Pimozide-Induced Depression in Men Who Stutter

Miki Bloch, M.D., Sheila Stager, Ph.D., Allen Braun, M.D., Karim A. Calis, Pharm.D., Nanette M. Turcasso, Pharm.D., Dale R. Grothe, Pharm.D., and David R. Rubinow, M.D.

Background: Neuroleptic-related dysphoric reactions are well recognized in the context of psychiatric disorders, especially in association with extrapyramidal side effects. Very few controlled data exist regarding the effects of neuroleptics on the mood of psychiatrically "normal" subjects. In this study, the depressogenic effect of the neuroleptic drug pimozide was assessed in men without psychiatric disorders.

Method: Eight men with developmental stuttering but no past or present psychiatric illness participated in a double-blind, placebo-controlled study assessing the effect of 6 weeks of pimozide treatment on speech fluency and mood.

Results: Four of the seven subjects who were compliant with the treatment developed marked depressive symptoms. No clear association was found between these reactions and pimozide dose, blood level, or degree of neurologic side effects. Symptoms abated soon after drug discontinuation.

Conclusion: Pimozide induced significant depressive symptoms in this group of psychiatrically normal men who stutter. Neuroleptic drugs may have a causal effect in the induction of depression in psychiatrically normal subjects, ostensibly independent of dose or severity of neurologic side effects.

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Received Oct. 22, 1996; accepted July 7, 1997. From the Department of Health and Human Services, National Institute of Mental Health (Drs. Bloch and Rubinow), National Institute of Deafness and Other Communication Disorders (Drs. Stager and Braun), and the Clinical Center of the National Institutes of Health (Drs. Calis, Grothe, and Turcasso), Bethesda, Md.

Reprint requests to: Miki Bloch, M.D., National Institute of Mental Health, Building 10, Room 3N238, 10 Center Drive MSC 1276, Bethesda, MD 20892-1276.

While the noradrenergic and serotonergic neurotransmitter systems are traditionally believed to underlie major depression, the dopaminergic system is also recognized as having a role in the pathogenesis of mood changes.[1] Several lines of evidence support the involvement of the dopaminergic system in depression, including the mood-elevating effect of dopamine agonists and the reported depressogenic effect of dopamine-antagonist antipsychotic medication (neuroleptics) in animal studies[2] and also in both psychiatrically ill and normal populations. Schizophrenic patients treated acutely with neuroleptic drugs show a higher prevalence of depressive symptoms than untreated patients.[3] Harrow et al.[4] have shown that schizophrenic and schizoaffective patients on chronic neuroleptic treatment are significantly more likely to show full depressive syndromes at follow-up than those who are not taking neuroleptics. This depression occurred in psychotic and nonpsychotic patients and was not found to be a function of extrapyramidal symptoms in this study and others.[5] However, other studies did find an association between depressive symptoms and neuroleptic-induced akathisia,[6] akinesia,[7] or other extrapyramidal symptoms.[3] Several studies have also described a dysphoric reaction to neuroleptic drugs in subjects without a psychiatric disorder.[8–10] However, most of these studies consist of anecdotal or incidental observations and do not formally attempt to diagnose depression or measure its severity.

The demonstration that neuroleptics can induce depression might influence therapeutic decision making in conditions like postpsychotic depression; i.e., reduction of the dose of neuroleptics in this disorder might be indicated. However, assessing the direct role of neuroleptic drugs in the induction of mood symptoms in patients with psychiatric disorders is difficult because of confounding factors such as postpsychotic regression, the natural course of the disease in bipolar patients, and neuroleptic-induced extrapyramidal symptoms.[11–13] Thus, the contribution of neuroleptics to depression might best be observed in normal controls.

In this study, the neuroleptic drug pimozide, administered for 6 weeks under double-blind conditions, was used to assess the effect of dopamine-2 antagonists on speech fluency and mood in psychiatrically normal men who stutter.

METHOD

The subjects recruited for the study were all healthy, unmedicated men, aged 18–46 years, all suffering from

chronic developmental stuttering. A psychiatric evaluation was carried out at baseline consisting of a Schedule for Affective Disorders and Schizophrenia-Lifetime (SADS-L) diagnostic interview,[14] Yale-Brown Obsessive Compulsive Scale,[15] Beck Depression Inventory (BDI),[16] and Spielberger State-Trait Anxiety Inventory (STAI).[17] Subjects were excluded from participation in the study if they had an Axis I diagnosis at the time of the screening.

Consenting subjects participated in a double-blind, placebo-controlled, crossover treatment study using two pharmacologic agents—the dopamine-2 antagonist pimozide and the serotonin selective reuptake inhibitor paroxetine (full results of the study to be published elsewhere). The drugs were administered for 6 weeks in increasing doses, separated by a 6-week placebo phase. Pimozide was started at 2 mg/day and increased to the highest tolerable dose according to a fixed time table (maximal dose = 10 mg/day). Blood levels of pimozide were measured at the end of the medication and placebo phases.

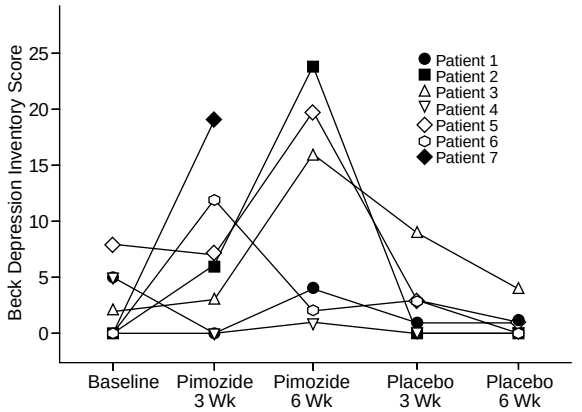
Throughout the study, subjects were assessed at 3-week intervals for mood symptoms (BDI and STAI), for fluency, and for the presence of side effects. Extrapyramidal symptoms were clinically monitored by a neurologist (A.B.) by assessing the presence or absence of akathisia and four cardinal parkinsonian signs—tremor, rigidity, bradykinesia, and postural instability. The study was terminated prematurely due to unexpected psychiatric side effects experienced during the withdrawal from paroxetine.[18]

RESULTS

Eight subjects participated in the pimozide arm of the study. One was found to be noncompliant (as determined by plasma pimozide levels). Five of the remaining seven subjects started the study on the pimozide arm, and two received pimozide after a 6-week paroxetine phase and a 6-week placebo phase. One subject dropped out of the study due to severe depressive symptoms after 4 weeks of pimozide treatment and did not participate in the placebo phase. He developed severe anhedonia, depressed mood, and insomnia and also reported suicidal ideation, which resolved when he discontinued the medication.

Altogether, four of seven patients developed a depressive syndrome (three major and one minor depression) during pimozide treatment according to BDI scores and a clinical interview (Figure 1). Three subjects developed serious depressive symptoms during the first phase of the study while under treatment with pimozide, one of them after 2 weeks of medication and two during the last 3 weeks of the 6-week pimozide phase. Two of these men met criteria for major depression and the third for minor depression. All three subjects became euthymic between 7 to 15 days (mean = 12) after discontinuation of pimozide (two during the placebo phase and one after the study discontinuation). The fourth subject received pimozide during the third phase of the study (after placebo) and developed a severe major depression that was successfully treated with an antidepressant; euthymia returned after 4 weeks. Of the four depressed subjects, one had akathisia and three had mild parkinsonian symptoms. Another subject (Patient 6 in Figure 1) had some mild mood symptoms, in association with moderately severe extrapyramidal symptoms, that resolved with a decrease in the medication dose. Of the two subjects who never experienced any mood symptoms, one had mild parkinsonian signs and the other did not.

Figure 1. Beck Depression Inventory Scores During Pimozide and Placebo Treatment*



*Two patients (Patients 2 and 4) received pimozide after the placebo phase as opposed to the other five patients, who started with pimozide and then switched to placebo. Because placebo scores were very similar to baseline scores, all patients were graphed with pimozide preceding placebo.

The group data comparing BDI and STAI scores at baseline and after 3 weeks and 6 weeks of pimozide and placebo treatment are presented in Table 1. In the six subjects who completed both arms of the study, there was no correlation between BDI scores and pimozide dose or plasma levels.

DISCUSSION

In this treatment study of men who stutter, four (57%) of seven subjects who received pimozide developed marked depressive syndromes, which resolved within 2 weeks of the drug's discontinuation (and with subsequent antidepressant treatment in one case). The severity of the depressive reaction is indicated by the significantly elevated BDI ratings in the whole group of subjects 6 weeks after initiation of pimozide treatment, as well as by the fact that one subject dropped out because of depressive symptoms and another required antidepressant treatment. Our observation of pimozide-induced depression is consistent with anecdotal reports of haloperidol-induced depressive symptoms in persons who stutter.[19,20]

Table 1. Effects of Pimozide and Placebo on Mood Ratings in Six Men*

Variable	Baseline	Pimozide 3 Weeks	Pimozide 6 Weeks	Placebo 3 Weeks	Placebo 6 Weeks	ANOVA-Repeated
Beck Depression Inventory, mean ± SD	2.5 ± 2.9	6.1 ± 6.2	11.5 ± 8.6[a]	2.7 ± 3.1	1.7 ± 2.2	p < .02
Spielberger State-Trait Anxiety Inventory, mean ± SD	45.4 ± 10.8	47.5 ± 6.8	53.8 ± 10.8	41.8 ± 5.3	41.8 ± 5.3	NS
Dose (mg/d), mean ± SD	0	5.1 ± 2.6	4.3 ± 2.7	0	0	
Drug level (ng/mL), mean ± SD			3.4 ± 1.4		Undetected	
Extrapyramidal symptoms (No. of subjects)	0	2	4	0	0	

*Subjects who completed both pimozide and placebo arms of the study.
[a]p < .05 for post hoc paired sample t test with the Bonferroni correction for comparison with both placebo-6 weeks and baseline.

Because of the limited sample size of this study, a statistical correlation between extrapyramidal symptoms and symptom severity could not be performed. However, whereas subjects who developed depressive symptoms did have some extrapyramidal symptoms, no clear association was found between the observed depressive symptoms and the severity of either parkinsonian symptoms or akathisia; i.e., extrapyramidal symptoms appeared without depression in one of five subjects with extrapyramidal symptoms, and severe depression appeared in face of rather mild neurologic symptoms (mild parkinsonian facies and mild akathisia in one case, and mild rigidity in the other case). While previous studies have suggested an association between neuroleptic use and depressive syndromes, our study provides evidence for a possible causal relationship: the depression may appear consequent to the effects of pimozide on brain neurochemistry and not necessarily consequent to severe neurologic side effects or expression of the illness. In support of this possibility are reports of the following: (1) in patients with Parkinson's disease, depressive symptoms are more frequent than in controls but do not appear to correlate with the severity of the disorder,[21–23] and (2) levodopa treatment of parkinsonian patients may alleviate mood symptoms independent of motor effects.[24]

Although the results of our study cannot be regarded as definitive due to its small sample size, the double-blind, placebo-controlled design strengthens the inference that the depression resulted from taking pimozide and not simply from taking a "medication," as symptoms were absent during the placebo phase (and during the paroxetine phase as well). In addition to its small sample size, another possible limitation of this study is the "normality" of the sample population. Despite the fact that no subject had present or past history of Axis I psychiatric disorders, the underlying neurobiology of stuttering may have predisposed to depression or to an increased sensitivity to antipsychotic medication.

The concept that depressive syndromes can be induced by neuroleptic treatment in the absence of significant extrapyramidal symptoms has important implications for our understanding of depression and for the treatment of certain clinical conditions. The induction of depression by pimozide, a relatively selective dopamine-2 antagonist, adds to the growing body of evidence supporting the involvement of the dopaminergic system in the pathogenesis of depression. In clinical practice, the differential diagnosis of disorders such as postpsychotic depression, depression complicating psychotic episodes, and bipolar disorder with breakthrough depression should be expanded to include the possible depressogenic effect of antipsychotic medications. In such disorders, clinicians should consider lowering neuroleptic dose or, if possible, stopping it altogether. Furthermore, as dysphoria is often a clinically significant residuum in psychotic patients taking antipsychotic medication,[25] the detection and treatment of medication-related depression should improve treatment compliance. Although an association between depressive symptoms and pimozide dose was not clearly seen in this study, the effect of neuroleptic dose on depressive symptoms requires further study.

Drug names: haloperidol (Haldol and others), levodopa (Larodopa), paroxetine (Paxil), pimozide (Orap).

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