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How to cite

HUGHES, John R et al. Withdrawal symptoms from e-cigarette abstinence among adult never-smokers: a pilot experimental study. In: Nicotine & Tobacco Research, 2020, vol. 22, n° 5, p. 740–746. doi: 10.1093/ntr/ntz169

This publication URL: https://archive-ouverte.unige.ch/unige:143932
Publication DOI: 10.1093/ntr/ntz169

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doi:10.1093/ntr/ntz169
Original Investigation
Received July 12, 2019; Editorial Decision August 28, 2019; Accepted August 31, 2019

Original Investigation

Withdrawal Symptoms From E-Cigarette Abstinence Among Adult Never-Smokers: A Pilot Experimental Study

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Abstract

Introduction: Use of e-cigarettes among never-smokers has substantially increased; yet there are few descriptions of the consequences of such use. We assessed whether adult never-smokers can have withdrawal from cessation of e-cigarettes.

Methods: In an un-blinded pre-post clinical trial, 30 never-smoker daily e-cigarette users used their own nicotine-containing e-cigarette for 7 days followed by 6 days of biologically confirmed abstinence. Participants monitored symptoms of nicotine withdrawal nightly via an Interactive Voice Response system. They attended three lab visits/week to provide expired carbon monoxide and urine samples to determine compliance.

Findings: Abstinence increased all the DSM5 symptoms of tobacco withdrawal and this occurred in the majority of participants. The increase in severity of withdrawal was small and rarely impaired functioning.

Conclusions: Our finding suggests that withdrawal symptoms can occur in never-smokers who stop e-cigarettes abruptly. However, the severity of withdrawal appears to be small and may not be of clinical or regulatory significance. Although our sample size was small and thus replication tests of our results are indicated, it may be prudent to warn never-smokers that withdrawal symptoms may occur.

Implications: This study indicates that withdrawal symptoms can occur in never-smokers who are daily e-cigarette users. However, the severity of withdrawal from e-cigarette abstinence in never-smokers appears to be small and may not be of clinical or regulatory significance. Given our small sample size, replication of our results is warranted. Nevertheless, it might be prudent to warn never-smokers of addiction to e-cigarettes.

Clinical Trial Registration = NCT02825459

Introduction

The use of e-cigarettes among US adult never-smokers has increased substantially in the last few years[1–3] (Although this may not be the case in other countries.)[4] One of the major concerns about such use is that it may serve as a gateway to tobacco cigarette use.[5] Another concern is that, even if such use does not lead to tobacco use, it

may lead to nicotine dependence on e-cigarettes themselves[5] and long-term use of nicotine. Such use could produce cardiovascular problems.[6] The ability of nicotine to induce dependence in the absence of current or past tobacco use is unclear.[7–9] Dependence on nicotine replacement therapy (NRT) in never-smokers appears to be extremely rare.[10,11] NRTs produce nicotine levels with slow onset and nicotine levels less than half of that of cigarettes; in contrast, e-cigarettes can produce rapid uptake of large amounts of nicotine and thus are more likely to induce dependence in never-smokers.[5]

We could locate only one study on addiction to e-cigarettes among never-smokers.[12] This study recruited 19 adult never-smokers, 64 current smokers, and 237 former smokers who used e-cigarettes daily. Only 16% of the never smokers used e-cigarettes within 30 min of awakening (a validated marker of nicotine dependence),[13] whereas 64% of the current smokers and 62% of the former-smoker daily e-cigarette users did so.

During the conduct of our study on whether former smoker daily e-cigarette users would have withdrawal symptoms when they stopped vaping,[14] a substantial number of never-smokers applied for the study. Given adult never-smokers who are daily e-cigarette users are rare[1–3] but a group of concern, we amended our study protocol to allow such users to enroll in our study and now report on their results.

Our study focused on the presence of withdrawal upon abstinence because this is a major indicator of nicotine dependence, is clinically important because it makes cessation difficult, can produce functional consequences such as trouble sleeping or inability to concentrate, and is a sign of more severe addiction.[15,16] Since e-cigarettes contain nicotine but not other psychoactive tobacco ingredients, if e-cigarettes were found to cause withdrawal upon abstinence in never-smokers, this would suggest de novo dependence can occur upon use of nicotine per se. It would also suggest the risk of withdrawal upon abstinence should be conveyed in the product promotion and labeling of e-cigarettes as well as being recognized as a factor in the risk/benefit assessment of e-cigarettes.[17]

Methods

The methods we used for never-smokers were identical to those we used for our study of former smokers[14] and, thus, will be only described briefly. We recruited never-smokers, defined as those who used < 100 cigarettes in their lifetime and had no current "regular use" of other nicotine/tobacco products other than current e-cigarette use. They also had to currently use refillable nicotine containing e-cigarettes daily and currently use no other nicotine or tobacco products. Participants vaped their own e-cigarettes for 1 week and then abstained from e-cigarettes for a second week. We monitored withdrawal symptoms with nightly calls to an Interactive Voice Responding (IVR) system. Our major hypothesis was that the withdrawal scores would increase with abstinence. The study was conducted at Burlington VT and Baltimore MD sites. The study was approved by the University of Vermont and Battelle institutional review boards and was registered at clinicaltrials.gov (NCT02825459).

Participants

The major inclusion criteria were (1) ≥18 years old, (2) had not smoked ≥100 cigarettes in their lifetime and had no current "regular" use of tobacco or nicotine products other than e-cigarettes, (3) no current use of marijuana, (4) using a refillable tank e-cigarette, or drips liquid directly onto the heating coil (to obtain those more likely to evidence withdrawal[18]), (5) using nicotine-containing e-cigarette daily for the last 2 months, (6) had no current psychiatric problems, and (7) had a breath carbon monoxide level of ≤ 8 ppm, a urinary cotinine level of ≥100 ng/mL, and a negative marijuana dipstick. We included never-smokers in the study between 6/17 and 10/18. Our optimal sample size would be identical to that for our former smoker study (n = 60) but we were able to recruit only 30 participants during the funding period. The major methods of recruitment were Facebook, Instagram, and referral. The two major reasons for exclusion were recent marijuana use and use of a disposable or cartridge e-cigarette (see flowchart in Appendix).

Procedures

Participants were instructed to continue abstinence from all tobacco and nicotine products other than their own e-cigarettes and from marijuana during the entire study period. They were to use their own nicotine-containing e-cigarette as usual for the first week and to abstain from e-cigarettes in the second week. We used monetary contingencies to increase abstinence and compliance to obtaining measures. Participants attended three lab visits each week to provide breath and urine samples for verification of abstinence. In the first week of vaping as usual, they were required to have a carbon monoxide levels of 8 ppm or less, and positive cotinine tests via NicAlert dipstick tests.[19] During the abstinence week, they were required to have lower urinary cotinine tests. Our definition of abstinence compliance was no report of use of e-cigarettes or other tobacco or nicotine products and that the NicAlert had decreased by at least one level by the end of the week. During both phases, participants were required to have a negative breath carbon monoxide and urine marijuana dipstick tests, attend all laboratory sessions, and complete at least three IVR calls/week. If a participant was compliant to completing measures and abstinence, they would earn an extra US$15 on a Monday session, US$20 if still compliant on a Wednesday session, and US$25 if still compliant at the Friday session.

Measures

Withdrawal symptoms were collected via nightly IVR calls. Participants were reimbursed US$2/IVR call with a bonus of US$10 for each week in which all seven daily calls were completed. The IVR asked the two urge questions of the Mood and Physical Symptoms Scale.[20]The urge strength rating scale is 0 = No urges, 1 = Slight, 2 = Moderate, 3 = Strong, 4 = Very Strong, and 5 = Extremely strong urges. The frequency of urges scale is 0 = Not at all, 1 = A little of the time, 2 = Some of the time, 3 = A lot of the time, and 4 = All the time. The IVR next asked participants to rate the seven DSM-5 withdrawal criteria (anger, anxiety, difficulty concentrating, depression, hunger insomnia, and restlessness)[21] plus four plausible withdrawal symptoms (anhedonia, impulsivity, mood swings, and positive affect) and three control symptoms known not to increase with withdrawal (diarrhea, headache, and tremor) on a 0–3 scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe.[15,16] It also asked participants to state whether the withdrawal symptoms "interfered with their functioning." Finally, the IVR asked about any use of tobacco cigarettes, smokeless, cigars, marijuana, or nicotine replacement. At the lab visits, we also obtained weight and heart rate. Finally, participants completed an e-cigarette purchase task that measures motivation to continue to use e-cigarettes.[22] This outcome will be reported elsewhere.

Data Analysis

Our major hypothesis was that, among the 18 compliant participants, the withdrawal scores would increase during abstinence. Our major outcome was the average score across the seven DSM symptoms. Because withdrawal symptoms peak on the first 2 days,[15] we compared the mean score on the last 2 days of the vaping week with the mean score on the first 2 days of abstinence week. In all analyses, we assumed missing data represented a lack of abstinence. Our major analysis was based on those compliant for the entire study, i.e., 18 (60%) of the 30 enrolled. We also conducted a sensitivity test in which we only required abstinence on the first 2 days of abstinence to obtain a less selective sample (n = 23, 77%). Secondary analyses examined whether individual withdrawal symptoms, craving scores, newly proposed withdrawal symptoms, and verified nonsymptoms of withdrawal changed with abstinence.[15] To examine whether symptoms exhibited the expected inverted U time pattern of a withdrawal effect we tested whether the symptoms decreased from the peak time in the first 2 days to the end of the study, i.e., during days 3–6 of abstinence. We also tested whether the increase in withdrawal prospectively predicted the inability to abstain at the end of the study. Vaping versus abstinence comparisons were tested with paired t-tests. We used a two-tailed $p \leq .05$ to determine statistical significance.

Results

Participants

As in prior studies of never-smokers who use e-cigarettes,[2,3] participants were mostly young White men (Table 1). The average duration of e-cigarette use was about 2 years. Compliant and noncompliant participants were similar except compliant participants had lower cotinine levels. Few participants said they were unable to quit e-cigarettes and the mean rating of addiction was midway on a 10-point scale. None reported 4+ DSM-5 symptoms (needed for DSM-defined withdrawal) during past abstinence. We calculated mean nicotine intake during the vaping period by multiplying the mL of e-liquid used daily by the mg of nicotine and found the average nicotine intake to be 21 mg/day. Among the 18 compliant participants, five reported using hookahs and one reported using cigars "regularly" in the past but not currently. Nonstatistical examination suggested similar results for those who had and had not used other products regularly in the past. More detailed information on the tobacco and e-cigarette use of these never-smokers was obtained in a semistructured interview during the study and will be reported elsewhere. The 18 compliant (60%) and the 12 noncompliant participants were similar on demographics, and measures of e-cigarette and tobacco use (Table 1). Among those compliant, the NicAlert reduced one level with abstinence in five participants, reduced two levels in six participants, three levels in six participants, and five levels in one participant. Among the compliant participants, withdrawal ratings during vaping in the first week were stable or decreasing over time. The three nonwithdrawal symptom ratings were almost zero and did not change over time.

Tests of Major Hypotheses

Among the 18 compliant participants, the mean withdrawal score increased with abstinence and peaked on days 1 or 2 (Figure 1; Table 2). The increase in the mean withdrawal score among compliant participants was 0.23 units on the 0–3 scale (95% CI = 0.09, 0.37). In comparison, in our prior study of e-cigarette withdrawal among former smokers using identical procedures, the increase was 0.41 units (95% CI = 0.29, 0.54). In two prior studies of using the similar methods and the same scale, the increase with cessation of tobacco cigarettes was 0.55 units[23] and for cessation of nicotine gum was 0.57 units.[24] All seven of the DSM-5 withdrawal symptoms increased with abstinence (Table 2). Craving e-cigarettes and irritability increased somewhat more, and depression and insomnia somewhat less, than other symptoms. Weight did not increase during abstinence. Heart rate decreased from 77.1 to 69.3 bpm (p = .0005). Among the designated possible withdrawal symptoms, impulsivity and mood swings increased but decreased positive mood and loss of enjoyment of pleasant events did not (Table 2). Similar findings for all the above occurred in the sensitivity analysis.

Table 1. Participant Characteristics*

	Compliant	Non-Compliant	PATH Wave 1
	N = 18	N = 12	Unweighted n = 11 Weighted n = 27,600
Demographics			
Age*	22 (4)	21 (2)	26
% Female	39%	33%	73%
% > High school	83%	75%	77%
% Unemployed	11%	8%	13%
% Caucasian	83%	67%	52%
E-Cigarette Use			
Cotinine Level (0–6)**	4.5 (4–6)	6 (6-6)	
Duration*(months)	20 (14)	20 (19)	
% stated unable to stop using ecigs	6%	18%	
Current addiction to ecigs on 0–10 scale)*	5.7 (2.6)	5.6 (3.2)	
% ever stopped ecigs ≥3 days	67%	92%	
Among those who stopped, % with ≥4 of 7 DSM5 withdrawal symptoms	0%	0%	

PATH= Population Assessment of Tobacco and Health

*Mean and (standard deviation).

**Median (interquartile range); Wilcoxon Rank Sum Test, p = .004.

PATH participants were daily users using nicotine, non-refillable e-cigs who smoked <100 cigarettes in lifetime and no use of other tobacco products in last 30 days. No significant differences between compliers and noncompliers.

To test for the typical inverted U time pattern of withdrawal, we tested whether the total withdrawal score decreased after the first 2 days. In a regression, the slope was not consistently negative (−0.03, p = NS). Half (50%) of participants continued to have withdrawal symptoms at the end of the study; i.e., their total withdrawal score at the end of the study was numerically higher than their mean preabstinence vaping scores.

The mean withdrawal score increased from the last 2 days of vaping to the first 2 days of abstinence in 67% of participants and the strength of craving for e-cigarettes increased in 56%. When asked about whether withdrawal symptoms interfered with functioning, this increased from 11% or participants during vaping to 33% during abstinence. A few (22%) participants had an increase on 4+ symptoms and thus met the symptom number criterion for DSM5 nicotine withdrawal. When symptoms were also required to interfere with functioning, 17% met full DSM5 criteria. No participants had an adverse event that was rated as severe. We examined several baseline possible moderators. Those with greater negative expectancies from abstinence, and those with greater withdrawal when having stopped e-cigarettes in the past (among those who had abstained) had greater increases in withdrawal. Age, sex, baseline cotinine, the decline in cotinine levels with abstinence, psychiatric problems, e-cigarette liquid nicotine content, duration of using e-cigarettes, and rating of current addiction did not predict the increase in total withdrawal.

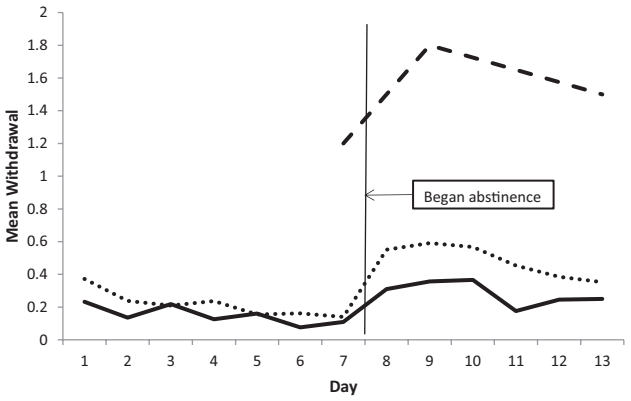

Figure 1. Mean withdrawal score (0–3) before and after abstinence from e-cigarettes in never-smokers in the current study (solid line); after abstinence from e-cigarettes in former smokers in our prior study (dotted line); and after abstinence from tobacco in abstinent smokers in our prior study (dashed line).

Discussion

The main findings of this pilot investigation were (1) withdrawal can occur in never-smokers who stop e-cigarette use, (2) the severity of withdrawal from e-cigarette abstinence in never-smokers appears to be less than that from abstinence from e-cigarettes in former smokers and from cigarette abstinence, and (3) the incidence and, severity, of e-cigarette withdrawal in never-smokers may not be of clinical or regulatory significance.

One limitation of our results is that the study was confined to never-smokers who are daily e-cigarette users. The prevalence of current use of e-cigarettes in never-smokers is 1.4%, and 18% of never smokes who use e-cigarettes are daily users.[2] Thus, our results apply to only a small group of e-cigarette users. We employed a convenience sample and this was likely influenced by locale (e.g., the Burlington site was on a college campus). We also enrolled only those who used refillable

Table 2. Mean Change in Withdrawal and Control Symptoms with Abstinence Among Compliers (n = 18)

	Vaping	Abstinent	Increase		
	Mean	Mean	Mean (SD)	t value*	*P*
Withdrawal (0–3)					
Total	0.10	0.33	0.23 (0.28)	3.4	0.003
Angry, irritable	0.06	0.44	0.39 (0.53)	3.1	0.006
Anxious, nervous	0.14	0.42	0.28 (0.65)	1.8	0.09
Increased appetite	0.06	0.33	0.28 (0.71)	1.7	0.12
Difficulty concentrating	0.06	0.33	0.28 (0.52)	2.3	0.04
Depressed, sad	0.14	0.25	0.11 (0.63)	0.7	0.47
Insomnia	0.14	0.25	0.11 (0.27)	1.7	0.10
Restlessness	0.14	0.31	0.17 (0.34)	2.1	0.05
Craving					
Ecig craving					
How much of time urge (0–4)	1.44	2.08	0.64 (0.97)	2.8	0.01
How strong urge (0–5)	1.47	2.19	0.72 (1.00)	3.1	0.007
Tobacco cigarette craving					
How much of time urge (0–4)	0.17	0.31	0.14 (0.41)	1.4	0.17
How strong urge (0–5)	0.19	0.31	0.11 (0.44)	1.1	0.30
Potential Withdrawal Items (0–3)					
Impatient, impulsive	0.08	0.33	0.25 (0.39)	2.7	0.02
Enjoy pleasant events less	0.03	0.06	0.03 (0.27)	0.4	0.67
Less positive outlook	0.06	0.06	0.00 (0.17)	0.0	1.00
Mood swings	0.00	0.14	0.14 (0.29)	2.1	0.06
Control Items (0–3)					
Diarrhea	0.08	0.19	0.11 (0.61)	0.8	0.45
Headache	0.11	0.42	0.31 (0.82)	1.6	0.13
Tremors	0.00	0.03	0.03 (0.12)	1.0	0.33

*Based on paired t-test (17 df).

e-cigarettes, which produce higher nicotine levels and are more likely to induce dependence.[5] On the other hand, with the exception of under-representation of women, the characteristics of our participants were similar to never-smoker daily e-cigarette users in a population-based sample.[25] Our sample size was small and, thus, may have produced false negative results. Recent studies suggest testing participants who are actively trying to quit increases the sensitivity of human laboratory studies of abstinence[26]; thus, our use of those not trying to quit may also have produced false negatives. Participants and experimenters were not blind to the manipulation; thus, our results may be over-estimates due to expectancy effects as indicated in our moderator analyses. We compared our withdrawal results from e-cigarette abstinence with those among former smoker e-cigarette users who abstain, and with tobacco cigarette smokers who stopped smoking using historical controls. Such cross-study comparisons can be misleading.

On the other hand, our experimental design had several strengths; i.e., use of (1) never-smokers of who had no history of regular use of other tobacco products, (2) never-smokers who used the more potent refillable e-cigarettes, (3) a within-participants design, (4) measures at multiple time points during each condition, (5) methods to increase the incidence of abstinence, (6) a validated withdrawal scale, (7) inclusion of measures of the functional significance of withdrawal effects, and (8) inclusion of newly proposed withdrawal symptoms.

Our results have basic science, clinical, and regulatory implications. In terms of science, the evidence that nicotine per se can induce dependence has been described as poor in some reviews.[27] Our results do suggest nicotine per se can at least induce withdrawal which can be a marker for dependence. In addition, the finding that 40% of e-cigarette users were unable to stop e-cigarette use for only a week, even when given significant financial incentives, does suggest some dependence potential in e-cigarette users. In terms of clinical implications, our study suggests that clinicians should be aware that some complaints of irritability, etc., among e-cigarettes users could be due to e-cigarette withdrawal. On the other hand, given withdrawal symptom severity in never-smokers was less than that in former smokers, had a small effect on functioning, and did not appear to predict the inability to abstain, this suggests that withdrawal from e-cigarettes may not of sufficient severity to be of clinical significance. In terms of regulation of e-cigarettes, our results suggest that the ability to induce withdrawal symptoms upon abstinence should be part of a risk/benefit factor analyses of the public health impact of e-cigarettes. In addition, they suggest that never-smoker e-cigarette users should be warned that they may suffer withdrawal upon abstinence.

Like many pilot studies, ours had several methodological weaknesses; thus, we believe our results are preliminary and that replication will be necessary to validate our findings. Our study only assessed withdrawal. We believe experimental studies examining behavioral dependence (e.g., inability to stop use) using behavioral economics or diagnostic criteria are especially needed. Given the increase in use of e-cigarettes in adult never-smokers and the increased use of more potent e-cigarette products, the possibility of addiction to e-cigarettes in never-smokers warrants further study.

Funding

Funded by National Cancer Institute grant CA-192940

Declaration of Interest

JRH has received consulting and speaking fees from several companies that develop or market pharmacological and behavioral treatments for smoking cessation or harm reduction and from several nonprofit organizations that promote tobacco control. He currently receives consulting fees from Swedish Match and has received fees in the past from Altria and Philip Morris to assist their efforts to develop less-risky tobacco products such as e-cigarettes. CP-M's spouse's employer markets nicotine replacement products. J-FE, PWC, ENP, EO, and NM have nothing to disclose.

Acknowledgments

We thank Joy Benner, Quintella Bester, Konstantinos Farsalinos, Jessie McNabb, Shelly Naud, Jennifer Oletsky, Jeff Priest, Saul Shiffman, Joel Vincent, and Lauren Viray, for help in the conduct of the study or in interpretation of the study results.

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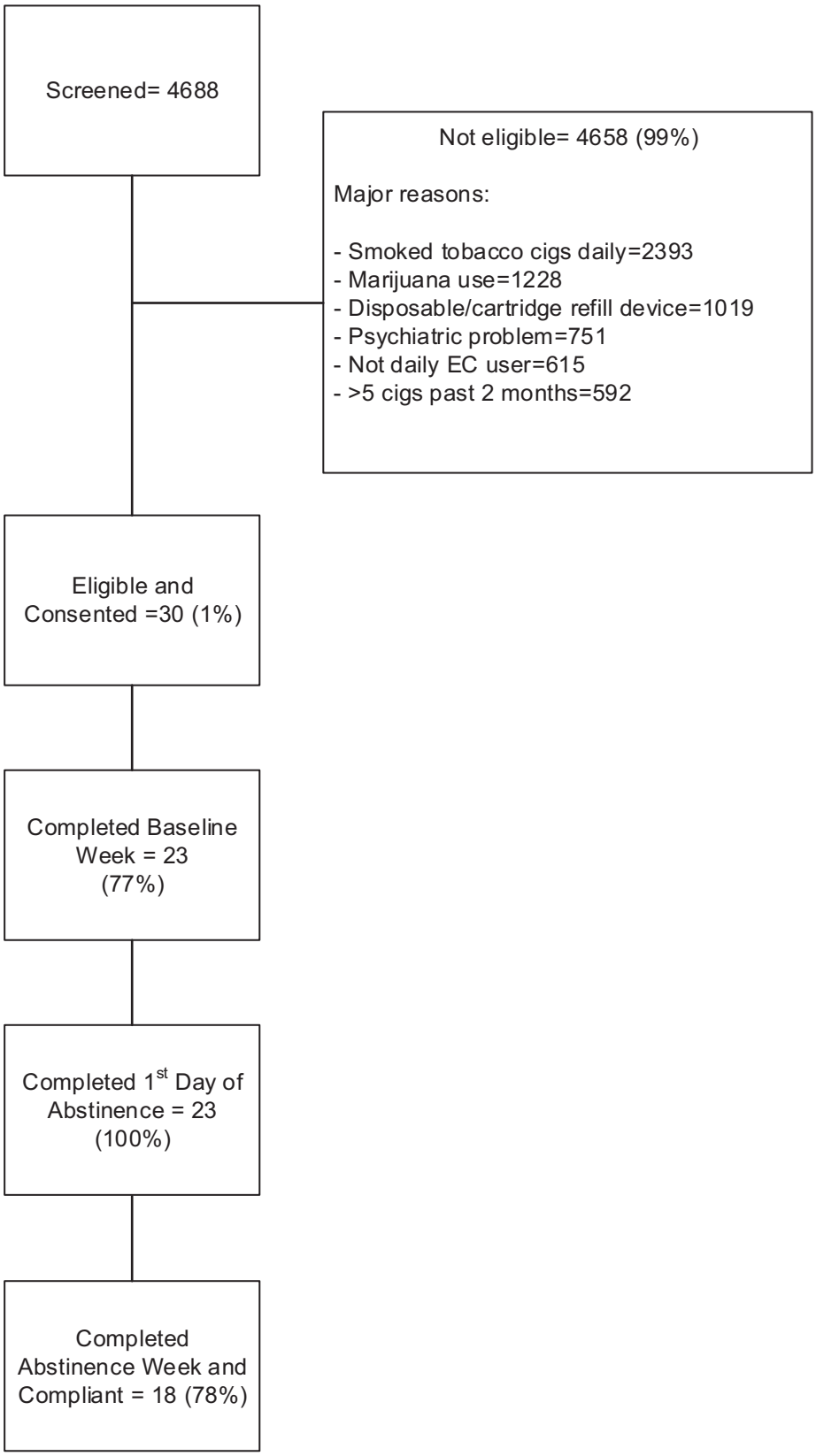
Appendix


Screened= 4688
Not eligible= 4658 (99%)
Major reasons:
- Smoked tobacco cigs daily=2393
- Marijuana use=1228
- Disposable/cartridge refill device=1019
- Psychiatric problem=751
- Not daily EC user=615
- >5 cigs past 2 months=592
Eligible and Consented =30 (1%)
Completed Baseline Week = 23 (77%)
Completed 1st Day of Abstinence = 23 (100%)
Completed Abstinence Week and Compliant = 18 (78%)