

Why Do Schizophrenic Patients Refuse to Take Their Drugs?

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Patients with schizophrenia often do not take their prescribed phenothiazines. This survey focused on the drug-taking behavior of 85 mostly chronic schizophrenic patients during a two-year period.

Thirty-nine (46%) of these patients took less antipsychotic drug than the amount prescribed. The reluctance to take antipsychotic medication was significantly associated with extrapyramidal symptoms—most notably a subtle akathisia.

It is proposed that drug reluctance and dysphoric response to antipsychotic drugs are often extrapyramidally based.

The reluctance of patients with schizophrenia to take their prescribed phenothiazines is the bane of the psychiatrist. Readmissions are commonly precipitated by drug reluctance, and it has been estimated that a large proportion of schizophrenic outpatients (from 24% to 63%) take less antipsychotic drug than the amount prescribed.¹⁻⁶ Even psychiatric inpatients (from 15% to 33%) take less drug than the amount administered.^{5,7-10} Since most of these studies are based on one or two spot Forrester urine tests, which make no distinction between a recently ingested low dose and a previously taken higher dose,⁸ these percentages are almost certainly conservative. In spite of its magnitude, there are few studies that focus on why schizophrenic patients refuse their drugs.

Wilson and Enoch⁹ found that covert rejection of chlorpromazine tablets in schizophrenic inpatients was associated with paranoid delusions, and that drug rejection could be alleviated by dispensing chlorpromazine syrup. Michaux¹¹ and Raskin¹² studied resistance to drug treatment in 180 Veterans Administration outpatients with mixed diagnosis randomly assigned to chlorpromazine hydrochloride 100 mg daily, a placebo, phenobarbital 60 mg daily, and meprobamate 1,600 mg daily. They found side effects, drug resistance, and dosage deviation to be unrelated to type of medication. Resisters to medication—when compared with the accepters—were more hostile and used the drugs as “a convenient focal point for their hostile and aggressive impulses.” Richards⁹ found that 58 (33%) out of 191 chronically hospitalized VA patients were

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chronic refusers of phenothiazine. He viewed their refusal of phenothiazine in terms of intrapsychic conflict and speculated that phenothiazine refusers as a group refuse to take their drug, because they object to being told what to do. McClellan and Cowan⁴ studied 286 VA outpatients with mixed diagnoses and found that at least 24% were taking less phenothiazine than the amount prescribed. They speculated that patients tend to adjust their phenothiazine dosage downward "in accordance with their own self-identified needs." Other proposed reasons for phenothiazine reluctance are: side effects in general (particularly sedation)^{3,6,13}; complexity of regime (multiple medications discourage compliance)¹³; social supervision (schizophrenics who live alone are most noncompliant)^{1,3,6}; severity of schizophrenia (default rates were highest in those schizophrenics who were most ill at time of discharge)^{3,13}; and the doctor's attitude.^{5,13}

Klein and Davis¹⁴ (pp 17-32) emphasize the importance of enlisting the patient's cooperation in the taking of psychotropic drugs. They believe that the most important reason for drug resistance is that the acceptance of medication forces the patient to admit that he is sick. Other patients desire to be in complete control of their lives, and view the drug as an external dominating agent or identify the drug with irrational authority or dominating parents.

Aside from these various reasons for resistance to medication, a dysphoric response to the phenothiazines could lead to an understandable drug reluctance. Sarwer-Foner,^{15,16} a pioneer in the dynamic aspects of drug response, has emphasized that the sedative, extrapyramidal, or other physiologic effects of antipsychotic drugs can precipitate panic reactions, further psychotic deterioration, and increased somatization. Extrapyramidal symptoms—the most common side effect of the potent neuroleptics—are often subjectively very stressful^{15,17,18} and may be incompatible with clinical improvement.^{19,22}

For the past two years we have carefully coded drug-induced extrapyramidal symptoms. Out of clinical necessity, we also focused on the habitual drug reluctance of some psychotic patients. As data accumulated, we noted an association between drug reluctance and drug-induced extrapyramidal effects. The hypothesis that much drug reluctance is attributable to extrapyramidal symptoms is examined.

Method

Since the hospital setting, the attitude of personnel, and the treatment philosophy have much to do with the manner of drug administration and the consciously perceived drug effect,^{16,23-31} these factors will be described in some detail.

The setting is a 30-bed teaching service in a university affiliated veterans hospital. For the psychotic patient our focus is on optimal chemotherapy. Optimal chemotherapy requires a continuous assessment of the interactions between the pharmacological effects as perceived by the patient and the patient's mental status on the one hand, and the total situation (including the social setting, transference, and countertransference) on the other. Dosage is adjusted frequently. Drug administration occurs in as non-authoritarian fashion as possible; patients—as soon as some working alliance can be established—are encouraged to report their view of the drug effect and thus participate in selection of optimal dosage. Since it is our belief that gross extrapyramidal effects are

incompatible with clinical improvement, this is a "low-dosage" ward.

The patients selected for this study had to meet two criteria: (1) They required maintenance with an antipsychotic drug in that discontinuation of medication would precipitate severe anxiety, the breakthrough of secondary symptoms or relapse. Cyclic schizophrenics who do not require interim medication were excluded. (2) That the ward director (author) and staff have known the patients as in- or outpatients for a minimum of two years. Patients who did not show up for outpatient treatment, but who were readmitted within two years were also included, provided accurate information about their drug-taking behavior could be obtained.

Eighty-five patients (17 men and 68 women) met these criteria. Eighty-two of these patients met strict Bleulerian criteria for schizophrenia and three patients were best classified as "borderline." The group averaged between three and four admissions. Many of these veterans were quite dependent on the hospital. Most were middle aged (range 21 to 64 years old) and carry the label of "poor-premord" or "process" schizophrenia.

The antipsychotic drugs utilized were: chlorpromazine (Thorazine), thioridazine (Mellaril), trifluoperazine (Stelazine), fluphenazine (Prolixin—both oral and the intramuscular enanthate), and haloperidol (Haldol). Trihexyphenidyl (Artane) was used to suppress extrapyramidal effects if these occurred.

"Dysphoric responder" refers to those patients who habitually complained about the drug effect. They felt "miserable" on the drug, and continually pleaded to have the drug stopped or dosage reduced.

Drug reluctance was categorized in terms of the patient's active refusal to take psychotropic medication.

Category 1.—Active and habitual refusal to continue taking any oral phenothiazines in the hospital. The patient may spit out or "tongue" the medication, and is convinced that it will harm or poison him.

Category 2.—Active and habitual refusal to take any phenothiazines after discharge, but will passively take phenothiazines in hospital.

Category 3.—Active and habitual refusal to take the prescribed phenothiazine dose, but will take a lesser dose.

Category 4.—Can be pressured into taking phenothiazines (particularly biweekly fluphenazine [Prolixin] enanthate), but strongly dislikes taking phenothiazines.

Category 5.—No drug reluctance. Patient usually "likes" the phenothiazines.

Drug reluctance was assessed by the nurses for the inpatients; for outpatients drug reluctance was assessed by the staff member who had the closest relationship with the patient (usually the treating psychiatric resident or social worker). At times, relatives were able to provide additional information on the patient's drug-taking behavior. Staff members were unaware of the hypothesis being tested.

The severity of extrapyramidal involvement (EPI) was judged by the following criteria:

Akathisia

Mild.—Patient feels "all nerved up," "squirmy inside," "up-tight," "nervous," "tense," "uncomfortable," "impatient." Characteristically, the milder akathisias are difficult to articulate; the patient does often volunteer that he has never experienced this feeling state before. Subjective feeling of ill-being may be accompanied by restless changes in posture. The milder akathisias are often evanescent.^{32,33}

Moderate.—Subjective complaints more intense; frequently complains of restlessness and inability to feel comfortable in any position. Feeling of ill-being accompanied by restless changes in posture (fidgetiness or crossing and uncrossing of legs). Patient may prefer to stand or pace.

Severe.—Restlessness to point of agitation. Patient cannot

sit still for even several minutes. Frequently, the sufferer is panicked.

Akinesia

Mild.—Patient is not somnolent, but complains of feeling "dead inside," "tired all the time," "no energy," "weakness," or "slowed up." Objectively, patient may appear apathetic, depressed, or emotionally indifferent.^{14 (pp163-168), 34-35} May manifest a decrease in ocular scanning.^{36,37} Associated movements (such as armswing) may be decreased. Facial expression may lack spontaneity. Muscle tone may be increased, decreased, or appear normal. Spontaneous muscular activity or normal fidgetiness during a stressful interview is reduced.

Moderate.—Subjective complaints more intense. Patient demonstrates some loss of associated movements, diminution of facial expression, some slowness of movement, and definite alteration of muscle tone.

Severe.—Loss of facial expression, obvious decrease of associated movement, definite motor slowing.

Tremor

Mild.—Seldom or intermittently present and mild.

Moderate.—Intermittently present.

Severe.—Usually present.

Dystonia

Mild.—Occasional and self-limited oculogyric crises, mild torticollis, trismus.

Moderate.—Dystonic reactions that are more severe and require medication, given intramuscularly or intravenously.

The EPI ratings were made by those trained staff members who knew the patient as a person—both off and on the drug. For documentation of the subtler akathisias or akinesias, biperiden (Akineton) hydrochloride 5 mg, intramuscularly, alternating with a placebo was administered as described in previous studies.^{32,33} If the biperiden-placebo procedure was inconclusive, the psychotropic drugs were stopped. Final EPI ratings were made at a "steady" state and at the *lowest* maintenance dose (with or without trihexyphenidyl) that seemed to best control psychotic symptoms. If the trihexyphenidyl completely suppressed the EPI, the patient was rated as having no EPI.

Although there was overlap between the raters for drug reluctance

and the raters for EPI, raters were unaware of any formal hypothesis being tested. (This, because the extrapyramidal ratings were originally collected for a different study having nothing to do with drug reluctance.)

Table 1.—Categories of Drug Reluctance

Category	Drug Reluctance	No. of Patients
1	Refuses to take drug; equates it with poison	10
2	Will not take drug as an out-patient, but passively takes drug in hospital	12
3	Takes less drug than prescribed	7
4	Can be pressured into taking Prolixin Enanthate biweekly	10
5	No drug reluctance	46
Total		85

Table 2.—Drug Reluctance and EPI

Category	No. of Patients	No. of Patients With No EPI, (% of Total)	No. of Patients With EPI, (% of Total)
1 + 2 + 3 + 4, drug reluctant	39	4 (11)	35 (89)
5, no drug reluctance	46	37 (80)	9 (20)

$\chi^2 = 41.629, df = 1, P < .001 (\chi^2_{.001} = 10.8).$

Table 3.—Dysphoric Response and EPI

	No. of Patients	No. of Patients With EPI (%)	No. of Patients Without EPI (%)
Dysphoric responders	33	31 (94)	2 (6)
Nondysphoric responders	52	11 (21)	41 (79)

$\chi^2 = 42.786, df = 1, P < .001.$

Table 4.—Types of EPI Associated With Drug Reluctance

EPI	Categories	
	1 + 2 + 3 + 4, Drug Reluctant	5, No Drug Reluctance
Akathisia		
No. of patients	39	46
No. of patients with akathisia	26 (67%)	1 (2%)
No. of patients with none	13 (33%)	45 (98%)
$\chi^2 = 40.50, df = 1, P < .001$		
Akinesia		
No. of patients	39	46
No. of patients with akinesia	21 (54%)	6 (13%)
No. of patients with none	18 (46%)	40 (87%)
$\chi^2 = 16.21, df = 1, P < .001$		
Tremor		
No. of patients	39	46
No. of patients with tremor	14 (36%)	2 (4%)
No. of patients with none	25 (64%)	44 (96%)
$\chi^2 = 13.748, df = 1, P < .001$		
Dystonia		
No. of patients	39	46
No. of patients with dystonia	8 (20%)	0
No. of patients with none	31 (80%)	46
No. of cases too small for χ^2 test to be appropriate; Fisher exact test significant at $P < .001$		

Results

Drug reluctance, when defined in terms of active refusal to take an antipsychotic drug, was distributed as shown in Table 1. Thus, some 46% of the patients were drug reluctant to some degree.

A comparison between the 39 drug-reluctant and 46 nondrug-reluctant patients, revealed a strong association between drug reluctance and EPI. Of the drug-reluctant patients, 89% experienced EPI, whereas only 20% of nondrug-reluctant patients experienced EPI ($P < .001$; Table 2). Most (80%) nondrug-reluctant patients did not experience any EPI. The nondrug-reluctant patients without EPI usually "liked" the medication; many have stopped the medication on their own for a few days or a week but all soon concluded that they felt better on medication.

Severity of EPI was not related to the degree of drug reluctance. There appeared to be, however, an interaction between EPI, drug reluctance, and type of schizophrenia in that the hostile paranoid schizophrenics were most intolerant of any extrapyramidal side effects. Thus, eight out of the ten most drug-reluctant patients (category 1) were chronic paranoid schizophrenics who interpreted the subtlest extrapyramidal symptoms as further proof that they were being poisoned or controlled by sinister outside forces.

A dysphoric response to antipsychotic drug was also strongly associated with EPI ($P < .001$; Table 3). These patients complained bitterly about the drug and 32 of the dysphoric responders were strongly drug reluctant. Many of these patients craved increases of antiparkinson drugs, and private stores of antiparkinson drugs were not uncommon in this group.

Table 4 shows that drug-reluctant patients experienced more akathisia, more akinesia, more dystonia, and more tremor, than nondrug-reluctant patients ($P < .001$; Table 4). Akathisia was most notably associated with drug reluctance. Only one nondrug-reluctant patient tolerated a mild akathisia over time, and this particular schizophrenic woman was uncritically compliant to whatever the doctor ordered. Akinesia was similarly associated with drug reluctance, but the results suggest that at least some patients can tolerate a mild akinesia (five nondrug-reluctant patients tolerated a mild akinesia over time). Only one nondrug-reluctant patient tolerated a moderate akinesia over time; this particular schizophrenic woman seemed to prefer an akinesia possibly because her drug-induced immobility helped with her overwhelming rage.³⁸ The experiencing of intermittent dystonia or tremor is similarly associated with drug reluctance.

Association does not mean cause. Do drug-reluctant patients refuse to take their medication because they cannot tolerate the drug-induced EPI? Clinical experience suggests that this is so; that is, most drug-reluctant patients find life with chronic EPI unbearable. The life-impact of even the milder extrapyramidal involvements will be illustrated by a few case examples:

Mild Akathisia

This 42-year-old woman with the diagnosis of chronic process schizophrenia was strongly drug reluctant to oral antipsychotic

drugs, but could be pressured into taking fluphenazine enanthate 6 mg, intramuscularly, every three weeks (class 4). She willingly took trihexyphenidyl (Artane) 4 mg, twice a day. On maintenance fluphenazine enanthate she experienced no secondary symptoms, but continued to lead a very empty and aimless life.

Without maintenance fluphenazine she invariably relapsed into a florid delusional psychosis. For the first seven days after her fluphenazine injection she experienced an "unbearably funny feeling" particularly on arising. "It may not mean much to you but I feel all squishy inside in the morning. Kind of jittery-like. I just don't feel comfortable. The Artane helps but doesn't do away with the feeling. I used to work in an office, but I can't do that anymore. I just can't sit all day. So now I'm a waitress. I know that you think the medicine (fluphenazine) is good for me . . . and I respect your opinion, but I'd rather be crazy than have that squishy feeling. Besides, I have more fun when I'm crazy" (laughter).

Akinesia

This 50-year-old woman had a chronic, fixed delusional system to the effect that she possessed an "atomic secret" that had great implications for the "universe." She dissimulated rather well, but at times of even minimal stress relapsed into a florid paranoid psychosis. She would not take any antipsychotic drug, claiming that these made her worse. She was finally persuaded into a trial of thioridazine 100 mg, at bedtime. After seven days she complained of unbearable "fatigue" . . . "I have slowed down. I talk slower and move slower (objectively this was apparent only after she called our attention to it). I feel like an old lady. I get tired from walking around the block. I feel discouraged about the future; I have no enthusiasm. I can't type nearly as fast at my job (clerk typist) . . . I want my own personality." Biperiden 5 mg, intramuscularly, completely suppressed the akinesia; the placebo, given intramuscularly, had no effect. Maintenance trihexyphenidyl did not completely suppress the akinesia.

Dystonia

This 28-year-old very muscular black man with the diagnosis of chronic paranoid schizophrenia could be pressured into taking fluphenazine enanthate 12.5 mg, intramuscularly, every two weeks (class 4). On maintenance fluphenazine secondary symptoms were diminished and he could do factory work; without maintenance fluphenazine he relapsed into a florid paranoid psychosis. Even on trihexyphenidyl, 12 mg, daily (a high dose) he experienced episodic oculogyric crises. "I'm telling you I can't take this medicine. It makes my eyes flip to the top of my head. The other day on the freeway I almost got into an accident. It's embarrassing. When I'm around my friends and my eyes flip up I just rub my eyes so they won't notice."

The experiences with the seven patients, who habitually took less drug than the amount prescribed (category 3), lend further support to the finding that EPI is difficult to bear over time. These patients invariably self-titrated their dosage to the point of minimal or no EPI. At least three of these patients functioned better on their self-prescribed lower dose, thus supporting the possibility that the patient's view of optimal dosage is very much worth listening to.

Comment

The data reported here suggest that the reluctance to take chemotherapeutic agents and the dysphoric response to antipsychotic drugs are usually related to EPI. While gross EPI can be tolerated for a short interim within the supportive confines of the hospital, even mild EPI over a prolonged interim is difficult to tolerate for an outpatient.

The EPI may not be compatible with a useful life in the community; an akinesia may cost a clerk typist her job; an oculogyric crisis may imperil the life of a man who needs to drive; or a tremor can be socially incapacitating to a self-conscious woman. Denber,¹⁷ who focused on the psychodynamic aspects of EPI, found that drug-induced rigidity and immobility were often equated with "paralysis," and that in many cases "the prime verbalized fear was death." Singh and Smith²¹ also noted an association between dysphoric response to haloperidol and persistent EPI, but they did not believe that the dysphoric response was extrapyramidally based.

Drug reluctance is most notably associated with akathisia. This extrapyramidal manifestation is entirely subjective and, in its milder form, is virtually impossible to distinguish from dynamically determined anxiety. The well-established interaction between anxiety and extrapyramidal symptoms makes it even more difficult to distinguish a mild or subclinical akathisia from anxiety. Kalinowsky³⁹ states that akathisia can be "more difficult to endure than any of the symptoms for which (the patient) was originally treated," and Fouks et al⁴⁰ refer to akathisia as the "syndrome of impatience" and stress that it often is associated with severe anxiety, peculiar bodily sensations, and bizarre mentation. A moderate akathisia can preclude sitting through the dinner hour or a movie—let alone a sedentary job.

The reader may wonder whether the milder akathisias and akinesias, which are mostly subjective, were truly drug induced. Side effects of "restlessness and excitement" and "weakness and fatigue" occur with the placebo as well.¹¹ It is unlikely that EPI was confounded with the placebo effect, because in order for a subjective complaint to be rated as an akinesia or akathisia it had to pass the following test: improvement on biperiden, 5 mg, given intramuscularly, and no improvement on the placebo, given intramuscularly (double-blind), or, if this biperiden-placebo procedure was inconclusive, disappearance after the antipsychotic drug was stopped.

This study has its shortcomings. First, there was overlap between raters. Although the extrapyramidal ratings were originally collected for a different study having nothing to do with drug reluctance, thus making the raters unaware of the hypothesis being tested, rater bias cannot be ruled out. Second, the mere inquiry into subtle EPI by the same staff involved with the patient's treatment may have blown their importance out of proportion. Theoretically, EPI ratings should have been made by independent trained raters. However, the subtlety and evanescence of the milder EPI often require a closer and more continuous relationship for their detection than exists between subject and an independent rater.

Our experiences suggest that a schizophrenic outpatient on maintenance phenothiazines is more likely to continue taking his medication as prescribed if great care is taken to avoid even mild EPI—particularly the akathisias. This is particularly true for the paranoid patient who is most intolerant of any EPI. In this sample of 85 patients, 17 were converted from drug-reluctant categories by reduction of dosage and, usually; the addition of trihexyphenidyl (these patients were classified as nondrug re-

luctant, category 5). Unfortunately, a happy marriage between maximal antipsychotic effect and freedom from mild EPI cannot always be achieved. In 28 patients trihexyphenidyl in customary dosages (up to 12 mg daily) attenuated, but did not eliminate, a troublesome EPI. Furthermore, in 18 out of the 85 patients, the extrapyramidal threshold changed over time (sometimes very suddenly), so that a patient could be optimally medicated on one visit, and experience an akathisia or other EPI on the same dosage of phenothiazines two weeks later. These patients need to be seen more frequently and often profit from an as needed supply of antiparkinson drugs.

Our data cannot answer the important question of whether antiparkinson drugs should be regularly used. For one, the relationship between extrapyramidal symptoms and clinical efficacy has always been fraught with confusion and equivocal results.^{19-21,37} Bishop et al²⁰ in a controlled study, found that "obvious extrapyramidal symptoms" were incompatible with a good clinical response. He emphasized, however, that patients with drug-induced parkinsonism were often rated as showing mild improvement, because their akinesia indirectly resulted in decreased agitation, less verbal expression of psychotic material, and improved manageability on the ward, even though there was no substantial change in the underlying psychotic process. For another, there are complex and, for some patients, probably antitherapeutic interactions between phenothiazines and antiparkinson agents that can only be unraveled by a different design.^{41,42}

This study focused on EPI, not on side effects in general. In our experience the sedative and anticholinergic effects usually do not pose a major problem. Tolerance usually develops to the sedative effects, and most patients find life with a dry mouth or occasional blurriness of near vision possible. Sexual dysfunction in men could pose a major problem, but was not observed in our 17 men. The question does arise whether drug reluctance is mostly extrapyramidally based in other schizophrenic populations. Our population consisted mostly of chronic middle-aged female schizophrenics who were rather passive and morbidly dependent on the hospital. It may well be that drug reluctance in younger acute schizophrenic men is determined to a greater degree by personality factors. Nevertheless, on the low-dosage ward in which this study was conducted, much of the EPI that led to drug reluctance was of the "mild" or subclinical type which is apparent only to the careful observer who knows the patient both off and on a drug. Even mild EPI is difficult to bear on a maintenance basis, regardless of personality type.

Once it is established that maintenance on an antipsychotic drug is necessary, every effort should be made to avoid the development of even mild EPI. There is no uniformity in the criteria for assessing the presence or absence of extrapyramidal effects, and the subtler extrapyramidal symptoms often go unrecognized by the physician³⁶—but not by the patient! Even mild extrapyramidal involvement can be unbearable and lead to outright drug reluctance or self-prescribed reduction of dosage.

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