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# Evaluation of the information processing and mood effects of a transdermal nicotine patch

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**Abstract** The purpose of this study was to determine whether a transdermal nicotine patch will produce the same effects on performance and mood as cigarette smoking. The nicotine patch improved attentional processing and produced some improvements in memory. It produced the calming effects of smoking and induced feelings of happiness which were increased with smoking. These effects were obtained 6 h after application of the patch, showing that acute tolerance for these behavioural effects had not developed completely, if at all, after exposure to nicotine, although it is still possible that tolerance might occur with longer exposure.

**Key words** Nicotine · Tolerance · Cognition · Attention · Memory · Mood · Sensory effects · Transdermal nicotine patch

## Introduction

Beneficial psychological effects of nicotine have been reported in a variety of performance measures by many people. Performance on vigilance and information processing tasks was improved by nicotine (e.g. Wesnes et al. 1983; Parrott and Winder 1989; Sahakian et al. 1989; Jones et al. 1992) and cigarette smoking (e.g. Wesnes and Warburton 1983; Revell 1988; Warburton and Arnall 1994), as well as smokeless tobacco (e.g. Landers et al. 1990). This research has been reviewed by Warburton (1990), by Sherwood (1993) and Heishman et al. (1994). With a few exceptions of nicotine given to non-smokers (Wesnes and Warburton 1983; Sahakian et al. 1989; Jones et al. 1992), the methodological aspects of this early research can be criticised, because a wash-out period was used to ensure that the participants were drug-free prior to testing. Thus, participants are asked to abstain from smoking some hours before testing, so that positive psychological effects were attributed to the reversal of a nicotine withdrawal syndrome (Hughes 1991; Sherwood 1993).

Another major methodological problem for cigarette smoking studies stems from the type of control which is used. The availability of an effective placebo cigarette is questionable, since herbal or low nicotine cigarettes (less than 0.1 mg) are easily distinguishable by most regular smokers immediately after the first puff (Rose 1988) and sham smoking (used by Revell 1988) is not a blind procedure.

Transdermal nicotine delivery systems (nicotine patch) avoid these methodological problems for several reasons. Participants are not in abstinence when they are tested. Their rate of nicotine absorption is controlled, leading to steady-state levels of plasma nicotine after 5 or 6 h (Benowitz et al. 1991; Srivastava et al. 1991). Placebo patches can be used for a double blind design. Moreover, patches avoid any confounding effects of the sensory-motor effects of the smoking act.

Estimates of the efficacy of the transdermal nicotine patch over placebo in smoking cessation have ranged from 6% to 13%, overall 9% (Tang et al. 1994). However, some studies have argued that acute tolerance to the pleasant effects of nicotine builds-up during continuous absorption of nicotine from the patch (Foulds et al. 1992). Thus, nicotine replacement by the patch may not be satisfying the needs of the smoker. This suggestion is supported by studies showing that some individuals using the patch continue to smoke

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(Transdermal Nicotine Group 1991; Foulds et al. 1992).

Thus, the purpose of the study was to determine whether a transdermal nicotine patch will produce the same effects on performance and mood as cigarette smoking.

## Materials and methods

### Nicotine patch

For the study, the 21 mg transdermal patch (Nicotinell; Habitrol, Ciba-Geigy) was used. This dose was selected on the basis of having few adverse effects and yet, after 6 h, this patch produces average levels of nicotine similar to the trough levels which are found in a smoker during a smoking day, i.e. about half of the peak levels achieved at the end of each cigarette (Benowitz et al. 1991; Srivastava et al. 1991). A matching placebo patch was constructed from the patch with a plastic filmover the nicotine reservoir, in order to prevent absorption of the nicotine, but still give the odour of the active patch.

### Participants

Twenty healthy, male smokers (over 15 cigarettes per day) between the ages of 18–25, and with weights of 55–85 kg, were recruited from the student population of the University. All participants were free from cardiovascular disorders as determined by medical history. Any volunteers who were receiving, or had received in the 2 weeks prior to entry into the study, any centrally acting medications, were not admitted to the study. In studies with a nicotine patch, 50% of 664 patients have reported transient itching, particularly following application and removal after 24 h (Transdermal Nicotine Study Group 1991). Consequently, anyone with a history of skin problems was excluded.

Prior to the study, all volunteers were informed about the nature of the study and possible adverse experiences. In a study with a similar patch (Srivastava et al. 1991), none of the smokers who participated in the study had any unpleasant effects or symptoms (other than transient itching), while wearing a patch for 24 h, although some non-smokers experienced mild lightheadedness and nausea.

In addition, any volunteers who were receiving, or had received any centrally acting medication in the 2 weeks prior to entry into the study, were not admitted to the study.

Volunteers were not allowed to take alcohol in the 24-h period before and after each experimental session. They were required to abstain from caffeine (coffee, cola and tea) during the 12-h period preceding each experimental session. Use of other "substances" for 3 days prior to the study was prohibited.

They abstained from smoking for 12 h prior to testing. End-tidal, carbon monoxide samples were taken before each session in order to ensure compliance with the smoking abstinence restrictions. Given the persistence of carbon monoxide in the bloodstream with lack of exercise, a cut-off of 10 ppm was used. Urine samples were also taken before each session, but none of the samples was actually analyzed.

In addition, participants were told not to indulge in strenuous exercise, while the patch was on the skin, because it increases nicotine absorption rate. In order to prevent loss of the patch, they were not be allowed to bathe, while the patch was on the skin. After the patches were removed, the participants were told not to smoke for 6 h.

The study was not disallowed by the University Ethics Committee and written informed consent was given in the presence of a person who was not involved in the study.

### Psychological testing

Four types of tests were used – attention testing, memory tests, problem solving and mood assessment. Baseline tests on each of the tasks were included as part of the evaluation and so that the results could be described with respect to baseline. BBC Master computers in individual experimental rooms presented each of the tasks and collected the data generated by each subject.

#### *Attentional testing*

The rapid visual information processing task is a vigilance task in which participants monitor digits presented sequentially on the computer screen at a rate of 100 per minute. Numerous studies have shown its sensitivity to smoking and nicotine (e.g. Wesnes and Warburton 1983; Wesnes et al. 1983; Sahakian et al. 1989; Jones et al. 1992; Rusted and Warburton 1992; Warburton and Arnall 1994).

Participants were instructed to detect and respond as quickly as possible to targets of three consecutive odd or three consecutive even digits. Independent measures are made of both accuracy (hit rate) and speed (reaction time) of decision making. Testing was carried out for 10 min.

#### *Memory testing*

Both verbal and non-verbal memory were assessed.

### Verbal memory

Verbal memory was assessed using immediate free recall.

The test consist of a list of 72 words given in blocks of four, which enabled a serial position curve analysis to determine whether there is a direct effect on memory or an effect mediated, via attention. Two lists of 32 words were used. Each list was matched for frequency (Kucera and Francis 1967), concreteness (Colorado Concreteness Norms 1973) and number of syllables.

At the end of each list, participants completed a written recall of as many items as they can remember. Delayed recall was also assessed by repeating the procedure at the end of the session. This test has been shown to be sensitive to the effects of smoking and nicotine tablets (Warburton et al. 1992a,b).

### Non-verbal memory

A subset of the CANTAB computerised non-verbal test battery (Morris et al. 1987) was modified for use in this study. The tests included pattern recognition, memory for spatial location and a test of visuo-spatial memory. The tasks make use of touch sensitive screens, with participants indicating their selection by touching the appropriate item or position on the screen.

In the pattern recognition test, participants are shown a 12-item set of patterns which appear consecutively on the screen. At the end of the set, 12 pairs of items are presented, one of which occurred in the previous set. The task is to select the test item from each pair. The sequence is then repeated with 12 more items. For this study, random shapes were generated by a computer program, with the aim of minimising meaningful verbal coding of the shapes. Non-target items for the recognition phase were derived from the test items by systematically adding to or removing sections of the original shape.

For the spatial recognition task, the program presents a five-item sequence of boxes, each in a different location on the screen. This was followed by a five-trial recognition phase in which participants

selected the correctly located box from a choice of two locations. There was a total of five novel sequences in this task.

In the delayed response test of visuo-spatial memory, participants are required to remember the locations of abstract visual stimuli hidden in a set of eight boxes. Each box opens in turn to reveal the shape inside. Then the shapes appear in turn in the centre of the screen and participants indicate the box in which each appeared. The sequence of presentation and test trials is repeated until the subject remembers the correct location of all eight items on a single trial. The original program for this test was modified so that all test items occurred in the same colour, to assess memory for location of each shape in the absence of colour cues.

*Problem solving*

Problem solving skills were examined using the Semantic Verification Test (Baddeley 1968). In this task, a sentence describing the order of two letters (e.g. A follows B) is presented on the screen along with the two letters (e.g. AB or BA). Participants are required to evaluate the veracity of the sentence as a description of the order of the letters "YES" and "NO" responses and reaction times to make these responses were recorded for each sentence. The response to the sentence initiated presentation of the next problem in the series. There were 64 sentences involving four different grammatical constructions; three different letter pairs were randomly used in the three sessions.

*Mood assessment*

The participants completed visual analogue, mood scales which were a modification of those devised by Bond and Lader (1974). Visual analogue scaling is a well researched method for assessing mood-changing agents. With a visual analogue scale, the subject places a mark on a horizontal line equivalent to the strength of a particular feeling at that time. The words at each end of the lines are words, such as "calm" and "excited".

Our version consisted of 12 bipolar scales assessing various aspects of mood. Each scale was presented successively on the computer screen and subjective ratings of mood were made by moving a centrally positioned cursor to the appropriate position on the scale. The visual analogue scales were completed once during the test session. With these scales, we have found that smoking can improve mood (Warburton et al. 1988).

*Adverse reactions*

Although none were anticipated on the basis of the literature on the 21 mg nicotine patch (Srivastava et al. 1991; Transdermal Nicotine Study Group, 1991), participants were questioned about any adverse experiences.

Design

All participants underwent training on the experimental tasks on separate days prior to the test sessions. This training familiarised them with the experimental procedures and minimised the possibility that practice effects would interfere with the assessment of the effects of the transdermal patch.

Participants completed two experimental sessions, active and placebo transdermal patch. The testing was carried out double-blind and the order of administration of doses over sessions was counterbalanced among participants. Successive sessions were separated by at least a week. Participants were only tested on Tuesday, Wednesday, Thursday or Friday in order to avoid the "week-end effect".

Then the transdermal patch was placed on the arm of the participants at 0930 hours and they left the laboratory and were told not to do anything unusual, e.g. strenuous exercise. Testing was at 6 h after placement of the patch, i.e. 1530 hours and the patch was only removed after testing.

On each test day, the participants were given a baseline test on the rapid visual information processing test and the mood assessment, prior to placing the patch. This procedure enabled us to control statistically for a sessions effect, if necessary. At 6 h, the tests were presented in the order – attention testing, memory tests, problem solving and mood assessment.

## Results

Baseline test performance on the rapid visual information processing task immediately prior to dosing did not differ and so no difference from baseline analysis was carried out.

### Attentional testing

*Rapid visual information processing*

The data collected for the rapid visual information processing task permitted a minute-by-minute evaluation of the effects of the nicotine patch. The number of correctly identified targets and reaction time to correct targets provided two independent measures of performance on this task.

More correct detections were made minute-by-minute after 6 h using the nicotine patch than with the placebo. The mean number of correct detections were 5.71 for the nicotine patch condition (5.38–6.48) and 5.15 for the placebo condition (range of 4.64–6.43), a 10.8% superiority for the nicotine patch condition. Analyses of variance of the minute-by-minute correct detection data revealed a significant effect of condition [$F(1, 19) = 11.52$, $P < 0.005$].

*Reaction times*

The mean reaction times were longer, 444 ms (range of 416–472) for the placebo condition, in comparison with 427 ms (range 416–432) after the nicotine patch, about a 4% improvement. Analyses of variance of the minute-by-minute data confirmed that the reaction times were significantly shorter in the nicotine patch condition in comparison with the placebo [$F(1, 19) = 9.34$, $P < 0.01$].

*Commission errors*

The average number of commission errors were less than one per condition and so commission errors were not analyzed statistically.

### Memory testing

#### *Immediate recall of word lists*

A difference score was calculated for each subject, such that a positive score indicated a facilitation of memory by the nicotine patch. There were more scores greater than zero and an analysis of the difference showed a significant effect of nicotine ($t = 2.63$; $P < 0.02$, with 19 *df*). Nevertheless, it was clearly not a universal phenomenon, with some participants not showing improved recall in the nicotine condition.

#### *Delayed recall of word lists*

For delayed recall, there were no effects of nicotine on the error data. An improvement in number of correctly recalled items was significant in the analysis of raw scores [$t = 2.98$, $df = 19$, $P < 0.01$].

#### *Nonverbal memory*

Neither recognition memory for abstract shapes nor memory for spatial location was affected by nicotine.

### Problem solving

The nicotine patch did not affect either number of correct responses or reaction time to make correct responses on the semantic verification test.

### Mood assessment

The 12 mood scales assessed three main factors, namely, alertness, happiness and calmness, with four scales contributing to each. In the analysis of raw scores on the individual scales, there were significant effects of nicotine on the calmness scales. For Calm-Excited, the participants were significantly calmer [$t = 3.11$, $df = 19$, $P < 0.01$]. For Tranquil-Troubled, the participants were significantly more tranquil [$t = 2.73$, $df = 19$, $P < 0.02$]. For Relaxed-Tense, the participants were significantly more relaxed [$t = 2.92$, $df = 19$, $P < 0.02$].

There were also significant effects of nicotine on the happiness scales. For Happy-Sad, the participants were significantly happier [$t = 3.26$, $df = 19$, $P < 0.01$]. For Contented-Discontented, the participants were significantly more contented [$t = 2.63$, $df = 19$, $P < 0.02$]. For Friendly-Unfriendly, the participants were significantly more friendly [$t = 1.32$, $df = 19$, $P > 0.1$) and for Sociable-Unsociable, there were no significant effects [$t = 1.63$, $df = 19$, $P > 0.1$].

There were no significant effects on the alertness, as in previous work with this computerised mood scale (Warburton et al. 1988).

### Adverse reactions

None of the volunteers who participated in the study had any unpleasant effects or symptoms, while wearing the 21 mg nicotine patch for six h.

## Discussion

A neglected aspect of nicotine replacement strategies is the need to provide the abstaining smoker with the psychological benefits which were previously being obtained from smoking. Abundant research has shown that cigarette smoking combines both performance enhancement with mood-altering properties (Warburton 1990) and the question posed in this research was whether the transdermal nicotine patch can provide any of these effects.

From the attentional testing, it is clear that the transdermal nicotine patch can produce improved attentional performance by 10.8% and 4% for correct detections and reaction times, respectively, of a similar order of magnitude to cigarette smoking (Wesnes and Warburton 1983; Warburton and Arnall 1994). In those studies, cigarettes produced average improvements of 14.1% and 7.8% for correct detections and reaction times, respectively, during the first 5 min of smoking and this was maintained throughout the cigarette. An improvement of around 10% was also obtained with acute dosing with nicotine tablets (Wesnes and Warburton 1983; Wesnes et al. 1983) and nicotine gum (Parrott and Winder 1989).

In addition, the transdermal nicotine patch improved both immediate and delayed recall in the task with which smoking (Warburton et al. 1992a) and nicotine (Warburton et al. 1992) improves performance. Smoking and nicotine improve memory in a number of delayed recall tests. For example, smoking a cigarette before the test improved verbal memory and pattern recognition (Warburton et al 1986).

The findings are less consistent for the effects of nicotine and smoking on immediate memory. Positive effects were found by Peeke and Peeke (1984) in two studies for verbal material and a nicotine tablet improved immediate memory for a 48-word list (Warburton et al. 1986). In other studies, no significant effects of smoking on immediate recall were found by Williams (1980), Peters and McGee (1982) and Kusendorf and Wignes (1985), and in Alzheimer patient studies (Sahakian et al. 1989; Jones et al. 1992).

It has even been claimed recently that nicotine impairs working memory tasks (Spilich et al. 1992). In

our study, working memory was assessed by the non-verbal memory tasks and the problem solving test. We found no evidence that the nicotine patch impaired working memory performance, although these tests are sensitive to impairing drugs such as scopolamine and diazepam (Rusted and Warburton 1989, 1991). Thus, these results are consistent with the findings of no effect rather those of Spilich et al. (1992).

A particularly intriguing finding was the evidence that the nicotine patch can produce calming effects (calmer, more tranquil and more relaxed) and improve mood as assessed by the happiness scales (happier and more contented, but not friendlier or more sociable). In our smoking studies, participants became significantly more calm, more tranquil and more relaxed, after successive puffs on the cigarette (Warburton et al. 1988). However, the same participants also rated themselves as happier, more contented, more friendly and more sociable, as they smoked. These findings with the patch are in accord with the mood assessments, which have been made in other studies of the 21 mg nicotine patch (Transdermal Nicotine Group 1991).

Foulds et al. (1992) have argued for acute tolerance occurring for the pleasant effects of nicotine with the transdermal patch. Certainly, partial, acute tolerance develops for heart rate, but not for skin temperature (Benowitz et al. 1982). However, the similarity of the psychological effects of the transdermal nicotine patch argues that tolerance for these pleasant effects, after 6 h exposure to nicotine, is not complete, if it is occurring at all.

This conclusion leaves us with the problem of accounting for the continued smoking by individuals on the patch, both in the real world (Transdermal Nicotine Group 1991; Foulds et al. 1992) and in the laboratory (Foulds et al. 1992). One explanation may lie in the absence of sensory effects with the transdermal nicotine patch. The importance of sensory effects for the smoking habit has been emphasised by Rose (1988) on the basis of his numerous studies showing the importance of upper airways stimulation for satisfying desire for cigarettes.

Recent support for this view has come from a study, which showed that a nicotine-free cigarettes can suppress craving ratings in a manner similar to nicotine-containing cigarettes (Gross et al. 1997). In fact, Rose warned that this need for sensory stimulation would not be satisfied by transdermal nicotine patches in his early evaluation of the patches (Rose 1986).

In summary, the nicotine patch can provide some substitute for cigarette smoking, by giving many of the benefits of smoking. It can produce the calming effects of smoking and some of the feelings of happiness which are increased with smoking. In addition, the nicotine patch improves attentional processing and memory. Acute tolerance to nicotine does not develop to these effects after 6 h exposure, although it is still possible that tolerance might occur with longer exposure.

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