Depression in Schizophrenia: Are Neuroleptics, Akinesia, or Anhedonia Involved?

by Martin Harrow, Cynthia A. Yonan, James R. Sands, and Joanne Marengo

Abstract

To investigate the presence of a full depressive syndrome in schizophrenia years after the acute phase and factors linked to these depressive syndromes, 75 schizophrenia and schizoaffective patients and 32 patients with bipolar affective disorders were studied prospectively at index hospitalization and followed up 4.5 years later as part of the Chicago Followup Study. Over 30 percent of the schizophrenia patients showed full depressive syndromes during the followup year. Schizophrenia patients on neuroleptics were significantly more likely to show full depressive syndromes than those not on neuroleptics during the followup year. This relationship held after the level of posthospital psychosis was controlled. The data suggest that neuroleptic use is one factor linked to the depressive-like syndromes found in the posthospital phase in non-chronic schizophrenia samples. The results did not support the view that these depressive-like syndromes are only a function of akinesia, although they suggest that akinesia is probably one factor involved. The data indicate a strong link between neuroleptic use and anhedonia. These data suggest that one factor involved in the depressive-like symptoms found in schizophrenia patients could be interference by neuroleptics with the mesolimbic dopamine reinforcement system or the dopamine reward system.


The present study was designed to investigate whether posthospital depression occurs in schizophrenia years after the acute phase and, if it does occur, to provide data on factors that may be involved in posthospital depression, with a particular focus on neuroleptic use. Recent research has provided evidence of posthospital depression in some schizophrenia patients. However, most of the research in this area has been on depression within the first year after entering the hospital (Bowers and Astrachan 1967; Shanfield et al. 1970; Mandel et al. 1982; Munro et al. 1984; Siris et al. 1984; House et al. 1987; Hirsch et al. 1989; Siris 1991), with a few studies extending over several years (e.g., Johnson 1981, 1988; Summers et al. 1983). In contrast, there is a lack of data on recurring depressive syndromes in the longitudinal course of schizophrenia and a lack of comparative data to reveal whether individuals with schizophrenia experience posthospital depressive syndromes more or less frequently than persons with other major psychotic disorders. Research has been scant on whether depression can be found, or is frequent, in schizophrenia many years after the acute phase, and most of the long-term studies have been based on retrospective studies and retrospective chart reviews (Planansky and Johnston 1980; Roy 1980, 1981; Guze et al. 1983; Martin et al. 1985). The present study was designed to assess the frequency of depressive syndromes in schizophrenia years after the acute period of hospitalization and to...
compare schizophrenia patients with patients with other major psychotic disorders on the presence of posthospital depressive syndromes.

A factor that may be involved in the depressive-like symptoms found in some schizophrenia patients is the use of neuroleptics. Since the introduction of chlorpromazine in the early 1950s, treatment of, hospitalization patterns of, and outlook toward schizophrenia have changed drastically in a positive direction. Neuroleptics are still the major type of antipsychotic medications used today, both in this country and abroad. Over the years, a number of minor and some possible major side effects have been reported to be associated with the use of neuroleptics. There is solid evidence concerning a number of these potential side effects, particularly extrapyramidal side effects, which include a variety of parkinsonian symptoms. Among these symptoms is akinesia.

However, there are other adverse effects, equally or even more important, that have been in dispute and that could drastically change the clinical picture. A possible major side effect concerns the potential of neuroleptic medications to lead to depressed mood or even to a full depressive syndrome (Ayd 1975; Rifkin et al. 1975; Van Putten and May 1978; Johnson 1981, 1988; Mandel et al. 1982; Galdi 1983; Siris 1987, 1991; Emerich and Sanberg 1991; Harrow et al. 1991). The research reported here was designed to study this potential, within a naturalistic research design, in both a sample of schizophrenia patients and a sample of other types of psychotic patients. One factor linked to neuroleptic use that could potentially account for some of the depressive-like features seen in some schizophrenia patients is akinesia. Throughout the literature on depression in schizophrenia, references are made to neuroleptic-induced akinesia and its relationship to depression (Ayd 1975; Rifkin et al. 1975; Van Putten and May 1978; Johnson 1981; Siris 1987; Van Putten and Marder 1987). Akinesia is an extrapyramidal side effect of antipsychotic drugs that has been described by Rifkin et al. (1975). Their description of the manifestations of akinesia is similar to some aspects of the symptom profile seen in depression. Thus, a series of investigators have proposed that the apparent depression in some postacute schizophrenia patients may be closely linked to (or a part of) an extrapyramidal reaction such as akinesia (Ayd 1975; Johnson 1981).

Another possible factor, which has not received any attention in the literature on potential depression in schizophrenia, is the effect of possible interference with the dopamine reward system or dopamine reinforcing system as a result of neuroleptic use. Anhedonia has been proposed as a factor in the psychopathology of some or many schizophrenia patients, and there has been some research into anhedonia in schizophrenia (e.g., Meehl 1962; Harrow et al. 1977; Andreasen et al. 1982). However, a possible link between anhedonia and neuroleptic use in schizophrenia has not been investigated in a systematic fashion. The present study, in which we analyzed data on anhedonia in schizophrenia, investigated this possibility.

The present study was designed to study the issue of depression in a sample of schizophrenia patients studied prospectively at the acute phase and then followed up 4.5 years later. The following specific questions were addressed:

1. Do schizophrenia patients show full depressive syndromes when studied 4.5 years after the acute phase?
2. Do schizophrenia patients show as much depression as patients with other types of psychotic and affective disorders, such as schizoaffective and bipolar disorders?
3. Are neuroleptic medications involved in the posthospital depression that may be found in some schizophrenia patients?
4. Are the depressive-like symptoms of neuroleptically treated schizophrenia patients linked to akinesia?
5. Could these depressive-like symptoms be linked to neuroleptic interference with hedonic capacity or with the dopamine reward system?

**Method**

**Sample.** The research reported here is based on data obtained from the Chicago Followup Study, a prospective, longitudinal research program based at Michael Reese Hospital and the University of Illinois at Chicago. This research program was designed to study (1) the course over time of schizophrenia and affective disorders (Grinker and Harrow 1987; Harrow et al. 1990; Carone et al. 1991; Grossman et al. 1991) and (2) factors involved in thought disorders and positive and deficit-negative symptoms (Harrow et al. 1985, 1989; Harrow and Quinlan 1985; Pogue-Geile and Harrow 1985). The present sample consisted of 107 relatively young patients who
were assessed prospectively at the acute phase, reassessed afterward, and then followed up 4.5 years later. At the 4.5-year followup, complete data were obtained on the patients' affective symptoms, their overall functioning and adjustment, and potential psychotic symptoms. The sample, diagnosed according to Research Diagnostic Criteria (RDC; Spitzer et al. 1978) included 54 patients with schizophrenia, 21 with schizoaffective disorders, and 32 with bipolar affective disorders who were experiencing manic episodes at index hospitalization. All of the schizophrenia and schizoaffective patients were psychotic at index, but none of the patients with schizophrenia exhibited a full depressive syndrome at acute hospitalization.

The inpatients included in this study were recruited from among patients experiencing the acute phase of their disorders who were admitted to a private hospital (Michael Reese Hospital) or a public hospital (Illinois State Psychiatric Institute) as part of the same research program. At index, all patients received structured diagnostic interviews. The similar followup assessments were administered by trained research assistants who were blind to the patient's diagnosis. The RDC diagnoses for the patients were based on one or both of two structured interviews: the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978) and the Schizophrenic State Inventory (Grinker and Harrow 1987).

The sample selected consisted of relatively young patients, between the ages of 17 and 30 years at index hospitalization, with limited chronicity of illness. Fifty-seven percent had had no or only one hospitalization before index admission, 24 percent had had two or three previous hospitalizations, and only 19 percent had had more than three previous hospitalizations. Within each diagnostic group, there were no significant differences in overall outcome between the patients with and without previous hospitalizations.

At index hospitalization, the patients had a mean age of 24 years and had completed an average of 13 years of education. Sixty-one percent were males. Seventy-six percent had never married.

At followup, of the 105 patients for whom clear medication data are available, 33 of the 53 schizophrenia patients (62%) were being treated with neuroleptics, as were 14 of the 21 schizoaffective patients (67%) and 12 of the 31 bipolar patients (39%). Less than 10 percent of the sample (only 8 of the 105 patients for whom medication data are available) were on tricyclic antidepressant medications at followup.

**Followup Assessments.** The followup assessments were conducted an average of 4.5 years after index hospitalization. The followup interviews consisted of a semistructured interview, performance tests, and questionnaires (Harrow et al. 1990; Carone et al. 1991). The SADS was the major instrument used to assess the presence of a major depressive disorder or full affective syndrome (the two are used synonymously here) during the followup year, and it provided detailed information about each patient's depressive symptoms. These symptoms included 17 major depressive symptoms such as depressed mood, hopelessness, excessive guilt, reduced concentration, insomnia, and psychomotor retardation, which were rated on a scale from 1 (symptom not present) to 6 or 7 (symptom present in severe form). Anhedonia, one of the depressive symptoms, was subjected to special analysis because of our hypotheses about its potential importance in the symptom picture. The rating for anhedonia from the SADS is based on a 6-point scale ranging from a score of 1 (no anhedonia) to 6 (very severe anhedonia). Information from the SADS interview was used to determine whether a full depressive syndrome or major depressive disorder was present according to criteria taken from the RDC.

The SADS was also used to assess delusions and hallucinations during the followup year and the month preceding the followup interview. Each type of delusion and each type of hallucination was rated on a 3-point scale: 1 = absent, 2 = suspected or likely, 3 = definite. Separate overall scales that we developed were used to rate the presence of delusions and/or hallucinations; these scales are based on the highest score in any area for delusions or hallucinations. Thus, a patient with a full delusion present in one or more areas is usually viewed as delusional and a patient with a full hallucination in one or more areas is usually viewed as hallucinatory. This scale has been used in previously reported research (Harrow and Silverstein 1977; Harrow et al. 1985; Pogue-Geile and Harrow 1985).

**Results**

**Depressive Syndromes in Schizophrenia at Followup.** Table 1 presents data on posthospital depression in schizophrenia at the 4.5-year followup. Thirty-seven
Table 1. Presence of depression at 4.5-year followup for patients in each diagnostic group

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Some or no depression</th>
<th>Full depressive syndrome</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Schizophrenia (n = 54)</td>
<td>34</td>
<td>63</td>
</tr>
<tr>
<td>Schizoaffective disorders (n = 21)</td>
<td>13</td>
<td>62</td>
</tr>
<tr>
<td>Bipolar disorders (n = 32)</td>
<td>18</td>
<td>56</td>
</tr>
</tbody>
</table>

percent of the schizophrenia patients showed a major depressive disorder at some point during the followup year. The patients' symptom profiles were categorized according to RDC, which require that patients exhibit not only mood- or sadness-related symptoms but an array of other symptoms to meet the criteria for a full depressive syndrome. According to the RDC, a major depressive disorder includes mood-linked symptoms (e.g., depressed mood, excessive guilt, hopelessness), cognitive-motor symptoms (e.g., fatigue, reduced concentration, indecisiveness, psychomotor retardation), and vegetative symptoms (e.g., loss of appetite, insomnia, weight loss). More than 35 percent of the schizoaffective patients and the bipolar patients also showed full depressive syndromes during the followup year studied.

Relationship Between Posthospital Depression in Schizophrenia and Neuroleptic Medications.

Table 2 presents data on the relationship between neuroleptic use and depression, controlling for level of psychosis. An analysis of major variables that may and posthospital depression in schizophrenia. Significantly more of the schizophrenia patients being treated with neuroleptics than those not treated with neuroleptics showed a major depressive disorder at the 4.5-year followup ($\chi^2 = 10.52, df = 1, p < 0.01$): 55 percent of these young patients with non-chronic schizophrenia who were on neuroleptics experienced a full depressive syndrome during the followup year.

The data for the schizoaffective patients show a trend similar to that found for the schizophrenia patients. Major depressive disorders were found in a larger percentage of the schizoaffective patients who were receiving neuroleptics (50%) than those not receiving neuroleptics (14%); however, partly because of the small size of the sample, this trend did not achieve statistical significance $\chi^2 = 2.52, df = 1, p = 0.11$.

Table 2. Presence of depression at 4.5-year followup in patients who were not on neuroleptics and in those on neuroleptics

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Not on neuroleptics</th>
<th>On neuroleptics$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some or no depression</td>
<td>Full depressive syndrome</td>
</tr>
<tr>
<td>------------------------------</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Schizophrenia (n = 53)</td>
<td>18</td>
<td>90</td>
</tr>
<tr>
<td>Schizoaffective disorders (n = 21)</td>
<td>6</td>
<td>86</td>
</tr>
<tr>
<td>Bipolar disorders (n = 31)</td>
<td>11</td>
<td>58</td>
</tr>
</tbody>
</table>

$^1$Complete data on neuroleptic treatment were not available for 2 of the 107 patients studied.
be related to depression in our sample, and thus may influence the level of depression in schizophrenia, showed that depression was significantly related to psychosis for the schizophrenia patients ($\chi^2 = 4.71, df = 1, p < 0.05$). Sixty-three percent of the schizophrenia patients with a full depressive syndrome also exhibited psychotic symptoms, compared with only 32 percent of those who were not depressed. The bipolar patients showed a similar trend: 39 percent of those who were depressed also exhibited psychotic symptoms, versus only 11 percent of those who were not depressed ($\chi^2 = 3.23, df = 1, p = 0.07$). The relationship for the schizoaffective patients was not significant (NS).

As a result of the potential of a significant relationship between depression and psychosis, the data on neuroleptic treatment were also analyzed while controlling for the level of posthospital psychosis. The level of posthospital psychosis was controlled for by conducting separate comparisons of the extent of depression for only those patients who were not psychotic at followup who were on neuroleptics versus those not on neuroleptics. We also conducted separate comparisons of only those patients who were psychotic at followup. When the schizophrenia patients who were not psychotic at followup were looked at separately, there was a trend for more depression among those who were not on neuroleptics (65%) than among those who were not ($\chi^2 = 3.11, df = 1, p = 0.08$).

In the combined sample of schizophrenia, schizoaffective, and bipolar patients who were not psychotic at the 4.5-year followup, we found significantly more frequent posthospital depression for those patients receiving neuroleptic medications than for those not receiving neuroleptic medications ($\chi^2 = 7.56, df = 1, p < 0.01$). In the combined sample of patients who were psychotic at followup, the data did not show a significant trend for more depression among patients receiving neuroleptics than among those not receiving neuroleptics ($\chi^2 = 0.12, df = 1, NS$).

**Akinesia and Neuroleptic Use in Schizophrenia.** To investigate whether the depressive-like symptoms found in some schizophrenia patients on neuroleptics in the posthospital period might be due to akinesia rather than depression, we conducted two different types of analyses. The first analysis involved studying whether there were fewer depressive-like symptoms in neuroleptically treated schizophrenia patients taking antiparkinsonian medications; the second involved studying the specific types of depressive-like symptoms found in schizophrenia patients after the acute phase.

In regard to the first of these analyses, if the depressive-like symptoms found after the acute phase in some schizophrenia patients on neuroleptics are due only to akinesia, one might expect a lower rate of depressive symptoms in neuroleptically treated schizophrenia patients who are also on antiparkinsonian medications, for example, an anticholinergic agent such as benztropine or trihexyphenidyl (Ayd 1975; Rifkin et al. 1975; Van Putten and May 1978; Siris 1987). Table 3 presents data comparing the extent of depression in schizophrenia patients on neuroleptics who were not receiving anticholinergic medications versus those receiving a combination of neuroleptics and anticholinergics. Analysis of the data shown in table 3 indicated that there were no significant or near-significant differences between these two groups ($\chi^2 = 0.004, df = 1, NS$).

In the second analysis, we examined the relationship between neuroleptic administration and major symptom groupings found in depression. If the depressive-like picture seen in a number of schizophrenia patients is only a function of akinesia, one would expect the depressive-like symptoms commonly associated with akinesia to be the ones that are primarily

<table>
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<tr>
<th>Type of medication</th>
<th>Some or no depression</th>
<th>Full depressive syndrome</th>
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<tbody>
<tr>
<td>Neuroleptics and anticholinergics</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Neuroleptics, no anticholinergics</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

*Note.* $\chi^2 = 0.004, df = 1$, not significant.
linked to neuroleptic use. Strictly defined, akinesia, an extrapyramidal system symptom, involves diminished or slow motor movements and rigid motor movements, although at times it has been viewed much more broadly as leading to mood-related problems and a number of other symptoms associated with depression. If the depressive-like symptoms found in many schizophrenia patients on neuroleptics are almost entirely due to akinesia as defined narrowly, one might expect schizophrenia patients on neuroleptics to have predominantly cognitive-motor symptoms and few or no mood-related symptoms.

To study more closely the relationship between neuroleptic use and both depression and akinesia, we grouped depressive symptoms into three symptom clusters and related each of these clusters to neuroleptic use. The three symptom clusters included (1) five mood-related symptoms (depressed mood, hopelessness, negative self-evaluations, suicidal tendencies, and excessive guilt); (2) five cognitive-motor symptoms (loss of energy/fatigue, indecisiveness, reduced concentration, psychomotor retardation, and psychomotor agitation); and (3) three vegetative symptoms (insomnia or hypersomnia, appetite loss or appetite gain, weight loss or weight gain). The score for each patient on each cluster was based on the sum of the number of symptoms in each cluster; thus, scores could range from 0 to 5 for the mood-related symptoms and the cognitive-motor symptoms and from 0 to 3 for the vegetative symptoms.

The data indicate that the schizophrenia patients on neuroleptics experienced significantly more mood-related symptoms than those not on neuroleptics ($t = 2.10, p < 0.05$). We should note that although anhedonia is a mood-related symptom, it was not included in this analysis because we examined separately hypotheses about the relationship between neuroleptic use and anhedonia in regard to formulations about potential interference with the dopamine reward system. However, a separate analysis of the mood-related symptom group, including anhedonia as a sixth symptom, also showed a significant difference (and even a slightly larger difference) between schizophrenia patients on neuroleptics versus those not on neuroleptics; there were more mood-related symptoms in the former group ($t = 2.75, p < 0.01$).

There was also a significant trend for schizophrenia patients on neuroleptics to experience more cognitive-motor symptoms than those not on neuroleptics ($t = 2.82, p < 0.01$). In contrast, those on neuroleptics did not differ significantly from those not on neuroleptics in the presence of vegetative symptoms ($t = 0.63, NS$).

### Neuraleptic Use in Schizophrenia and the Dopamine Reward System

A factor we studied as a possible influence on depressive-like syndromes in schizophrenia patients treated with neuroleptics is potential disruption or interference with the dopamine reward or dopamine reinforcement system. One might propose that neuroleptic use could interfere with effective functioning of this hypothesized dopamine reward system and lead to anhedonia, one of the depressive symptoms. The present study was designed to explore this possibility.

Table 4 presents data on the relationship between neuroleptic use and anhedonia at followup for the schizophrenia patients. A detailed look at the 20 patients who were not on neuroleptics indicates that none of these 20 patients showed anhedonia. In contrast, 10 of the 33 schizophrenia patients who were on neuroleptics experienced moderate to severe levels of anhedonia, and another 4 experienced mild levels of anhedonia. Thus, none of the schizophrenia patients who were not on neuroleptics showed anhedonia, whereas 42 percent of these who were on neuroleptics showed at least mild evidence of anhedonia. A comparison of the anhedonia scores (using the 6-point scale) for the patients on neuroleptics versus patients not on neuroleptics.

<table>
<thead>
<tr>
<th>Level of anhedonia</th>
<th>Not on neuroleptics</th>
<th>On neuroleptics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
</tr>
<tr>
<td>None/slight</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

Note. $t$ (using a 6-point anhedonia scale) = 3.54, $df = 51, p < 0.001$ for patients on neuroleptics versus patients not on neuroleptics.
those not on neuroleptics showed significant differences (t = 3.54, df = 51, p < 0.001). Overall, the strongest association between neuroleptic use and an individual depressive symptom was with anhedonia.

Discussion

Do Many Schizophrenia Patients Experience Posthospital Depression and Are These Depressive-like Syndromes Limited to the Immediate Posthospital Phase? The data clearly indicate that years after the acute phase, some or many schizophrenia patients are vulnerable to major depressive disorders. Despite the fact that these patients did not have full depressive syndromes at hospitalization, they nevertheless developed later depressive syndromes at a rate comparable to that of other formal affective disorders. Previous research has indicated that during the immediate postacute phase, and in short-term followups, a number of schizophrenia patients show some depressive symptoms (Shanfield et al. 1970; McGlashan and Carpenter 1976; Johnson 1981, 1988; Mandel et al. 1982; Summers et al. 1983; Becker et al. 1985; Hirsch et al. 1989; Siris 1991). Several reports have indicated that this occurrence may be even more likely for those schizophrenia patients who originally had depressive features at the time of hospitalization (Shanfield et al. 1970; House et al. 1987).

In comparison to the present results, which show 37 percent of the schizophrenia patients with major depressive disorders during the followup year, other investigators have reported rates of depressive episodes in schizophrenia ranging from 30 to 60 percent (Falloon et al. 1978; Johnson 1981; Knights and Hirsch 1981; Roy 1981; Siris 1991).

Prospective research on young patients with acute schizophrenia years after the immediate posthospital period is relatively rare. The present results indicate that one may expect depression in young schizophrenia patients not just in the immediate postacute phase, but during a more extended period. Breier et al. (1991), using a long-term followup similar to ours (mean = 6 years) but studying a more chronic sample of patients, reported that 24 percent of their schizophrenia sample experienced at least one episode of RDC major depression. Thus, our results and those of Breier et al. indicate that depressive syndromes in schizophrenia can be found years after the immediate postacute phase, and these results are in accord with other results obtained with shorter followups. Our results provide evidence against diagnostic criteria that view postacute depression in schizophrenia as being limited to the first year after an acute schizophrenic break (see Siris 1991 for a discussion of this diagnostic issue).

The overall evidence indicates that later affective syndromes are not exclusively a phenomenon associated with unipolar and bipolar affective disorders, and it raises the question of whether some individuals with schizophrenia are as likely to become depressed during the course of their disorder as members of other diagnostic groups. It has been proposed that the depression found in some schizophrenia patients under these conditions is a depressive reaction to the original acute psychosis. Data indicating that depression can be found in some schizophrenia patients many years later call this view into question.

Such data, and the data of a number of other investigators (e.g., Knights and Hirsch 1981; House et al. 1987; Hirsch et al. 1989; Green et al. 1990; Siris 1991) showing a moderate percentage of schizophrenia patients with major depressive disorders years later, pose a clear problem for any diagnostic system that stipulates that schizophrenia patients should not have a depressive syndrome at any point during the course of their disorder.

In addition, data showing a clear subgroup of more than 30 percent of schizophrenia patients with postpsychotic depression years after the acute phase also pose a problem for research programs that have reported that none of their schizophrenia subjects ever showed any affective syndromes during a prolonged posthospital period. It is possible that research programs reporting such results have not studied their patients systematically over time at several different points in the posthospital period but rather have taken only one look at their patients many years later. However, the present data suggest that even in this type of one-frame analysis one would expect to find at least some schizophrenia patients with a full depressive syndrome.

Is Posthospital Depression in Schizophrenia Linked to the Use of Neuroleptic Medications? The data suggest that neuroleptic use may be linked to the depressive-like syndromes found in more than a third of young nonchronic schizophrenia patients. The majority of the schizophrenia patients who showed depressive syndromes were being treated with neuroleptics, and the results seem to sug-
gest that neuroleptic use is one factor contributing to this picture. Depression was relatively frequent among the patients who were taking neuroleptics. The data also indicated that depression is relatively infrequent among the schizophrenia patients who were not on neuroleptics; fewer than 20 percent of these patients showed a major depressive disorder at followup.

Two possible side effects of neuroleptic use, extrapyramidal symptoms and movement disorders (especially tardive dyskinesia), are usually seen as major drawbacks to neuroleptic treatment. The results of the present study suggest another drawback as well when neuroleptics are used on a prolonged basis after the acute phase: our data suggest that depressive-like syndromes are a potential concomitant of neuroleptic use that must be carefully monitored by clinicians. Work by other investigators has also raised this issue, with results emerging on both sides of the controversy (Van Putten and May 1978; Johnson 1981, 1988; Knights and Hirsch 1981; Galdi 1983; Hogarty and Munetz 1984; Hirsch et al. 1989; Emerich and Sanberg 1991; Siris 1991). The issue has not been completely resolved, since the association between neuroleptic use and a depressive syndrome is suggestive but does not provide definitive evidence that this is a causal relationship. If neuroleptics do increase the probability of depressive symptoms in those schizophrenia patients who are vulnerable to depression, it is possible that this effect could occur by a variety of mechanisms. Thus, each of several different mechanisms could account for a part of the variance in this area.

In addition, it is quite possible that there may be some features of those schizophrenia patients who are vulnerable to depression who also make them more likely to be treated with neuroleptics. The correlation of depression with psychosis suggests that psychosis may be one factor that influences both neuroleptic use and depression, although one would expect that other factors are involved, since the relationship between neuroleptic use and depression was still significant even when controls for psychosis were used in the analysis.

We should note that previous research analyzing the relationship between depression and neuroleptic use has not controlled as clearly for factors such as psychosis as was done in the present investigation. However, in future research studying this relationship, the analysis would be enhanced if it also controlled for other symptom ratings.

Overall, the use of neuroleptic medications for schizophrenia and for other psychotic disorders presents many positive features and some negative features. Important positive features have already been well documented—for instance, the potential reduction of the frequency and flagrance of positive symptoms, which must be kept in mind when reviewing the total picture associated with neuroleptic use.

Since there were some schizophrenia patients not on neuroleptics who did show depressive syndromes, the present results indicate that depression is not solely a function of neuroleptic use in all schizophrenia patients who manifest depression. However, the data suggest that neuroleptic use is one factor that contributes to depression, although conclusions in this area should be drawn with caution.

One viewpoint would be that a moderate percentage of schizophrenia patients (perhaps from 40% to 60%) are vulnerable to potential depression and under certain circumstances are likely to manifest this depression. In this view, neuroleptic use is the most common factor that results in depression in some vulnerable schizophrenia patients. Clearly, it is not the only factor.

If neuroleptics are associated with depressive syndromes among schizophrenia patients, the issue arises as to whether depression is also frequent among schizoaffective patients being treated with neuroleptics. Indeed, this was the case in the present study. Posthospital major depressive disorder was more frequent in the combined sample of schizophrenia and schizoaffective patients taking neuroleptics than in those not taking neuroleptics.

Is the Depressive-like Syndrome Found To Be Only a Function of Neuroleptic-Induced Akinesia?

In the past, some have questioned whether the depressive-like symptoms found in a number of schizophrenia patients after the acute phase are "only" a function of akinesia (Ayd 1975; Johnson 1981). In general, our data do not support this view. However, the resolution of this question depends on how one defines akinesia. Akinesia is an extrapyramidal system symptom. The definition of akinesia, which originally was characterized as involving a motor disorder (e.g., slowed and/or rigid motor movements), has at times been extended to include a wide variety of nonmotor symptoms. The in-
increased depressive-like symptomatology of schizophrenia patients would fit under the extended definition of akinesia. On the one hand, the view of an extended and broad definition of akinesia can be justified (e.g., Bermanzohn and Siris 1992). On the other hand, this could be a matter of making a phenomenon “true” by broadening the definition used, and to do so does not automatically advance knowledge in the area.

The present data suggest that the depressive syndromes found in schizophrenia are associated with some depressive-like symptoms that would fit under a narrow definition of akinesia, and they also include a number of other symptoms that do not fit under a narrow definition of akinesia. Thus, the depressive syndromes observed in the schizophrenia patients were experiencing showed both cognitive-motor features and mood-related and vegetative features. Our results would fit with those of other investigators who have found evidence suggesting that the depressive-like symptoms found in a number of schizophrenia patients are not just a function of narrowly defined akinesia (Hogarty and Munetz 1984; Hirsch et al. 1989). However, investigators such as Bermanzohn and Siris (1992) have pointed out the potential complexity of akinesia and how it might include a variety of different disorders.

While the present data suggest that the depressive-like symptoms found in a number of schizophrenia patients are not just a function of narrowly defined akinesia, this issue could be better looked at in a study where data are available on the exact dose range and adequacy of the antiparkinsonian medications to facilitate further comparisons. In addition, the most complete assessment of hypotheses about akinesia would include measures of depressive-like symptoms that have been linked to akinesia and would also include a direct scale assessing akinesia and extrapyramidal symptoms. Therefore, the present results should be viewed as providing tentative data on whether akinesia is one of the factors involved in the depressive-like symptoms found in posthospital schizophrenia over the long term.

When our results are looked at from a different viewpoint—in terms of the potential relationship between neuroleptic use and akinesia—they show a significant relationship between neuroleptic use and several key depressive-like symptoms that would fit in with an akinetic picture. These symptoms include the cognitive-motor grouping of symptoms (p < 0.01). However, neuroleptic use also showed a significant relationship with several other key depressive-spectrum symptoms that do not fit under a narrow definition of akinesia. These symptoms include the cluster of mood-related symptoms (p < 0.05); individual symptoms such as guilt and suicidal tendencies are significantly related to neuroleptic use among the schizophrenia patients. Hence, while the present data suggest that neuroleptic use may be one factor contributing to the depressive-like symptoms found in a number of schizophrenia patients after the acute phase, this relationship is not only a function of neuroleptically induced akinesia. The relationship between neuroleptic use and depressive-like symptoms also extends to other symptoms that are not classically linked to akinesia when akinesia is defined only in terms of motor symptoms.

Neuroleptic Use and Possible Interference With the Dopamine Reward System. Our results clearly suggest that malfunction of the dopamine reinforcement system, or the dopamine reward system, could be a factor at least as important as the possible relationship between depressive-like symptoms and neuroleptic-induced akinesia. Research using several different techniques (Weeks 1962; Corbett and Wise 1980; Sherman et al. 1980) has provided strong evidence that the mesolimbic dopaminergic system mediates some of the reinforcing properties of brain stimulation reward for use of drugs such as cocaine and amphetamine and that it probably is one of several different mechanisms involved in the reinforcing properties of opiates (Schwartz and Marchok 1974; Wise 1978; Sypkra et al. 1982; Fibiger and Phillips 1988). Neuroleptics such as haloperidol have been used in animal research to decrease the reinforcing properties of brain stimulation and also to block previously conditioned place preferences (Wise 1978; Sypkra et al. 1982). The precise details of some of the mechanisms involved in this system await further definitive research. In addition, the overall picture does not lend itself to simplistic formulations, since the reinforcing properties of some drugs can probably be mediated by several different mechanisms in different brain locations (Fibiger and Phillips 1988).

Despite the lack of uniformity, the cumulative evidence in the field on the presence and importance of a mesolimbic dopamine...
reward system in human behavior is substantial. The present data indicating a strong link between neuroleptic use and anhedonia would fit in closely with an interpretation concerning neuroleptic interference with the dopamine reward system for a number of schizophrenia patients. The view would be that such neuroleptic use leads to a possible interference with this system for some, but not all, schizophrenia patients and for some patients with other types of psychotic disorders, increasing the chances of anhedonia.

Again, it is unlikely that all of the data on depressive-like features in schizophrenia can be explained on this basis, since there were some schizophrenia patients in our sample who showed a depressive syndrome without anhedonia and there were a number of schizophrenia patients on neuroleptics who did not experience depression. However, the data could support such interference with hedonic capacity as one influence, possibly an important influence.

The Link Between Psychosis and Depression in Schizophrenia. Our data showed a relationship between psychosis and depression for the schizophrenia patients, and this relationship could indicate that psychosis increases the chances for depression in those schizophrenia patients who are vulnerable to depression. However, one cannot assume that psychosis automatically leads to depression in vulnerable schizophrenia patients. Thus, for some schizophrenia patients both depression and psychosis could be features of some common diathesis or other predisposing factors. Such predisposing factors could include stress, anxiety, and emotional turmoil, which, in schizophrenia patients, could increase the chances for the overt appearance of psychosis or for an increase in the flagrancy of already existent psychosis. Increased stress could also increase the probability of depression in schizophrenia patients who are vulnerable to depression.

In other research on patients with unipolar depression, we have found evidence suggesting that the appearance of posthospital depressive episodes drastically increases the likelihood of overt psychosis for depressive patients who were psychotic at acute hospitalization (Sands and Harrow, in press). However, here again it is quite possible that both depression and psychosis could be features of a common diathesis for patients with unipolar psychotic depression.

Depressive-like Symptoms and the Involvement of Multiple Factors. Our data could be interpreted as suggesting that multiple factors are involved in the depressive-like symptoms found in the posthospital phase for a number of relatively young nonchronic schizophrenia patients. These factors include neuroleptic use, although there was a small subgroup of schizophrenia patients who showed vulnerability to depressive syndromes even though they were not on neuroleptics. Among the factors associated with the depressive-like symptoms were possible akinesia and probable neuroleptic interference with the mesolimbic dopamine reward system. The data showing a strong relationship with anhedonia would support the latter potential influence.

The present evidence on depression and anhedonia and other evidence on motor symptoms and sluggishness suggest that during the long-term postacute phase of schizophrenia, neuroleptic treatment may present a mixed picture. Such treatment has some very important positive effects on symptoms that are central to schizophrenia (i.e., it reduces the flagrancy of psychotic activity); it also involves some negative features, among which is anhedonia. The effects of neuroleptic treatment should be monitored carefully.

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The Authors

Martin Harrow, Ph.D., is Professor and Director of Psychology, Department of Psychiatry, University of Illinois College of Medicine and Director of Psychology, Michael Reese Hospital and Medical Center, Chicago, IL. Cynthia A. Yonan, B.S., is a graduate student, Department of Psychology, Washington University, St. Louis, MO. James R. Sands, Ph.D., is Assistant Professor, Department of Psychiatry, University of Illinois College of Medicine, Chicago, IL. Joanne Marengo, Ph.D., is Associate Professor, Department of Psychiatry, Northwestern University Medical School, Evanston, IL.