Phenothiazine-Induced Decompensation

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Adverse mental reactions to phenothiazines have been anecdotally reported. In a systematic study 80 patients with the diagnosis of schizophrenia received phenothiazines in conventional dosages. Nine patients experienced dramatic exacerbations of psychosis on phenothiazines with a piperazine side group—particularly fluphenazine enanthate.

These exacerbations of psychosis are associated with a subtle akathisia. Exacerbations of psychosis were promptly reversed by biperiden (Akineton)—an anticholinergic drug, given intramuscularly.

It is proposed that extrapyramidal involvement can have a prominent mental component which resembles an exacerbation of schizophrenia.

This paper reports a study of a heretofore uninvestigated type of behavioral toxicity associated with antipsychotic compounds. There are several different types of behavioral toxicity associated with antipsychotic compounds; however, this study will focus on a behavioral syndrome characterized by sudden and dramatic exacerbations of psychosis, an experience of abject terror, and subtle extrapyramidal symptoms. This behavioral syndrome appears to be an expression of extrapyramidal involvement.

Evidence that these exacerbations of psychosis are extrapyramidally based is that they occur with phenothiazines associated with a high incidence of extrapyramidal side effects—namely, fluphenazine and trifluoperazine hydrochloride. Second, the syndrome is always associated with akathisia. Third, the syndrome is dose related as are extrapyramidal side effects. Fourth, a similar syndrome has been reported in Parkinson disease.[1] Lastly, the exacerbations of psychosis are dramatically reversed by the administration of antiparkinsonian agents. Response to the antiparkinsonian agent, biperiden, given intramuscularly, is so prompt, that it can be used as a diagnostic test.

Method

Observations were made, over an eight-month period, on a 30-bed psychiatric unit in a university affiliated Veterans Administration hospital. The emphasis is on active treatment and staff patient ratio is high. About 80% of patients were on physician's choice of phenothiazine. Polypharmacy is discouraged. Antiparkinsonian drugs are used only once when extrapyramidal involvement occurs.

Patients on phenothiazines were watched around the clock for exacerbations of psychosis or conspicuous regressions. Once a deterioration of mental status was reported, an attempt was made to establish consensus between the treating resident, nursing staff, and director that a definite deterioration had actually occurred. Biperiden (Akineton) 5 mg, given intramuscularly, or a placebo were then administered in double-blind fashion on an every other incident basis, if there was even subtle evidence of extrapyramidal involvement, such as mild tremor, akinesia, or evidence of restlessness suggestive of an akathisia. "Double-blind" was not successful, however, since spontaneous complaints of dry mouth invariably tipped off at least the rater. Biperiden, 5 mg, given intramuscularly, was chosen because of its prompt onset of action and documented effectiveness in reversing drug-induced EPS.[2] The patient was evaluated by a brief interview and the Brief Psychiatric Rating Scale (BPRS) administered by two experienced clinicians, both before and one to two hours after the injection of biperiden. Since these exacerbations were often sudden and at odd times, it was not always possible to have two raters. In that event, the patient was rated by the senior investigator.

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Results

In most reported cases of regression, immediate consensus between nursing staff, treating resident, and ward director was reached, because the exacerbations of psychosis were often sudden and dramatic.

Eighty patients received phenothiazines in conventional dosages. Nine patients (11%) experienced sudden decompensations in association with extrapyramidal symptoms. The exacerbations of psychosis occurred on phenothiazines with a piperazine side chain—intramuscular fluphenazine enanthate, given intramuscularly, and fluphenazine and trifluoperazine, given orally. No other piperazine phenothiazine was used. Dosages were conventional; the highest prescribed dose of fluphenazine enanthate was 25 mg, given intramuscularly, every two weeks and the usual prescribed dose of trifluoperazine was 15 to 30 mg daily. All nine patients experienced decompensations on IM fluphenazine enanthate, given intramuscularly—this amounts to 35% of patients on fluphenazine enanthate! Two of these nine patients also experienced identical decompensations on trifluoperazine hydrochloride (Stelazine) and fluphenazine given orally (Table 1). Outside of the nine patients who experienced decompensations in association with their extrapyramidal involvement, 23 other patients (out of 46 patients on piperazine phenothiazine) experienced their akathisia, parkinsonism, or dystonia as "annoying," "irritating," or "frightening," but no more.

The extrapyramidal involvement associated with mental exacerbation was always of the akathisia type (Table 1). It is important to emphasize that often the akathisia was evanescent and most subtle. Akathisia in most consisted of nothing more than frequent minor changes in posture, fidgetiness, subjective complaints of not being able to feel comfortable, and occasional pacing. The restless changes in posture and evanescent pacing are easily interpreted as a manifestation of anxiety.

The drug-induced regressions resemble the original psychoses so precisely, that at the beginning of the study the treatment team (including the ward director) always explained the decompensation in plausible dynamic terms. Often, the patient himself agreed with the dynamic formulation. During the decompensation secondary symptoms recurred, thought processes again became fragmented, and several complained of an abject terror, the likes of which they had never experienced. Even the articulate found it difficult to describe their dysphoric affective state. Statements, such as "It's a horrible feeling; I can't describe it" or "If this feeling continues, I'd rather be dead" were not unusual. Signs of a toxic psychosis, such as vivid visual hallucinations and clouded sensorium, were entirely lacking. In several cases the mental symptoms preceded the extrapyramidal symptoms by as much as an hour. The only clinical tip-off to the drug-induced regression is a rather sudden onset and the presence of an akathisia.

Table 1.—Nature of Decompensation

Case	Phenothiazine	Timing of Decompensation	Extrapyramidal Symptoms	Nature of Decompensation
1	Fluphenazine enanthate 25 mg, intramuscularly	Started five days after dose	Mild akathisia Mild tremor, mild hyperventilation	Anxiety of annihilation proportions, terror
2	Fluphenazine enanthate 25 mg, intramuscularly	Started six days after dose	Mild akathisia Barely noticeable tremor	Fulminant psychosis characterized by bizarre somatic delusions, terror, and strong suicidal preoccupation
3	Fluphenazine enanthate 25 mg, intramuscularly	Started eight days after dose	Mild akathisia Mild dystonia 2 days before decompensation	Severe withdrawal
4	Fluphenazine enanthate 25 mg, intramuscularly	Started five days after dose	Mild akathisia Mild tremor	Fulminant psychosis with bizarre somatic delusions and terror
5	Fluphenazine enanthate 12.5 mg, intramuscularly	Started five days after dose	Mild akathisia	Fear, upsurge of paranoia and peculiar auditory hallucination of "tires screeching"
6	Fluphenazine enanthate 25 mg, intramuscularly	Started two days after dose	Mild akathisia Involuntary extension of tongue	Terror, bizarre thought content, and rage
7	Fluphenazine enanthate 25 mg, intramuscularly	Started four days after dose	Moderate akathisia	Terror, suicidal preoccupation, loosening of associations
8	Fluphenazine enanthate 12.5 mg, intramuscularly	Started seven days after dose	Very mild akathisia	Bizarre thought content, fear, posturing, and suicidal ideation
	Fluphenazine 5 mg, three times a day	Started on the fifth day	Very mild akathisia	Same decompensation
9	Fluphenazine enanthate 12.5 mg, intramuscularly	Started four days after dose	Very mild akathisia	Overwhelming anxiety, terror, regression to childish pleading
	Trifluoperazine hydrochloride, 60 mg, daily	Started on seventh day	Very mild akathisia	Same
	Trifluoperazine hydrochloride, 20 mg, daily, and chlorpromazine, 250 mg, daily	Started on ninth day	Very mild akathisia	Same

Decompensations associated with akathisia were reversed by biperiden, 5 mg given intramuscularly, in all nine cases. In one case, however, biperiden was very effective in reversing some sudden regressions but was ineffective at other times. Onset of action occurred at approximately 20 minutes and duration of action averaged about four hours. Reversal of regression was dramatic. Quality of contact improved, secondary symptoms abated, thinking became more reality oriented, and patients invariably stated that they felt more "at ease," "calmer," and "less tense."

Results of the BPRS (Table 2) confirm the clinically observed reversals of regression with biperiden. These results are based upon ten episodes of decompensation in seven different patients. The BPRS was administered by two independent raters immediately before biperiden injection and at one hour postinjection. The results indicate a significant over all reversal of regression; specifically increased reality contact (Conceptual Disorganization, Unusual Thought Content, and Somatic Concern Scales), improved quality of contact (Blunted Affect, Suspiciousness, and Hostility Scales), and decrease in dysphoric affective state (Anxiety, Tension, Depressive Mood, and Excitement Scales).

The BPRS ratings were collected for six cases of pre- and postplacebo injections. These ratings show no postplacebo improvement. Statistical analysis on this small number of cases was not deemed meaningful.

Atropine sulfate-like toxic psychoses were not observed. Patients "liked" the biperiden, given intramuscularly, and would ask for an "as necessary" order, in case symptoms recurred. Some patients saved up a private store of antiparkinsonian drugs "just in case that horrible feeling comes back."

The sample is too small to come to a conclusion as to which patient is at risk for a piperazine phenothiazine-induced decompensation. In the nine patients, who experienced decompensations, ages ranged from 20 to 52 and both sexes were proportionally represented. Duration or severity of illness, dynamic make up, previous response to nonpiperazine phenothiazines, or diagnostic type of schizophrenia seem to have no predictive value. We can say that patients on fluphenazine (Prolixin) enanthate should be watched closely for decompensations.

Report of Cases

CASE 1.—This 51-year-old divorced, white female registered nurse was admitted because of suicidal preoccupation, inability to cope, and a strong fear that she would lose control over her suicidal drive. Over the past decade she had numerous neuropsychiatric admissions and extensive private outpatient treatment because of recurrent depressions, several severe suicidal attempts, and general inability to cope. She carries the diagnosis of schizo-affective reaction depressed type. Over the years she had been treated with most of the phenothiazines and tricyclic antidepressants with notable lack of success, and had developed the

Table 2.—Analysis of BPRS Administered Pre and Postinjections of Biperiden for Ten Cases

BPRS Item	Mean Pre	Mean Post	Variance	t
Somatic Concern	3.45	1.70	1.87	2.96*
Anxiety	5.10	3.00	1.65	4.04†
Emotional Withdrawal	3.70	3.10	1.24	1.53
Conceptual Disorganization	3.80	2.85	1.36	2.91‡
Guilt Feelings	2.55	2.55	0.94	0.00
Tension	4.25	2.40	1.25	4.69§
Mannerisms and Posturing	1.80	1.35	0.95	1.49
Grandiosity	1.20	1.20	0.00	0.00
Depressive Mood	3.90	2.50	1.26	3.51†
Hostility	2.70	1.20	1.71	2.77‡
Suspiciousness	2.70	1.40	1.70	2.42*
Hallucinatory Behavior	1.90	1.30	1.35	1.41
Motor Retardation	2.95	2.15	1.11	2.28*
Uncooperativeness	2.25	1.30	1.38	2.17
Unusual Thought Content	4.35	2.40	1.67	3.69†
Blunted Affect	4.10	2.80	1.16	3.55†
Excitement	3.45	1.20	1.75	4.07†
Disorientation	1.00	1.00	0.00	0.00
Elevated Mood	1.00	1.00	0.00	0.00

* $P < .05$. ‡ $P < .02$.
† $P < .01$. § $P < .001$.

conviction that she was "allergic" to the phenothiazines—particularly trifluoperazine hydrochloride. On the ward, she was initially treated with chlorpromazine hydrochloride, 200 mg daily. She improved somewhat but remained depressed, apathetic, and rather withdrawn. Chlorpromazine hydrochloride was stopped and trifluoperazine hydrochloride, 30 mg daily, was instituted. She improved, became quite likable, and started work as an electrocardiogram technician on the grounds. Two weeks later she became "anxious" and "lost confidence." Patient and staff agreed that the anxiety was due to "pressures and conflicts of her job." Trifluoperazine hydrochloride was increased to 60 mg, daily. Seven days later she became agitated, exhibited overwhelming anxiety of annihilation proportions and regressed to very childish pleading behavior. "Please do something for me. Please!" Chlorpromazine hydrochloride, given intramuscularly, was added to the trifluoperazine hydrochloride. She regressed further, became convinced that most of her difficulties were attributable to the trifluoperazine hydrochloride and angrily pleaded to have it stopped. The usual interpretations made her furious and it was finally decided to stop the phenothiazines lest the transference became completely unworkable. Over the next three weeks she improved somewhat. (This would be compatible with the notion of a gradually declining plasma phenothiazine level from a toxic to a therapeutic range.) From then on the patient deteriorated to her admission level of functioning, in spite of a very active treatment program. It was decided to reinstitute the trifluoperazine hydrochloride, regardless of the patient's objections. On liquid trifluoperazine hydrochloride, 20 mg daily, and liquid chlorpromazine hydrochloride, 250 mg daily (we emphasize "liquid" because of the findings by Curry et al[3] that "liquid" chlorpromazine hydrochloride results in higher plasma levels than pill form). The patient again, after an initial spurt of improvement, regressed to childish pleading. Anxiety was so severe that no rational conversation could take place. "I feel very frightened. I can't take these attacks. This awful feeling just came on me. It hits me like that (three hours after medication time which coincides with peak plasma level following liquid administration[3]). I have lost all confidence. I am afraid of people. Please, doctor, (tearfully) please help me. It's a horrible feeling, like going through hell. I feel I'll lose my mind completely." Restless changes in posture and intermittent pacing were noted. There was no other extrapyramidal involvement. Biperiden, 5 mg, given intramuscularly, produced a most dramatic improvement in mental status. Thirty minutes after the biperiden she was no longer tearful, spoke coherently and rationally, had regained her usual sense of humor and discussed realistic concerns. Restless changes in posture had ceased. Vague somatic complaints of "tightness" in the chest and a sensation of "feeling swollen up inside" also ceased. Placebo injections produced subjective mention of improvement but little objective improvement. This procedure of biperiden-placebo was repeated four times with very consistent results.

Because of her drug reluctance she was switched to fluphenazine enanthate, 12.5 mg, given intramuscularly every two weeks (a low dose). On the fourth morning following the injection she awoke early with a feeling of extreme "fear," "confusion," and "deep depression," which the patient plausibly explained in terms of pressures of her job. She had barely noticeable body shaking and appeared restless. Biperiden, given intramuscularly, again produced remarkable improvement. Anxiety and somatic complaints were much diminished, depression improved, and feelings of nameless fear abated. This same improvement was replicated in subsequent fluphenazine injections with biperiden-placebo injections. She is now functioning very well on fluphenazine enanthate, 12.5 mg, given intramuscularly every two weeks and trihexyphenidyl hydrochloride (Artane) 16 mg, daily. If the trihexyphenidyl is reduced below 16 mg, daily, a subtle akathisia together with an anxious regression appears.

"Fulminant psychotic episodes" following fluphenazine enanthate have been described.[4]

CASE 2.—This 48-year-old married white woman was admitted with a long-standing and well-organized delusional system to the effect that a NASA computer system controlled her mind and actions. She was quite calm and conversed quite rationally as long as the delusional system was avoided. She was placed on liquid fluphenazine, 5 mg, three times a day, which exerted no noticeable effect. Fluphenazine, given orally, was stopped and 12.5 mg, fluphenazine enanthate, given intramuscularly, was administered. Again there was no noticeable response. Fluphenazine enanthate was increased to 25 mg. For the next four days she remained quietly delusional. On the fifth day following the injection she burst into my office panic stricken. She was extremely agitated and talking in pressured fashion. "I was hit by ultrasonic sound. A war machine has been used against me. You can get polio with these lasers. Please, can't you see I'm wasting away. Touch me. . . ." No rational contact could be established. She had a mild parkinsonian tremor of her fingers and would not sit down. One hour after biperiden, 5 mg given intramuscularly, she was a changed person. She felt "relaxed" and spoke very coherently. Six hours after the biperiden moderate anxiety recurred. A placebo injection had no effect.

Comment

Behavioral toxicity to phenothiazines is a poorly explored area. Some anecdotally reported adverse mental reactions to phenothiazines have all the earmarks of a toxic psychosis with clouded sensorium, vivid visual and auditory hallucinations, confusion, memory impairment, slurred speech, etc.[5-8] Others[7-12] have described the intensification or development of depersonalization phenomenon, depression, unreality feelings, and mood changes when phenothiazines were administered to nonpsychotic patients. These adverse reactions often occurred on very low dosages and support the clinical impression that phenothiazines are the drug of choice in psychosis only El-Yousef and co-workers[13] have recently reported an anticholinergically based exacerbation of psychosis in patients maintained on moderate dosages of antipsychotic drugs and antiparkinson agents. These exacerbations can be reversed by physostigmine—a cholinergic agent. Curry[14] has also reported "enhanced signs of schizophrenia" in a few

patients with high chlorpromazine blood levels. Others[15-19] have attributed phenothiazine-induced exacerbations of schizophrenia to a subtle interaction between phenothiazine drug effect and premorbid personality. In this psychodynamic view, exacerbations of the disease process occur because the pharmacologic action of the drug has particular emotional meaning and significance to the subject. Most phenothiazine-induced exacerbations of psychosis seem to occur with the more potent piperazine phenothiazines (prochlorperazine, fluphenazine, trifluoperazine, etc) which regularly cause extrapyramidal involvement.[4,9-11,20-23] This raises the possibility that these exacerbations of psychosis are extrapyramidally based.

In the nine patients decompensations—like extrapyramidal symptoms—were dose related. Since the exacerbation mimic the original psychosis, the clinical impulse was always to raise the dosage. When dosage was increased, a more florid psychosis together with obvious extrapyramidal symptoms occurred. Lowering of dosage just short of a subtle akathisia kept the patient well controlled. Decompensations and associated akathisia could be suppressed with maintenance antiparkinson drugs, given orally, in all nine patients. If the antiparkinson dosage was decreased, a subtle akathisia together with an anxious regression appeared.

Akathisia is a subjective state and "refers not to any type or pattern of movements but rather to a subjective need or desire to move."[24] This urge to move is always accompanied by affective distress and, objectively, is manifested by restless pacing, inability to sit still, and continuous alterations in posture. With the more subclinical akathisias, the patient may not use the word, "restless" and complain instead of "jitteriness," inability to feel "comfortable," "impatience," "irritability," feeling "keyed up," or being a "bundle of nerves." The well-established interaction between anxiety and extrapyramidal symptoms makes it even more difficult to distinguish a subclinical akathisia from anxiety.

Mental manifestations do occur in documented basal ganglia disease. Schwabb et al[1] have reported paroxysmal attacks of altered mental functioning in Parkinson disease. These attacks are often associated with oculogyric crisis and frequently disappear when antiparkinsonian drugs are administered. Davison and Bagley[25] also report an increased incidence of schizophrenia-like psychoses in such basal ganglia disorders as Huntington chorea, Wilson disease, torsion spasm, essential hereditary tremor, and midbrain reticulosis. They conclude that "basal ganglia dysfunction often has a prominent mental component which may take a psychotic form."

Since biperiden—an anticholinergic drug—reversed these decompensations, the question arises whether biperiden, by itself, might exert a therapeutic effect in schizophrenia. Anticholinergic agents alone, however, seem to activate schizophrenic symptoms, whereas cholinergic drugs have been reported to cause lucid intervals in schizophrenics.[26]

It seems reasonable to conclude that akathisia, a presumed basal ganglia dysfunction, can have a prominent mental component which resembles an exacerbation of the original schizophrenia. Exacerbations of psychosis, which are reversed by biperiden, can thus be viewed as an extrapyramidal equivalent. In some predisposed schizophrenics a conventional dose of a piperazine phenothiazine can be a toxic dose. The clinical tip-offs to such a drug-induced exacerbation are a sudden exacerbation of psychosis together with a subtle akathisia, complaints of a diffuse horrible sensation which has never been experienced before, and prompt response to biperiden or other antiparkinsonian drugs.

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