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BRIEF REPORT

RELATIONSHIP BETWEEN NICOTINE TOLERANCE QUESTIONNAIRE SCORES AND PLASMA COTININE

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Abstract — The Fagerström Tolerance Questionnaire (TQ) is often used in both research and treatment contexts to evaluate nicotine tolerance and physiological dependence in cigarette smokers. Recently, however, questions about its validity and its usefulness in comparison to other easily collected measures have been raised. In the present study, 100 male subjects reporting for experimental sessions (Sample I) and 50 male and female subjects entering a smoking cessation clinic program (Sample II) were administered the TQ and determinations of plasma cotinine during ad libitum smoking were made. TQ scores were found to be correlated with cotinine levels in both samples, and several of the individual items proved to have statistically significant discriminatory value. Other schemes for determining degree of dependence were considered and found not to be superior to the TQ. Suggestions for further refining the TQ are reviewed.

The consequences of nicotine use have been shown to include both the usual indices of addiction (e.g., tolerance and withdrawal, Henningfield, 1984; Hughes & Hatsukami, 1986) and situation-specific factors (e.g., improvement of performance, relief of anxiety, Pomerleau & Pomerleau, 1984). Moreover, sensitivity to nicotine, and presumably degree of dependence, appear to be stable over time, at least over the short run (Jones, 1986). For this reason, a simple, noninvasive test that could provide a valid and reliable index of degree of dependence would be of considerable value to researchers attempting to specify factors involved in the reinforcement of tobacco use. Because it has been argued that identification of differences among smokers would allow the development of treatment methods tailored to individual needs (Fagerström, 1978; Pomerleau, Adkins, & Pertschuk, 1978), such a test would be of clinical value as well. Recent evidence that nicotine replacement therapy is more effective in highly dependent smokers (Jarvik & Schneider, 1984), and that higher doses of nicotine gum might be more appropriate for such smokers (Tønnesen, 1988), have considerably enhanced the potential clinical utility of such a tool.

An instrument widely used by both researchers and clinicians to classify smokers on the basis of nicotine dependence is the Tolerance Questionnaire (TQ) developed by Fagerström (1978). This scale consists of 8 items believed to be related to physiological dependence. It yields scores ranging from 0 to 11 points, with scores of ≥ 7 usually taken to indicate a high degree of dependence and scores of ≤ 6 a low degree of dependence. To validate the TQ, Fagerström used change in body temperature in 26 subjects as a measure of withdrawal and heart rate increase in 19 subjects as a measure of degree of acquired tolerance; he later reported a significant correlation with outcome in smoking cessation and other variables (Fagerström, 1980). Hughes (1984) has reviewed studies demonstrating the TQ's ability to predict tolerance, withdrawal, nicotine self-administration, and response to nicotine-gum

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treatment. Pinto, Abrams, Monti, and Jacobus (1987) found that highly dependent (TQ $\geq$ 6) smokers were significantly less likely to quit than their less dependent counterparts in a nicotine-fading treatment program. Hughes and Hatsukami (1986), however, reported that the scale did not predict signs and symptoms of tobacco withdrawal. More recently, Lombardo, Hughes, and Fross (1988) have reported a failure to replicate Fagerström's finding of physiological tolerance in two different studies, looking at heart rate change divided by nicotine boost and adjusted for body weight (but not age) in one and heart rate, skin temperature, skin conductance level, and blood volume pulse as indices in the other. (Findings for the second study hinge on the success of their fixed-dosing procedure, which was not confirmed by direct measurement of plasma nicotine.) These investigators conclude that the TQ measures "behavioral" or "perceived" dependence rather than physiological dependence.

Two other studies have raised additional questions about the validity and usefulness of the TQ. McNabb (1985), analyzing data from 97 persons entering a smoking cessation clinic, found no correlation between TQ scores and afternoon plasma nicotine levels. He also found that none of the individual items discriminated between highly dependent and less dependent smokers, again based on plasma nicotine levels. Lichtenstein and Mermelstein (1986), performing factor analyses and internal consistency analyses on two moderately large samples (N = 179 and N = 150), concluded that the items on the TQ do not form a unidimensional measure of an underlying construct.

Lichtenstein and Mermelstein (1986) went on to suggest that some items or subsets of items may constitute better indices of dependence than full scale scores — with the caveat that to be a valid and useful measure of nicotine dependence, the TQ should measure more than rate. Various schemes for subdividing the TQ have in fact been proposed. Pomerleau, Fertig, and Shanahan (1983), for example, distinguished between Intake (questions 1–3) and Pattern (questions 4–8); using plasma cotinine as the criterion variable, correlations for 27 subjects were + .57 ($p < .001$, 1-tailed) and + .34 ($p < .05$, 1-tailed), respectively. Jerome et al. (1984), using outcome in 45 postmyocardial infarction patients as the criterion variable, found that rate, latency to first cigarette, and smoking-when-ill discriminated quitters from nonquitters, with latency being the best predictor.

The present study represents a reassessment of the utility of the TQ using data from two widely differing subject samples: I. 100 male smokers who were recruited to serve as subjects in a series of laboratory experiments and who were not trying to quit; and II. 50 male and female patients enrolling in a smoking-cessation program. TQ scores and individual items were subjected to the same analyses employed by McNabb (1985), except that plasma cotinine rather than plasma nicotine was used as the biochemical validator. The data were also examined in the light of various suggestions for using subscales that might increase the predictive value of the TQ.

Cotinine, the principal metabolite of nicotine, was chosen as a validator because it has a biological half-life of approximately 30 hours and is relatively insensitive to the immediate effects of smoking (Matsukura et al. 1979). It therefore constitutes a more stable measure of chronic intake than plasma nicotine, which is very responsive to time since last cigarette. Pomerleau et al. (1983) found high-cotinine subjects to be consistently more nicotine-dependent than low-cotinine subjects, using several biological measures of tolerance/dependence, including changes in heart rate and skin temperature and ability to regulate nicotine intake when smoking high- versus low-nicotine cigarettes. Further evidence of the stability of this measure is provided by unpublished test-retest reliability checks from our laboratory (r = + .82, $p < .0001$; N = 46), based on data from Sample II subjects collected approximately one week apart, before initiation of treatment.

Table 1. Demographic and smoking data on subjects in Samples I and II

	Sample I	Sample II		
	Males $N = 100$	Males $N = 20$	Females $N = 30$	All subjects $N = 50$
Age	32.5 (±11.9)	42.7 (±11.7)	44.2 (±11.6)	43.6 (±11.5)
Years smoked	16.9 (±12.0)	24.4 (±11.2)	25.8 (±11.3)	25.2 (±11.5)
Weight (lbs.)	166.7 (±24.5)	181.9 (±41.6)	148.8 (±31.0)	162.0 (±38.8)
Height (in.)	70.2 (±2.9)	69.3 (±2.8)	64.5 (±2.6)	66.4 (±3.6)
Cigarettes/day	30.0 (±11.9)	31.7 (±9.9)	28.2 (±11.2)	29.5 (±12.7)
Mg/cigarette	0.98 (±0.23)	0.83 (±0.26)	0.70 (±0.32)	0.75 (±0.30)
Mg/day (mg/cig × cig/day)	29.0 (±12.1)	25.8 (±11.3)	19.7 (±11.9)	22.2 (±11.9)
Exposure per pound $\left(\frac{\text{mg/day}}{\text{weight}}\right)$	0.18 (±0.08)	0.15 (±0.07)	0.14 (±0.09)	0.14 (±0.08)
TQ score	6.4 (±2.0)	6.3 (±1.6)	5.8 (±1.8)	6.0 (±1.7)
Plasma cotinine (ng/mL)	275.7 (±138.1)	273.2 (±148.7)	277.2 (±109.6)	275.6 (±125.2)

Means (± SD)

METHOD

Subjects

Subjects in Sample I were 100 male smokers, in good health and not on psychoactive medications, who participated in experiments in our laboratory between 1981 and 1986. Although subject selection criteria varied across experiments, most were recruited for being moderate to heavy smokers who smoked at least 20 cigarettes per day and who had smoked for at least five years. All were paid for their participation.

Subjects in Sample II were 50 smokers (20 males and 30 females) who enrolled in a double-blind, placebo-controlled clinical trial of a pharmacological agent as a possible aid in smoking cessation. (All data presented in the present study were collected prior to administration of drug or placebo, and before subjects were asked to cut down or quit.) Subjects were paid for participating in the clinical trial. To be included, subjects were required to be in good health, at least 18 years of age, with a history of having smoked at least 20 cigarettes per day for one or more years, not pregnant, and not regular users of psychotropic medication.

Table 1 presents data on demographic and smoking variables for all subjects in Sample I and for males, females, and all subjects in Sample II.

Assays

For subjects in Sample I, plasma cotinine was quantitated by radioimmunoassay (RIA) as

Table 2a. Nicotine tolerance questions and plasma cotinine levels for samples I and II

		No. Ss	Sample I (N = 100)	$p <$	No. Ss	Sample II (N = 50)	$p <$
1. How many cigarettes a day do you smoke?	(0) ≤ 15	8	206.1 ± 152.4		4	145.5 ± 84.8	
	(1) 16–25	36	288.0 ± 147.7	NS	17	218.2 ± 95.9	.05
	(2) ≥ 26	56	277.8 ± 129.3		29	327.2 ± 117.9	
2. What brand do you smoke? (nicotine yield)	(0) ≤ 0.9 mg	29	220.0 ± 97.3		32	269.1 ± 121.8	
	(1) 1.0–1.2	61	280.6 ± 131.9	.005	17	290.2 ± 137.5	NS
	(2) ≥ 1.3	10	407.7 ± 187.0		1	237.0 ± 137.5	
3. Do you inhale?	(0) never	0			1	192.0	
	(1) sometimes	8	177.0 ± 113.9	.05	1	272.0	NS
	(2) always	92	284.3 ± 137.3		48	277.4 ± 127.3	
4. Do you smoke more during the morning than during the rest of the day?	(1) yes	27	312.0 ± 114.1	NS	19	279.3 ± 82.2	NS
	(0) no	73	262.3 ± 144.4		31	273.4 ± 146.8	
5. How soon after you wake up do you smoke your first cigarette?	(1) ≤ 30 min	81	289.9 ± 130.0	.05	37	302.7 ± 127.4	.01
	(0) > 30 min	19	215.4 ± 158.6		13	198.5 ± 81.5	
6. Which cigarette would you hate to give up?	(1) 1st in a.m.	29	273.2 ± 132.7	NS	20	274.1 ± 120.2	NS
	(0) other	71	276.8 ± 141.2		30	276.6 ± 130.5	
7. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., church, library, theater?	(1) yes	41	297.6 ± 138.5	NS	13	289.2 ± 120.5	NS
	(0) no	59	260.5 ± 137.0		37	270.9 ± 128.1	
8. Do you smoke if you are so ill that you are in bed most of the day?	(1) yes	42	312.3 ± 140.6	.05	21	313.9 ± 74.7	.05
	(0) no	58	249.3 ± 131.3		29	247.9 ± 147.0	

(Mean ± SD)

described by Langone, Gjika, and Van Vunakis (1973). Analyses were conducted under the supervision of Nancy Haley, Ph.D., at the American Health Foundation in Valhalla, NY (Hill, Haley, & Wynder, 1983). For Sample II subjects, plasma cotinine was quantitated using gas chromatography with alkali flame ionization (nitrogen-phosphorus) detection and a structural analogue of cotinine as an internal standard, as described by Jacob, Wilson, and Benowitz (1981). Analyses were conducted by Neal Benowitz, M.D., Division of Clinical Pharmacology, San Francisco General Hospital Medical Center.

Procedure

Subjects in Sample I were participants in several experiments and were deprived for periods ranging from 1/2 hour to overnight. TQ scores and demographic data were collected at a screening session (in a context of ad libitum smoking), at which time informed consent was also obtained. Experimental sessions were conducted at various times of the day, generally ranging from 1000 to 1600 hours. On experimental days, blood samples were drawn from a forearm vein, using an indwelling scalp-vein needle and a 1 m infusion-exfusion tubing flushed with heparin. Cotinine analysis was based on baseline samples collected before the first smoking trial. Blood was collected in heparinized plastic tubes, chilled in ice water, centrifuged at 4 °C, and kept frozen at −80 °C until it could be sent out for assay.

Table 2b. Nicotine tolerance questions and plasma cotinine levels for sample II by sex

		No. Ss	Males (N = 20)	$p <$	No. Ss	Females (N = 30)	$p <$
1. How many cigarettes a day do you smoke?	(0) ≤ 15	1	154.0		3	142.7 ± 103.7	
	(1) 16–25	4	158.0 ± 134.2	NS	13	236.7 ± 83.5	.05
	(2) ≥ 26	15	311.9 ± 140.5		14	343.7 ± 90.1	
2. What brand do you smoke? (nicotine yield)	(0) ≤ 0.9mg	10	291.3 ± 132.5		22	258.9 ± 118.4	
	(1) 1.0–1.2	10	255.1 ± 168.5	NS	7	340.4 ± 52.9	NS
	(2) ≥ 1.3	0			1	237.0	
3. Do you inhale?	(0) never	0			1	192.0	
	(1) sometimes	0			1	272.0	NS
	(2) always	20	273.2 ± 148.7		28	280.5 ± 112.3	
4. Do you smoke more during the morning than during the rest of the day?	(1) yes	6	288.5 ± 98.3	NS	13	275.1 ± 77.7	NS
	(0) no	14	266.6 ± 168.7		17	278.9 ± 131.2	
5. How soon after you wake up do you smoke your first cigarette?	(1) ≤ 30min	15	302.7 ± 160.0	.05	22	302.8 ± 103.7	.05
	(0) > 30 min	5	184.8 ± 49.4		8	207.0 ± 98.9	
6. Which cigarette would you hate to give up?	(1) 1st in a.m.	8	291.3 ± 135.1	NS	12	262.7 ± 114.0	NS
	(0) other	12	261.2 ± 161.8		18	286.9 ± 108.7	
7. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., church, library, theater?	(1) yes	6	302.3 ± 177.3	NS	7	277.9 ± 50.2	NS
	(0) no	14	260.7 ± 140.3		23	277.0 ± 123.0	
8. Do you smoke if you are so ill that you are in bed most of the day?	(1) yes	7	297.1 ± 92.3	NS	14	322.3 ± 66.3	.05
	(0) no	13	260.3 ± 173.9		16	237.8 ± 125.9	

(Mean ± SD)

Data were collected from participants in the drug study (Sample II) at individually scheduled initial interviews, prior to their assignment to drug condition. These interviews were scheduled throughout the day. Blood was collected in serum separator tubes, centrifuged at room temperature, and kept frozen at −80 °C until it could be sent out for assay.

Because of differences in the nature of the samples as well as in the assay procedures, it was deemed inappropriate to make any attempt to pool data from the two samples.

RESULTS

TQ scores were significantly correlated with plasma cotinine levels for both Sample I (r = + .33, $p < .001$) and Sample II (r = + .42, $p < .005$). When Sample II was analyzed by sex, TQ was significantly correlated with plasma cotinine for females (r = + .51, $p <$ .005) but not for the males (r = + .34, n.s.).

Table 2a presents an analysis of responses to the individual items, using t tests to determine whether different responses were associated with significantly different mean levels of plasma cotinine. In keeping with McNabb's (1985) procedure, responses of 0 were tested against all other responses (with the exception of item 3, "Do you inhale?" where

Table 3. Correlations of mean plasma cotinine levels with TQ subscales and with non-TQ variables

	Sample I	Sample II		
	Males $N = 100$	Males $N = 20$	Females $N = 30$	All Subjects $N = 50$
TQ (Fagerström, 1978)	0.33 ($p < .001$)	0.34 (NS)	0.51 ($p<.005$)	0.42 ($p<.005$)
Intake (TQ Items 1–3) (Pomerleau et al., 1983)	0.34 ($p < .0005$)	0.26 (NS)	0.59 ($p<.001$)	0.41 ($p<.005$)
Pattern (TQ Items 4–8) (Pomerleau et al., 1983)	0.24 ($p < .05$)	0.27 (NS)	0.24 (NS)	0.25 (NS)
Predictors (TQ Items 1,5, 8) (Jerome et al., 1984)	0.20 ($p < .05$)	0.46 ($p<.05$)	0.68 ($p<.0001$)	0.57 ($p<.0001$)
Cigarettes/day	0.02 (NS)	0.41 ($.10> p > .05$)	0.56 ($p<.001$)	0.47 ($p<.0005$)
Mg/cigarette	0.28 ($p < .005$)	−0.07 (NS)	0.25 (NS)	0.11 (NS)
Mg/day (mg/cig × cig/day)	0.14 (NS)	0.26 (NS)	0.48 ($p<.01$)	0.35 ($p<.05$)
Exposure per pound $\left(\frac{\text{mg/day}}{\text{weight}}\right)$	0.22 ($p < .05$)	0.23 (NS)	0.51 ($P<.005$)	0.38 ($p<.01$)

there were no responses of 0 in Sample I and only 1 in Sample II; for this item, pooled responses of 0 and 1 were tested against responses of 2). (Because 5 of the 8 questions are dichotomous, this strategy was deemed more appropriate than multiple regression techniques.) For Sample I, items 2, 3, 5, and 8 successfully discriminated between respondent groups; for sample II, items 1, 5, and 8 discriminated between respondent groups. In Table 2b, Sample II is further broken down by sex. The discriminative value of items 1, 5, and 8 persisted for the female subset; for the smaller male subset, only item 5 retained discriminative value.

Coefficient Alphas, like those reported by Lichtenstein and Mermelstein (1986), were low (.58 for Sample I and .41 for Sample II). Two previously suggested schemes for subdividing the TQ were tested: The Intake (questions 1–3) and Pattern subscales (questions 4–8) proposed by Pomerleau et al. (1983) and the combined score for the 3 variables singled out by Jerome et al. (1984). Finally, several easily determined non-TQ variables were tested to determine whether they might serve as better indicators of dependence than the TQ. Results are shown in Table 3.

DISCUSSION

Using plasma cotinine as the criterion variable, significant and moderately strong correlations with the TQ were found in two separate samples with widely differing

demographic characteristics, smoking histories, and motivational sets. When Sample II was broken down by sex, the females clearly contributed more to the significant relationship than did the males. Since the correlation coefficient for the males in Sample II is strikingly similar to that for the all-male Sample I (+ .34 vs. + .33), however, it is likely that a larger number of males in Sample II would have produced a significant correlation as well.

Except for item 6 in Sample II, individual items produced results in the expected direction, even when they failed to reach significance. Two items, 5 and 8, had discriminative value in both samples. The strong predictive value of item 5, which deals with latency to first cigarette of the day, is consistent with the findings of previous investigators using other criterion variables (e.g., Jerome et al., 1984; Lichtenstein & Mermelstein, 1986).

In Sample I, strength of cigarette (item 2) discriminated among subjects, but rate (item 1) did not; in Sample II, the opposite situation prevailed. Sample I subjects smoked considerably stronger cigarettes than Sample II subjects; possibly lower-nicotine cigarettes encourage subjects to maximize nicotine intake with each cigarette, thus tying intake more closely to rate. Moreover, Sample I data were collected over the course of five years, so changes in cigarettes and smoking patterns, as well as the possibility of slight assay drift (although we did not detect appreciable shifts in cotinine means over the period), may also have contributed to the somewhat puzzling lack of correlation between cotinine and rate by introducing extraneous sources of variability. Since over 90% of subjects in both our samples always inhaled, item 3 may be of limited value; in populations including larger numbers of light smokers, however, it could add a useful dimension.

Items 4, 6, and 7 proved to be weak discriminators in both samples. Moore, Schneider, and Ryan (1987) have recently pointed out that item 4 has been mistranslated from the Swedish; possibly if it referred to "the first two hours of the day" rather than to "the morning," its information value would be enhanced. The benefits of making such a change, however, must be weighed against the fact that comparisons with data collected using the earlier version will be difficult to interpret. Item 6 also suffers from a translational problem. "Which cigarette would you hate to give up?" (Fagerström, 1978) is not idiomatic English and clearly confuses some respondents; a frequent response in our laboratory is "all," which might result in artificially low TQ scores for highly dependent smokers. If altered to read, "Which cigarette of the day would you *most* hate to give up?" item 6 might prove more useful. (Such a change is currently in effect in our laboratory). A similar modification was apparently used by McNabb (1985).

Overall, none of the proposed subscales or alternative noninvasive measures provided a consistent improvement over TQ scores as a predictor of cotinine level. We conclude that the TQ, in the absence of measures of plasma cotinine, can be accepted as a useful measure of chronic nicotine intake, particularly if the linguistic ambiguities in items 4 and 6 can be resolved. Evidence of its lack of internal consistency and mixed findings in the literature regarding its ability to predict physiological tolerance and withdrawal suggest that further research will be required to resolve fully the issue of whether the TQ as a whole actually measures nicotine dependence.

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