United States Patent [19]

Hutchinson et al.

[11] **3,870,794**

[45] **Mar. 11, 1975**

[54] **TREATMENT OF CERTAIN EMOTIONAL DISORDERS WITH NICOTINE COMPOUNDS**

[75] Inventors: **Ronald R. Hutchinson**, Augusta; **Grace S. Emley**, Ross Township, Kalamazoo County; **Edward R. Hallin**, Barry Township, Barry County; **Nancy J. Murray**, Charlestown Township, Kalamazoo County, all of Mich.

[73] Assignee: **Foundation for Behavioral Research**, Kalamazoo, Mich.

[22] Filed: **Feb. 20, 1974**

[21] Appl. No.: **444,035**

[52] **U.S. Cl.** **424/264**

[51] **Int. Cl.** **A61l 27/00**

[58] **Field of Search** 424/264

[56] **References Cited**

UNITED STATES PATENTS

3,048,520 8/1962 McKennis, Jr. et al. 424/264

OTHER PUBLICATIONS

Merck Index, 7th Ed. (1960), p. 719.

Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Woodhams, Blanchard and Flynn

[57] **ABSTRACT**

Nicotine and nicotine derivatives are employed in medicinal treatment routines in a manner which produces unique and beneficial changes in particular emotional disorders. Administration of the compounds causes prompt and discrete reductions of anger, hostility, irritability, and frustration. Simultaneously reactions indicative of fear and anxiety are reduced without general sedation effects. These excessive emotional states are rather supplanted by improved focus upon and performance of necessary tasks. The compounds can be administered in a variety of dosage forms and are effective for the above-described purposes when administered in amounts far less than toxic amounts.

8 Claims, No Drawings

TREATMENT OF CERTAIN EMOTIONAL DISORDERS WITH NICOTINE COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a new and useful medicinal treatment effective in alleviating emotional states characterized by anger, irritability, tension and concomitant fears and anxieties resulting from stressful or frustrative living conditions. The treatment acts to alter emotional balance and expression by two different processes. Anger, hostility, irritability, frustration, and feelings of tension are reduced but without general response depression, drowsiness, or sedation. Simultaneously, reactions of fear, anxiety, and nervousness are reduced and supplanted by improved focus upon and performance of necessary tasks.

The successful treatment of emotional disorders by chemical means has been hampered historically by the lack of objective laboratory methods for quantitative assessment of specific emotional processes. Previously available tests have relied upon gross visual observations of humans and animals in either natural living settings or special artificial social settings. The variability inherent in such tests contributed greatly to the uncertainty of the findings. During the past decade, precise, objective, and efficient methods have been discovered for the measurement of anger, hostility and aggressivity in both man and animals. The techniques, now well established, allow the simultaneous differential assessment of anger and aggressivity versus fear and anxiety. The efficacy of the medicinal treatment according to this invention has been verified by employing these precise testing methods.

Insofar as we are aware, no prior scientifically based disclosure regarding the benefits of nicotine upon emotional processes, behavioral expression, or performance has occurred. The long standing practice in numerous cultures through many hundreds of years of using tobacco products containing nicotine is well known. Nicotine or nicotine related substances have previously been employed or proposed for employment as a treatment for colic (U.S. Pat. No. 101,145), tobacco substitute (U.S. Pat. Nos. 904,521 and 2,981,641), insecticide and parasiticide (U.S. Pat. No. 2,175,980), muscle relaxant (U.S. Pat. No. 3,048,520), snake repellent (U.S. Pat. No. 3,069,314), antihistamine potentiator (U.S. Pat. No. 3,126,319), swine food additive (U.S. Pat. No. 3,252,802) and skin care agent (U.S. Pat. No. 2,437,561).

SUMMARY OF THE INVENTION

This invention is based on the unexpected discovery that the administration of very small quantities of nicotine or nicotine derivatives to mammals, including human beings, produces in the subject treated immediate and substantial reductions in anger or aggressivity and improved task performance, without general response sedation or reduction.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a new and useful medicinal treatment effective in reducing emotional states characterized by anger, irritability, tension and concomitant fears and anxieties resulting from stressful or frustrative living conditions. The treatment acts to alter the emotional balance and expression of the subject

treated by two different processes. Anger, hostility, irritability, frustration, and feelings of tension are reduced but without general response depression, drowsiness, or sedation. Simultaneously, reactions of fear, anxiety, and nervousness are reduced and supplanted by improved focus upon and performance of necessary tasks.

Specifically the treatment involves the administration to a mammal, especially human beings, in a pharmaceutically acceptable dosage form, of a therapeutically effective amount of nicotine or its pharmacologically acceptable acid addition salts, especially nicotine tartrate, nicotine bitartrate, nicotine hydrochloride and nicotine sulfate, or a metabolite of nicotine, especially nornicotine or cotinine (available from K & K Laboratories, Plainview, N.Y.). The drug can be administered in any of several forms and dosages suitable to maximum convenience and desired effect. Administration can be (1) oral — in the form of powder, capsules, tablet, pill, elixir, syrup, lozenge, or chewable mastic. Representative compositions for oral dosage forms are:

Preparation 1A - Capsule - Two piece gelatin capsules containing 5 mg of essential active ingredient are prepared as follows:

Nicotine tartrate	5 mg
Lactose U.S.P.	195 mg

These ingredients are powdered and mixed together and filled into gelatin capsules.

Preparation 1B - Syrup - A teaspoon (10 cc) of syrup containing 5 mg of essential active ingredient is prepared as follows:

Nicotine tartrate	5 mg
Wild Cherry Syrup	10 cc

The nicotine tartrate is stirred, with wild cherry syrup until uniformly distributed.

(2) inhalation of insufflation from an atomizer, inhaler or insufflator. A representative composition of this dosage form is as follows:

Preparation 2A - Inhalation and insufflation devices can be used as the means of administering the drug. The constituents described in Example 1A can be used in these devices.

(3) parenteral administration via standard hypodermic procedures.

A representative composition of this dosage form is as follows:

Preparation 3A - Parenteral - Each injection (2cc) contains 2 mg of essential active ingredients is prepared as follows:

Nicotine tartrate	2 mg
Normal Saline for injection	2 cc

The nicotine tartrate is dissolved in the normal saline for subcutaneous injections.

Pharmaceutical preparations can be designed to provide delayed and/or prolonged release of effective agent in accordance with conventional practice. Buffering by conventional pharmaceutical buffering agents can be useful to facilitate drug uptake and minimization of tissue irritation.

Thus, the process of the present invention is accomplished by oral inhalation, insufflation and parenteral

administration of pharmaceutical compositions for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions containing suitable quantities of nicotine or its pharmacologically acceptable acid addition salts or metabolites.

For oral administration, either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, the principal active ingredient is mixed with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methylcellulose, and functionally similar materials as pharmaceutical diluents or carriers. The tablets can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or predetermined successive action of the enclosed medication. For example, the tablet can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings such materials including a number of polymeric acids or mixture of polymeric acids with such materials as shellac, cetyl alcohol, cellulose acetate phthalate, styrene maleic acid copolymer and the like. Wafers are prepared in the same manner as tablets, differing only in shape and the inclusion of sucrose or other sweetener and flavor. In their simplest embodiment, capsules, like tablets, are prepared by mixing the compound of the formulation with an inert pharmaceutical diluent and filling the mixture into a hard gelatin capsule of appropriate size. In another embodiment, capsules are prepared by filling hard gelatin capsules with polymeric acid coated beads containing the compound of the formula 1. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the nicotine compound with an acceptable vegetable oil, light liquid petrolatum or other inert oil.

Fluid unit dosage forms for oral administration such as syrups, elixirs, and suspensions can be prepared. The water-soluble forms of the nicotine compounds 1 can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydroalcoholic (ethanol) vehicle with suitable sweeteners such as sucrose together with an aromatic flavoring agent. Suspensions can be prepared of the insoluble forms with a syrup vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

For parenteral administration, fluid unit dosage forms are prepared utilizing a nicotine compound and a sterile vehicle, water being preferred. The compound, depending on the form and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, a water-soluble form of the nicotine compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampul and sealing. Advantageously, adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection is supplied to reconstitute the powder prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle.

The term "unit dosage form" as used in the specification and claims refers to physically discrete units suitable as unitary dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the novel unit dosage forms of this invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for therapeutic use in humans and animals. Examples of suitable unit dosage forms in accord with this invention are tablets, capsules, pills, troches, suppositories, powder packets, granules, wafers, cachets, teaspoonfuls, tablespoonfuls, dropperfuls, ampuls, vials, segregated multiples of any of the foregoing, and other forms as herein described.

Nicotine, its pharmacologically acceptable acid addition salts and metabolites thereof when administered in the dosage amounts specified in this application are not toxic to a normal human adults. The drug is rapidly metabolized by the body to relatively inactive, low toxicity substances and is excreted. Tolerance can develop following repeated usage.

The dosage of the nicotine compound for treatment depends on the route and frequency of administration; the age, weight and condition of the patient; and the severity of the particular emotional condition to be treated. Therapeutically effective dosages appropriate for clinically sufficient results can vary from 0.0002 to 0.2 mg/kg per hour, preferably from 0.005 to 0.05 mg/kg per hour, especially about 0.0125 mg/kg per hour. For continuous (chronic) treatment the nicotine compound can be administered in appropriately sized dosages 3 or 4 times a day so as to supply, in total, the indicated amount of compound per day. For intermittent or occasional treatment, as the need arises, the individual acute dosage (single dosage) needed to promptly produce the described effects will, in most cases for adult humans, lie in the 0.001 – 0.10 mg/kg range. Preferred unit dosage forms contain about 0.07 mg/kg for oral administration, 0.02 mg/kg for subcutaneous administration and 0.002 mg/kg for intravenous administration. The initial dosage can suitably be one-half these amounts and the optimal dose for achieving the desired results can be determined by successive trials of ascending or descending dosage strength.

The duration and periodicity of treatment will necessarily depend upon the nature and chronicity of stressful living conditions. Optimally the drug therapy regimen will be used as an adjunct to other social and psychiatric efforts toward more stress-free living routines.

EXAMPLE 1

Three squirrel monkeys (*Saimiri sciureus*) served as subjects. In the test apparatus the subjects were par-

tially restrained from the waist down. Painful electric shocks delivered to the tail of the test subject produced subsequent biting attack upon a pneumatic hose suspended in front of the animal (Hutchinson, R. R., et al., J. exp. Anal. Behav., 1966, 9, 233–237). Prior to shock delivery the subjects engaged in motor performances of lever pressing and chain pulling (Hutchinson, R.R., et al., J. exp. Anal. Behav., 1971, 15, 141–166). d-Amphetamine in doses from 0.06 – 0.5 mg/kg increased both responses. Morphine in doses from 0.06 – 2.0 mg/kg reduced both responses. Administration of nicotine in doses from 0.04 – 0.8 mg/kg caused a progressive dose dependent reduction in biting attack reactions but left the other motor responses (lever response) substantially unaffected or actually increased. This differential effect of nicotine upon aggression and attack responses, in relation to motor responses is similar to the reported effects of chlorpromazine, a major tranquilizer. The test data is presented in the following table. The data given shows increases (+) and decreases (−) in the number of the indicated responses, in comparison to the responses of the same test subjects tested previously without administration of the compounds (controls). This shows the effect of acute administration of a single dosage.

TABLE 1

	DOSAGE (mg/kg)									
	d-Amphetamine				Chlorpromazine					
	.06	.12	.25	.5	.06	.12	.25	.5	1.0	2.0
Lever Response Change	+5	+12	+30	+60	+20	+25	+50	+5	+10	−8
Bite Response Change	−25	+180	+400	+600+	−10	−20	−100	−110	−150	−150
	Morphine						Nicotine			
	.06	.12	.25	.5	1.0	2.0	.04	.16	.32	.64	.8
Lever Response Change	−7	−20	−10	−35	−50	−45	+5	+10	+5	+20	+8
Bite Response Change	−5	−25	−35	−100	−150	−190	−45	+25	−75	−125	−45

These effects are statistically significant.

Wilcoxon Signed Ranks Test

	Lever	Bite
d-amphetamine	p<.02	p<.01
chlorpromazine	p<.05	p<.01
morphine	p<.01	p<.01
nicotine	p<.02	p<.05

EXAMPLE 2

Four squirrel monkey (*Saimiri sciureus*) subjects ingested various concentrations of nicotine in their drinking water continuously for several weeks. Nicotine dosage was altered in a counterbalanced design. Daily one hour tests of aggressivity and other motor responses, as described in Example 1, produced for all subjects a progressive, dose dependent, reduction in attack responses immediately after shock, while over a portion of the dosage range pre-shock responses were elevated or unaffected. This shows the effect of a chronic administration of nicotine over an extended time period.

TABLE 2

		NICOTINE DOSAGE mg/kg/day						
		.002	.005	.01	.03	.06	.1	.2
Difference from Controls	pre-shock responses	+57	+4	+41	+30	−77	−35	−30
	post-shock responses	+53	+3	−28	−51	−25	−56	−30

EXAMPLE 3

Four volunteer adult male human subjects were tested in 30 minute daily sessions in which a repetitive intense pure tone (110 decibel, 3,000 hertz) was delivered for 2 seconds each 3 minutes and their jaw contractions (masseter muscle) were recorded. This loud noise caused jaw clenching immediately after the tone delivery. The values recorded on 2 days prior to nicotine administration are set forth in the column entitled "Before Nicotine Administration." On two subsequent days 5 milligrams of nicotine in 5 ounces of water was administered 15 minutes before the test. All subjects showed marked reductions in jaw contractions produced by the tone while other motor responses were left unaffected. These values are shown in the column entitled "During Nicotine Administration." On the following day, nicotine was not administered and the test was repeated. The values for this test are shown in the column entitled "After Nicotine Administration." The data for "Average Response Ratio (before/after)" is the ratio of jaw contractions occurring in the last two-thirds of the intertone interval relative to contractions occurring in the first third of the intertone interval. These effects are statistically significant.

TABLE 3

	Before Nicotine Administration	During Nicotine Administration	After Nicotine Administration
Average number of masseter contractions	7.9	2.1	5.5
Average contraction force (μvolts)	34	12	29
Average response ratio (before/after)	1.7	4.25	2.8

EXAMPLE 4

Eleven food deprived albino rats were studied in a test in which they responded on a switch for food. Aperiodically during this test a tone was presented and followed by an electric shock (Estes, W. K. and Skinner, B. F., J. exp. Psychol., 1941, 29, 390–400). Stabilized performance showed all subjects to be responding for food except during the tone preceding shock. Administration of nicotine in a dosage range from 0.05 – 0.4 mg/kg produced recovery of responding in this anxiety producing situation during the tone. Responding during other portions of the test was unaffected. This result is similar to the reported effects of chlorpromazine, a major tranquilizer.

TABLE 4

	NICOTINE DOSAGE (mg/kg)						
	.025	.05	.1	.2	.4	.8	1.6
Response Increase Suppression Ratio Difference from Controls	−.07	+.12	+.04	+.04	+.19	−.02	−.05

These results are statistically significant.

EXAMPLE 5

Four squirrel monkey subjects were tested in a procedure as in Example 4. Stable performance showed a suppression of responding for food during the tone preceding shock. Administration of nicotine in dosages from 0.1 – 0.4 mg/kg produced a return of responding during the tone signalling shock. Performances in the other portions of the test were unaffected by the drug administration. This result is similar to the reported effects of chlorpromazine, a major tranquilizer.

TABLE 5

	NICOTINE DOSAGE (mg/kg)					
	.05	.1	.2	.4	.6	1.2
Response Increase Suppression Ratio Difference from Controls	−.03	+.13*	+.07*	+.09*	−.18	−.34

*Wilcoxon Signed Ranks Test $p < .05$

Subsequent to our invention, we reported some of these results in "Smoking Behavior; Motives and Incentives," W. L. Dunn (ed.), V. H. Winston (Washington, D.C.), 1973, 171–195. This article and the references listed therein are incorporated herein by reference, particularly with regard to the significance of our test results.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method of producing (A) reduction of anger, hostility, irritability, frustration and the behavioral expression of these emotions, without producing general depression, drowsiness or sedation, or (B) reduction of fear, anxiety, nervousness and the behavioral expression of these emotions, with the simultaneous increase in focus upon and performance of necessary tasks, in mammals requiring such treatment, which comprises administering to such a mammal a unit dosage form of a therapeutic composition containing an effective, nontoxic amount of nicotine, pharmaceutically acceptable acid addition salt of nicotine, nornicotine or cotinine, with a pharmaceutically acceptable carrier, diluent or vehicle.

2. A method in accordance with claim **1**, wherein the mammal is a human and the effective amount is in the range of about 0.0002 mg/kg per hour to about 0.2

mg/kg per hour, administered daily in divided doses.

3. A method in accordance with claim **2,** wherein the mammal is a human and the effective amount is in the range of 0.005 mg/kg per hour to 0.05 mg/kg per hour.

4. A method in accordance with claim **1,** wherein the mammal is a human and the effective amount is in the range of about 0.001 mg/kg to about 0.10 mg/kg administered in a single dosage.

5. A method according to claim **1** in which said salt

is selected from the group consisting of nicotine tartrate, nicotine bitartrate, nicotine hydrochloride and nicotine sulfate.

6. A method according to claim **1,** in which said composition is administered orally.

7. A method according to claim **1,** in which said composition is administered parenterally.

8. A method according to claim **1,** in which said composition is administered by inhalation or insufflation.

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