

The Use of Anticholinergic Drugs for Smoking Cessation: A Pilot Study

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Abstract

A pilot study of 500 cases drawn from a total population of 3,700 patients reports on a smoking cessation program in a private practice clinic. A new protocol offers promise for treatment based on an initial injected dose of atropine, scopolamine, and chlorpromazine administered subcutaneously to eliminate physiological withdrawal symptoms, followed by a 2-week oral medication regimen, and follow-up every 2 months for a 12-month period. The study held that 92.1% of the male patients and 80.7% of female patients remained nonsmokers at the end of 2 months; 42.3% of the men and 36.9% of the women remained nonsmokers at the end of 12 months, a cumulative total of 39.8%.

INTRODUCTION

Since the introduction of tobacco into Europe by the Spaniards, nicotine has become the most widespread form of substance dependency in the world (Corti, 1932; Russell, 1971). Cigarette smoking is legal and heavily advertised; thus, it is encouraged as an acceptable mode of public behavior though cigarette smoking probably causes more morbidity and mortality than all other drugs combined (*Why People Smoke*, 1983). It is the single major cause of cancer mortality in the United States (MFMWZ, 1982). Recent studies show that the inci-

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dence of developing coronary heart disease (CHD) is directly related to the number of cigarettes smoked; those smoking more than 20 cigarettes a day and those who begin smoking before the age of 20 are three to five times more likely to suffer coronary heart disease than nonsmokers (Ramisdale et al.). Up to 30% of deaths from CHD can be attributed to cigarette smoking (MMWR, 1984; Cashin et al., 1984). The expense of treating diseases caused by smoking is currently being assessed. Oster et al. (1984) estimate that "male heavy smokers between the ages of 40 and 44 will generate, on [the] average, over \$56,000 in additional costs of illness during their lifetimes, while for women, these costs will be over \$19,000" (p. 384).

The decision to cease smoking does not ensure permanent cessation. Although definitive data are not available, over the past decade it has been estimated that three-fourths of the smokers have tried to stop, but only about 20 to 25% actually succeed (*Why People Smoke*, 1983; Russell, 1971). Recidivism among those who quit smoking equals that of heroin addicts—75% (Russell and Feyerabend, 1978; Pomerleau, Adkins, and Pierichuk, 1978).

Clinical experience and a search of the literature indicate that a decision to stop smoking often means choosing a support program (Hunt and Bespalec, 1981). This study reports encouraging results found in a pilot test of new medical protocols not previously described or reported.

The program consists of a prescribed anticholinergic drug regimen aimed at eliminating physiological withdrawal symptoms. Treatment achieves positive effects for persons who enroll in the program with the intention of remaining nonsmokers. Drug intervention treatment reduces the extreme discomfort of withdrawal usually experienced by smokers that urges them to return to smoking. The scientific basis of this medical technique is described in the next section (Theory).

This yearlong pilot study had four purposes:

1. To test through medical observation if a prescribed drug regimen does, in effect, eliminate physiological withdrawal symptoms.
2. To identify and describe demographic characteristics common to a sampling of patients in the program.
3. To monitor for both expected and unexpected immediate effect.
4. To track cessation behavior.

The underlying assumption held that the absence of uncomfortable physiological withdrawal symptoms and the perception of this relief serve as a positive reinforcement for cessation, increasing the chance of a smoker's changing his behavior.

Research during the past decade has emphasized responsibility for one's own health and the need to educate the public about the physical benefits of

smoking cessation. A number of approaches have been attempted including electroshock, hypnosis, psychotherapy, and counselling through support groups (Myrsten, Elegerot, and Edgren, 1977; Pederson, Scrimgeour, and Lefcoe, 1979; Gross, 1978-1979).

However, it is well documented that a smoker desiring to cease smoking and remain a nonsmoker must address both physiological and psychosocial effects. For best success, the patient must have a specific motivational reason (SMR) to stop smoking, and social reasons seem to impose stronger motivation than medical reasons (Russell and Feyerabend, 1978; Eiser and Sutton, 1978; Malotte et al., 1981).

THEORY

Nicotine is addictive, having a neurobiochemical basis (Jarvik, 1979). Nicotine has an agonistic action at the nicotine receptor sites in the cholinergic nervous system (Birdsall, Burgen, and Hulme, 1978; Rosecrans, 1979) (Fig. 1). Its primary action upon prolonged use is that of a blocking agent. While this activity is less documented in the central than in the peripheral nervous systems, the preponderance of such nicotine receptors appears to be located centrally at the midbrain level (Weiner, 1974; Popot and Changeux, 1984). With chronic nicotine use, biochemical tolerance and physiological dependency are developed by increased acetylcholine accumulation mediated by enzyme induction and/or derepression through choline acetyltransferase (Brimblecombe, 1974; Wills, 1970; Dahlstrom, Booi, Heiwall, and Larsson, 1980; Ketchum et al., 1973) (Fig. 2).

A "tobacco withdrawal syndrome" providing for nicotine abstinence thus comes about by elimination of the nicotine blockade at specific nicotine-cholinergic synapses. Tolerance and dependency, developed by increased acetylcholine synthesis activity, are replaced by withdrawal, which results from excessive acetylcholine rebound stimulation (Jarvik, 1979; Dahlstrom et al., 1980; Ketchum et al., 1973) (Fig. 3).

The final biochemical interpretation of nicotine withdrawal is through acetylcholine intersynaptic stimulation of predominately muscarinic cholinergic sites at higher neuronal levels, including the cerebral cortex (Hirschorn and Rosecrans, 1974). Usual clinical symptoms include a decrease in heart rate and blood pressure, increased irritability, nervousness, gastrointestinal disturbances, electroencephalogram changes, and a temporary decrease in the ability to concentrate.

Tests of a variety of anticholinergic and other drugs found that only scopolamine and di-amphetamine decreased smoking (pudding pattern) in monkeys. By using animal paradigms as a model for human nicotine dependency, Chick, Jarvik, and Nakamura (1970) showed the effectiveness of parasympathetic nervous system antagonists. Clinical data gathered from medical patients, as reported

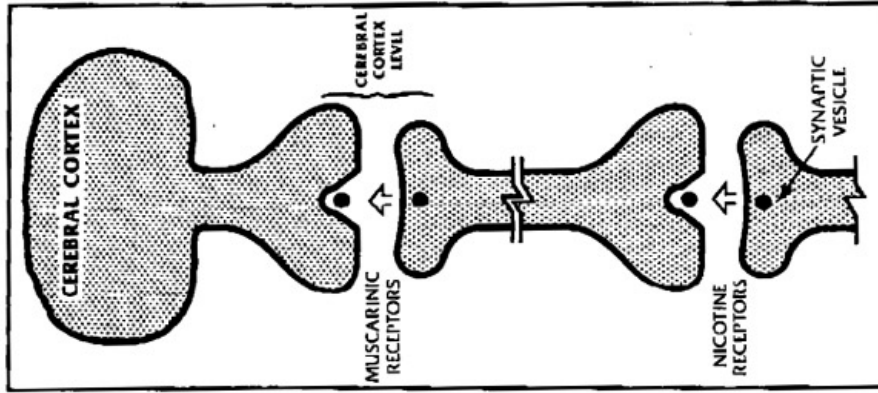


Fig. 1. Normal cholinergic transmission.

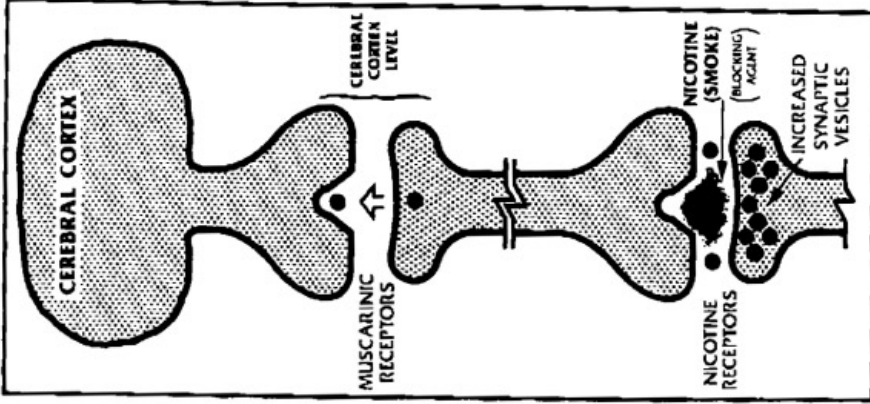


Fig. 2. Nicotine blockade: increased neurotransmitter synthesis.

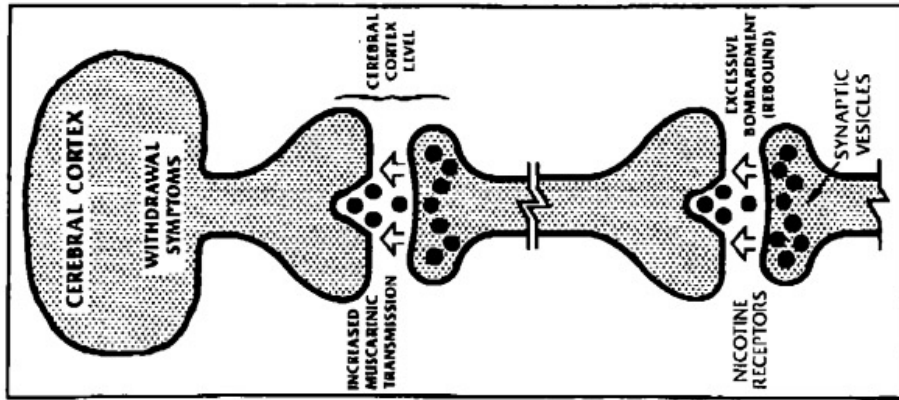


Fig. 3. Nicotine withdrawal: rebound stimulation.

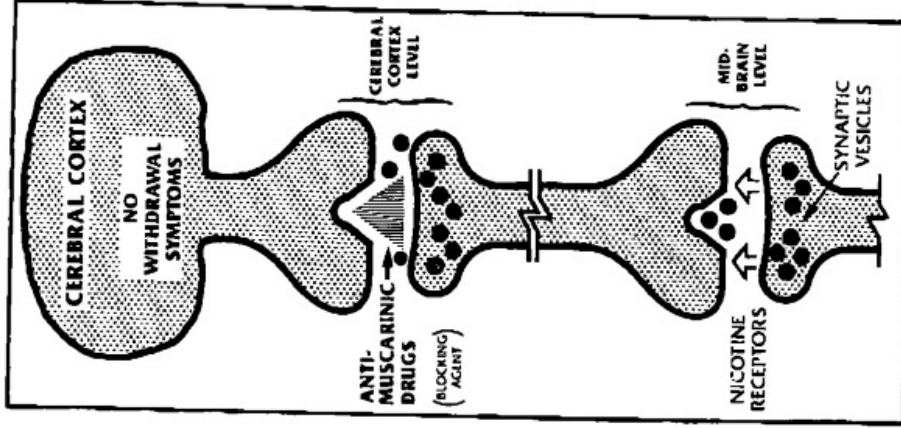


Fig. 4. Anticholinergic blockade of nicotine withdrawal.

in this pilot study, demonstrate the usefulness of their research. Anticholinergic drugs act predominantly at muscarinic sites in the cerebral cortex. By blocking these sites, we prevent the ultimate interpretation of the intersynaptic rebound phenomenon caused by excessive acetylcholine stimulation at lower nicotine midbrain-level receptors created by cessation of chronic nicotine (tobacco) use (Fig. 4).

Since withdrawal symptoms to nicotine cessation are most pronounced during the first 24-48 hours, immediate and high levels of anticholinergic activity are achieved by injecting described anticholinergic drugs in the subcutaneous areas over the mastoids. Nicotine is eliminated in approximately 3 days, but it may take approximately 2 weeks to reduce withdrawal symptoms (Goldstein and Goldstein, 1968). Consequently, oral medication is recommended to maintain a low level of anticholinergic activity for a period up to 2 weeks. This technique is based on laboratory evidence that approximately 2 weeks are required for a significant decrease in enzyme synthesis of the end product (acetylcholine).

The anticholinergic method helps patients develop an aversion to cigarettes by also affecting taste and sensory receptors. The effect of dry mouth, for example, while disadvantageous in many instances, is helpful where it is a consequence of therapeutic techniques.

METHODS

For this pilot study, retrospective, longitudinal data were collected over a 2½-year period, 1980 to mid-1983, using the smoking cessation protocol. For purposes of this initial report, demographic and other characteristics of the program's self-selecting population were combined to better profile the smoker who is likely to seek out and complete this approach to smoking cessation.

Four primary variables were used to describe the program population and the pilot group:

- Age at entrance into the program
- Sex
- Number of cigarettes smoked per day
- Reason for wanting to stop smoking

The pilot study describes a single treatment group consisting of a cohort of 500 adult patients from a total study population of 3,700 patients tracked for a 12-month period (Tables 1 and 2). A systematic convenience sample was drawn from patients' charts and clinic recordings on follow-up log books. Patients for the treatment program were self-referrals, those attracted by public advertisement, media, and physician referrals. They paid for the program by private payment or medical insurance coverage.

Table 1
Smoking Cessation Record (500 Cases)^a

Age range	Cases	Years smoking	Cases	No. cigarettes smoked per day	Cases	Months	Non-smokers after 12 months
15-25	35	1-5	19	1-10	2	0	500
26-35	158	6-10	71	11-20	70	2	435
36-45	141	11-15	86	21-30	111	4	344
46-55	115	16-20	77	31-40	168	6	327
56-55	44	21-25	51	41-50	99	8	302
66-75	6	26-30	98	61-80	50	12	199
76-80	1	31-40	76				
		41-50	22				

Mean: 39.9 yr
SD: 11.4

Mean: 19.5 yr
SD: 10.9

Mean: 35.4 cigs
SD: 14.9

Median: 6.5 mo
nonsmoking time

^aData were gathered retrospectively from charts of the Physicians' Clinic.

Criteria for acceptance into the program included:

1. The desire and willingness to stop smoking
2. No medical contraindications for the use of anticholinergic drugs, as with acute-angle glaucoma, prostatic hypertrophy, or cardiac arrhythmias (Cashin et al., 1984)

The baseline screening protocol included^b but was not limited to, these check-points:

1. Assessment of medical history
2. Routine chest X-ray
3. Urinalysis
4. Electrocardiogram
5. Blood work, complete blood count, serum electrolytes, and an SMA-12 panel
6. Assessment of surgical history for previous occurrence of idiosyncratic or prolonged refractory times in the dissipation of anticholinergic drug effects

All patients meeting the program criteria signed an informed consent to treatment which spells out the expected effects as well as possible—but not necessarily anticipated—untoward reactions.

Table 2
Baseline Average of Years Smoked and Number of Cigarettes
Smoked per Day by Sex

	Average years smoked	Average number of cigarettes smoked per day
Male	21.4	37.8
Female	20.8	33.6
Total	21.1	35.5

THE PROTOCOLS OF TREATMENT

Having consented to treatment with anticholinergic drugs, patients submitted to the following set of protocols:

1. The patient receives an initial intramuscular injection of a 2-ml saline solution with scopolamine 0.2 mg and atropine 0.2 mg.
2. The patient is monitored in the physician's office with the room darkened for a minimum period of 5 minutes, followed by an assessment of normal pupillary constriction and mild xerostomia.
3. Given that factors in Step 2 are within normal limits, two additional injections are administered subcutaneously over each mastoid area. The total drug regimen is atropine 0.2 mg, scopolamine 0.2 mg, and chlorpromazine 10 mg. One-half of the total solution is injected in each site.
4. The patient again is monitored in the physician's office for a minimum period of 5 minutes.
5. Given that the response is within the range of anticipated effects, the patient is allowed to leave the office with instructions not to drive, not to consume alcohol, and not to take medications with a synergistic effect for 24 hours. Acceptable anticipated effects include moderate xerostomia, lightheadedness, and some difficulty in focusing.
6. Day 2 through Day 14, the patient is to take a prescribed oral anticholinergic drug that is known to act on the central, rather than the peripheral, nervous system. The most commonly used drugs are trihexphenidyl hydrochloride, benztropine mesylate, or scopolamine patches.

Tracking patients during the 12-month period was a task requiring systematic review. Subjects responded favorably to follow-up activity, for periodic contacts provided them with motivation to continue cessation. Follow-up information on smoking status was self-reported by patients' responses to telephone contacts every 2 months and mailings utilizing a brief, tersely worded

questionnaire (see the Appendix). Results were tabulated by staff of the Physicians' Clinic and entered into patient charts. The interplay between SMR and medical intervention could further refine knowledge of factors that enhance or inhibit success and affect a smoker's chance for long-term cessation (Goldstein and Goldstein, 1968).

RESULTS

1. Preliminary findings indicate that this treatment protocol is successful for a large number of patients. Success is described at two points in time: cross-sectionally, where the patient has or has not ceased to smoke, and longitudinally, to determine the length of smoking abstinence over a 12-month observation period. The use of anticholinergic drugs for smoking cessation is a technique easily administered in the office of a private practitioner and accessible to most practicing physicians.

Future intake should focus on a thorough physical assessment (workup) since treatment is by physical (chemical) means. Psychological assessment may be worthwhile to determine SMRs, but this may prove a self-selection process because patients would not choose to participate without a good or immediate reason to do so.

2. Findings support the main purpose of the study, indicating that 434 (86.8%) of the 500 patients of the pilot study stopped smoking at 2 months; 199 (39.8%) remained nonsmokers at the end of the year. Results of the program are higher than the general population of smokers who attempt to stop smoking (Conditte and Lichtenstein, 1981) (Fig. 5). Further study is needed to report with confidence an anticipated program success rate for this particular smoking cessation protocol. If, however, the average smoking cessation program finds an average of 20% of the patients abstinent at 6 months (Hunt and Lespalec, 1981), this methodology may offer the possibility of cessation to a greater percentage of smokers.

3. Table 3 summarizes motivational characteristics of subjects tested at the beginning of the cessation program. The study concluded that in long-term cessation, the patient must perceive a *specific motivational reason* [SMR] to stop smoking. Smokers who could clearly identify in SMR were more successful in smoking cessation than those who could not. Social reasons represented a SMR among 63.6% of the patients who stopped smoking a full 12 months—the need to satisfy a spouse, children, friends, or employe conditions—whereas only 30.7% stopped who had medical reasons for doing so. SMRs include such concerns as (1) social acceptance in a peer group; (2) interpersonal relationships; (3) intolerance in a work station or business site; (4) pressure from a sexual partner; (5) parental disapproval; (6) cosmetic effects, including stained teeth and wrinkled lips; and (7) complaints about the stench of tobacco.

Table 4
Nicotine Levels at Baseline and Two Follow-Up Periods

Nicotine level	Smoker baseline		2 mo nonsmoker		12 mo nonsmoker	
	N	%	N	%	N	%
Low (0.3 mg)	288	57.6	244	56.9	125	62.8
High (1.3 mg)	212	42.4	191	43.1	74	37.1

4. Table 4 indicates that a greater percentage of smokers of low-nicotine cigarettes were able to stop smoking for a period of 12 months than smokers of high-nicotine cigarettes. We are cognizant of the fact that 60.8% of the participants enrolled in the program entered as smokers of low-nicotine cigarettes. (See Table 1.) Therefore, we encountered a design group with positive motivation to stop smoking since the majority had, in this way, demonstrated a practice intended to reduce nicotine dependency. In 1964 the World Health Organization substituted the single term "dependence" to describe physical or psychological "habituation" or "addiction." Physical dependence includes "tolerance of the effects of... [a] drug due primarily to changes at synapses and "withdrawal symptoms resulting from rebound over-activity at synapses when intake of the drug is reduced or discontinued" (Russell, 1971, p. 2). Nicotine dependency is characterized as increased acetylcholine synthetic activity resulting from nicotine blockade at specific nicotine-cholinergic synapses. Chronic nicotine use causes increased acetylcholine accumulation. Smokers of low-nicotine cigarettes help themselves because lower levels of acetylcholine buildup enable earlier and less painful withdrawal.

5. Experience in this pilot group showed that 39.5% of those who stopped smoking a period of 12 months used regular cigarettes; but only 11% of those who smoked mentholated cigarettes were able to stop. It is possible that smokers of mentholated cigarettes may have a greater level of nicotine dependency because mentholatum has a soothing action on the respiratory membrane, thus permitting deeper inhalation and retention of smoke with higher levels of nicotine (titration and dependency).

CONCLUSIONS

1. Development of a rigorous program of smoking cessation using anticholinergic drugs requires establishment of protocols for (1) patient selection, (2) conduct of a physical examination, (3) administration of drugs, (4) follow-up activity, and (5) evaluation of short-term and long-term success and failure. The short-term measure is completion and compliance within treatment of the

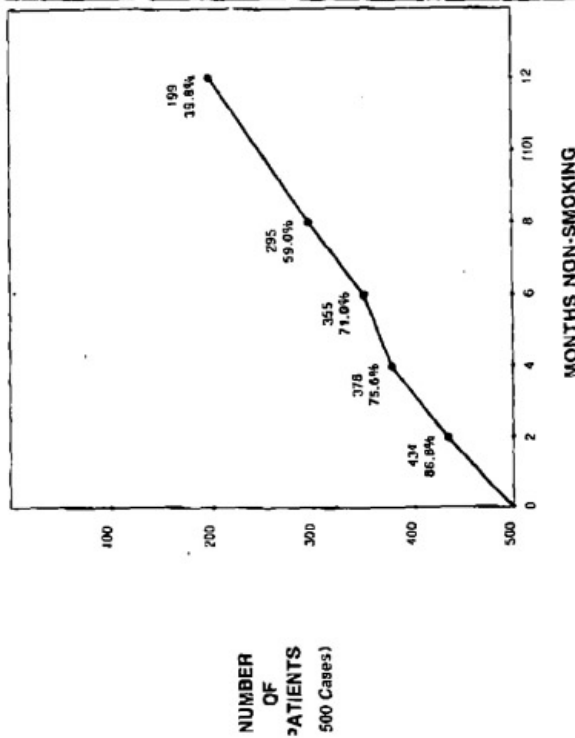


Fig. 5. Successful nonsmokers.

Table 3
Reason for Entering the Program

Reason	Male		Female		Total	
	N	%	N	%	N	%
Social	185	(37.0)	133	(26.6)	318	(63.6)
Medical	62	(12.4)	54	(10.8)	116	(23.2)
Missing values	35	(07.0)	31	(06.2)	66	(13.2)
Total	282	(56.4)	218	(43.6)	500	(100.0)

program. The intermediary, long-term measure requires follow-up of past treatment. By establishing criteria for protocols and following these protocols in clinical practice, physicians could obtain data for a longitudinal study of smoking cessation based upon medical intervention techniques.

2. A sustained research effort is desirable in aspects of smoking cessation with drug intervention protocols. Specifically, medical science would benefit from scientific reports treating the following concerns:

- A prospective longitudinal study with supporting standardized intervention, recordkeeping, and administrative follow-up.
- Improved behavioral modification support to complement physical/medical treatment.
- Outcome measures related to smoking cessation, including quit levels, patient evaluations of the program (strong points and weak points), and physiological measures (including self-reporting) such as improvements in respiratory or cardiovascular status reported in postcessation or self-worth assays.
- Development of an operational definition of a program's "success" or "failure" at both the individual level and the clinic program level.
- Articulation of demographic sociopsychological descriptors to afford more precise intake data (patient profiles) and complementary follow-up information (changes in status).

APPENDIX

THE PHYSICIANS' CLINIC
6535 SOUTHWEST FREEWAY
HOUSTON, TEXAS 77074

SMOKING CESSATION PROGRAM
PATIENT FOLLOW-UP LETTER

Dear

In our continuing follow-up to determine the effectiveness of our Clinic's smoking treatment program, we ask that you answer the questions below.

ANTICHOLINERGIC DRUGS FOR SMOKING CESSATION

When you have completed this form, please return it to us in the enclosed self-addressed envelope.

Thank you.

1. Are you smoking now? YES _____ NO _____
2. If your answer to question 1 was "yes," how many months after completing the Clinic's treatment did you re-start?
1 2 3 4 5 6 7 8 9 10 11 12
CIRCLE ONE
3. If you have re-started smoking, why?

STRESS _____ HABIT _____
(Check one or both)
Other [Please explain]: _____

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