Neuroleptic Withdrawal in Schizophrenic Patients

A Review of the Literature

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In the treatment of chronic schizophrenia, there are risks associated with both neuroleptic maintenance (eg, tardive dyskinesia) and neuroleptic withdrawal (eg, psychotic exacerbation or relapse). We reviewed 66 studies on neuroleptic withdrawal involving 4365 patients with schizophrenia. The mean cumulative relapse rate was 53% in patients withdrawn from neuroleptic therapy and 16% in those maintained on neuroleptic therapy over a mean follow-up period of 9.7 months. The relapse rate was positively associated with length of follow-up. Predictors of relapse reported in individual studies included younger age, higher baseline neuroleptic dosage, and shorter length of hospitalization. Adverse effects of neuroleptic withdrawal other than relapse were usually mild and transient. The risk-benefit ratio of neuroleptic maintenance vs withdrawal should be assessed carefully in individual patients. A slow taper to the lowest effective dosage may be the preferred strategy in many patients. *(Arch Gen Psychiatry. 1995;52:173-188)*

Neuroleptic or antipsychotic drugs are the mainstay of treatment for patients with schizophrenia. The efficacy of these medications in reducing both the severity of psychotic symptoms and the risk of psychotic relapse has been well documented.[1-3] It has been suggested that early treatment with neuroleptic medication reduces morbidity in some patients with schizophrenia.[4] Many patients with chronic schizophrenia need to be maintained on neuroleptic therapy for prolonged periods. In a recent review, Schooler[5] concluded that alternatives to continuous long-term neuroleptic treatment (eg, targeted medication strategies) may be feasible in some patients, yet they also carry significant risks and should be studied further. At the same time, continued treatment with neuroleptic drugs is also associated with an increased risk of serious side effects, such as orthostatic hypotension, extrapyramidal symptoms, and, of particular concern, persistent tardive dyskinesia (TD).[6-8] Kane et al[9] reported an annual incidence of TD of 4% to 5% in neuroleptic-treated young adults. Saltz et al[10] as well as Jeste and Caligiuri[11] reported an incidence of TD that was at least six times greater in older psychiatric patients.

The issue of prolonged neuroleptic treatment in a patient with chronic schizophrenia places the clinician on the horns of a dilemma. Since neuroleptic treatment does not cure schizophrenia, a large majority of such patients need long-term treatment. At the same time, prolonged use of these drugs carries a high risk of adverse effects, including TD. It is therefore recommended that continued prescription of antipsychotic drugs over a long period not be undertaken without adequate justification for both clinical and medicolegal purposes.[1,7,11] This may imply attempts at neuroleptic withdrawal. Drug withdrawal, however, is associated with a risk of psychotic relapse. To complicate matters further, a number of patients withdrawn from antipsychotic therapy do not experience relapse, at least over a short period, while some patients maintained on therapy do experience relapse. Thus, the clinician and the patient have to choose between two unwelcome risks: relapse and adverse effects of continued treatment.

Neuroleptic withdrawal is also important yet problematic from a research

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perspective. Neuroleptic use is frequently a confounding factor in interpreting neurochemical and other findings in schizophrenia. It would be ideal to keep patients off neuroleptic drugs for as long as is possible, provided they can be maintained in a clinically stable state, ie, without relapse. Unfortunately, there is no clear guidance in the available literature about what type of patients can be withdrawn from antipsychotic drug therapy and for how long, as well as the optimal way of stopping drug therapy. To our knowledge, there has been no recent, comprehensive review of this important but controversial topic. Hence, we undertook the following review.

We asked the following questions: What is the risk of relapse in patients with schizophrenia after neuroleptic therapy has been stopped; in other words, what proportion of patients can be withdrawn from neuroleptic therapy without precipitating a relapse? Similarly, what is the likelihood of relapse in patients maintained on antipsychotic therapy over a comparable period? What are the other consequences of stopping neuroleptic therapy? Finally, what patient-related and treatment-related factors are associated with an increased or decreased danger of relapse and other adverse effects of stopping neuroleptic therapy?

METHODS

SELECTION OF STUDIES

We performed a computerized search of the literature on the MELVYL MEDLINE system using the following key words: *schizophrenia, antipsychotic, neuroleptic, withdrawal, discontinuation,* and *taper.* Cross-references were obtained from the bibliographies of the retrieved articles. We included English- and foreign-language articles about a minimum of 10 subjects with a diagnosis of schizophrenia or schizoaffective disorder. We included only articles with new data; review articles, such as that by Davis,[12] were thus excluded from our analyses. Because of unspecified or small sample sizes (fewer than 10 subjects each), we excluded from our analyses reports by Spivak et al,[13] Melamed et al,[14] Kushnir,[15] and Calev et al.[16] (We will, however, refer to these studies in discussing various adverse effects of neuroleptic withdrawal.) We included seven studies[17-23] that contained mixed diagnostic groups, but we excluded nonschizophrenic subjects in those studies from our analyses. Twenty-nine (44%) of the 66 studies included patients maintained on neuroleptic therapy who served as matched control groups for the neuroleptic withdrawal groups. The neuroleptic withdrawal groups from these 29 studies will be referred to in this review as "matched neuroleptic withdrawal groups." The term *matched* is used here for lack of a more suitable alternative. In a majority of these studies, the "control" groups were obtained by random assignment,[17,19,23-45] whereas five studies[46-50] specifically selected controls matched for age, diagnosis, duration of illness, and other variables.

A few research groups have published several sequential studies on neuroleptic withdrawal. Hence, data on individual subjects might have been used in more than one publication. We went through each article carefully and excluded the earlier publications from which data had been reused in later studies by the same group of investigators. Occasionally, however, it was not possible to weed out overlapping data. We cannot therefore exclude the possibility of a small bias resulting from the individual subjects' data being represented more than once in the cumulative data analysis. This was, however, not a major problem in our review, which involved more than 4000 patients.

SELECTION OF VARIABLES

For each study we examined the rate of relapse as well as possible predictors of relapse, such as age, gender, duration of illness, length of hospitalization, neuroleptic type and dose, length of neuroleptic taper, and length of follow-up. For the data analysis we selected those relevant variables on which at least 30 out of the 66 studies reviewed had provided usable information. (The only exception was percentage of patients receiving anticholinergic therapy, for which data were available in only 20 studies; we thought it to be too important a variable to be excluded.) We also reviewed other clinical or neurochemical effects of neuroleptic withdrawal in both the neuroleptic withdrawal and neuroleptic maintenance groups (when present).

STATISTICAL ANALYSIS

For each study we extracted the following descriptive summary statistics for both the neuroleptic withdrawal group and the neuroleptic maintenance (control) group, if present: the "average" values for age, duration of illness, length of hospitalization, baseline neuroleptic dose in milligram chlorpromazine equivalents (mg CPZE),[6] length of taper, and length of follow-up period. The means of the variables were utilized if these had been provided by the authors, but the midpoint of the range was substituted (as "averages") if the authors had provided that information instead of the mean. Study characteristics were noted, and the percentage of studies specifying diagnostic criteria as well as the percentage of studies with different designs (open, nonblind, single blind, or double blind) were determined.

To summarize the information in these studies, we computed unweighted means and SDs across studies from the individual study averages (means or midpoints), percentages, or sample sizes for the neuroleptic withdrawal groups and for the neuroleptic maintenance groups.

The matched neuroleptic withdrawal groups were compared with the matched neuroleptic maintenance groups by paired t tests. We used Bonferroni-corrected criterion α levels to limit the chance of a type I error from multiple comparisons. The matched neuroleptic withdrawal groups were also compared with the unmatched neuroleptic withdrawal groups on each of the listed variables using t tests, Mann-Whitney U Tests, or χ^2 analyses as appropriate, using Bonferroni-corrected criterion α levels.

Since the average length of fol-

low-up varied considerably from study to study, we attempted to relate the relapse rate of a study to its average length of follow-up. Because the follow-up time was positively skewed, a common logarithm was taken of the sum of the length of follow-up (in months) plus 1 for each group (neuroleptic withdrawal and neuroleptic maintenance) in each study that had both groups before this variable was related to others. This transformation also improved the linearity of any associations. A linear regression of relapse rate on the log transformation of the average length of follow-up was performed separately for all the neuroleptic withdrawal groups, the unmatched and the matched neuroleptic withdrawal groups, and the matched neuroleptic maintenance groups. Because the matched pairs of groups had the same average length of follow-up, we were also able to regress the difference in relapse rates between the matched groups on the log-transformed average length of follow-up.[51]

We also attempted to improve on the linear association between the relapse rate and the logarithm of the average length of follow-up and between the differences in relapse rates and the logarithm of the average length of follow-up by employing the empirical unweighted logit transformation of the relapse rate and the difference in logits, respectively. Occasional studies had relapse rates of zero; since one cannot take the logarithm of zero, we added 0.5 to each cell count.[52]

Finally, we attempted to improve the prediction of the relapse rate or logarithmic odds of the relapse rate or their respective differences between the matched withdrawal and matched maintenance groups by substituting or adding any of the other potential predictors in the data by means of a stepwise multiple regression analysis.

RESULTS

In the literature reviewed, 64 articles containing 66 studies* (each of two articles[47,56] reported two separate studies) including a total of 4365 subjects (3141 subjects withdrawn from neuroleptic therapy and 1224 comparison subjects maintained on neuroleptic therapy) met our inclusion criterion, ie, a minimum of 10 subjects with schizophrenia or schizoaffective disorder. **Table 1** summarizes descriptive features of the 66 studies reviewed.[86,87]

We derived summary data from the 66 studies, including the relapse rate. The descriptive statistics based on the summary data are shown in **Table 2**.

METHODOLOGICAL ASPECTS OF THE STUDIES REVIEWED

Sample Size

The sample sizes ranged from 10 to 519, with the average number of subjects in the neuroleptic withdrawal groups being 47.6.

Amount of Other Information Available

In general, the amount of information provided by the individual studies varied greatly. For example, in terms of age, 28 studies gave mean age only, nine reported age range only, 22 reported both mean age and range, while seven studies did not specify age at all.

Diagnostic Criteria

None of the 30 articles prior to 1981 defined or utilized specific diagnostic criteria for schizophrenia. If any reference was made to diagnosis, it was only noted that the subjects were "diagnosed by two psychiatrists."[19,24,26,30] Beginning in 1981, however, all of the studies reviewed except for one[62] employed specific diagnostic criteria, such as Research Diagnostic Criteria (RDC), *DSM-III, International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), and *DSM-III-R*.

Study Design

Thirty-seven of the 66 withdrawal studies (n=38) were double blind. Twenty-nine studies utilized a control group, ie, patients maintained on neuroleptic therapy. (Double-blind studies without control groups used placebo during neuroleptic withdrawal and had both patients and raters "blind" to the medication status.)

Medication Type and Dose

The neuroleptic medication used varied from study to study in terms of specific type and daily dosage. Phenothiazines and haloperidol were the most commonly prescribed neuroleptic agents. The average daily dosages, where stated, ranged from 228 to 1736 mg/d CPZE, with an average of 630.0 mg/d CPZE.

Of the 20 studies that specified concurrent medications, only one study specifically excluded patients receiving anticholinergic medication.[69]

Length of Neuroleptic Taper

Neuroleptic therapy was withdrawn acutely over 1 day in 42 of the studies where information about taper was given. The remaining studies used taper periods ranging from 2 to 60 days.

Length of Follow-up

The follow-up period after neuroleptic withdrawal ranged from 0.5 to 24 months, with an average of 6.3 months for all 66 studies and 9.7 months for the 29 studies with control groups. Since most studies did not specify the exact time of relapse in individual patients, we used the mean follow-up period. The matched withdrawal groups had a significantly longer average length of follow-up (Mann-Whitney *U* Test, $P=.0001$) and logarithmic follow-up ($t=5.47$, $df=64$, $P<.0001$) than the unmatched withdrawal groups.

Definition of Relapse

Twenty-two studies did not provide any definition of relapse.† *Relapse* was defined as a "return to active medication" in 11 studies.‡ The

*References 17-34, 37-43, 45-50, 53-85.

†References 17, 19-22, 25, 47, 53-57, 61, 62, 69, 71, 73, 76, 79, 80, 85.

‡References 18, 24, 26, 27, 30, 41, 60, 63, 72, 75, 81.

Table 1. Literature Review on Neuroleptic Withdrawal*

Source, y	No./Sex	Mean (Range) Age, y	Mean (Range) Duration of Illness, y	Mean (Range) Length of Hospitalization, y	Diagnostic Criteria	Study Design
Good et al,[53] 1958	112/M	(22-50)	NS	(0.2-?)	NS	DB
Brooks,[54] 1959	28/F	40.4 (19-53)	NS (chronic)	(1-25)	NS	SB
Diamond and Marks,[46] 1960	E: 20 C: 20	46.3	NS	E: 11.4 C: 11.6	NS	DB with control group
Rothstein,[55] 1960	17	45.2	NS (chronic)	8.4	NS	SB
Blackburn and Allen,[27] 1961	E: 28/M C: 25/M	(20-40)	Chronic	(0.3-10.8)	NS	Open with control group
Judah et al,[56] 1961 (two studies)	87	NS	NS (chronic)	(2-5)	NS	SB
	519	NS	NS	NS	NS	SB
Gross and Reeves,[57] 1961	E: 70 C: 36	41.8 (19-66)	NS	4.6 (0.5-10)	NS	DB with control group
Freeman and Alson,[17] 1962	E: 46/M (42 with SZ) C: 44/M	E: 41.1 C: 46.2	NS	E: 13.2 C: 11.3	NS	DB with control group
Olson and Peterson,[47] 1962 (two studies)	E: 60 C: 30	51 (21-78)	NS (chronic)	(>1.5)	NS	DB with control group
	E: 30 C: 30	51 (21-78)	NS (chronic)	(>1.5)	NS	DB
Whitaker and Hoy,[30] 1963	E: 26/M C: 13/M	E: 50 (27-66) C: 51.8	NS	E: 15.5 C: 19.9	NS (2 psychiatrists agreed)	DB with control group
Caffey et al,[32] 1964	E: 171/M C: 88/M	40	NS	10	NS	DB with control group
Marjerrison et al,[58] 1964	31 (15/M, 16/F)	47	(13-21)	(13-20)	NS	DB
Garfield et al,[33] 1966	E: 18/F C: 9/F	E: 42.4 (22-59) C: 42.6	NS	E: 11.4 C: 11.2	NS	DB with control group
Melnyk et al,[59] 1966	E: 20 (7/M, 13/F) C: 20	NS	12.8 (3-32)	1.5 (0.3-3)	NS	DB with control group
Hughes and Little,[18] 1967	21/F (12 with SZ)	57 (26-74)	NS (chronic)	10	NS	SB
Morton,[24] 1968	E: 20/M C: 20/M	(25-55)	NS	(≥2)	NS (2 psychiatrists agreed)	DB with control group
Prien et al,[60] 1968	210 (30 each at 7 hospitals)	41.6 (61% >40)	NS	14.5	NS	DB
Prien et al,[37] 1969	E: 120 C: 240	41.8	NS (chronic)	15 (2-33)	NS	DB with control group
Gleser et al,[65] 1970	74 (35/M, 39/F)	42.9 (24-54)	NS	11	NS	DB
Rassidakis et al,[19] 1970	E: 43 (36/M, 7/F) (33 with SZ) C: 28	E: 49.3 (26-74) C: 42.8 (33-60)	E: 23.5 (4-45) C: 18.1 (3-38)	NS	NS (2 psychiatrists agreed)	Open with control groups
Baro et al,[38] 1970	E: 26 C: 12	(24-71)	NS	NS	NS	DB with control group
Leff and Wing,[39] 1971	E: 15 C: 20	(16-55)	NS	NS	NS	DB with control group
Hershon et al,[50] 1972	E: 32 (17/M, 15/F) C: 30 (15/M, 15/F)	E: 53.6 (M), 60.4 (F) C: 57.3	NS (chronic)	NS	NS	DB with control group
Hirsch et al,[40] 1973	E: 41 (27/M, 14/F) C: 40 (25/M, 15/F)	E: 44.3±10.0† C: 42.6±10.5†	NS	NS	NS (case records)	DB with control group
Andrews et al,[26] 1976	E: 17/M C: 14/M	(50-63)	NS	6	Psychiatrist confirmed	DB with control group

Neuroleptic Type/Mean (Range) Dosage, mg/d	Mean (Range) Length of Taper, d	Mean (Range) Length of Follow-up, mo	Definition of Relapse	Relapse Rate, %	Predictors of Relapse
CPZ/(200-800)	1 (Acute)	6	NS	NS	NS
CPZ/(150-600), reserpine/(1.5-4)	1 (Acute)	0.5	NS	NS	NS
CPZ/400 (300-800), trifluopromazine/150 (50-300)	1 (Acute)	6	Worsening clinical condition	E: 70 C: 25	NS
CPZ	1 (Acute)	3	NS	6	NS
Phenothiazines	1 (Acute)	4	(1) Rating score decreased by 1 SE from baseline (2) Emergent resumption of medications (3) Transfer to closed ward	E: 46 C: 12	NS
CPZ, other phenothiazines	1 (Acute)	5	NS	60	NS
CPZ/(300-600)	1 (Acute)	3	Hyperactive, mute, threatening behavior	72	NS
Mainly CPZ	60 (28-150)	6	NS	E: 75.7 C: 13.9	NS
CPZ/228	1 (Acute)	6	NS	E: 31 C: 13	NS
CPZ, thioridazine	1 (Acute)	6	NS	29 (with placebo)	None
CPZ, thioridazine	1 (Acute)	6	NS	85 (without placebo)	NS
Perphenazine	1 (Acute)	2.5	Major relapse, return to medications	E: 39 C: 7.7	NS
CPZ/400, thioridazine/350	4	4	Withdrawal agitation, thinking disturbance	45	None
Trifluoperazine, chlorprothixene	1 (Acute)	7	Behavioral worsening	NS	NS
CPZ/610, other phenothiazines	7	5	Difference of ±2 on IMPS[86] factor scores and of ±4 on morbidity scores indicated positive or negative change	E: 31 C: 13	NS
CPZ, thioridazine	1 (Acute)	1.5	Return of symptoms similar to before drug treatment	E: 50 C: 0	NS
CPZ/(75-450)	1 (Acute)	18	Return to medications	19	NS
Trifluoperazine, CPZ	1 (Acute)	6	Return to medications	E: 70 C: 25	NS
CPZ	1 (Acute)	6	Regressed, returned to neuroleptic medication before end of 6 mo	40	(1) Higher prior dose of medications (2) Younger patients (<40 y)
Trifluoperazine/(15-80)	1 (Acute)	6	Deteriorated behavior	E: 45 C: 20	Longer hospitalization, type of phenothiazine medication
Phenothiazines	1 (Acute)	1	Assaultive or suicidal	5.4	NS
Thioridazine, haloperidol, CPZ	1 (Acute)	9	NS	E: 58.1 C: 34.1	Younger age at onset, younger current age, and nonparanoid subtype
R16341/20 (10-40)	1 (Acute)	2.5	Disorganization, agitation, abnormal thought process	E: 100 C: 0	NS
CPZ/(100-300), trifluoperazine/(5-15)	1 (Acute)	12	Return to SZ symptoms	E: 80 C: 35	Younger age, male, situational anxiety
Trifluoperazine/17	1 (Acute)	4	Delusions, hallucinations, aggression, regressed behavior	E: 28.1 C: 6.7	Younger current age, longer duration of neuroleptic treatment, higher prior medication dose
Fluphenazine decanoate/25 mg/mo	1 (Acute)	9	Deteriorated condition	E: 66 C: 8	NS
CPZ/(50-450)	1 (Acute)	10.5	Deteriorated behavior and return to medications	E: 35 C: 7	Higher prior medication dose

(continued)

Table 1. Literature Review on Neuroleptic Withdrawal* (cont)

Source, y	No./Sex	Mean (Range) Age, y	Mean (Range) Duration of Illness, y	Mean (Range) Length of Hospitalization, y	Diagnostic Criteria	Study Design
Rifkin et al,[34] 1977	E: 51 (34/M, 17/F) C: 22 (16/M, 6/F)	E: 23.7 (17-38) C: (17-30)	NS NS	NS NS	Kraepelinian signs of SZ	DB with control group
Lacoursiere et al,[61] 1976	48	37	NS	6	NS	DB
Hogarty and Goldberg,[41] 1973	E: 182 C: 192	34.4 (18-55)	NS	NS	Confirmed by research psychiatrist	DB with control group
Levine et al,[42] 1980	E: 50 C: 17	NS	NS	NS	NS	DB with control group
Zander et al,[62] 1981	13 (8/M, 5/F)	45.2±6.5‡	22	13.6	NS	NS
Brown and Laughren,[63] 1981	28/M	(28-66)	NS	NS	RDC	Open
Branchey et al,[49] 1981	E: 21 (13/M, 8/F) C: 11 (6/M, 5/F)	E: 51.4±9.6† (27-62) C: 52.2±8.9† (33-62)	NS	E: 25.4±8.6† (7-40) C: 25.9±10.3† (10-39)	RDC	DB with control group
Herz et al,[64] 1982	13 (6/M, 7/F)	43.5	NS	NS	*DSM-III*	Open
Kane et al,[23] 1982	E: 17 C: 11	E: 22.1±3.6† C: 21.5±5.4†	NS	NS	RDC	DB with control group
Kirch et al,[20] 1983	19 (13/M, 6/F) (12 with SZ)	19-56	NS	NS	*DSM-III*	Open
Johnson et al,[48] 1983	E: 60 (group A: 20, group B: 20, group C: 20) C: 56 (group A: 20, group B: 20, group C: 16)	E: 31.97 (group A: 29.4, group B: 31.4, group C: 35.1) C: 33.8 (group A: 31.1, group B: 32.7, group C: 37.6)	NS	NS	First-rank symptoms of Schneider	Open with control group
Naber et al,[65] 1985	36/M	46±11† (27-60)	17	16	*ICD-9-CM*	SB
Pietzcker et al,[25] 1986	E: 34 (17/M, 17/F) C: 14 (7/M, 7/F)	E: 41 C: 34	E: 9.9 C: 8.6	NS	*ICD-9* and RDC	Randomized, open with control group
Pickar et al,[57] 1986	11 (7/M, 4/F)	28±2.8§	NS	NS	*DSM-III*	DB
Crow et al,[43] 1986	E: 66 (39/M, 27/F) C: 54 (35/M, 19/F)	E: 24.3 (16-56) C: 28.2 (17-59)	E: (0.1-7.7) C: (0.1-8.4)	NS	RDC	DB with control group
Lieberman et al,[58] 1987	29	29.1±2.5† (18-50)	7.2	NS	RDC	DB

Neuroleptic Type/Mean (Range) Dosage, mg/d	Mean (Range) Length of Taper, d	Mean (Range) Length of Follow-up, mo	Definition of Relapse	Relapse Rate, %	Predictors of Relapse
Oral fluphenazine/(5-30), fluphenazine decanoate/12.5 mg biweekly	1 (Acute)	12	Substantial clinical deterioration	E: 68 C: 10	NS
CPZE/800	1 (Acute)	1	NS	NS	NS
CPZ	1 (Acute)	12	Return to medications	E: 67.5 C: 30.9	Younger age, earlier onset of illness
NS	1 (Acute)	12	Rehospitalization or deterioration of clinical condition	E: 46 C: 24	NS
CPZE/(273-396)	1 (Acute)	4.8	NS	61.5	Early relapsers: younger age, shortest duration of psychosis, shortest duration of medical therapy and hospitalization
CPZE/(75-1250)	14	10	Development of symptoms requiring return to medications	29	NS
E: Loxapine/70.9±44.7 (10-130), Loxapine/66.4±44.3 (20-160)	28	6	Development of new or worsening of preexisting symptoms	E: 76 C: 18	Higher baseline neuroleptic dose
CPZE/340 (100-690)	56	8	Low rating on GAS	23	Younger age at onset, recent hospitalization, higher medication doses
Oral fluphenazine or fluphenazine decanoate	1 (Acute)	12	Clinical deterioration	E: 41.2 C: 0	Poorer social adjustment
CPZE/807	1 (Acute)	0.5	NS	NS	NS
Depot neuroleptics: fluphenazine decanoate, flupenthixol decanoate	NS	E: 12 C: 18	Worsening of previous psychotic symptoms causing a 20% increase in the BPRS score and the Krawiecka Scale[87] or appearance of new SZ symptoms	E (12 mo): 65 (group A: 70, group B: 65, group C: 60) E (18 mo): 80 group A: 80, group B: 90, group C: 70) C (12 mo): 16 (group A: 25, group B: 10, group C: 13) C (18 mo): 23 (group A: 35, group B: 15, group C: 19)	NS
CPZE/560	1 (Acute)	0.5	Increase in total BPRS score ≥7 points or ≥5 points on subscales	11	NS
NS	Gradual	6	NS	E: 21 C: 0	NS
Fluphenazine	1 (Acute)	1.3	Worsening of symptoms or increase in pHVA level	NS	Increase in pHVA level
CPZ	30	24	Readmission to psychiatric care	62 46	Duration of illness prior to starting medication
NS	20 (oral medications), 42 (fluphenazine decanoate)	12	(1) Increase of 10 points on BPRS factors III, IV, V (2) Increase of 2 points on SADS Psychosis and Disorganization items	70.6	(1) Patients with TD relapsed sooner (2) Positive responders to Ritalin (methylphenidate hydrochloride) relapsed sooner

(continued)

Table 1. Literature Review on Neuroleptic Withdrawal* (cont)

Source, y	No./Sex	Mean (Range) Age, y	Mean (Range) Duration of Illness, y	Mean (Range) Length of Hospitalization, y	Diagnostic Criteria	Study Design
Dufresne and Wagner,[69] 1988	27 (13/M, 14/F)	32.7±9.9† (M) 33.1±11.2† (F)	12.0	NS	*DSM-III*	Open
Kirch et al,[70] 1988	22 (14/M, 8/F)	27 (18-41)	8	NS	*DSM-III*	DB
Kuhs and Eikelmann,[71] 1988	21 (11/M, 10/F)	25±6†	1.9	NS	*ICD-9-CM*	Open
Baron et al,[21] 1989	22 (18/M, 4/F) (17 with SZ)	46 (21-83)	NS	NS	*DSM-III*	Open
Glazer et al,[72] 1989	19	51	27	4.8	RDC	SB
Thaker et al,[73] 1989	10	28±5.3†	NS	NS	RDC	Open
van Kammen et al,[74] 1989	32/M	34.2±7.61†	11.2 (SD, 6.6)	NS	*DSM-III*	DB
Jolley et al,[44] 1990	E: 27 (10/M, 17/F) C: 27 (13/M, 14/F)	E: 41 C: 42	E: 12 C: 13	NS	*DSM-III*	DB with control group
Glazer et al,[22] 1990	49 (15/M, 34/F) (10 with SZ)	54±13†	32	0.5	RDC	Open
Green et al,[75] 1990	22/M	(22-66)	(4-25)	NS	RDC	Open
Khan et al,[76] 1990	32/M	39.1±11.4	22.8±4.7	NS	*DSM-III*	Open
Singh et al,[77] 1990	10	40.5	(11-32)	NS	*DSM-III-R* and SSP	DB
Carpenter et al,[29] 1990	E: 57 (34/M, 23/F) C: 59 (37/M, 22/F)	E: 28.4 C: 27.8	5.5 4.6	NS	RDC	SB with control group
Davidson et al,[78] 1991	23	38.5±11.2†	16.4±10.5	8.0±6.4	RDC and *DSM-III-R*	Open
Harvey et al,[79] 1991	24/M	36±10†	(22-23)	(3-10)	*DSM-III* and RDC	SB
Ruskin and Nyman,[31] 1991	E: 10 C: 8	60.1	NS	NS	*DSM-III*	DB with control group
Wolf et al,[80] 1991	20	(33-37)	NS	7	*DSM-III*	Open
Herz et al,[45] 1991	E: 50 (28/M, 22/F) C: 51 (26/M, 25/F)	E: 34.6±10.8† C: 37.4±11.7†	NS	NS	RDC	DB with control group
Glovinsky et al,[81] 1992	45 (28/M, 17/F)	29.5 (18-45)	9.5	NS	*DSM-III* and *DSM-III-R*	DB
Neylan et al,[82] 1992	18/M	35±6† (26-45)	10.7±6.7	NS	*DSM-III-R*	DB

Neuroleptic Type/Mean (Range) Dosage, mg/d	Mean (Range) Length of Taper, d	Mean (Range) Length of Follow-up, mo	Definition of Relapse	Relapse Rate, %	Predictors of Relapse
Haloperidol/(5-40), thioridazine, molindone	2	0.5	NS	NS	NS
Mostly haloperidol, CPZE/1736	1 (Acute)	1.5	Increase of 36% in BPRS score	NS	Increase in pMHPG level, increase in pHVA level
Mostly haloperidol/(10-30)	1 (Acute)	1	NS	NS	NS
Phenothiazines or haloperidol, CPZE/(1.4-285.4)	NS	2	NS	NS	NS
CPZE/326	(7-10)	0.5	Required return to medications (behavioral changes, psychosis)	26	Increase in pHVA level after withdrawal, lower baseline pHVA level, higher prior medication dose, higher BPRS score during withdrawal, longer neuroleptic exposure
Mostly haloperidol/(5-40)	1 (Acute)	0.5	NS	NS	NS
Haloperidol/12.8±9.5	7	1.5	Increase of 10 points on BPRS psychosis subscale and 3 points on Bunney-Hamburg psychosis item	43.8	Increase in CSF NE level
	NS	24	Reemergence of severe psychiatric symptoms	E: 50 C: 12	NS
CPZE/255	30	12	NS	NS	NS
CPZE/(50-1350)	21	10	Developed symptoms requiring return to neuroleptic medication	NS	Low prolactin level during neuroleptic treatment
NS	1 (Acute)	1.5	NS	NS	NS
CPZE/(413-930)	1 (Acute)	0.5	Any increase from baseline BPRS score	None	NS
NS	1 (Acute)	24	Hospitalization	E: 53 C: 36	NS
NS	1 (Acute)	1.5	Increase of ≥2 points on BPRS psychosis items for 2 wk	39.1	pHVA level was higher in decompensated group
CPZE/500	1 (Acute)	1.5	NS	50 (nonkraepelinian)	NS
Haloperidol, CPZE/324.7	14	6	Significant clinical decline per research psychiatrist (new psychotic symptoms, increase in old psychotic symptoms, or prodromal symptoms with anxiety/insomnia)	E: 50 C: 12.5	Younger age, higher prior medication dose, higher baseline BPRS score, recent psychiatric hospitalization
CPZE/(2000-2600)	42	1.5	NS	NS	NS
E: CPZE/322.8±270.0 C: CPZE/259.0±150.1	42	24	Increase in certain psychotic symptoms	E: 30 C: 16	NS
NS	NS	2	Symptom worsening, return to medications	NS	NS
Haloperidol	1 (Acute)	1.5	Mean increase ≥3 points on global psychosis item of Bunney-Hamburg Scale	50	None found

(continued)

Table 1. Literature Review on Neuroleptic Withdrawal* (cont)

Source, y	No./Sex	Mean (Range) Age, y	Mean (Range) Duration of Illness, y	Mean (Range) Length of Hospitalization, y	Diagnostic Criteria	Study Design
Kirkpatrick et al,[83] 1992	18/M	30 (18-39)	9.5	NS	RDC	Open
Jeste et al,[84] 1993	20/M	48.4 (33-68)	21.3 (1-37)	4.6 (0-20)	*DSM-III-R*	SB
Arndt et al,[85] 1993	43 (30/M, 13/F)	32.7±9.7† (22-56)	NS	NS	*DSM-III-R*	Open

**NS indicates not specified; DB, double blind; CPZ, chlorpromazine; SB, single blind; E, experimental; C, control; SZ, schizophrenia; IMPS, Inpatient Multidimensional Psychiatric Scale; CPZE, chlorpromazine equivalent; RDC, Research Diagnostic Criteria; GAS, Global Assessment Scale; BPRS, Brief Psychiatric Rating Scale;* ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-9, International Statistical Classification of Diseases, Injuries, and Causes of Death, Based on the Recommendations of the Ninth Revision Conference; *pHVA, plasma homovanillic acid; TD, tardive dyskinesia; pMHPG, plasma methoxyhydroxyphenylglycol; SADS, Schedule for Affective Disorders and Schizophrenia; CSF, cerebrospinal fluid; NE, norepinephrine; SSP, supersensitivity psychosis; and CGI, Clinical Global Impression.*

†Value is mean± SD.

‡Meaning of plus-or-minus value not specified.

§Value is mean± SEM.

remaining 33 studies defined *relapse* as either emergence of "behavioral worsening" (with agitation, aggression, insomnia, anxiety, hallucinations, delusions, or assaultive or suicidal behavior) or a specified change seen on clinical rating scales, such as the Brief Psychiatric Rating Scale (BPRS).[88]

RATE OF RELAPSE

Relationship of Relapse Rate to Neuroleptic Withdrawal

The rate of relapse in the 66 studies of neuroleptic withdrawal groups ranged from 0% to 100%. We found a significant difference (t=10.64, df=28, P<.0001) in the mean rate of relapse for the matched withdrawal groups (53.2%) vs matched maintenance groups (15.6%) in the 29 studies that included control groups. The mean rate of relapse in the neuroleptic withdrawal groups from all the 66 studies was 46.6%. There was an outlier study[38] with a relapse rate of 100% in the neuroleptic withdrawal patients and 0% in the neuroleptic maintenance patients (n=13 each) at 2.5 months of follow-up. This difference in the percentage relapse rate was more than 3 SDs from the mean difference for all 29 studies. With this group excluded, the mean relapse rates for the withdrawal and maintenance groups were 51.5% and 16.2%, respectively (paired t=12.48, df=27, P=.0001).

Relationship of Relapse Rate to Length of Follow-up

With the outlier study[38] removed and with percentage relapse expressed as a natural logarithm (odds) and follow-up time expressed as logarithmic follow-up, there was a significant association between relapse and follow-up for all the withdrawal groups (r=.500, df=45, P=.001), for the unmatched withdrawal groups (r=.493, df=17, P=.032), and for the matched maintenance groups (r=.503, df=26, P<.006). The matched withdrawal groups exhibited a nonsignificant positive association (r=.231, df=26, P=.237). The two regression lines for the matched withdrawal and matched maintenance groups were, however, converging with significantly different slopes, as indicated by the significant regression of the natural logarithm (odds ratio) on logarithmic follow-up (r=−.383, df=26, P=.044): ln (odds ratio) = ln (odds for withdrawal groups) − ln (odds for maintenance groups), where ln indicates natural logarithm. The negative correlation indicated that the differences in ln (odds) were diminishing over follow-up time (**Figure**).

Other Predictors of Relapse

Even without Bonferroni corrections, other study characteristics (eg, average duration of illness, use of specific diagnostic criteria for schizophrenia) made no significant contributions to the prediction of the logit transform of the relapse rate beyond that of the logarithm of the length of follow-up. Individual studies, however, reported that certain individual characteristics were predictors of relapse after neuroleptic therapy was stopped. These included younger current age,[19,31,39,50,60,62] earlier age of onset of illness,[19,64] higher baseline neuroleptic dose,[26,31,49,50,60,64,72] nonparanoid subtype of schizophrenia,[19] recent psychiatric hospitalization,[31,64] poor social adjustment,[23] male gender,[39] and nonpiperazine type of phenothiazine medication.[37]

Response to Reinstitution of Neuroleptics

Patients who experienced relapse after neuroleptic withdrawal were usually found to have a rapid return to baseline when neuroleptic therapy was reinstituted.[31,53,55,81] Recompensation was observed within 3 days to 3 weeks after neuroleptic treatment was restarted.

Neuroleptic Type/Mean (Range) Dosage, mg/d	Mean (Range) Length of Taper, d	Mean (Range) Length of Follow-up, mo	Definition of Relapse	Relapse Rate, %	Predictors of Relapse
Fluphenazine, haloperidol, trifluoperazine	NS	1	Increase in or reappearance of psychotic symptoms	NS	No relationship between prolactin concentration and time to subsequent relapse
Variable, CPZE/(379±533)	7	0.5	Increase ≥2 points on BPRS or CGI Scale, or dangerousness to self or others	0	Not applicable
Variable	3.2 (2-4)	1	NS	NS	NS

OTHER CLINICAL EFFECTS OF NEUROLEPTIC WITHDRAWAL

Cholinergic Rebound

In the first 2 weeks after neuroleptic therapy was stopped, patients were reported to experience a variety of symptoms consistent with cholinergic rebound, including nausea, malaise, diaphoresis, vomiting, and insomnia.[54,61,89,90] These effects were generally mild and transient and did not require treatment.

Withdrawal-Emergent Dyskinesia

Dufresne and Wagner[69] reported the occurrence of withdrawal-emergent dyskinesia 2 weeks after neuroleptic therapy was stopped. Maintaining patients with withdrawal-emergent dyskinesia or TD off neuroleptic drugs for long periods tended to improve the dyskinesia,[20] especially in younger patients.[72]

Other Adverse Effects

There have been anecdotal case reports of neuroleptic malignant syndrome,[13] tardive akathisia,[69] progressive parkinsonism,[14] and even hematemesis[20] following neuroleptic withdrawal. Such untoward reactions must be very rare, however.

Neuropsychological Effects

Orzak et al[91] and Spohn et al[92] compared patients with schizophrenia maintained on neuroleptic therapy with those withdrawn from neuroleptic therapy and found improved performance on tests of attention and information processing in the neuroleptic maintenance group. Simon,[93] however, found no significant difference between the neuroleptic maintenance and withdrawal groups on the Trail Making Test, while Depue et al[94] observed no change in Wechsler Adult Intelligence Scale (WAIS) IQ score after neuroleptic withdrawal.

Changes in Sleep Architecture

Thaker et al[73] reported decreased total sleep time, decreased rapid eye movement sleep, and decreased rapid eye movement latency after neuroleptic withdrawal. Neylan et al[82] found similar changes but also noted that relapsers had greater decreases than nonrelapsers in total sleep time, in non–rapid eye movement sleep, and in stage 2 sleep.

Neurochemical Effects

The following neurochemical changes were reported after neuroleptic withdrawal, although not all studies yielded consistent results: increased concentrations of plasma homovanillic acid, a metabolite of dopamine[20,67,72,76]; increased concentrations of plasma 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of norepinephrine[70]; initial decrease followed by an increase in plasma prolactin concentrations[73,75,95]; decreased plasma prolactin concentrations during neuroleptic treatment associated with earlier relapse[75]; lower baseline plasma prolactin concentrations associated with earlier relapse[63]; decreased plasma norepinephrine concentrations[62,66]; and increased cerebrospinal fluid norepinephrine concentrations in relapsers.[74] Finally, some investigators reported increased plasma cortisol concentrations,[66] increased plasma β-endorphin concentrations,[66] and increased density of striatal dopamine D_2 receptors on positron emission tomography scan after neuroleptic withdrawal.[21]

COMMENT

The limitations of this report stem in part from methodologic aspects of the studies reviewed, such as differences in methods and materials, variable and sometimes small sample sizes, a lack of specific diagnostic cri-

Table 2. Summary Characteristics

Variable	Unweighted Mean (SD) [Sample Size*] All Neuroleptic Withdrawal Groups (N=66)	Unmatched Neuroleptic Withdrawal Groups (N=37)	Matched Neuroleptic Withdrawal Groups (N=29)	Matched Neuroleptic Maintenance Groups (N=29)
Sample size, No. of subjects†	47.6 (70.6) [N=66]	48.5 (87.4) [N=37]	46.4 (41.8) [N=29]	42.2 (51.5) [N=29]
Male, %	69.1 (29.7) [n=43]	69.7 (31.0) [n=25]	68.2 (28.6) [n=18]	69.8 (27.0) [n=18]
Average‡ age, y	40.0 (9.0) [n=62]	39.5 (8.2) [n=35]	40.4 (10.4) [n=25]	40.8 (10.4) [n=25]
Average‡ duration of illness, y	14.9 (7.5) [n=25]	16.0 (7.6) [n=19]	11.4 (7.1) [n=6]	10.0 (5.3) [n=6]
Average‡ length of hospitalization, y	8.7 (5.9) [n=31]	8.1 (5.2) [n=18]	9.5 (6.9) [n=13]	9.7 (7.4) [n=13]
% Specifying diagnostic criteria§	34 (52) [n=65]	25 (68) [N=37]	9 (35) [n=26]	9 (35) [n=26]
Study design, No. (%)§				
Open	18 (28) [n=65]	14 (39) [n=36]	4 (14) [N=29]	4 (14) [N=29]
Single blind	9 (14) [n=65]	8 (22) [n=36]	1 (3) [N=29]	1 (3) [N=29]
Double blind	38 (58) [n=65]	14 (39) [n=36]	24 (83) [N=29]	24 (83) [N=29]
Average‡ baseline neuroleptic dose, mg/d (chlorpromazine equivalent)	630.0 (453.7) [n=32]	713.7 (506.4) [n=22]	445.8 (236.4) [n=10]	439.2 (234.7) [n=10]
Average‡ length of taper, d	7.5 (14.0) [n=60]	7.2 (13.3) [n=34]	7.9 (15.1) [n=26]	NA‖
Patients receiving anticholinergic therapy, %	75.0 [n=20]	75.0 [n=16]	75.0 [n=4]	75.0 [n=4]
Average‡ length of follow-up, mo	6.3 (6.3) [N=66]	3.7 (4.2) [N=37]	9.7 (6.9) [N=29]	9.7 (6.9) [N=29]
Definition of relapse, No. (%)§				
No definition	22 (3.3)	15 (41)	5 (17)	5 (17)
Returned to neuroleptic medication	11 (17)	4 (11)	4 (14)	4 (14)
Other definition	33 (50) [N=66]	18 (49) [N=37]	20 (69) [N=29]	20 (69) [N=29]
Relapse rate, ¶	46.6 (23.5) [n=48]	36.7 (25.9) [n=19]	53.2 (19.6) [N=29]	15.6 (12.4) [N=29]

**In each cell, the sample size is the number of studies that provided the specific information. For the two matched groups, both groups needed to have the data for the variable to be included in the summary statistic for that variable.*

†The matched neuroleptic withdrawal groups had a significantly larger log-transformed sample size than the matched neuroleptic maintenance groups ($t=2.95$, $df=28$, $P<.01$), but the difference was not significant after the Bonferroni correction.

§These values are numbers and percentages of studies rather than unweighted means and SDs.

‡Average indicates study mean or midpoint of range.

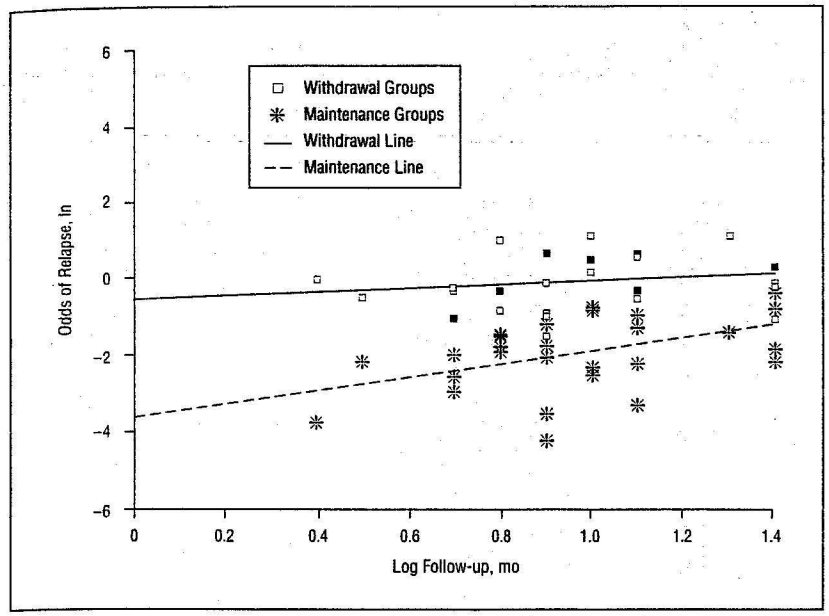
‖NA indicates not applicable.

¶The matched neuroleptic withdrawal groups had a significantly larger relapse rate ($t=10.64$, $df=28$, $P<.0001$) that was still significant after the Bonferroni correction.

teria for schizophrenia in earlier studies, and incomplete presentation of information. One particularly vexing problem relates to the variable definitions of *relapse;* better terms might be *symptom recurrence* or *exacerbation.* Moreover, not all the work undertaken has been published. Thus, there may be a bias; studies with negative results may not see print. Furthermore, in spite of our best efforts, we may not have accessed every available article on the subject of neuroleptic withdrawal. Another limitation is inherent in our attempt to infer relationships in individuals from the aggregate data provided by a literature review. Finally, it is conceivable that relapse rates in research settings may differ from those in "the real world" because of patient-related as well as methodological biases.

Nevertheless, we attempted to perform and present a search of the literature on neuroleptic withdrawal that was as extensive and complete as possible. Next, in an attempt to overcome the difficulties noted in some of the studies, we reanalyzed the data in different ways. Although only 29 of the 66 studies reviewed used neuroleptic maintenance (control) groups, the overall results of neuroleptic withdrawal in these 29 studies were generally similar to those in the total group of 66 studies, indicating generalizability of their findings.

Of all the variables examined, only the mean relapse rate was significantly different between the groups of patients withdrawn from neuroleptic therapy and those maintained on neuroleptic therapy. Groups of patients with schizophrenia withdrawn from neuroleptic therapy had a relapse rate more than three times higher than the rate of those maintained on neuroleptic therapy. On the other hand, approximately half of all the patients withdrawn from neuroleptic therapy remained stable without relapse over



The natural logarithm of the relapse rate vs the logarithmic average length of follow-up in the matched withdrawal and maintenance groups (N=28).[38] A study of an outlier pair of matched withdrawal and maintenance groups was omitted. (See the text for details.)

average follow-up periods of 6.3 to 9.7 months, while, despite neuroleptic maintenance, 15.6% patients relapsed over an average follow-up period of 7.9 months. The rate of relapse was associated positively with the length of follow-up.

Individual studies have reported predictors of relapse such as younger age, earlier age of onset of illness, higher neuroleptic dose at baseline, and recent psychiatric hospitalization. In our aggregate data analysis, however, we did not find any specific predictors of relapse except for average length of follow-up. This may be caused in part by reduced sample sizes because of missing data as well as by the expected insensitivity resulting from the use of aggregate data; our analysis used summary measures from each study in lieu of the ranges of values within individual studies. Perhaps, however, there are few across-the-board predictors of schizophrenic relapse just as there are few consistent predictors of long-term prognosis of schizophrenia (except for chronicity).[96,97]

Patients who underwent decompensation after neuroleptic therapy was stopped were seen to recompensate quickly when treatment was restarted.[31,53,55,81] This suggests that even when patients experience psychotic symptoms after neuroleptic withdrawal, they are generally not subjected to any prolonged exacerbation if neuroleptic therapy is restarted soon.

Finally, concerning other adverse effects of neuroleptic withdrawal, some of the serious symptoms described in the case reports, such as hematemesis or neuroleptic malignant syndrome, were not common and might be associated only with abrupt neuroleptic withdrawal. Other side effects (eg, insomnia, vomiting) were usually mild and transient.

RESEARCH RECOMMENDATIONS

A proposed study of neuroleptic withdrawal should have clinically justifiable criteria for selection of patients; a proper consenting procedure; an adequate sample size based on power analysis; specific diagnostic criteria for schizophrenia, such as *DSM-IV*[98]; an appropriate comparison group maintained on neuroleptic therapy; quantitative double-blind assessments using standardized rating scales that have significant and high interrater reliability; neurochemical determinations of possible antecedents of relapse, such as changes in plasma homovanillic acid concentrations[72]; and suitable statistical analyses, such as survival analysis with covariates. A comprehensive baseline evaluation of patients is necessary for a better delineation of patients who can tolerate maintenance off neuroleptic therapy without relapsing. Certain measures should perhaps be assessed at regular intervals after baseline, eg, indicators of movement disorder. Neurological, neuropsychological, and brain imaging assessments have rarely been done in such studies and may be useful. For example, it is not known whether patients with neurological "soft" signs, cognitive impairment, and structural brain abnormalities on magnetic resonance imaging are more or less likely to relapse after neuroleptic withdrawal, although such patients are known to be less responsive to neuroleptic therapy.[99] Close monitoring of the patients is necessary throughout the study period to detect and treat any early unacceptable exacerbation or recurrence of psychotic symptoms to avoid a full-blown relapse. Different taper schedules (eg, acute vs gradual withdrawal of neuroleptic therapy) have not been systematically compared, except in isolated instances,[100] and this should be done. Special populations, such as first-break patients or the elderly, need to be studied from the viewpoint of the relative risks and benefits of neuroleptic withdrawal. Given that the risk of relapse is lower in the first few days or weeks after neuroleptic therapy is stopped, short-term withdrawal, such as that entailed in placebo-controlled studies of the acute efficacy of new antipsychotic drugs, would appear to be less hazardous. Whether still-persisting small amounts of neuroleptic agents from previous therapy delay relapse in early stages should also be tested.

CLINICAL RECOMMENDATIONS

It is possible to make divergent clinical recommendations based on our findings. On the one hand, it could be argued that neuroleptic withdrawal is extremely risky, with the chances of relapse more than three times greater than with neuroleptic maintenance. Psychotic relapse is associated with a possibility of pa-