17-2.50; *p*=0.005).

Conclusions: Using an extended care model combining NRT with evidence-based psychosocial treatment, a digital therapeutic intervention (Quit Genius) produces continuous abstinence rates that are notably higher than those typically observed in the literature.

Trial Registration: The trial was registered in the ISRCTN database on December 18, 2018 (https://www.isrctn.com/ISRCTN65853476).

Abbreviations

ACT: acceptance and commitment therapy

CBT: cognitive behavioral therapy

CO: carbon monoxide

DTI: digital therapeutic intervention

ITT: intention-to-treat

Mhealth: Mobile Health

NRT: nicotine replacement therapy

PP: per-protocol

SOP: standard operating procedure

QG: quit genius

RCT: randomized controlled trial

VBA: very brief advice

Introduction

Smoking is the leading cause of preventable death worldwide, causing more than 8 million deaths each year (1) with a total annual global economic cost of more than $1.4 trillion (2). Despite advances in pharmacological and behavioral smoking cessation treatment approaches over the past few decades, even when evidence-based treatments are combined in accordance with best practice guidelines, long-term abstinence rates remain relatively low, frequently falling below 20% at 1 year post-intervention (3,4). One possible explanation for the paucity of longer-term success is that the most commonly used treatment models do not align well with the scientific understanding of addiction as a chronic illness. Given that tobacco addiction, like addiction to alcohol and other drugs, is characterized by a chronic and relapsing clinical course, extended treatment models that support multiple transitions between relapse and recovery may optimize outcomes (5). Though traditional smoking cessation support involves low intensity motivational advice, a handful of studies combining pharmacological smoking cessation treatment with extended, evidence-based counselling ranging from 6 (5,6) to 12 months in duration (7) have demonstrated that sustained treatment models produce superior clinical outcomes, both in terms of effective relapse prevention and abstinence rates. Nevertheless, utilization rates of evidence-based smoking cessation treatment programs are astonishingly low, with as few as 5% of smokers accessing care (8). Moreover, given the limited scalability of face-to-face smoking cessation treatment models, novel approaches to broadening the reach of evidence-based treatment strategies are urgently needed.

Fortunately, progress in mobile technology has led to the proliferation of mobile health (mHealth) approaches to smoking cessation. The use of mHealth platforms for providing behavioral treatment confers many advantages over traditional face-to-face approaches, including low cost, greater accessibility, customizable features to support individuals through different psychological stages of behavior change, and scalability. Nevertheless, scientific support for the relatively large existing base of mHealth tobacco cessation interventions is lacking. According to a recent systematic review, among the 50 most highly recommended apps suggested by the leading app stores, only 4% had any scientific support (9), and the majority of existing mHealth apps underutilize recommended evidence-based treatment strategies.

Following evidence-based treatment guidelines to optimize smoking cessation treatment outcomes, our group developed Quit Genius, a digital therapeutic intervention combining pharmacotherapy with cognitive behavioral therapy (CBT) within an extended treatment model. Quit Genius is a 52-week cessation program combining a digitally delivered, self-guided CBT journey with individualized coaching support delivered asynchronously within the Quit Genius app. Concurrent access to nicotine replacement therapy (NRT) is provided to each participant. In 2020, we reported promising preliminary outcomes of Quit Genius for short-term behavior change, with a CO-verified 4-week quit rate of 44.5% (risk ratio 1.55, 1.23-1.96) (10). However, the extent to which these short-term outcomes are sustained over an extended follow up period remains unknown. As such, in the present study, extending the findings reported previously, we examine the effect of Quit Genius on longer term outcomes through 52 weeks post-quit date. To achieve this, we evaluated sustained smoking abstinence at 4-, 26- and 52 weeks post-quit date. The impact of Quit Genius, relative to the control condition on secondary outcomes including quit attempts, psychological well-being, and self-efficacy was also examined.

Methods

Study Design and Participants

We conducted a single-blinded, two-arm parallel design, randomized controlled trial (1:1 allocation ratio), with 4-, 26- and 52-week follow-up. Here we report the outcomes at 4, 26, and 52 weeks post-quit date. This study complies with the Declaration of Helsinki and ethical approval was granted by the Health and Social Care Research Ethics Committee A (HSC REC A; reference 18/NI/0171). The study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines..

Participants were recruited via social media advertisements and referrals from primary care practices in the United Kingdom between January and November 2019. Participants were directed to a study website, where they were provided with study information and prompted to complete a questionnaire to determine eligibility. Following this screening, they were invited to attend an in-person baseline assessment in which eligibility was reconfirmed upon review of the questionnaire responses. Subsequently, informed consent was obtained and baseline data were collected.

Individuals were eligible to participate if they were adult smokers (aged ≥18 years), smoked at least 5 cigarettes a day for the past year, had the required mobile phone functionality (5th generation or higher for Apple iPhone or version 18 or higher for Android) and were not using any other form of behavioral or pharmacological support for smoking cessation. Exclusionary criteria included not speaking English, pregnancy, COPD, currently taking psychiatric medication, and any serious health conditions that would substantially hinder completion of the study procedures as determined by the study team. A total of 556 participants consented to participate, completed screening, were offered NRT and randomly assigned to either Quit Genius or the Very Brief Advice control condition.

Randomization and blinding

Participants were randomized with an allocation ratio of 1:1 (treatment:control) using a block size of 4 participants. An online research management system (curebase) was used, with researchers blinded to treatment allocation until after randomization had been performed.

Treatment Intervention: Quit Genius

Quit Genius (QG) (11) is a 52-week digital therapeutic intervention informed by the principles of cognitive behavior therapy (CBT) (Screenshots shown in Figure 1). Designed to support the user pre and post quit-date, QG comprises a smartphone application with self-guided CBT content for therapeutic skills acquisition, coupled with a dedicated quit coach who provides asynchronous messaging to support and reinforce the use of CBT skills to initiate and sustain cessation. QG utilizes components that have demonstrated efficacy in promoting smoking cessation, including encouraging medication adherence, progress feedback, goal setting and self-monitoring. The application automatically collects user data via in-app metrics that help personalize the pace, feedback, and content each participant experiences during the program. The variables that inform personalization include app utilization, program completion, motivations for quitting smoking, reasons for continuing to smoke, and quit-date.

Tailored content is delivered in the form of animated videos, audio sessions, reflective exercises, and quizzes. The user is prompted to complete a series of consecutive self-paced steps, based on principles of motivational enhancement therapy and cognitive behavioral therapy, on their smoking cessation journey. QG's content is divided into the 'Essentials' stage, and the 'Sustain' stage. In the Essentials stage, which is recommended to be completed prior to the quit date, the user is prompted to complete a series of steps

comprising digitally delivered psychoeducation and motivational exercises including preparing for the quit date, review of the research evidence supporting use of NRT as part of cessation treatment, how NRT works, how to use it, and thinking about their personal reasons for quitting. In the ‘Sustain’ stage, the user completes after their quit date, focuses on principles of relapse prevention, helping the user to remain abstinent in the long-term. On a daily basis, users are encouraged to monitor their smoking habits by logging the number of cigarettes smoked, their smoking triggers, and the intensity of their cravings. After quitting smoking, participants are encouraged to log their current smoking status when they open the app. Accordingly, participants receive tailored feedback concerning abstinence status and associated health benefits over the course of their involvement in the program.

All QG participants had access to a ‘Quit Coach’, an advisor qualified by the National Centre for Smoking Cessation and Training (NCSCT). The coach provides personalized CBT and motivational support via the in-app chat service and phone. At treatment entry, participants are scheduled for a 30 minute phone call with their Quit Coach. During this call, participants receive an introduction to the Quit Genius program, a detailed formulation and discussion of the individual’s quit plan using CBT and MI, and guidance concerning the availability, types, and methods of using NRT. Subsequently, and for the duration of treatment, interactions with the quit coach transition to the in-app chat platform. Features include: (1) the ability for individuals to monitor their progress via the app, which details health improvements and financial benefits gained from being abstinent and sustaining abstinence over time,and (2) access to a ‘Craving Toolbox’ comprising audio delivered mindfulness, meditation and short breathing exercises designed to help the user manage cravings.

The QG app also provides content addressing mental health and well being, including CBT based skills training targeting common mental health concerns linked with tobacco use, such as anxiety, low mood, stress, self-esteem and social skills. The app also contains content addressing general health and well-being concerns such as diet, exercise, and self-care.

Cognitive and behavioral techniques include goal setting, cognitive restructuring, graded exposure, progressive muscle relaxation, mindfulness, assertiveness and communication training, and problem-solving skills. QG uses push notifications to remind users to engage with the app. All participants in the treatment group received access to the QG intervention for a period of 52 weeks.

Control Intervention: Very Brief Advice

VBA is a type of smoking cessation advice designed to be used by healthcare professionals and follows the Ask, Advise, Act structure as recommended by the UK government. Participants were advised to contact their local stop smoking service to access behavioral support and other forms of pharmacotherapy to help them quit smoking. Research assistants with a BA level of education who had completed the NCSCT smoking cessation course were trained to deliver VBA, a 15 minute face-to-face intervention, as per NCSCT guidelines (https://elearning.ncsct.co.uk). Of the control group participants allocated a CO device, a mobile-app (ASH-app) was also provided to the participant. The ASH-app enabled participants to view their CO results. The control group mobile-app was only used in conjunction with the CO device and contained no therapeutic counselling content.

Nicotine Replacement Therapy

All participants were given the option of nicotine replacement therapy (NRT; 2mg or 4mg gum and/or 16hr or 24hr patches) free for 12 weeks, with the first two-weeks supplied at the baseline visit. Participants were also allowed to use other forms of oral NRT.

Carbon Monoxide Monitor

Due to cost considerations, a random sample of half of the participants in each treatment group were issued a carbon monoxide (CO) monitor for biochemical verification of self-reported smoking status (Smokerlyzer, coVita Inc.). CO levels were self-reported at 4-,

26- and 52-weeks post quit-date. The CO devices connected via headphone/charging slot of participants' smartphones, and were only used in conjunction with the QG and the Analyzing Smoking Habits (ASH) app, which was used to record CO measurement data. At each of the follow-up visits, participants were asked to submit a reading from their device via phone or online to validate their self-reported abstinence status. Following NCSCT guidelines, a CO reading <10ppm was considered indicative of abstinence.

Outcome measures

Outcome measures were collected via phone or online at baseline, 4-, 26- and 52-weeks post-quit date. Participants received £10 to offset travel costs and were compensated for each follow-up data collection visit as follows: £10 (26 weeks) and £20 (4- and 52- week follow-ups). The primary dependent variable was continuous smoking abstinence at 26- and 52- week follow-up. Continuous smoking abstinence at each of the follow up timepoints was defined as smoking no more than 5 cigarettes from the quit date to 26- and 52- week follow-up, respectively. Those who smoked more than 5 cigarettes from their quit date to the specified time point were considered to have relapsed to smoking status. Continuous smoking abstinence status was indicated by self-reported abstinence, and expired-air CO levels of 10 ppm or lower (among the subset of individuals for whom biochemical verification was conducted). Secondary outcomes included: (1) self-reported 7-day point prevalence abstinence from cigarettes (not even a puff of smoke for the past 7 days) at 26- and 52-weeks post-quit date, (2) number of quit attempts at 26- and 52-weeks post-quit date, and (3) self-reported average number of cigarettes smoked per day at 26- and 52-weeks post-quit date.

In addition, we administered a standard demographics questionnaire, Fagerstrom Test for Nicotine Dependence (FTND) (12), the Smoking Abstinence Self-efficacy Questionnaire (SASEQ) (13), a 6-item measure used to assess changes in self-efficacy before and after the intervention within different emotional and situational contexts (24-point scale); and the

Warwick-Edinburgh mental wellbeing scale (WEMWBS), a 12-item measure used to assess general positive mental health (56-point scale) (14). Measurements were collected via online questionnaires in a trial management system (Curebase Inc) (15).

Statistical Analysis

The sample size was determined on the basis of requirements linked with the primary hypothesis: evaluating differences in self-reported abstinence rates across weeks 4 through 52. Power was set at 80%, with a Type I error rate of 0.05. The estimated effect size was based upon prior literature (16) and factored in the anticipated attrition rate of 20%. Statistical analyses were conducted with SAS version 9.4 software (SAS Institute, Cary, NC). To determine smoking abstinence rates, both intention-to-treat (ITT) and per-protocol analyses (PP) were used. ITT analyses are considered the most conservative and are standard for psychosocial clinical trials targeting smoking cessation (17). Using the ITT approach, all participant data in each respective study condition were analyzed, with unknown smoking status assumed to reflect continued tobacco use, resulting in conservative estimates of treatment efficacy. PP analyses excluded those for whom there were missing or unknown smoking status data and are presented herein for informational purposes, to enable comparison to ITT results.

Continuous abstinence across weeks 4, 26, and 52, based on sustained 7-day self-reported point prevalence abstinence at each timepoint, was compared among those who received Quit Genius, relative to the control condition using mixed effects models, controlling for variables known to be associated with smoking cessation treatment outcomes, including gender, race, employment, education, and nicotine dependence severity (indicated by the Fagerstrom Test for Nicotine Dependence). Seven-day abstinence rates were calculated for each timepoint. Relative Risk ratios (RRs) were used to assess the outcomes for Quit Genius relative to the control group, and chi-square tests were used to test for statistical

significance. Comparison of secondary outcome variables between the Quit Genius and control groups was achieved by using 2-sample *t* tests for continuous measures and chi-square tests for binary measures.

Results

Participants

Figure 2 displays the participants who were screened, assigned to each intervention condition, and participated at each of the follow-up assessments. 2195 individuals were assessed for study eligibility, of which 693 were ineligible. Of the 1502 individuals eligible for inclusion, 946 failed to attend their in-person baseline visit. The remaining 556 participants eligible for inclusion in the study were randomized to study conditions (treatment n=277, control n=279). The ITT analysis included 530 participants (n=265 in each arm; 11 excluded before trial registration, and 15 for baseline protocol violations). Follow-up completion was 81.6.% at 26 weeks, and 79.4% at 52 weeks, with no difference in follow-up rates between those assigned to Quit Genius versus the control condition. As shown in Table 1, participants were, on average, 41 (SD=12) years of age (range: 19 to 78). The overall sample included 291 (54.9%) men, and was predominantly Caucasian (65.5%), employed (80%), and educated, with more than two-thirds of participants reporting educational attainment beyond high school. On average, participants reported smoking 14.5 (SD=7) cigarettes per day, with an average FTND nicotine dependence score of 4 (SD=2). The vast majority of participants (85.0%, n=451) had previously made one or more quit attempts, largely by going cold turkey (48%) or using e-cigarettes (42%) and NRT (30%). There were no significant differences between the two study conditions in age, ethnicity, educational attainment, gender distribution, or employment status. There also were no significant baseline differences between the study conditions in smoking frequency, nicotine dependence severity, and previous quit attempts.

Abstinence

The hypothesis that the Quit Genius condition would have higher continuous abstinence rates across the 52-week post-quit period, compared to the control condition was supported. In regards to the primary outcome, according to ITT analyses, after controlling for gender, demographics, and nicotine dependence severity, the odds of smoking abstinence over the 52-week course of treatment were significantly higher in the Quit Genius treatment condition, relative to the control group (OR = 4.16, 95% CI= 2.01, 8.59; $p<0.0001$). Likewise, the Quit Genius condition produced consistently higher continuous abstinence rates relative to controls at week 26 (27.2% versus 16.6%, $p=0.003$) and week 52 (22.6% versus 13.2%, $p=0.005$) (see Table 2 and Figure 3). Moreover, relative risk ratios indicated that those who received the Quit Genius intervention and had quit successfully at 4-weeks were 70% more likely to report continuous abstinence at week 26 (95% CI = 1.22, 2.37, $p=0.003$) and 71% more likely to remain abstinent through week 52 (95% CI = 1.17, 2.50, $p=0.005$). Seven-day biochemically verified continuous abstinence rates by condition, according to both ITT and PP analyses, are shown in Table 2.

Among participants who were assigned a CO monitor, 97.1% (n=134) in the Quit Genius condition and 97.9% (n=139) in the control group provided a baseline CO reading. Among those who subsequently reported abstinence, at 4-weeks post-quit date the expired-air CO levels of 10 ppm or lower corresponded with participant self-report for nearly all (96.4%; n= 80) participants. At 26- and 52-weeks, self-reported abstinence was biochemically verified among 98.4% and 95.5% of participants, respectively.

Regarding secondary outcomes, the Quit Genius condition produced consistently higher continuous abstinence rates at weeks 4, 26, and 52, and self-reported 7-day point prevalence abstinence relative to the control group ($p<0.01$ at each assessment point), with the exception of self-reported 7-day point prevalence of abstinence at 52 weeks ($p>0.05$) (See Table 3). Based on 7-day point prevalence rates, Quit Genius participants evidenced

higher rates of sustained abstinence compared with those who received the control intervention, both at 26-weeks (RR=1.82, 95% CI, 1.29 -2.58 ;27.5% vs 15.1% quit rate) and at 52-weeks (RR= 1.93, 95% CI 1.30, 2.91; 21.9% vs 11.3% quit rate).

As shown in Table 3, for the first 26-weeks of the study, there was no difference between treatment conditions in additional quit attempts after the initial quit date (Quit Genius = 35% versus Control = 43%, p>0.05). At 52-weeks, however, participants in the control group were significantly more likely to have reported additional quit attempts (RR= 0.77, 95% CI 0.64 - 0.93).

The hypothesis that those who were assigned to the Quit Genius condition would demonstrate greater changes in putative mechanisms of action of CBT relative to those assigned to the control intervention, including self-efficacy and mental well-being, was partially supported. Though differences in self-efficacy for managing smoking urges were not observed at week 4 (p=0.09), a difference emerged at week 26, with larger increases in self-efficacy observed among those who received the Quit Genius intervention, t(506) = 2.6, p=0.01. However, at 52-weeks, that effect had diminished with no significant differences detected between groups (p=0.12). No differences between groups were detected in regards to participant mental well-being at any of the 3 timepoints.

Discussion

The purpose of the present investigation was to evaluate Quit Genius, an extended CBT-based digital therapeutic intervention model combining pharmacotherapy and behavioral treatment for smoking cessation. Based on the well accepted chronic disease model of addiction (18), the 52-week Quit Genius treatment program produced continuous abstinence rates at 26 and 52 weeks post-quit date that are substantially higher than those typically reported in the literature. Quit Genius participants who effectively quit smoking 4 weeks post-quit date were 1.70 times more likely to remain abstinent relative to control

group participants at week 26 (27.2% abstinent versus 16.6% abstinent), and 1.71 times more likely to remain abstinent at week 52 (22.6% abstinent versus 13.2% abstinent).

Importantly, these findings extend the preliminary outcomes previously reported, establishing not only the short-term efficacy of the Quit Genius intervention in producing high abstinence rates (44.5% at 4 weeks post-QD, according to ITT analyses), but also its superiority in helping smokers achieve repeated abstinence over the course of one year. The intervention approach used in this study differs from others reported in the literature in that it combines psychosocial and pharmacological modalities, and concurrently provides access to the psychosocial component over an extended time period, regardless of participants' abstinence status over that timeframe. Thus, the current study advances the evidence base for extended, digital health intervention models for smoking cessation. Although point prevalence abstinence rates have been reported across various randomized clinical trials of digital health interventions, according to a recent Cochrane review of smartphone and app-based smoking cessation interventions, 6-month abstinence rates ranged from 4% to 18% (19), suggesting that the extended, multi-modality approach inherent to the Quit Genius program is an advance compared with existing digital interventions for individuals with tobacco addiction. Moreover, longer term quit rates reported in the literature typically refer to the proportion of individuals abstinent at a given point in time, rather than capturing continuous abstinence across multiple follow-ups, a more stringent measurement of favorable treatment outcomes. Thus, the 26-week point prevalence abstinence rate of 35.9% observed among Quit Genius participants not only exceeds long term quit rates reported for other digital smoking cessation interventions, such as iCanQuit, an ACT-based smoking cessation application (29.6% quit rate at 6 months post-treatment) (20) , and Craving to Quit, a mobile app based mindfulness training program (11% abstinence rate at 6 months post-baseline) (21), but our primary outcome of continuous abstinence at 6 and 12 months (27.2% and 22.6%, respectively) far exceeds those reported for various digital programs,

including iCanQuit (prolonged abstinence rate of 13.8% at 12 months post-treatment) (20), Happy Quit, a text messaging based intervention (6.5% at 6 months post-treatment) (22), and is comparable to Pivot's 23.8% (ITT) continuous abstinence at 7 months post-enrollment (23).

While there is a paucity of literature surrounding digital therapeutic interventions for smoking cessation beyond 6 months post-treatment, the continuous abstinence rate observed at 52 week follow-up in the present study is substantially higher than that observed in the handful of studies of digital smoking cessation treatments with long-term follow up measurements, in which prolonged abstinence rates are below 10% by 12 months (20).

Methodological limitations of extant studies, including the use of single-arm designs, coupled with the absence of biochemical verification of self-report data, pose challenges to interpretation and generalizability of prior findings. To overcome these limitations, the present study employed a 2-arm parallel-group RCT design with biochemical verification. Despite verifying the CO of a subset of participants, the high correspondence between CO readings in this study and and self-reported abstinence is consistent with conclusions of a review by the Society for Research on Nicotine and Tobacco (SRNT) Subcommittee on Biochemical Verification (24), indicating that biochemical validation is not always necessary in smoking cessation studies, because the levels of misrepresentation are generally low (0–8.8%).

There were no significant group differences in quit-attempts at 4- and 26-weeks; however, at 52-weeks, despite having lower quit rates, participants in the control group were significantly more likely to have reported additional quit attempts beyond their initial QD that those in the treatment group, suggesting that they continued to attempt, albeit less successfully, to stop smoking. Focusing on re-engaging individuals in the treatment group who initially failed to

quit and increasing their motivation to reinitiate quit attempts will likely improve future success rates of the Quit Genius intervention.

Self-efficacy is a critical ingredient for enhancing a smoker's intention to quit, thereby leading to successful smoking abstinence outcomes (25,26). Improvement in self-efficacy was greater among those who received the Quit Genius intervention, relative to controls, an effect that emerged at 26-weeks post-QD. These findings replicate and extend the increase in reported quit-confidence and self-efficacy observed in Webb et al's (2020) preliminary outcome findings, indicating that digital CBT based interventions can affect similar psychological process variables to face-to-face treatments (10). These differences in self-efficacy diminished at 52-weeks post-QD, suggesting that understanding and addressing barriers to maintaining confidence is a potential target for future intervention refinement. Though overall mental well being improved generally among participants, there were no group differences in the magnitude of improvement, suggesting that further research is needed to build upon our understanding of how digital interventions can positively target mental wellness among smokers. Nevertheless, given that those receiving psychiatric medication were excluded from participation in this study, the absence of effects on mental well-being may be attributable to a restricted range of mental well being in the study sample.

Strengths and limitations

There are several strengths of this study, including a large sample size, the randomized controlled design, the use of remote biochemical verification and high correspondence between self-reported smoking status and CO measurements, the high retention rate of study participants and examination of long-term outcomes.

This study also has some limitations. First, Quit Genius was not compared to another digital intervention. VBA was used as the control intervention due to its frequent use as the first-line intervention for smoking cessation in the United Kingdom, and for the participants not allocated a CO device, no mobile-app was provided. To control fully for time and attention, future studies should consider incorporating a digital intervention control condition.

Second, this study relied largely on self-reported smoking abstinence status, which may have been exaggerated. To mitigate this, we verified self-reported outcomes using a measurement device to assess CO levels in the breath of the participant. These devices were allocated pseudorandomly to 50% of participants in each study condition. Despite the limited biochemical verification data, the consistently high level of agreement between the CO readings and self-reported abstinence across all study timepoints suggests that, in the context of this study, self-report is a reliable indicator for true smoking abstinence.

Third, researchers were unblinded to participant group allocation, and could have introduced bias. Finally, there are some limitations to the generalizability of the study findings, in light of the characteristics of the study sample. Participants with serious health conditions and/or who were using psychiatric medication were excluded as a safety consideration. In light of the high rates of psychiatric comorbidity among smokers, replication and extension of the study to include those with co-occurring mental health conditions appears warranted. Further, given that the study sample comprises a largely urban population, the long term efficacy of a digital health intervention such as Quit Genius among rural groups of smokers, who could benefit tremendously from the accessibility of this approach, remains largely unknown.

Conclusion

Quit Genius, a DTI utilizing an extended care model combining NRT with evidence-based psychosocial treatment for smoking cessation, was highly effective in achieving continuous smoking cessation at 4-, 26- and 52-weeks compared to the control group using VBA.

Still, opportunities exist to improve psychological outcomes such as mental well-being and self-efficacy through future intervention refinement. Future research into the effectiveness of Quit Genius among more diverse populations of smokers is warranted.

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Conflict of Interests

The study was funded by the company that produced the DTI (Quit Genius; Digital Therapeutics, Inc). PS and AA are paid statistical consultants. All other authors except AM received a salary from or own equity in Digital Therapeutics, Inc.

References

1. Tobacco [Internet]. [cited 2021 Aug 18]. Available from: https://www.who.int/news-room/fact-sheets/detail/tobacco
2. Goodchild M, Nargis N, d'Espaignet ET. Global economic cost of smoking-attributable diseases. Tob Control. 2018;27(1):58–64.
3. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. JAMA. 2000 Jun 28;283(24):3244–54.
4. Panel TU and DG. Treating Tobacco Use and Dependence: 2008 Update. US Department of Health and Human Services; 2008.

5. Park ER, Perez GK, Regan S, Muzikansky A, Levy DE, Temel JS, et al. Effect of Sustained Smoking Cessation Counseling and Provision of Medication vs Shorter-term Counseling and Medication Advice on Smoking Abstinence in Patients Recently Diagnosed With Cancer: A Randomized Clinical Trial. JAMA. 2020 Oct 13;324(14):1406–18.
6. Killen JD, Fortmann SP, Murphy GM, Hayward C, Arredondo C, Cromp D, et al. Extended treatment with bupropion SR for cigarette smoking cessation. J Consult Clin Psychol. 2006 Apr;74(2):286–94.
7. Hall SM, Humfleet GL, Muñoz RF, Reus VI, Prochaska JJ, Robbins JA. Using Extended Cognitive Behavioral Treatment and Medication to Treat Dependent Smokers. Am J Public Health. 2011 Dec 1;101(12):2349–56.
8. Brunette MF, Ferron JC, Aschbrenner KA, Pratt SI, Geiger P, Kosydar S. Attitudes about smoking cessation treatment, intention to quit, and cessation treatment utilization among young adult smokers with severe mental illnesses. Addict Behav. 2019;89:248–55.
9. Haskins BL, Lesperance D, Gibbons P, Boudreaux ED. A systematic review of smartphone applications for smoking cessation. Transl Behav Med. 2017;7(2):292–9.
10. Webb J, Peerbux S, Smittenaar P, Siddiqui S, Sherwani Y, Ahmed M, et al. Preliminary Outcomes of a Digital Therapeutic Intervention for Smoking Cessation in Adult Smokers: Randomized Controlled Trial. JMIR Ment Health. 2020 Oct 6;7(10):e22833.
11. Quit Genius | Behavior Change Program for Quitting Smoking, Vaping, Alcohol and Opioid. [Internet]. [cited 2020 Sep 15]. Available from: https://www.quitgenius.com/
12. Heatherton TF, Kozlowski LT, Frecker RC, FAGERSTROM K-O. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991;86(9):1119–27.
13. Spek V, Lemmens F, Chatrou M, van Kempen S, Pouwer F, Pop V. Development of a smoking abstinence self-efficacy questionnaire. Int J Behav Med. 2013;20(3):444–9.
14. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, et al. The

Warwick-Edinburgh mental well-being scale (WEMWBS): development and UK validation. Health Qual Life Outcomes. 2007;5(1):63.

15. Curebase - Distributed clinical trials [Internet]. [cited 2020 Sep 15]. Available from: https://web.curebase.com/home
16. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev. 2016 Apr 10;4:CD006611.
17. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addict Abingdon Engl. 2005 Mar;100(3):299–303.
18. Volkow ND, Koob GF, McLellan AT. Neurobiologic Advances from the Brain Disease Model of Addiction. N Engl J Med. 2016 Jan 28;374(4):363–71.
19. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y, Dobson R. Mobile phone text messaging and app-based interventions for smoking cessation. Cochrane Database Syst Rev. 2019;(10).
20. Bricker JB, Watson NL, Mull KE, Sullivan BM, Heffner JL. Efficacy of Smartphone Applications for Smoking Cessation: A Randomized Clinical Trial. JAMA Intern Med. 2020 Nov 1;180(11):1472–80.
21. Garrison KA, Pal P, O'Malley SS, Pittman BP, Gueorguieva R, Rojiani R, et al. Craving to Quit: A Randomized Controlled Trial of Smartphone App-Based Mindfulness Training for Smoking Cessation. Nicotine Tob Res Off J Soc Res Nicotine Tob. 2020 Mar 16;22(3):324–31.
22. Liao Y, Wu Q, Kelly BC, Zhang F, Tang Y-Y, Wang Q, et al. Effectiveness of a text-messaging-based smoking cessation intervention ("Happy Quit") for smoking cessation in China: A randomized controlled trial. PLOS Med. 2018 Dec 18;15(12):e1002713.
23. Marler JD, Fujii CA, Galanko JA, Balbierz DJ, Utley DS. Durability of Abstinence After Completing a Comprehensive Digital Smoking Cessation Program Incorporating a Mobile App, Breath Sensor, and Coaching: Cohort Study. J Med Internet Res. 2021 Feb

15;23(2):e25578.

24. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. Nicotine Tob Res Off J Soc Res Nicotine Tob. 2002 May;4(2):149–59.

25. Gwaltney CJ, Metrik J, Kahler CW, Shiffman S. Self-efficacy and smoking cessation: a meta-analysis. Psychol Addict Behav J Soc Psychol Addict Behav. 2009 Mar;23(1):56–66.

26. Rajani NB, Mastellos N, Filippidis FT. Impact of Gamification on the Self-Efficacy and Motivation to Quit of Smokers: Observational Study of Two Gamified Smoking Cessation Mobile Apps. JMIR Serious Games. 2021 Apr 27;9(2):e27290.

Tables and Figures

Table 1: Sample characteristics.

	Treatment	Control
Number of participants	265	265
Age (SD)	40 (12)	42 (12)
Female	46.0%	44.0%
Ethnicity		
Caucasian/White	69.0%	62.0%
Black/Caribbean/African/Black	9.0%	11.0%
Asian	7.0%	9.0%
Arab	1.0%	2.0%
Mixed	9.0%	9.0%
Other	3.0%	4.0%
Prefer not to say	2.0%	3.0%
Education		
GCSE or lower	22.0%	23.0%
A-level	25.0%	19.0%
Undergraduate degree	29.0%	29.0%
Postgraduate degree	17.0%	19.0%
PhD	2.0%	1.0%
Prefer not to say	6.0%	9.0%
Employed	79.0%	81.0%
Type of employment (if employed)		
Managerial or professional	60.0%	53.0%
Routine or manual	10.0%	15.0%
Intermediate	10.0%	9.0%
Other	18.0%	19.0%
Prefer not to say	1.0%	3.0%

Cigarettes per day (SD)	14 (6)	15 (7)
Fagerström Test for Nicotine Dependence (range 0-10; SD)	4 (2)	4 (2)
Any past attempt to quit smoking	84.0%	86.0%
Method previously used (if past attempts)		
Cold turkey	47.0%	49.0%
E-cigarettes	42.0%	42.0%
NRT	31.0%	28.0%
Prescription medication	11.0%	15.0%
Smartphone app	9.0%	10.0%
Hypnotherapy	4.0%	7.0%
Psychological Therapy	2.0%	2.0%

NRT: nicotine replacement therapy.

Table 2: Primary Smoking Outcomes at 4-, 26, and 52 weeks Post-Quit Date

Continuous abstinence	Treatment	Control	χ^2	P-value	RR (95% CI)
4-weeks:					
7-day abstinence ITT (n=530)	118 (44.5%)	75 (29.3%)	13.7	<.001***	1.55 (1.23-1.96)
7-day abstinence PP (n=456)	118 (52.4%)	75 (32.5%)	17.8	<.001***	1.62(1.29-2.0)
26-weeks:					
7-day abstinence ITT (n=530)	72 (27.2%)	44 (16.6%)	8.7	0.003**	1.70 (1.22- 2.37)
7-day abstinence PP (n=433)	72 (33.8%)	44 (20.0%)	10.5	0.001**	1.79 (1.30-2.46)
(abstinent 4- and 26-weeks)					
52-weeks:					
7-day abstinence ITT (n=530)	60 (22.6%)	35 (13.2%)	8.01	0.005**	1.71 (1.17-2.50)
7-day abstinence PP (n=421)	60 (28.7%)	35 (16.5%)	8.9	0.003**	1.77 (1.22-2.54)
(abstinent at 4-, 26- and 52-weeks)					

RR, Relative Risk ratio
ITT, Intention-to-treat analysis
PP, Per-protocol analysis
**p<0.01
**p<0.001

Table 3: Secondary Smoking Outcomes at 4-, 26-, and 52 weeks

Outcome	treatment	control	χ^2	*t* test (*df*)	*P* value	RR[a]	95% CI
Quit attempts beyond initial QD							
Week 4	68 (25.6%)	86 (32.6%)	2.6	N/A	0.10	0.79	0.60 to 1.03
Week 26	94 (35.5%)	115 (43.4%)	3.2		0.07	0.82	0.66 to 1.01
Week 52	104 (39.2%)	135 (50.9%)	6.9		0.009**	0.77	0.64 to 0.93
Change in Self-efficacy							
Week 4	4.2 (7.0)	3.1 (6.7)		1.7 (527)	0.09	N/A	1.0 (-0.16 to 2.17)
Week 26	3.8 (8.5)	2.0 (6.9)	N/A	2.6 (506)	0.01*		1.75 (0.42 to 3.07)
Week 52	3.3 (8.6)	2.2 (7.8)		1.6 (524)	0.12		1.12 (-0.28 to 2.52)
Change in Mental Well-being							
Week 4	0.7 (7.0)	0.6 (6.5)		0.2 (525)	0.83		0.13 (-1.02 to 1.28)
Week 26	1.4 (8.2)	1.0 (7.8)	N/A	0.7 (527)	0.51	N/A	0.45 (-0.90 to 1.81)
Week 52	1.5 (8.4)	0.1 (8.3)		1.9 (528)	0.06		1.39 (-0.03 to 2.82)
7-day point prevalence abstinence							
Week 4 (ITT)	118 (44.5%)	75 (29.3%)	13.7		<0.001***		1.55 (1.23 to 1.96)
Week 4 (PP)	118 (52.4%)	75 (32.5%)	17.8		<0.001***		1.62 (1.29 to 2.02)
Week 26 (ITT)	95 (35.9%)	73 (27.6%)	4.2		0.03*		1.32 (1.03 to 1.69)
Week 26 (PP)	95 (44.6%)	73 (33.2%)	5.9		0.01*		1.38 (1.08 to 1.75)
Week 52 (ITT)	92 (34.7%)	78 (29.4%)	1.7		0.19		1.20 (0.94, 1.54)
Week 52 (PP)	92 (44.0%)	78 (36.8%)	2.3		0.13		1.24 (0.99, 1.57)
Sustained abstinence, <=5 cigs since QD							
Week 26	73 (27.5%)	40 (15.1%)	11.5	N/A	<0.001***	1.82	1.29 to 2.58
Week 52	58 (21.9%)	30 (11.3%)	9.9		0.002**	1.93	1.29 to 2.90

χ^2 = Chi squared test
QD = Quit Date
*p<0.05
**p<0.01
***p<0.001

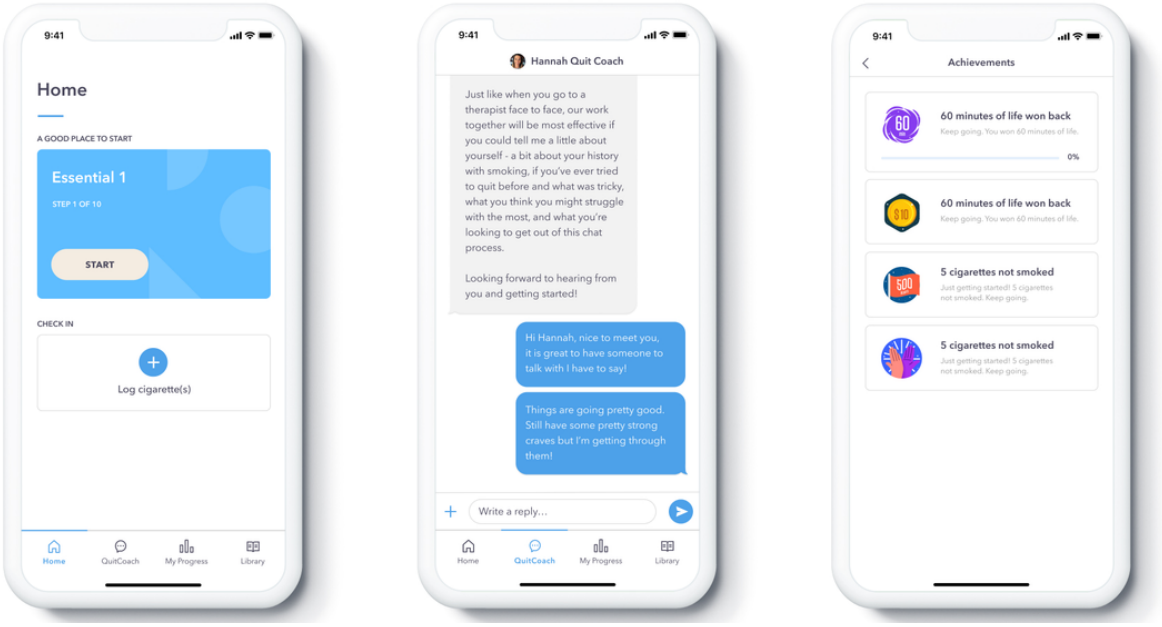

Figure 1: Screenshots of the digital therapeutic intervention Quit Genius.

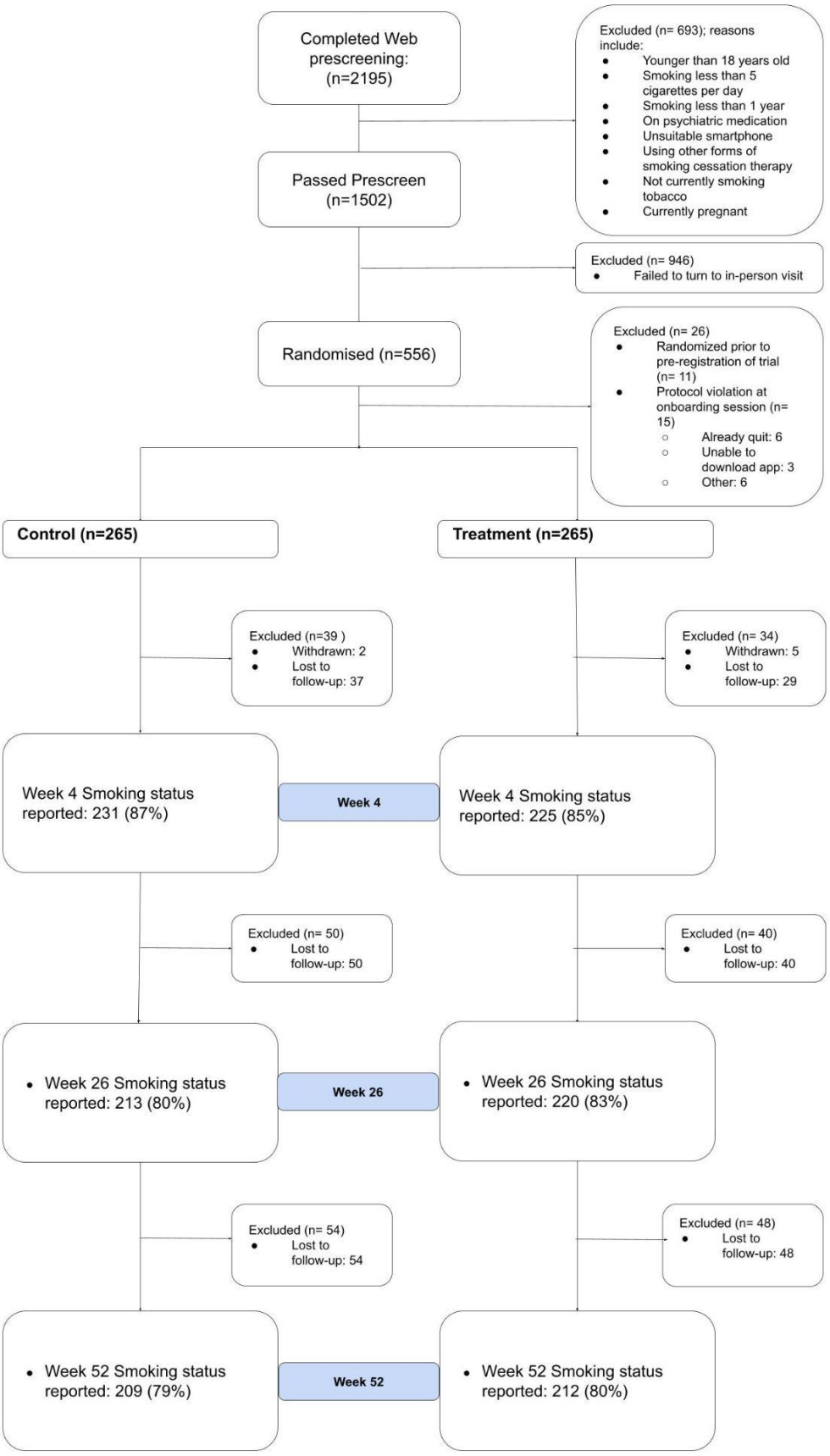

Figure 2: CONSORT Diagram

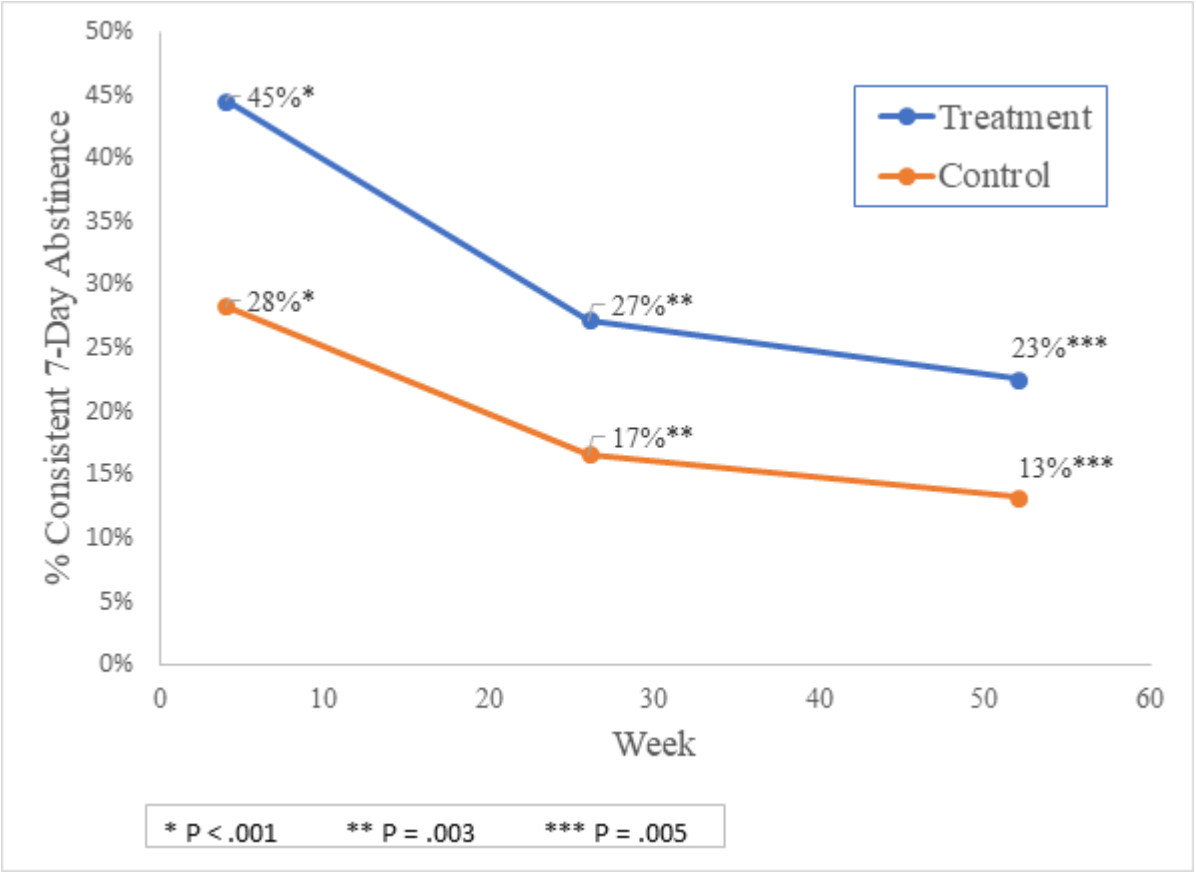

Figure.3. Change in Primary Outcome – 7-Day Point Prevalence Continuous Abstinence (ITT)