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METHOD OF TREATING DEPRESSION WITH 1-(2-PYRIDYL)PIPERAZINE

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ABSTRACT OF THE DISCLOSURE

Administration of 1-(2-pyridyl)piperazine or a pharmaceutically acceptable acid addition salt thereof is disclosed as a chemotherapeutic method of treating manifestations of depression in experimental mammals. Daily doses ranging from 2 mg./kg. to 60 mg./kg. per day are considered effective.

BACKGROUND OF THE INVENTION

Field of the invention

Depression is a psychiatric condition which may be diagnosed as a symptom, a syndrome, or a disease entity, depending upon the clinical situation of the patient. Although there is a lack of uniformity in classification, depression is clinically differentiated as reactive (interchangeably used with neurotic depression) or endogenous (also referred to as psychotic or involutional depression). Regardless of etiology, antidepressant drugs are a common form of therapy, and the disclosed new use of 1-(2-pyridyl)piperazine is a chemotherapeutic method of treating depression.

DESCRIPTION OF THE PRIOR ART

Antidepressant drugs fall into three broad categories of monoamine oxidase (MAO) inhibitors, certain tricyclic compounds, and amphetamine-like drugs.

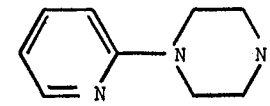
Among MAO inhibitors still in current use are isocarboxazide, nialimide, phenylzine, and tranylcypromine. Use of these compounds, however, is gradually becoming disfavored because their relatively low efficacy is countervailed by their relatively high toxicity. The most dangerous toxic effects caused by this class of drugs include hepato-toxicity, excessive central stimulation, orthostatic hypotension, and interaction with other drugs.

More widely used in depression is a family or tricyclic compounds including imipramine, desmethylimipramine, and amitriptyline. Although these drugs are more effective than MAO inhibitors and less toxic, they nevertheless cause a variety of untoward side effects. Among the latter are: atropine-like effects, including dryness of the mouth, constipation, dizziness, tachycardia, palpitations, and blurred vision; various cardiovascular difficulties, including orthostatic hypotension, myocardial infarction, arrhythmias, and tachycardia; persistent tremor; and psychiatric effects, such as a transition from depression to hypomanic or manic excitement, and hallucinations.

Although characterized as noncatecholamine sympathomimetic drugs, amphetamine sulfate, methamphetamine, and methylphenodate are effective in treating endogenous depression and the depressive phase of certain types of schizophrenia. In cases of chronic depression, tolerance is developed to the central effects of amphetamines, and the user often increases the dose to obtain the desired effect. Among other undesirable features are: abnormal mental conditions such as paranoid delusions and hallucinations; central effects, including restlessness, dizziness, tremor, hyperactive reflexes, irritability, insomnia, and tenseness; and gastrointestinal effects, as anorexin, nausea, emesis, and diarrhea.

For a discussion of antidepressant drugs, refer to: Jarvik, Muray E., "Drugs Used in the Treatment of Psychiatric Disorders, III. Drugs for Affective Disorders (Depression and Mania)," in The Pharmacological Basis of Therapeutics, 4th ed., L. S. Goodman and A. Gilman, editors, New York, Macmillan, 1970, chapter 12, pp. 181–192; and Innes, Ian R. and Nickerson, Mark, "Drugs Acting on Postganglionic Andrenergic Nerve Endings and Structures Innervated by Them (Sympathomimetic Drugs), II. Noncatecholamines," op. cit., chapter 24, pp. 500–520.

The compound 1-(2-pyridyl)piperazine is not related to the drugs described above and has the following structural formula:



The synthesis of 1-(2-pyridyl)piperazine is described by Hamlin et al. in J. Am. Chem. Soc. 71:2731–2743 (1949) and by Howard et al. in J. Org. Chem., 18:1484–1488 (1953). In the publication by Howard, 1-(2-pyridyl)piperazine was reported to have no analgesic or antifilarial activity. Although L. W. Roth in J. Pharmac. Exp. Ther., 110:157–165 (1954) reported the pharmacological activity of a series of substituted piperazines, 1-(2-pyridyl) piperazine was not tested.

SUMMARY OF THE INVENTION

The essential feature of this discovery is the utility of 1 - (2 - pyridyl)piperazine (hereinafter called compound A for convenience) in the treatment of depression as a symptom, syndrome, or a disease entity. Administration of an effective amount of compound A, generally in daily doses of from 2 mg./kg. to 60 mg./kg., produces an antidepressant effect in experimental animals. Pharmaceutically acceptable acid addition salts of compound A can be used in lieu of the parent compound. In comparative tests with imipramine as a reference, compound A exhibits greater efficacy than the reference drug.

Dose forms of compound A can be conveniently prepared by the addition of pharmaceutically acceptable vehicles generally used in formulations. Dose forms can be prepared in a solid or liquid state by methods known in the art for oral, intravenous, parenteral, intramuscular, and subcutaneous administration.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Example 1

The method of treating depression by administering 1-(2-pyridyl)piperazine to rats in an experimental model of depression is assessed according to the procedure developed by Horovitz et al., described in Int. J. Neuropharmacol., 5:405–411 (1966). The basis of this procedure is the neuropharmacological effect of antidepressant drugs in suppressing the spontaneous killing of mice (muricide) by selective "killer" rats. This "muricide test" has gained wide recognition among neuropharmacologists to test compounds for treating depression.

"Killer" rats of both sexes are easily ascertained as those which kill mice consistently within 5 seconds after confrontation. Experimental drugs are tested by observation of muricide responses at 15 minute intervals after intraperitoneal administration of the drugs. Table I summarizes the results of the "muricide test" for 1 - (2-pyridyl)piperazine dihydrochloride and a reference compound, imipramine, 5 - (3 - dimethylaminopropyl) - 10,11-dihydro - 5H - dibenz[b,f]azepine (U.S. Pat. No. 2,554,736, 1951). The median effective dose and 95% confidence limits are represented by the standard abbrevia-

tions ED_{50} and Cl_{95} respectively. The number of rats observed is indicated under the column N.

TABLE 1

Compound	Anti-muricide ED_{50} (mg./kg., i.p.)	CL_{95}	N
1-(2-pyridyl)piperazine dihydrochloride	1.7	1.2–2.5	40
Imipramine	12.0	8.1–17.6	25

Example 2

Because depression of the muricide response may be symptomatic of motor impairment, the method of treating depression by administering 1 - (2 - pyridyl)piperazine dihydrochloride was also evaluated by the rotarod test of Dunham and Miya described in J. Am. Pharm. Assoc. (sci. ed.), 46:208–209 (1957). In this test, rats are trained to walk for periods of 100 seconds on a wooden rod rotating at 13 r.p.m. After intraperitoneal administration of a drug walking times are recorded at zero time and at various 15 minute intervals afterwards.

Table II summarizes the results of the rotarod test for 1 - (2 - pyridyl)piperazine dihydrochloride and the reference drug imipramine.

TABLE II

Compound	Rotarod ED_{50} (mg./kg., i.p.)	CL_{95}	N
1-(2-pyridyl)piperazine dihydrochloride	28.0	19.3–40.4	25
Imipramine	18.0	10.8–29.7	25

The specificity of the anti-muricidal effect is measured by calculating the ratio of the rotarod ED_{50} to the anti-muricide ED_{50}. A ratio significantly greater than 1 indicates a specific anti-muricidal effect at non-debilitating doses. The ratio of rotarod ED_{50} to antimuricidal ED_{50} for 1 - (2 - pyridyl)piperazine dihydrochloride is 16.4, substantially in excess of unity, whereas the respective ratio for imipramine is 1.5.

The median lethal dose (LD_{50}, in mg./kg.) for 1-(2-pyridyl) piperazine dihydrochloride in rats is 681 mg./kg.

What is claimed is:

1. A method of treating a mammal having a symptom, a syndrome or a disease entity characterized as depression, which comprises:

administering to said mammal an effective amount of a compound selected from the group consisting essentially of 1 - (2 - pyridyl)piperazine and a pharmaceutically acceptable acid addition salt thereof.

2. A method as in claim 1, wherein said compound is 1-(2-pyridyl)piperazine dihydrochloride.

References Cited

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