Anxiety, Depression and Tobacco Abstinence

Ansiedad, depresión y deshabituación tabáquica

Virginia Almadana Pacheco*, Ana Paulina Gómez-Bastero Fernández*, Agustín Valido Morales*, Estefanía Luque Crespo*, Soledad Monserrat García*, Teodoro Montemayor Rubio*.

*UGC Neumología. Hospital Virgen Macarena. Avda. Dr. Fedriani s/n. 41003. Sevilla. España. Teléfono 600162576.

Abstract

There is evidence of the relationship between mental illness and smoking and increased risk of depressive episodes after quitting smoking, even with specific treatments for abstinence. Objective: To assess the influence of a cessation program on the emotional state of patients by measuring levels of anxiety / depression and differences depending on the presence of psychiatric history. Method: A prospective observational study of patients taking part in a combined program (pharmacological and cognitive-behavioral) for giving up smoking. Anxiety (A) and depression (D) were measured using the HADS questionnaire at baseline, first and third month of abstinence. Results: Anxiety and depression showed significant and progressive improvement during treatment (A: baseline 9.2 ± 4.5, 5.9 ± 3.6 1 month, 3 months 4.5 ± 3.1, p <0 05 / D: baseline 5.5 ± 4.1; 1 month 3 ± 3; 3 months 2.3 ± 2.1, p <0.05), in psychiatry population (A: baseline 11.3 ± 4 , 5; 1 month 7.1 ± 3.7, 5.3 ± 3.5 3 months, p <0.05 / D: baseline 7.4 ± 4.8, 4.2 ± 3.6 one month; 3 months 3 ± 2.9, p <0.05), regardless of treatment. Abstinence rate: 58.5%, unaffected by baseline levels of anxiety and depression. No significant neuropsychiatric side effects were detected. Conclusions: Anxiety and depression levels evolved favourably during the program, achieving good results regardless of the presence of psychiatric pathology.

Keywords: Anxiety; depression; tobacco; psychiatric patients; tobacco abstinence.

Resumen

Existe evidencia de la relación entre patología mental y tabaquismo y del mayor riesgo de sufrir un episodio depresivo al dejar de fumar, incluso con tratamientos específicos para la abstinencia. Objetivo: valorar la influencia de un programa de abandono del tabaco en el estado emocional de los pacientes mediante la medición de los niveles de ansiedad/depresión y las posibles diferencias en función de la presencia de antecedentes psiquiátricos. Método: estudio de cohortes observacional y prospectivo de pacientes que acudieron a dejar de fumar mediante programa combinado (farmacológico y cognitivo-conductual). Se midió ansiedad (A) y depresión (D) utilizando el cuestionario HADS al inicio, primer y tercer mes de abstinencia. Resultados: la ansiedad y la depresión presentaron mejoría significativa y progresiva a lo largo del tratamiento (A: basal 9,2±4,6; 1 mes 5,9±3,6; 3 meses 4,5±3,1; p<0,05 / D: basal 5,5±4,1; 1 mes 3±3; 3 meses 2,3±2,1; p<0,05), en la población psiquiátrica (A: basal 11,3±4,5; 1 mes 7,1±3,7; 3 meses 5,3±3,5; p<0,05 / D: basal 7,4±4,8; 1 mes 4,2±3,6; 3 meses 3±2,9; p<0,05), e independientemente del tratamiento. Tasa de abstinencia: 58,5%, no se vio afectada por los niveles basales de ansiedad y depresión. No se detectaron efectos secundarios neuropsiquiátricos relevantes. Conclusiones: los niveles de ansiedad y depresión evolucionan favorablemente durante el programa, alcanzándose buenos resultados, independientemente de la presencia de patología psiquiátrica.

Palabras clave: Ansiedad; depresión; tabaco; pacientes psiquiátricos; abstinencia tabáquica.

Evidence of the link between mental illness and tobacco dependence has been provided (Lawrence, Hafekost, Hull, Mitrou, & Zubrick, 2013), and the fact that those with psychiatric pathology have higher levels of anxiety and depression when compared to non-smokers has also been documented. Furthermore, quitting smoking carries a greater short-term risk of major depressive episodes, which can even be triggered by a sudden reduction in nicotine intake (Lagrue, Dupont, & Fakhfakh, 2002; Mykletun, Overland, Aaro, Liabo, & Stewart, 2008). Nevertheless, a review of studies using specific questionnaires with disparate results to assess the variation in levels of anxiety and depression after several weeks of not smoking shows that it is not yet completely clear how anxio-depressive symptomatology responds after a certain period of abstinence (Bolam, West, & Gunnell, 2011; Dawkins, Powell, Pickering, Powell, & West, 2009; Marqueta, Jimenez-Muro, Beamonte, Gargallo, & Nerin, 2010; McDermott, Marteau, Hollands, Hankins, & Aveyard, 2013; Sampablo et al., 2002; West & Hajek, 1997).

Not only do smokers have worse levels of anxiety and depression, or a greater susceptibility to mental pathology, but there is also a well-documented link between smoking and psychiatric pathology (Sobradiel & García-Vicent, 2007), with a prevalence of more than double among smokers compared to the general population. In addition, these patients carry a greater risk of relapse, higher drop-out rates, more severe withdrawal symptoms — all of which pose a serious challenge to a smoking cessation clinic.

There is sufficient evidence of the efficacy of first-line drugs for quitting smoking (nicotine replacement therapy (NPT), Bupropion and Varenicline) in healthy patients. The evidence with patients suffering mental illness is greater with NPT and Bupropion, and more limited with Varenicline given that patients with this profile did not take part in the marketing studies. Furthermore, following the approval of both drugs, cases began to appear in which the safety of the drug was questioned and the alarm was raised regarding the greater risk of serious neuropsychological effects in both patients with and without a history of psychiatric problems. As a result, the Food and Drug Administration (FDA) in the USA decided to include a "black alert" warning on the drug packaging which is still in place today (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm169988.htm). This in turn provided the motivation for a series of studies (Ahmed et al., 2013; Anthenelli et al., 2013; Cinciripini et al., 2013; Foulds et al., 2013; Garza, Murphy, Tseng, Riordan, & Chatterjee, 2011; Gunnel, Irvine, Wise, Davies, & Martin, 2009; McClure et al., 2009; Kasliwal, Wilton, & Shakir, 2009; McClure et al., 2010; Stapleton et al., 2008; Tonstad, Davies, Flammer, Russ, & Hughes, 2010),

some of which were even sponsored by the FDA, with a large range of methodologies and populations with the aim of analysing the possible neuropsychological effects of the drugs in general as well as their efficacy with mentally ill patients, although greater media attention fell on those involving Varenicline. Studies measuring levels of anxiety and depression in a standardised manner are fewer in number (Anthenelli et al., 2013; Cinciripini et al., 2013; Garza et al., 2011; McClure et al., 2009; McClure et al., 2010) and occasionally used complex questionnaires or were based on a measurement of withdrawal symptoms (Cinciripini et al., 2013), and at times limited to a small number of patients (Garza et al., 2011) with controversial results.

Research into the safety of these drugs is still ongoing today and although there are no contraindications to their use with psychiatric patients, careful monitoring of such patients is strongly advised.

Given the above, we attempt to evaluate the influence of a smoking cessation programme on the emotional state of patients by measuring their anxiety/depression levels throughout the treatment and whether a history of mental illness leads to possible differences. The programme was carried out in a secondary hospital unit for quitting smoking.

Material and Methodology

A prospective longitudinal observational cohort study was carried out with consecutive inclusion of patients attending the smoking cessation clinic at Seville's Hospital Universitario Virgen Macarena in order to quit smoking from March 2011 to October 2012. The STROBE declaration guidelines for the publication of observational studies were followed.

Participants

The study included smokers over the age of 18 with an accumulated smoking history of > 10 pack-years who agree to participate in a combined smoking cessation programme (pharmacological treatment plus cognitive behavioural therapy). Exclusion criteria were being an ex-smoker, being pregnant or attempting conception, lactation, inability to understand the questions in the anxiety/depression questionnaire, patients treated with nicotine patches, and refusal to take part in the study. The presence or a history of psychiatric pathology were not grounds for exclusion.

Smoking cessation treatment programme

A combined programme of pharmacological and individualised cognitive-behavioural psychological treatment was carried out with five control points: baseline, 15 days, first, second and third month. On the first visit, the pneumologist, who was the same in each case, established the clinical history, including psychiatric history, and decided on the pharmacological treatment based on the

Virginia Almadana, Ana Paulina Gómez-Bastero, Agustín Valido, Estefanía Luque, Soledad Monserrat García, Teodoro Montemayor

characteristics of each patient (comorbidity, concomitant medication, cost of treatment and preferences agreed with the patient): Bupropion (150 or 300 mg) or Varenicline (0.5 mg/day for 3 days; 0.5 mg/12 hours from the 4th to 7th day and 1 mg/12 hours from the 8th day on), with a duration of two months in both cases. Rescue nicotine gum was allowed at a decreasing rate over the first few days after complete cessation. The psychologist used a COoximeter of the type Micro-smokerlyzer (Model Micro Co, from Micro Medical Limited, Kent, UK) to measure exhaled CO, the HADS questionnaire (Hospital Anxiety and Depression Scale) (Zigmond & Snaith, 1983), the Fagerström test and the Richmond test. In other follow-up visits possible problems connected with the medication were assessed and abstinence was monitored.

Patients who did not complete the scheduled visits were telephoned to check for possible adverse effects, especially those of a neuropsychiatric nature. Patients who stopped smoking were asked to take a COoximeter test, and those whose abstinence could not be proved (impossible to contact patient and measure CO) were considered to have failed.

Variables:

- Principal variable:
  · Changes in the scores obtained for anxiety and depression symptoms after one month and at three months on the HADS questionnaire, which consists of 14 items divided into two subscales (anxiety and depression). The scores were reported as absolute scores for each subscale and scoring interval. Scores of 11 or above on either scale were considered to represent a high probability of suffering anxiety or depression disorder, scores between 8 and 10 were borderline and scores of 7 or below represented a low probability of this type of disorder.
- Secondary variables
  · Abstinence rate: established by measuring exhaled CO.
  · Adverse effects related to the medication for tobacco cessation: the most frequent adverse effects of the drugs employed, as well as those less frequent (anxiety, suicide ideation, suicide attempts, onset/worsening of psychiatric illness), were registered systematically. Any side effect or symptom that appeared and did not correspond to those mentioned was also recorded. Patients who did not attend follow-up visits were questioned by telephone. The moment symptoms appeared was recorded: early (first few days), first week, second week, third week, first month, second or third month. The intensity of symptoms was measured using a Likert scale from 0 to 3 (0: none, 1: light, 2: moderate, 3: strong).

- Other variables: epidemiological data and personal history, smoking history, motivation levels for quitting smoking (Richmond test) and nicotine dependence (Fagerström test) and assessment of withdrawal symptoms with a specific questionnaire of 12 questions connected to the most frequent symptoms and scored on a 4-point Likert scale from 0 to 3 (0: no withdrawal symptoms, 1: light withdrawal symptoms, 2: moderate, 3: severe).

Statistical analysis

To calculate the sample size, a preliminary analysis of the changes in anxiety/depression levels of a group of patients in the smoking cessation clinic was carried out. The mean baseline and first month anxiety score (which can be extrapolated to depression) was used. Using the program nQuery Advisor to calculate the difference (2.5 ± 2) it was found that 678 patients were needed to obtain a 95% confidence interval with statistical significance at 0.05. To counteract the expected dropout rate of 25% and 20% in the first and third month respectively, typical of a smoking cessation clinic like ours, we arrived at a total sample of 1140 patients.

SPSS version 22.0 (2014) was used for statistical analysis. The descriptive results were analysed for all patients included from the beginning. The abstinence rate was calculated through an intention-to-treat (ITT) analysis in which patients who dropped out during the follow-up were considered to be smokers. Comparisons between groups were made using the chi-square test for variable categories and the t-Student test for continuous variables. The comparison of anxiety and depression scores over time was carried out using a repeated measures analysis. The lowest significance level was considered to be $p < 0.05$. The point estimate was complemented by an estimation of 95% confidence intervals.

Ethical considerations: This study was presented and approved by the Clinical Ethics and Research Committee of the Hospital Universitario Virgen Macarena in Seville, Spain.

Results

Participants

The study included 1144 patients from March 2011 to October 2012. The dropout rate during patient follow-up was high at 25.6% in the first month and an additional 20.3% in the third (Figure 1) and due to programme abandonment in all cases. However, the likelihood of this was taken into account at the study design stage. An analysis of the population characteristics over the follow-up was made, and despite the losses, the population remained homogeneous. The characteristics of the study's final population of 678
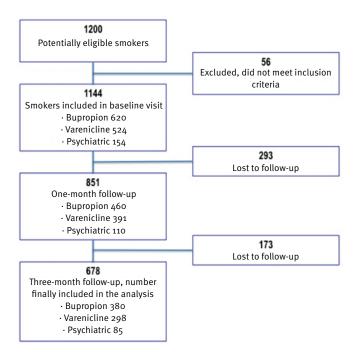
Figure 1. Data samples

point in their lives been diagnosed with psychiatric illness, the majority of which (63.5%) were cases of depression. The majority were highly motivated to quit smoking and almost half were heavily nicotine dependent.

Psychiatric patients

The prevalence of psychiatric symptoms at the clinic was 13.4%. Of these, 85 patients completed the programme. The general characteristics of this subgroup are detailed in Table 1. Depression was the most frequent of the psychiatric diagnoses (54 cases), followed by anxiety disorder (27 cases). Four patients were diagnosed with other problems: schizophrenia (1), phobias (2), bipolar (1). Twenty-four of the patients had been hospitalised for decompensation of their psychiatric symptoms at some point in their lives and seven had attempted suicide. Mean age was similar to that of other patients, although there was a clear predominance of women and less motivation to quit (7.7 ± 1.3 among those with psychiatric symptoms vs 8.1 ± 1.2 without; $p < 0.05$).

Drugs against psychiatric illnesses were taken by 72% (benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants, IMAOs, antipsychotics …).

Changes in anxiety and depression

The mean baseline score for anxiety was 9.2 ± 4.6 points, which is in the "borderline" category for screening. However, the mean baseline score for depression fell within the "low probability" range: 5.5 ± 4.1 (Table 2), and we can highlight

patients can be seen in Table 1. The patients who completed the follow-up were middle-aged (49.9 ± 11 years of age), with slightly more men than women and a relatively high accumulated tobacco consumption (37.4 ± 22.2 pack-years). Almost half showed cardiovascular risk factors (46.6%) and around 15% were diagnosed with COPD or sleep apnea syndrome. We found that 12.6% of the patients had at some

Table 1. *General characteristics of the population finally included in the study.*

Characteristics	Final population n=678	Non-psychiatric n=593	Psychiatric n=85	p
Age (years)	49.9 ± 11	49.7± 11	51.1± 11.8	0.593
Males (%)	57.5	61.7	28.2 **	**0.000**
Smoking onset age (years)	15.8 ± 5.2	15.6± 4.2	17.5± 9.3	0.578
Accumulated smoking (pack years)	37.4 ± 22.2	37.9± 22.5	34.2± 19.6	0.538
Comorbidity (%)				
COPD	15.2	15.3	14.1	0.718
CVRF†	46.6	45.7	52.9	0.834
OSAHS	15.6	16	12.9	0.640
Psychiatric#	12.6	---	---	---
Richmond Test Total+	8 ± 1.2	8.1± 1.2	7.7± 1.3 *	**0.033**
Low (%)	5.9	5.6	8.2	
Moderate (%)	5	4.9	5.9	
High (%)	89.1	89.5	85.9	
Fagerström Test Total+	6 ± 2.4	6± 2.4	6.2± 2.3 *	**0.012**
Light (%)	21.2	22.3	14.1	
Moderate (%)	32.7	32.9	31.8	
High (%)	46	44.9	54.1	
Treatment (%)				
Bupropion	56	59.7	30 **	**0.000**
Varenicline	44	40.3	70 **	**0.000**

Note. Data are expressed in means ± standard deviation and absolute frequency (%).
*p<0.05, **p<0.01; comparisons between smokers without and with psychiatric history.
† Cardiovascular risk factors (PAH, DM, DLP, ischemic cardiopathy)
#Includes anxiety, depression and others (schizophrenia, bipolar disorder, phobias, …)
+Richmond and Fagerström tests: total tests and by interval (≤4 points: low/light; 5-6 points: moderate and ≥ 7 points: high)

the fact that up to 70.3% of these patients also scored low for anxiety.

An analysis of what happened to anxiety and depression levels once the patients stopped smoking revealed a significant fall in the total HADS score as well as in both of its subscales (anxiety and depression) over the three months of the programme (Table 2, Figures 2 and 3). The significance was maintained when comparing the reductions of the beginning of the month with the first month, the first month with the third month, and the beginning with the third month in all of the cases. The decrease between the second and third month remained progressive and significant despite patients being free of medication at that point.

Psychiatric patients

The baseline HADS scores for this subgroup of patients were significantly higher in both subscales than those obtained by the non-psychiatric patients, falling within the high probability range in the case of anxiety. Despite this, scores for both anxiety and depression declined significantly over the course of treatment in both groups, with no differences being found at one month or at three months (Table 2, Figures 4 and 5).
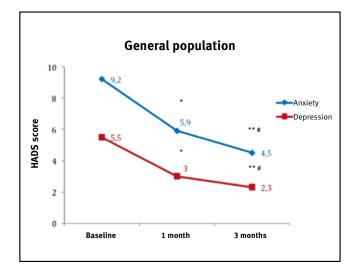
Treatment subgroup

Although the study was not designed to carry out a comparison between the different drugs involved, we did compare treatment groups and found that both groups were homogeneous in all the characteristics assessed.

At baseline, the scores for anxiety were higher in both treatment groups than those for depression. Independently of this, both scores decreased significantly during the follow-up period (Table 2, Figures 4 and 5).

Table 2. *Changes in the global levels of anxiety and depression over the duration of the programme and by population group.*
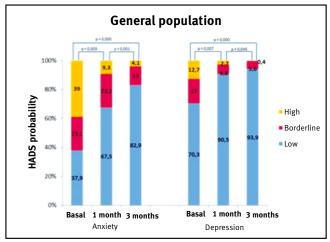
	Anxiety			Depression		
	Baseline	1 month	3 months	Baseline	1 month	3 months
Total population (n=678)	9,2±4,6	5,9±3,6 *	4,5±3,1 ** #	5,5±4,1	3±3 *	2,3±2,1 ** #
Non-psychiatric (n=593)	8,9±4,5	5,7±3,6 *	4,4±3** #	5,3±4	2,8±2,6 *	2,2±2,1 **#
Psychiatric (n=85)	11,3±4,5	7,1±3,7 *	5,3±3,5 ** #	7,4±4,8	4,2±3,6 *	3±2,9 ** #
Bupropion (n=380)	8,9±4,6	5,9±3,7*	4,4±3 ** #	5,4±4	2,9±2,5 *	2,2±2** #
Varenicline (n=298)	9,6±4,7	6±3,5 *	4,6±3,2** #	5,8±4,3	3±2,7 *	2,4±2,1** #

Note. Data is expressed in mean total scores obtained in the HADS questionnaire for each of the anxiety and depression subscales ± standard deviation. * p<0.001 Comparisons made between baseline and 1 month; ** p<0.001 Comparisons between baseline – 3 months; # p<0.001. Comparisons between 1 month – 3 months.
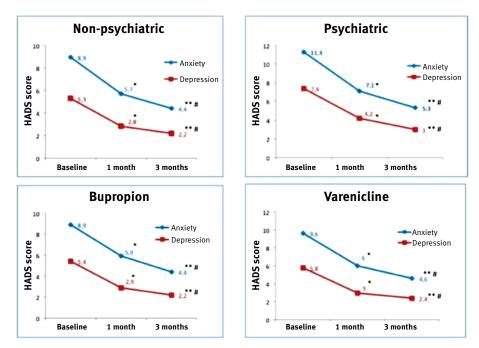
Note. The data is expressed as the mean of total points obtained in the HADS questionnaire for each of the anxiety and depression subscales.
* p<0.001 Comparisons between baseline – 1 month; ** p<0.001 Comparisons between baseline – 3 months; # p<0.001 Comparisons between 1 month – 3 months.

Figure 2. Change in global anxiety and depression levels based on HADS in the general population.

Note. Data are expressed as absolute frequency (%) of patients in each probability group for diagnosis of anxiety or depressive syndrome based on the HADS questionnaire scores for anxiety subscale (0-7 points: low probability, 8-10 points: borderline, › or equal to 11: high probability). Significant comparisons in all cases at p<0.05.

Figure 3. Changes in the levels of anxiety and depression by the probability of suffering anxiety or depression disorder during the programme in the general population.

Figure 4. Changes in global anxiety and depression levels based on the HADS questionnaire by population subgroup.

Note. The data are expressed as mean total points scored on the HADS questionnaire for each of the anxiety and depression subscales. * p<0.001 Comparisons between baseline – 1 month; ** p<0.001 Comparisons between baseline – 3 months; # p<0.001 Comparisons between 1 month – 3 months.

Figure 5. Changes in anxiety and depression levels depending on the probability of suffering anxiety or depression disorder during the programme by population subgroup.
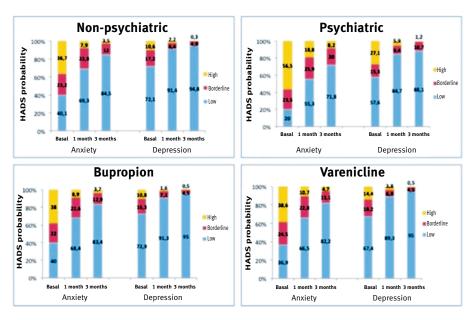
Note. The data are expressed as absolute frequency (%) of patients in each probability group for diagnosis of anxiety or depressive syndrome based on the HADS questionnaire scores for anxiety subscale (0-7 points: low probability, 8-10 points: borderline, › or equal to 11: high probability). Significant comparisons in all cases at p<0.05.

Results of the programme

The abstinence rate at three months on our programme was 58.5%, with 60.8% and 55% quit rates for those taking Bupropion and Varenicline respectively. Among psychiatric patients, abstinence was achieved by a slightly lower percentage (53.2%) than in the total. We found no differences in the baseline levels of anxiety and depression between the patients who managed to give up smoking and those who did not, either in the general population or the psychiatric patient subgroup (Table 3).

Analysis of adverse effects by treatment

An analysis was carried out of the impact of adverse effects reported during the course of treatment, with patients who dropped out being contacted by telephone. Those we did not manage to contact were labelled as lost to follow-up. This left a final total population of 1052 (92% of the sample). The most frequent adverse effects reported globally were nervousness (36.2%), nausea (22%), insomnia (18.9%) and dryness of the mouth (12.1%). Other adverse effects were present only on a very small scale. The majority were slight (98%) and appeared early. Serious side effects

Virginia Almadana, Ana Paulina Gómez-Bastero, Agustín Valido, Estefanía Luque, Soledad Monserrat García, Teodoro Montemayor

Table 3. *Abstinence rates at 3 months and baseline anxiety and depression values by smoker status.*

	Smoker	CO#	Anxiety	Depression	Non smoker	CO#	Anxiety	Depression
Total population (n=1144)	41,5	31,6±12,9	9,5±4,8	5,8±4	58,5	1,9±0,5	9,2±4,7	5,5±4,1
Psychiatric (n=154)	46,8	33,2±16,1	11,1±4,6	7±4,2	53,2	2±0,7	11,7±4,4	7,5±4,8

Note. Data is expressed as %age of patients who smoke and do not smoke, results of CO-oximetry in parts per billion (ppb) and total points obtained in the HADS questionnaire for each of the anxiety and depression subscales.
#CO: measurement of carbon monoxide in expired air by CO-oximetry.
*Significance at p<0.05, comparisons between smokers and non-smokers.

Table 4. *Global incidence of adverse effects connected with the treatment of withdrawal symptoms in the general and psychiatric populations.*

	General population (n: 1052)				Psychiatric population (n: 145)			
Adverse effect	Incidence	Slight	Moderate	Severe	Incidence	Slight	Moderate	Severe
Nausea	22	62,1	37,9	0	23,4	79,4	20,6	0
Vomiting	4,4	100	0	0	1,4	100	0	0
Constipation	1,4	80	20	0	3,4	80	25	0
Abdominal pain	2,7	55,5	44,5	0	2,7	100	0	0
Headaches	5,3	78,6	19,4	0	10,3	100	0	0
Dryness of the mouth	12,1	49,6	49,6	0,8	15,1	59	31,8	9,2
Pseudo flu	2,9	80,6	19,4	0	2,7	100	0	0
Insomnia	18,9	50	46,7	3,3	18,6	51,8	44,5	3,7
Nightmares	6,9	65,7	27,3	7	10,3	73,3	20	6,7
Nervousness	36,2	39,1	59,9	1	37,2	35,2	57,4	7,4
Mood disorders	3,2	52,9	44,1	3	4,8	100	0	0
Severe mental events*	0	0	0	0	0	0	0	0

Note. Results expressed as %ages. *Suicide ideation, hospitalization for exacerbated mental pathology.

were exceptional and only reported as nightmares (7%), insomnia (3.3%), mood disorders (3%), nervousness (1%) and dryness of the mouth (0.8%). In no case was it necessary to withdraw the drug (Table 4). The side effects reported by the psychiatric patients were similar to those described by the general population, as can be seen in Table 4, while Table 5 shows adverse effects by drug used.

Discussion

The results of our study display a notable and progressive reduction in levels of anxiety and depression over the duration of the smoking cessation programme, independently of baseline levels and whether or not patients suffered psychiatric symptoms prior to the start of treatment and even in the month after the end of treatment. Abstinence rates at three months were good, both for Bupropion and Varenicline, and initial levels of anxiety and depression did not appear to influence results.

With regard to initial anxiety and depression levels, the levels we found in smokers attended in our unit were not as high as the literature had led us to expect (Bolam et al.,

2011; Lagrue et al., 2002; Marqueta et al., 2010; Mykletun et al., 2008; Waal-Manning & de Hamel, 1978), and although their levels of anxiety were higher than those of depression, in no case were they of high probability for either diagnosis, according to the HADS. Nevertheless, our initial scores are in line with those found in studies such as Sampablo (2002) or Dawkins (2009) which used the same questionnaire in specific populations of smokers. Both studies, albeit with very small sample sizes, yielded higher scores for anxiety than depression, but in neither case did they fall in the pathological range.

The most relevant findings in our research were obtained when analysing the results of monitoring anxiety and depression levels at one and three months after quitting with a simple tool such as the HADS. Independently of baseline levels we found, for example, that there was a significant improvement in both throughout the follow-up, with a 4.7 point fall in anxiety at the end of the of the follow-up, and a 3.2 point drop in depression, reaching levels considered to be non-pathological. These results again match those reported by other authors (Anthenelli et al., 2013; Dawkins et al., 2009; Foulds et al., 2013; Marqueta et

Table 5. *Incidence of adverse effects connected with the treatment of withdrawal symptoms by drug used.*

Adverse effect	BUPROPION (n=554)				VARENICLINE (n=498)			
	Incidence Nº / %	Slight	Moderate	Severe	Incidence Nº / %	Slight	Moderate	Severe
Nausea	26 / 4,7	100	0	0	206 / 41,3	57,3	42,7	0
Vomiting	0 / 0	0	0	0	46 / 9,2	100	0	0
Constipation	1 / 0,2	100	0	0	14 / 2,8	78,6	21,4	0
Abdominal pain	5 / 0,9	100	0	0	13 / 2,6	38,5	61,5	0
Headaches	45 / 8,1	75,5	24,5	0	11 / 2,2	100	0	0
Dryness of the mouth	108 / 19,5	40,7	58,4	0,9	19 / 3,8	100	0	0
Pseudo flu	15 / 2,3	86,6	13,4	0	16 / 3,2	75	25	0
Insomnia	148 / 26,7	54	46	0	51 / 10,2	39,2	49	11,8
Nightmares	13 / 2,3	84,6	15,4	0	60 / 12	61,7	30	8,3
Nervousness	156 / 28,1	30,1	69,3	0,6	225 / 45,2	45,4	53,3	1,3
Mood disorders	9 / 1,6	45,5	55,5	0	25 / 5	56	40	4
Severe mental events*	0 / 0	0	0	0	0 / 0	0	0	0

Note. Results expressed as %ages. *Suicide ideation, hospitalization for exacerbated mental pathology. #Cases: number of cases with side effects compared to number of cases assessed.

al., 2010; McClure et al., 2009; McDermott et al., 2013; West et al., 1997), although different measurement approaches to ours were used (Anthenelli et al., 2013; Marqueta et al., 2010; McClure et al., 2009; McDermott et al., 2013) and/or a follow-up of just one month (West et al., 1997). The study by Marqueta (Marqueta et al., 2010) with more than 500 patients is notable, and although it only measured anxiety with the State-Trait Anxiety Inventory (STAI) it showed how this improved significantly until the third month of follow-up, albeit with an anxiety peak in the days leading up to and after quitting smoking. In line with our own research, the majority of these studies have revealed an improvement from the first month onward, a time when withdrawal symptoms are strongest (20 days without smoking), and some authors have attributed an anxiogenic effect to nicotine (West et al., 1997). In some cases, however, it appears that the improvement flattens out after the first month both for anxiety (Marqueta et al., 2010; Dawkins et al., 2009; McDermott et al., 2013) and for depression (Dawkins et al., 2009; McClure et al., 2009), although in our case it was persistent and significant.

The research of Sampablo (2002) provides a striking contrast to our results. He found that after 6 months of monitoring, those smokers who managed to give up appeared to have progressively higher anxiety levels than those who failed to stop, although the scores for depression were worse among those who continued to smoke. It should be noted, however, that the sample size was rather small (50 patients) and the treatment to quit smoking used Bupropion exclusively, without behavioural support. Similarly, Garza (2011), in a study with healthy patients treated with Varenicline versus placebo, did not show any improvement

in anxiety and depression scores either, with initial values practically normal in both groups and deterioration peaking in the third week (the height of withdrawal symptoms). It is worth mentioning that in our study, the smoking cessation programme combined pharmacological with behavioural treatment, and that psychological support was maintained throughout follow-up, which could be a determining factor behind the improvement.

Psychiatric patients

Psychiatric symptoms were found in 13.4% of cases, a level below that reported in other research (Gutiérrez, Otero, del Amo, & Ayesta, 2013; Marqueta et al., 2010; McDermott et al., 2013; Purvis, Mambourg, BalvanzMagallon, & Pham, 2009; Sobradiel et al., 2007; Stapleton et al., 2008), which estimated a prevalence of between 18.7% (McDermott et al., 2013) and 48% (in more selected populations) (Purvis et al., 2009) among smokers, and around 45% among those who request help to stop smoking (Sobradiel et al., 2007).

These patients had worse scores in anxiety and depression compared to healthy participants, although there was clear improvement over time even though more than half had previously been diagnosed with depressive syndrome. Our results are borne out by the findings of McClure (2009), in which higher initial depression scores were found on comparing smokers with and without depression, but with progressive improvement in both patient groups in the first month, which remained stable in the third. However, a recent study carried out exclusively with a group of more than 500 smokers diagnosed with depressive syndrome (Anthenelli et al., 2013) reports a mean score for their patients which could be considered normal for anxiety and

depression, although they did not include other psychiatric diagnoses.

Treatment subgroups

Although we have already stated that the aim of the present study was not to compare Bupropion and Varenicline, we did independently assess the development of anxiety and depression levels with each of the drugs involved. Both treatment groups showed clear improvements in these levels from the first month which were progressive and comparable until the third month for both Bupropion and Varenicline, even when taking into account that the latter was used over a shorter period than that recommended in order to improve treatment compliance. Because the decrease in anxiety and depression in the first two months could be conditioned by the pharmacological treatment applied, it is important to highlight the fact that once both drugs were stopped the differences between the second and third month remained significant and the symptoms continued to decrease.

Abstinence rate

The abstinence rate was high (58.5%) even when including the psychiatric group, which stopped smoking in more than half the cases (53%), possibly influenced by the characteristics of the study and the close patient follow-up. The results of the psychiatric population in particular stand out, despite what is described in the literature, where higher dropout ratios and greater difficulty in giving up smoking is reported in the psychiatric patient group (Killen et al., 2008). These results may be explained, however, by the fact that a broad range of patients were included under the concept of psychiatric pathology, from those who were diagnosed with a condition at the beginning of the study to those who had at some point in their lives suffered symptoms. There is a study, for example, which measured abstinence rates at 12 months with different treatment approaches and reported results in line with ours when comparing the same type of treatment (psychological plus pharmacological) at three months, and which did not find a link between abstinence results and psychiatric history either (Raich et al., 2015). Although most researchers assessing abstinence rates with different drugs exclude the psychiatric population from their methodology, there are some studies, such as that of McClure (McClure et al., 2009), which do not report differences in terms of abstinence between patients with and without depression treated with Varenicline and present similar rates to ours (48%), and even higher in the case of Stapleton (Stapleton et al., 2008). Conversely, data have been reported elsewhere which suggest abstinence rates up to 30% worse among psychiatric patients, as in the research carried out by Purvis (2009), albeit it with a very small and selected sample of patients. Recently, Cinciripini (2013) has reported abstinence rates of 38% and 37% for Bupropion and Varenicline respectively at three months, although in

a population with no psychiatric history. These results were similar to those of Anthinelli (2013) using Varenicline with depressive patients (36%), and although these rates are considerably lower than ours, the approach on which they are based did not include cognitive-behavioural treatment. Finally, it is worth pointing out that no baseline differences in anxiety and depression were found between those who managed to quit smoking and those who did not.

Side effects

An analysis of adverse events was even carried out one month after treatment ended and included possible long term effects. Varenicline produced a considerable number of side effects, with almost half the patients reporting nervousness (42.5%) and a large number suffering nausea (41.3%). It should be noted that, in terms of nausea, while these results are higher than those found in clinical trials carried out prior to the commercialization of the drug (Gonzalez et al., 2006; Jorenby et al., 2006) at around 29% or in more recent research (Cinciripini et al., 2013), they are more in line with other later series which included psychiatric patients (McClure et al., 2009; McClure et al., 2010; Stapleton et al., 2008; Kasliwal et al., 2009), which found a range of incidence rates between 38% and 63% in some cases. Nevertheless, the drug was well tolerated and in no case was it necessary to suspend treatment, although it is true that treatment was of shorter duration than normal. Bupropion had a lower incidence of adverse events, with nervousness and insomnia being the most frequent (28.1% and 26.7% respectively), in line with percentages described in the literature (Cinciripini et al., 2013; Gonzalez et al., 2006; Jorenby et al., 2006). Although our study is not powerful enough to detect unusual adverse events, it can be highlighted that no serious neuropsychiatric effects were registered with any of the drugs used. This is supported by the most recently published results in the literature (Meszaros et al., 2013; Thomas et al., 2013) and other classic studies (Tonstad et al., 2010), which in some cases include a psychiatric population, as we have done (Stapleton et al., 2008). In contrast to our findings, there are some controversial results in the literature, with some studies reporting a high risk of serious neuropsychiatric effects, in particular hospitalization and suicide ideation, in some cases with greater propensity if patients had a psychiatric history (Ahmed et al., 2013; Moore, Furberg, Glenmullen, Maltsberger, & Singh, 2011; Kasliwal et al., 2009).

Potential limitations

The above notwithstanding, our study is subject to a number of limitations. One of the most important is the losses to follow-up. These may produce a bias in the evaluation of results given that we cannot know the levels of anxiety and depression in the patients who abandoned the programme. In principle, this can be offset by the fact that

a comparison of the population's general characteristics was made at the beginning and finally included in the study which showed that they were very similar, including baseline scores for anxiety and depression. Therefore, at least the initial levels of anxiety and depression did not condition the losses to follow-up. Nevertheless, it would have been interesting to assess the levels of anxiety and depression at the point of dropout and to determine whether they gave rise to relapses.

A further limitation to take into account is the short duration of follow-up (three months) since it has been noted that depressive episodes can arise in the long term after quitting smoking. However, the aim of our research is to determine the connection of this type of symptomatology with the use of specific treatment for smoking cessation. Thus the three month follow-up period (which includes one month after the end of pharmacological treatment) guarantees the monitoring of any anxio-depressive symptomatology which could be linked to the actual taking of the medicine.

Conclusions

the smokers on our programme presented moderately high baseline levels of anxiety. Psychiatric patients, which made up 13.4% of the sample had even higher baseline anxiety levels. These levels, however, descended significantly over the three month duration of the smoking cessation programme. The improvement was more marked during the first month, when withdrawal symptoms are at their strongest. The psychiatric patients followed a similar pattern, although they started from a worse baseline situation. Furthermore, the programme achieved a high success rate at three months (58.5%), with similar results independently of the presence of psychiatric pathology. The improvement in anxiety and depression levels was brought about with the different drugs used, which were relatively safe given that although adverse effects were rather frequent, they were in general light and did not lead to an interruption of treatment. We should therefore provide multicomponent smoking cessation treatment even for patients with psychiatric illnesses, incorporating the monitoring of possible neuropsychiatric effects alongside anxiety and depression levels with simple tools integrated into the routine of smoking cessation consultation.

Acknowledgements

Conflict of interests

The authors declare no conflict of interest.

Bibliographic references

Ahmed, A. I., Ali, A. N., Kramers, C., Harmark, L. V., Burger, D. M. & Verhoeven, W. M. (2013). Neuropsychiatric adverse events of varenicline: A systematic review of published reports. *Journal of Clinical Psychopharmacology, 33*, 55-62. doi:10.1097/JCP.0b013e31827c0117.

Anthenelli, R. M., Morris, C., Ramey, T. S., Dubrava, S. J., Tsilkos, K., Russ, C. & Yunis, C. (2013). Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: A randomized trial. *Annals of Internal Medicine, 159*, 390-400. doi:10.7326/0003-4819-159-6-201309170-00005.

Bolam, B., West, R. & Gunnell, D. (2011). Does smoking cessation cause depression and anxiety? findings from the ATTEMPT cohort. *Nicotine & Tobacco Research, 13*, 209-214. doi:10.1093/ntr/ntq244.

Cinciripini, P. M., Robinson, J. D., Karam-Hage, M., Minnix, J. A., Lam, C., Versace, F., Brown, V. L., Engelmann, J. M. & Wetter, D. W. (2013). Effects of varenicline and bupropion sustained-release use plus intensive smoking cessation counseling on prolonged abstinence from smoking and on depression, negative affect, and other symptoms of nicotine withdrawal. *The Journal of the American Medical Association Psychiatry, 70*, 522-533. doi:10.1001/jamapsychiatry.2013.678.

Dawkins, L., Powell, J. H., Pickering, A., Powell, J. & West, R. (2009). Patterns of change in withdrawal symptoms, desire to smoke, reward motivation and response inhibition across 3 months of smoking abstinence. *Addiction, 104*, 850-858. doi:10.1111/j.1360-0443.2009.02522.x.

FDA requires new boxed warnings for the smoking cessation drugs chantix and zyban 2009. Retrieved from: http://www.fda.gov/Drugs/DrugSafety/Postmarket-Drug SafetyInformationforPatientsandProviders/Drug-Safety InformationforHeathcareProfessionals/PublicHealthAdvi sories/ucm169988.htm.

Foulds, J., Russ, C., Yu, C. R., Zou, K. H., Galaznik, A., Franzon, M.,… Hughes, JR. (2013). Effect of varenicline on individual nicotine withdrawal symptoms: A combined analysis of eight randomized, placebo-controlled trials. *Nicotine & Tobacco Research, 15*, 1849-1857. doi:10.1093/ntr/ntt066.

Garza, D., Murphy, M., Tseng, L. J., Riordan, H. J. & Chatterjee, A. (2011). A double-blind randomized placebo-controlled pilot study of neuropsychiatric adverse events in abstinent smokers treated with varenicline or placebo. *Biological Psychiatry, 69*, 1075-1082. doi:10.1016/j.biopsych.2010.12.005.

Gonzales, D., Rennard, S. I., Nides, M., Oncken, C., Azoulay, S., Billing, C.B.,… Reeves, K. R. (2006). Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. *The Journal of the American Medical Association, 296*, 47-55. doi:10.1001/jama.296.1.47.

Virginia Almadana, Ana Paulina Gómez-Bastero, Agustín Valido, Estefanía Luque, Soledad Monserrat García, Teodoro Montemayor

Gunnell, D., Irvine, D., Wise, L., Davies, C. & Martin, R. M. (2009). Varenicline and suicidal behaviour: A cohort study based on data from the general practice research database. *British Medical Journal, 339*, b3805. doi:10.1136/bmj.b3805.

Gutiérrez, L., Otero, L., del Amo, M. & Ayesta F. J. (2013). Evaluación de una intervención para dejar de fumar en personas con enfermedad mental. *Revista Española de Salud Pública, 87*, 651-657. doi:10.4321/S1135-57272013000600007.

Jorenby, D. E., Hays, J. T., Rigotti, N. A., Azoulay, S., Watsky, E. J., Williams, K. E.,… Reeves, K. R. (2006). Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. *The Journal of the American Medical Association, 296*, 56-63. doi:10.1001/jama.296.1.56.

Kasliwal, R., Wilton, L. V. & Shakir, S. A. (2009). Safety and drug utilization profile of varenicline as used in general practice in England: Interim results from a prescription-event monitoring study. *Drug Safety, 32,* 499-507. doi:10.2165/00002018-200932060-00006.

Killen, J. D., Fortmann, S. P., Schatzberg, A. F., Arredondo, C., Murphy, G., Hayward, C.,… Pandurangi, M. (2008). Extended congnitive behaviour therapy for cigarette smoking cessation. *Addiction, 103,* 1381-1390. doi:10.1111/j.1360-0443.2008.02273.x.

Lagrue, G., Dupont, P. & Fakhfakh, R. (2002). Anxiety and depressive disorders in tobacco dependence. *L'Encéphale, 28,* 374-377.

Lawrence, D., Hafekost, J., Hull, P., Mitrou, F. & Zubrick, S. R. (2013). Smoking, mental illness and socioeconomic disadvantage: Analysis of the Australian national survey of mental healrh and wellbeing. *BMC Pubilc Health, 13,* 462. doi:10.1186/1471-2458-13-462.

Marqueta, A., Jimenez-Muro, A., Beamonte, A., Gargallo, P. & Nerin, I. (2010). Evolution of anxiety during the smoking cessation process at a smoking cessation clinic. *Adicciones, 22,* 317-324. doi:10.20882/adicciones.173.

McClure, J. B., Swan, G. E., Jack, L., Catz, S. L., Zbikowski, S. M., McAfee, T. A.,… Javitz, H. S. (2009). Mood, side-effects and smoking outcomes among persons with and without probable lifetime depression taking varenicline. *Journal of General Internal Medicine, 24,* 563-569. doi:10.1007/s11606-009-0926-8.

McClure, J. B., Swan, G. E., Catz, S. L., Jack, L., Javitz, H., McAfee, T.,… Zbikowski, S. M. (2010). Smoking outcome by psychiatric history after behavioral and varenicline treatment. *Journal of Substance Abuse Treatment, 38,* 394-402. doi:10.1016/j.jsat.2010.03.007.

McDermott, M. S., Marteau, T. M., Hollands, G. J., Hankins, M. & Aveyard, P. (2013). Change in anxiety following successful and unsuccessful attempts at smoking cessation: Cohort study. *The British Journal of Psychiatry, 202,* 62-67. doi:10.1192/bjp.bp.112.114389.

Meszaros, Z. S., Abdul-Malak, Y., Dimmock, J. A., Wang, D., Ajagbe, T. O. & Batki, S. L. (2013) Varenicline treatment of concurrent alcohol and nicotine dependence in schizophrenia: A randomized, placebo-controlled pilot trial. *Journal of Clinical Psychopharmacology, 33,* 243-247. doi:10.1097/JCP.0b013e3182870551.

Moore, T. J., Furberg, C. D., Glenmullen, J., Maltsberger, J. T. & Singh, S. (2011). Suicidal behavior and depression in smoking cessation treatments. *PLoS One, 6,* e27016. doi:10.1371/journal.pone.0027016.

Mykletun, A., Overland, S., Aaro, L. E., Liabo, H. M. & Stewart, R. (2008). Smoking in relation to anxiety and depression: Evidence from a large population survey: The HUNT study. *European Psychiatry, 23,* 77-84.

Purvis, T. L., Mambourg, S. E., Balvanz, T. M., Magallon, H. E. & Pham, R. H. (2009). Safety and effectiveness of varenicline in a veteran population with a high prevalence of mental illness. *The Annals of Pharmacotherapy, 43,* 862-867. doi:10.1345/aph.1L661.

Raich, A., Martínez-Sánchez, J. M., Marquilles, E., Rubio, L., Fu, M. & Fernández, E. (2015). Abstinencia a los 12 meses de un programa multicomponente para dejar de fumar. *Adicciones, 27,* 37-46. doi:10.20882/adicciones.192.

Sampablo, I., Carreras, J. M., Lores, L., Quesada, M., Coll, F. & Sanchez Agudo, L. (2002) Smoking cessation and bupropion: Anxiety and depression as predictors of therapeutic efficacy. *Archivos de Bronconeumología, 38,* 351-355.

Sobradiel, N. & García-Vicent, V. (2007). Consumo de tabaco y patología psiquiátrica. *Trastornos Adictivos, 9,* 31-38.

Stapleton, J. A., Watson, L., Spirling, L. I., Smith, R., Milbrandt, A., Ratcliffe, M.,… Sutherland, G. (2008). Varenicline in the routine treatment of tobacco dependence: A pre-post comparison with nicotine replacement therapy and an evaluation in those with mental illness. *Addiction, 103,* 146-154. doi:10.1111/j.1360-0443.2007.02083.x.

Thomas, K. H., Martin, R. M., Davies, N. M., Metcalfe, C., Windmeijer, F. & Gunnell, D. (2013). Smoking cessation treatment and risk of depression, suicide, and self harm in the clinical practice research datalink: Prospective cohort study. *British Medical Journal, 347,* f5704. doi:10.1136/bmj.f5704.

Tonstad, S., Davies, S., Flammer, M., Russ, C. & Hughes, J. (2010). Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: A pooled analysis. *Drug Safety, 33,* 289-301. doi:10.2165/11319180-000000000-00000.

Waal-Manning, H. J. & de Hamel, F. A. (1978). Smoking habit and psychometric scores: A community study. *The New Zealand Medical Journal, 88,* 188-191.

West, R. & Hajek, P. (1997). What happens to anxiety levels on giving up smoking? *The American Journal of Psychiatry, 154*, 1589-1592.

Zigmond, A. S. & Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67,* 361-370.