CRAVING AND WITHDRAWAL SYMPTOMS, IN A SHORT TERM PERIOD (72 HOURS) OF ENFORCED SMOKING CESSATION, IN HEALTHY VOLUNTEERS

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ABSTRACT

Nicotine addiction is recognised as a primary process in the maintenance of smoking behaviour and general failure of treatment interventions (1). Nicotine deprivation causes craving for cigarettes and withdrawal symptoms (2-4).
Craving is considered to be the main cause for failure in smoking cessation and/or relapses after successful cessation (5).
The available pharmacological aids for smoking cessation are represented by Nicotine Replacement Treatments (NRTs) and Zyban® (bupropion sustained-release), a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine, the first available non-NRT (6).
We completed a previous study on craving and withdrawal symptoms in healthy volunteers going across 3 periods of: free smoke, enforced smoke cessation with NRT-patches or Placebo patches. The study showed that the intensity of craving was significantly lower with smoke and NRT than with Placebo, but no difference was found between those who smoked and those who had NRT (7).
The present study was double blind, randomised, 3 period, crossover, conducted in 21 healthy volunteers not intending to quit smoking.
The aim of the study was to investigate nicotine craving and withdrawal symptoms in an acute controlled setting.
Subjects went through three 72 hours periods of: free smoking, enforced smoking cessation with Zyban® (150mg P.O.) and enforced smoking cessation with Placebo. Active drug and Placebo were given as tablet twice a day at least 8 hours apart.
At predefined times three self-reported questionnaires were administered: the Tiffany Questionnaire on Smoking Craving/Urge, Short Form (QSU-SF), the Schneider Smoker Compliant Scale (SCS) the Shiffman-Jarvik Smoking Withdrawal Questionnaire (SWQ).
Craving was reported by 81% of subjects on Placebo, compared with 43% on smoking and 55% on Zyban®.
The intensity of craving was significantly lower with smoking and Zyban® than with Placebo. Craving was lower with smoking than with Zyban®. The intensity of withdrawal symptoms was significantly lower after smoking compared with Placebo and after smoking compared to Zyban®, but no difference was found between Zyban® and Placebo.
These results show that Zyban®, which has been demonstrated to be effective in clinical trials, is also effective in reducing craving in a short term setting. These data support our previous finding that craving and withdrawal symptoms could be sustained by different physiopathological pathways and therefore separable (7).

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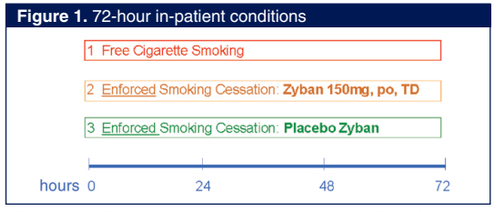
STUDY DESIGN

This was a double blind (according to the two non-smoking sessions: Zyban® versus Placebo tablets), randomised, three periods, crossover study. Each subject participated in the study had to go throughout three different in-patient conditions (Figure 1):

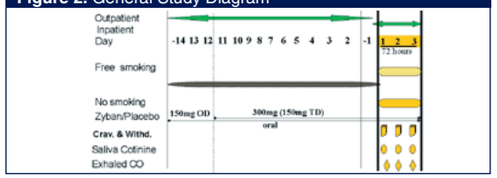
Figure 1. 72-hour in-patient conditions



- Two 72-hour (Days 1-3) non-smoking periods receiving Zyban® or Placebo tablet administration.
- One 72-hour (Days 1-3) smoking period, being allowed to smoke ad libitum.

Each of the two non-smoking periods was preceded by an out-patient period of 2 weeks (from Day -14 to Day -1) while subjects were allowed to smoke ad libitum, receiving Zyban® or Placebo tablet (Figure 2).

Figure 2. General Study Diagram



Ultimately Zyban® and Placebo tablets were administered for 17 consecutive days as follows:

- 1 tablet OD (morning) from Day -14 to Day-12
- 1 tablet TD (morning and afternoon) from Day -11 to Day 3

There was a wash out of at least ten days between each study conditions.
Each subject had to attend the Clinical Pharmacology Unit of GlaxoSmithKline in Verona (Italy) on 5 occasions: a pre-study screening visit, three 72-hour study periods, and a post-study follow- up visit.
The total duration of a subject's participation was approximately 8 weeks from the time of the screening visit to study discharge. A screening visit was performed within 21 days of admission to the research facility for the 1st study period. Subjects entered the research facility by 7 p.m. on the evening before the start of smoking deprivation (Day -1).

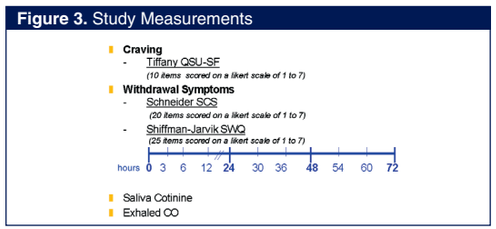
METHODS

A total of 23 healthy volunteers, 12 males and 11 females, were recruited from the panel of volunteers of the Clinical Pharmacology Unit. All these subjects were not intending to quit smoking. Inclusion criteria established that subjects: were at least eighteen years old; have smoked an average of 15 cigarettes or more a day for the past year; have Fagerström Tolerance Questionnaire (FTQ) scores of at least 7; were healthy as determined by physical, neurological and psychiatric examination, medical history, ECG and laboratory studies; were able to read, comprehend, and write in the language of the investigator, and sign and date a written informed consent prior to study participation. Exclusion criteria included any history of drug allergies, drug or alcohol abuse, use of long term medication, use of any drug within the previous 4 weeks, current use of any nicotine replacement therapy, alcohol intake during the 2 days prior the study or illness at the time of the study, and previous participation in any clinical study during the 6 months before the first study day.
Regulatory and ethical committee approval was obtained before the start of the study. The study was conducted in accordance with the Declaration of Helsinki.

Procedure
Subjects who met inclusion criteria were admitted to the Unit on the evening of Day -1 and remained until 6 hours after the end of each study period on Day 4. During each of the study periods, subjects had to observe the following restrictions: refrain from alcohol, avoid consumption of coffee, except for breakfast and lunch, avoid any prescribed concomitant medication and any over the counter preparations, refrain from strenuous exercise, refrain from all recreational drugs ("drugs of abuse" urine tests were performed during the study to monitor compliance with this restriction). Subjects that received Zyban® or Placebo tablets quitted smoking abruptly at 7:30 am of Day 1.

Measurements and Evaluations
The measurements were taken at various time intervals through the study. Time zero (0), around 8 am, was the beginning of the enforced abstinence, 30 minutes after the subject's last cigarette allowed (Figure 3).

Figure 3. Study Measurements



Self report questionnaires were administered at 0, 3, 6, 12, 24, 30, 36, 48, 54, 60 and 72 hours to evaluate craving and withdrawal symptoms:

The QSU-SF, to assess craving/urge to smoke, consists of 10 items scored on a likert scale of 1 (I strongly disagree) to 7 (I strongly agree).
The Average Total Score ranges from 1 to 7. Higher scores represents the presence of increased craving. The SWQ, to assess withdrawal symptoms, consists of 25 items scored on a likert scale of 1 (very definitely) to 7 (very definitely not). The scale allows for five Factors with scores ranging from 1 to 7. Higher scores represent the presence of lower levels of withdrawal symptoms.The SCS, to assess withdrawal symptoms, consists of 20 items scored on a likert scale of 1 (very definitely not) to 7 (very definitely).
The Sum Total Score ranges from 20 to 140. Higher scores represent the presence of higher levels of withdrawal symptoms.

Saliva samples for nicotine and cotinine levels were collected at 0, 6, 12, 24, 30, 36, 48, 54, 60 and 72 hours. Saliva samples were analysed for nicotine and cotinine levels using liquid-cromatography mass/mass (LC-MS/MS) assay at LOQ of 5ng/mL, using a 1mL sample.
Breath carbon monoxide (CO) measurements were performed at 0, 6, 12, 24, 30, 36, 48, 54, 60 and 72 hours using EC50 Micro III Smokerlyzer, Bedfont Instruments.

Statistical Methods
Total scores and factors of craving and withdrawal symptoms were at first summarised for each subject by the weighted mean over the 72 hours. This was calculated as the area under the measurement-time curve, divided by the time over which the measurements were taken, using the linear trapezoidal method. The weighted means of each total score and factor were then analysed by means of analysis of variance (ANOVA) taking into account subjects, periods and treatments.
The proportion of subjects with QSU-SF craving intensity ≥4 was compared between treatments on a pairwise basis by means of the nonparametric Sign Test. All analyses were performed using SAS Version 8 for Windows.

RESULTS

A total of 23 subjects (12 males and 11 females) participated in the study. Of the 23 subjects who entered the study, 20 completed all three 72 hours condition periods (Zyban® tablet, Placebo tablet, Free smoke).
Three of the original 23 subjects did not complete the study. Two received Placebo treatment only and withdrew for personal reasons before starting the in-patient period. One completed the Free smoke and the Placebo period, and withdrew during the Zyban® period because of nausea and headacke onset. Overall 21 subjects were treated and analysed.
An interval washout of at least 10 days between periods was maintained for all subjects who entered the study. The main study population characteristics are reported on Table 1.

Table 1. Study Population Characteristics

	Mean (± SD)	Range
N Enrolled	23	-
N Treated	21	-
Age (years)	34 (±13)	20-61
Male/Female	10/11	-
White Race	21/21	-
Height (cm)	170 (±7)	155-180
Weight (kg)	67 (±10)	50-87
FTQ	8 (±1)	7-10
N daily Cigarettes	23 (±6)	15-35

QSU-SF
The intensity of craving was summarised by the weighted mean over the 72 hours of the Average Total Score, Factor 1 and Factor 2 from the QSU-SF.
Key results in terms of treatments comparison are summarized in Table 2.

Table 2. Craving and Withdrawal Overall Results Comparisons

	Smoke vs Placebo	Zyban vs Placebo	Smoke vs Zyban
Tiffany QSU-SF	p<0.001	p<0.05	p<0.01
Factor 1	p<0.001	p<0.05	p<0.01
Factor 2	p<0.001	p=0.06	p<0.01
Schneider SCS	p<0.001	NS	p<0.05
Shiffman-Jarvik SWQ			
(Craving) Factor 1	p<0.001	p<0.05	p<0.001
(Psyc.Dis.) Factor 2	p<0.01	NS	p<0.05
(Phy.Sym.)Factor 3	p<0.05	NS	NS
(Sti./Sed.) Factor 4	NS	NS	NS
(Appetite) Factor 5	NS	p<0.05	NS

p<0.05 = *
p<0.01 = **
p <0.001 = ***

Figure 4. Tiffany QSU-SF: Craving Total Score

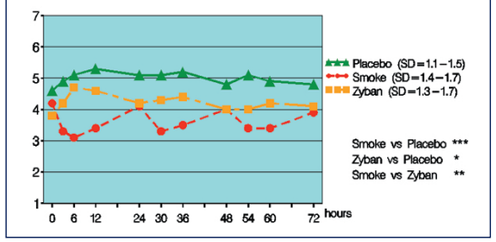
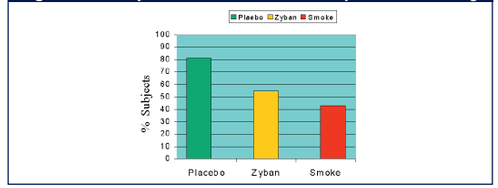


Figure 4 shows the mean 72-hours profile of the Average Total Score for each treatment. The figure shows that the intensity of craving was significantly higher (higher score) during Placebo than during Zyban® or Free Smoke. The figure also shows that during Placebo, craving seemed to have a circadian rhythm, with the lowest level in the morning and a progressive increase during the day. Craving achieved the maximum measured intensity around the 8 p.m. assessment, during each of the three abstinence study days. Over Zyban®, subjects tended to display a circadian rhythm profile similar to that seen during Placebo. Craving over the Zyban® treatment was generally lower than that observed during Placebo. During Free Smoke the overall levels of craving were significantly lower than during Placebo (p<0.001) and Zyban® (p<0.01). Moreover, the circadian rhythm during the Free Smoke tended to have an opposite direction compared to Placebo and Zyban® treatments.
Figure 5 shows that craving was reported by a significant higher proportion of subjects on Placebo (81%), compared to smoke (43%) and Zyban® (55%). Thus the repeated daily administration of the QSU-SF allowed us to recognise that: Free Smoke and Zyban® are able to significantly reduce the intensity and the proportion of subjects with craving, compared to Placebo; craving reduction is significantly higher with Free Smoke than with Zyban®.

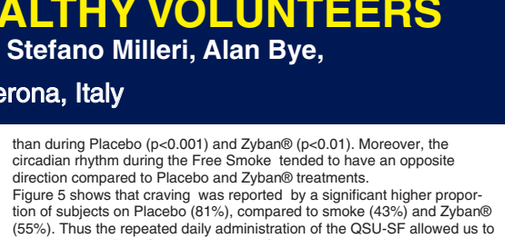
Figure 5. Tiffany QSU-SF Total Score: Subjects with Craving



SCS
The intensity of withdrawal was summarised by the weighted mean over the 72 hours of Sum Total Score.
Key results in terms of treatments comparisons are summarised in Table 2.

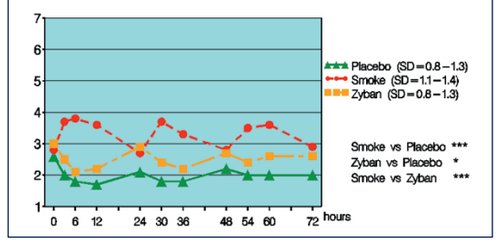
Figure 6 shows the mean 72- hours profile of Sum Total Scores for each treatment. The figure shows that withdrawal was significantly more intense (higher score) during Placebo than during Zyban® or Free Smoke.
Although withdrawal was somewhat stronger during Placebo than during Zyban®, this difference was on average not statistically significant. Thus, Zyban®, in contrast to craving, do not attenuate withdrawal symptoms. Furthermore, compared to craving, the circadian rhythm in the withdrawal scores appears to be less pronounced.

Figure 6. Schneider SCS: Withdrawal Sum Total Score



SWQ
The intensity of withdrawal was summarised by the weighted mean over the 72 hours of Factors 1-5 from the SWQ.
Key results in terms of treatments comparison are summarised in Table 2.
Figure 7 refers to the mean profiles of Factor 1, which explores craving.

Figure 7. Shiffman-Jarvik SWQ: Factor 1 - Craving Score

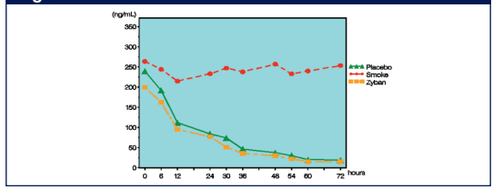


Craving factor was statistically significantly more intense (lower score) during Placebo than during Free Smoke and Zyban®, and during Zyban® than during Free Smoke. As with the QSU-SF, the figure shows that, during Placebo, craving levels, derived from the SWQ, seem to have a circadian rhythm, with the lowest intensity in the morning and a progressive increase during the day. A similar circadian rhythm profile seems to be present with Zyban®: parallel to Placebo but with a lower intensity.
During Free Smoke the circadian rhythm was evident with an opposite direction, compared to Placebo and Zyban®. Thus the repeated daily administration of the SWQ showed that: Free Smoke and Zyban® are able to significantly reduce the intensity of craving compared to Placebo, although the reduction with Free smoke is significantly higher than with Zyban®; craving can have a circadian rhythm during Free smoke, Placebo and Zyban®.

Factors 2-5 are summarised in Table 2.
Factor 2 explores Psychological Discomfort, Factor 3 explores Physical Symptoms, Factor 4 explores Stimulation/Sedation Symptoms, Factor 5 explores Appetite. However, among these only appetite shows to be sensitive to the Zyban® administration.

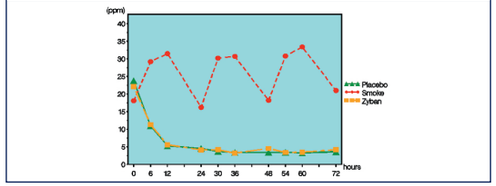
Saliva Cotinine
Figure 8 shows mean saliva cotinine concentration across days for each condition. As expected there were significantly higher levels of cotinine during Free Smoke than during Zyban® or Placebo.
With Zyban® and Placebo, the cotinine levels dropped (as expected) with a progressive reduction to very low level (<30ng/ml) within 54 hours from smoking cessation. Thus saliva cotinine levels proved to be a good indicator of nicotine intake during each study conditions.

Figure 8. Mean Saliva Cotinine Concentration



Exhaled CO
Figure 9 shows that, for Zyban® and Placebo, levels of exhaled CO dropped to a very low levels (< 6ppm) after 12 hours from smoke cessation.
In contrast CO reached very high levels during Free Smoke. The profile for this condition showed also a very clear circadian rhythm with the highest value in the evening and the lowest in the morning after wakeup. Thus the exhaled CO measurement is a good indicator of recent cigarette smoking.

Figure 9. Mean Exhaled CO



CONCLUSIONS

The study showed that:

- Free smoke and Zyban® were able to significantly reduce the intensity of craving, compared to Placebo, although the intensity of craving was significantly lower with smoke than with Zyban®.
- Free Smoke and Zyban® were also able to significantly reduce the proportion of subjects with craving compared to Placebo, although the proportion was significantly lower with smoke than with Zyban®.
- Free smoke was able to significantly reduce the intensity of withdrawal symptoms compared to Placebo and Zyban®, but no difference was found between Zyban® and Placebo.
- In addition, during Free smoke, Zyban® and Placebo, craving intensity seemed to display a circadian rhythm which was less evident for withdrawal symptoms.

These results show that Zyban®, which has been demonstrated to be effective in clinical trials, is also effective in reducing craving in a short term setting. Moreover these data support previous findings showing that: a high proportion of cigarette smokers report craving even during the free smoking period, craving and withdrawal symptoms seem to have a different temporal patterns. These could be sustained by different physiopathological pathways and their relationship needs further investigations . Finally the short term clinical setting we used to assess craving and withdrawal symptoms during the enforced smoking cessation, has proved to be sensitive with both NRT and Zyban®, the current available pharmacological aids for smoking cessation.

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