Schizophrenic Symptoms Improve with Apomorphine
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Source: *Science*, New Series, Vol. 200, No. 4341 (May 5, 1978), pp. 567-568
Published by: American Association for the Advancement of Science
Stable URL: http://www.jstor.org/stable/1746601
Accessed: 19-09-2016 19:56 UTC

18. Data for α^{1-24}-ACTH do not appear in Fig. 1A, nor for $\alpha_p{}^{1-39}$-ACTH in Fig. 1B, because their actions were similar and neither had a significant effect.
19. I thank R. E. Phillips for encouragement and support and P. P. G. Bateson for his comments on the manuscript. W. H. Burke donated the antiserum; H. M. Greven and Organon (Oss) donated the α^{1-10}-ACTH and α^{1-24}-ACTH; Schering AG (Berlin) contributed the $\alpha_p{}^{1-39}$-ACTH. Supported by National Institute of Child Health and Human Development postdoctoral fellowship HD 00495-02.

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31 August 1977; revised 28 December 1977

Schizophrenic Symptoms Improve with Apomorphine

Abstract. *Eighteen chronic schizophrenic patients received subcutaneous doses of apomorphine, a dopamine receptor agonist, and of placebo in separate trials. A significant improvement in psychotic symptoms occurred after apomorphine compared to placebo. The results are interpreted as a consequence of presynaptic dopamine receptor activation by apomorphine with a subsequent decrease in dopamine-mediated neural transmission.*

Much recent research has suggested that alterations in neural transmission mediated by dopamine (DA) may contribute to the development of schizophrenic symptoms (*1*). Support for this hypothesis derives mainly from the following pharmacologic observations. All clinically effective antipsychotic agents share the ability to block DA receptors. Indeed, the antipsychotic potency of neuroleptics in general parallels their DA receptor binding affinity (*2*). The antipsychotic effect of neuroleptic drugs is potentiated by α-methyl-*p*-tyrosine, a drug that blocks the DA-synthetic enzyme tyrosine hydroxylase (*3*). Furthermore, many drugs that augment DA transmission in brain, such as amphetamine or methylphenidate, can cause or exacerbate psychotic symptoms (*4*). In accord with these observations which underlie the DA theory of schizophrenia, apomorphine, a potent, centrally active DA receptor agonist (*5, 6*), should exacerbate psychotic symptoms.

Recent preclinical observations suggest, however, that at certain doses apomorphine might exert exactly the opposite effect. Dopamine receptors reside on DA cell bodies (*7*), and DA agonists appear to activate presynaptic DA receptors to inhibit DA synthesis and release (*8*). Accordingly, DA receptor agonists that preferentially affect presynaptic receptor sites may inhibit, not facilitate, DA-mediated transmission. Since apomorphine, when administered at relatively low doses, appears to mainly influence presynaptic receptor sites (*9*), beneficial rather than deleterious effects might accrue in schizophrenic patients. Here we report a significant improvement in psychotic symptoms in patients with chronic schizophrenia given apomorphine at a dose of 3 mg subcutaneously.

Eighteen patients (twelve males and six females) were studied. They were diagnosed as having chronic schizophrenia by the research diagnostic criteria of Spitzer and Endicott (*10*); in six, the disease was the paranoid type, in seven, the undifferentiated type, and in five, the schizoaffective type. Each patient had prominent psychotic symptoms despite ongoing treatment with neuroleptic medication. All patients received two separate drug trials, apomorphine (3 mg) and placebo (3 ml) in a double-blind, placebo-controlled design. The order of drug administration was randomized. No nausea or vomiting occurred because of the anti-emetic effect of the neuroleptic medication. Drug effects appeared within 20 minutes and lasted up to 60 minutes. Psychotic symptoms were scored using a modification of the New Haven schizophrenia scale (M-NHSS) (*11*). This scoring instrument records data elicited in a semistructured interview that is designed to demonstrate the thought patterns of psychotic subjects. The scale uses explicit criteria for noting a symptom and rating its intensity. In subsequent studies we have found that the M-NHSS items correlate with the thought disorder items on the Brief Psychiatric Rating Scale, but the M-NHSS is expanded and more detailed and the items are defined. Furthermore, it is designed to rate psychotic thought disturbances at intervals as frequent as 20 minutes. Reported scores derive from the consensus ratings of two interviewers who did not know what treatment had been given.

Apomorphine significantly decreased schizophrenic symptoms in these patients. The reduction (mean ± standard error of mean) in psychosis ratings with placebo was 1.67 ± 0.9, compared with a decrease of 6.22 ± 0.4 with apomorphine ($P < .02$). Paired data points from each patient during placebo and apomorphine treatment (Fig. 1) illustrate the reduction of 20 to 50 percent in psychotic symptoms in nine of the schizophrenics. In the responding patients, the decrease in psychotic symptoms, although transitory, was clinically remarkable. Certain patients temporarily stopped hallucinating, and others lost their delusions. A typical example of the symptomatic relief with apomorphine administration is provided by a 22-year-old male who suffered continual auditory hallucinations and thought control: "The voices are quite strong; they swear they are going to make me suffer, burn me, freeze me for seven years; I wish [the voices] were my mother and father, but they are an exodus." After apomorphine administra-

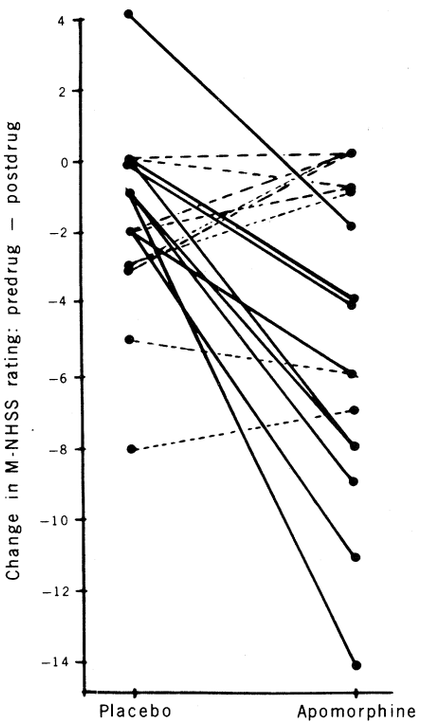

Fig. 1. Decrease in psychosis ratings in 60 minutes following placebo and apomorphine administration to each of 18 patients. Scores on the modified New Haven schizophrenic scale (M-NHSS) were determined before drug administration (baseline) and 30 and 60 minutes after drug or placebo was given. Change scores were calculated as (30-minute − baseline) + (60-minute − baseline). Significance was tested with Student's *t*-test. Solid lines represent the change in psychosis scores of the apomorphine-responding patients; the dotted lines represent the apomorphine nonresponders. Change scores of responders decreased 9.8 ± 0.02 points (mean ± standard error of mean) more after apomorphine than after placebo. For nonresponders the corresponding value was an increase of 2.0 ± 0.7. The decrease in psychosis, although transient, was 20 to 50 percent when it occurred.

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tion and for the duration of the drug effect, the patient reported no auditory hallucinations and he showed a transient improvement in cognitive organization. Of the remaining schizophrenic patients, four showed no change and five, a slight worsening with apomorphine. The frequency distribution of the apomorphine-induced change in psychosis ratings (Fig. 2) does not appear to be a normal distribution. While these data are suggestive of a bimodal response, neither age, sex, diagnosis, or type or dose of medication predicted the apomorphine-responding group. Because of some difference in pharmacokinetic handling of the drug, some patients may not have received the critical dose. Alternatively, these data may indicate an apomorphine-responsive subpopulation of schizophrenic subjects who have a common link in pathophysiology.

Before the discovery of the antipsychotic properties of phenothiazine drugs, apomorphine was administered to schizophrenics when temporary relief from psychotic symptoms was necessary. Case reports in the older literature describe its beneficial action as a short-acting "tranquilizer" (*12*). More recently, clinical studies of a number of neuropsychiatric disorders suggest that DA agonists may be useful in treating those illnesses in which dopaminergic function is thought to be augmented. Specifically, the involuntary choreiform movement disorders, including tardive dyskinesia, Huntington's chorea, and L-dopa–induced dyskinesias, have been reported to improve with various DA agonists, notably apomorphine (*13*). It is tempting to postulate that apomorphine diminishes schizophrenic symptoms and certain involuntary movements by inhibiting dopaminergic transmission through a predominant action at presynaptic DA receptors. This hypothesis is consistent with the neurochemical theories of schizophrenia and hyperkinetic extrapyramidal movement disorders, as well as with the results of preclinical studies of DA neuronal mechanisms. Alternative interpretations of the present results might be cited. Apomorphine could act as partial agonist at the postsynaptic receptor, diluting the concentration of the natural neurotransmitter in the synapse. A pharmacologic action of apomorphine not related to dopaminergic transmission could mediate the psychosis-remitting properties, possibly a residual pharmacologic action of apomorphine at the opioid receptor. These possibilities seem much less compelling, however, since there is no biochemical evidence that apomorphine acts through either of these mechanisms. Although the observations reported here need to be replicated and their mechanism elucidated, we propose that they can best be understood as a consequence of presynaptic DA receptor activation.

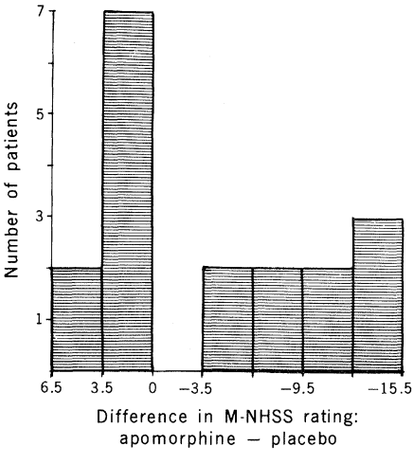

Fig. 2. Distribution frequency of the change in scores on the M-NHSS after administration of apomorphine. The values on the abcissa represent the net change in the M-NHSS score after apomorphine minus the net change in score after placebo. Those patients with a positive score had increased psychotic symptoms, while the group with negative scores sustained a decrease in their psychosis. The distribution appears to be bimodal and may suggest a nonhomogeneous schizophrenic population.

Given that apomorphine produces its transitory antipsychotic effect through activation of presynaptic DA receptors with a consequent decrease in DA synthesis, apomorphine at low doses may represent a new class of antipsychotic agents whose antischizophrenic properties derive from this presynaptic DA receptor action. The development of presynaptic agonist drugs in long-acting oral preparations may prove practical and effective as pharmacotherapy for schizophrenia. An optimal drug combination that includes presynaptic receptor activation with postsynaptic receptor blockade may maximize treatment of some schizophrenic and choreiform disorders. Furthermore, drugs that activate presynaptic DA receptors might lower the incidence of tardive dyskinesia by decreasing the requirement for neuroleptic drug.

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22 August 1977; revised 7 December 1977

Niemann-Pick Disease Experimental Model

Sakuragawa *et al.* (*1*) recommend compound AY-9944, an inhibitor of cholesterol biosynthesis, as an appropriate tool to create an animal model of the inherited sphingomyelinosis of man. While such experimental models are in demand, we would warn of being optimistic about the validity of the approach presented by Sakuragawa *et al.* (*1*). Undoubtedly, AY-9944 induces generalized accumulation of phospholipids, but the increase does not at all selectively affect

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