ORIGINAL ARTICLE

Clinical Risk Following Abrupt and Gradual Withdrawal of Maintenance Neuroleptic Treatment

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Background: Abrupt discontinuation of long-term psychotropic medication can be followed by a high risk of early relapse. This study aimed to quantify the relapse risk over time in patients with schizophrenia following discontinuation of maintenance neuroleptic treatment.

Methods: Data on the timing of relapses in patients with schizophrenia after withdrawal from neuroleptic therapy were located by a computerized literature search, combined with new data, and evaluated by survival analysis.

Results: Data were found for 1210 schizophrenic subjects: 1006 (795 inpatients and 211 outpatients) were withdrawn abruptly from oral neuroleptic therapy, and 204 discontinued treatment gradually (≥3 weeks) or stopped treatment with depot neuroleptic drugs. After abrupt discontinuation of oral medication, the risk of relapse reached 50% within 30 weeks, with remarkably little additional risk thereafter to 3.7 years; inpatients relapsed more rapidly than did outpatients (10 vs 18 weeks to a 25% relapse risk). In studies including subjects whose drug therapy was withdrawn abruptly (n=49) vs gradually (n=58), relapse was earlier after abrupt discontinuation (25% risk in 6 vs 10 weeks), with a persistent difference for at least 6 months.

Conclusions: The relapse risk was high within 6 months of discontinuing oral neuroleptic therapy, particularly in hospitalized patients. Most patients who remained stable for 6 months continued to do so for long periods without medication, indicating clinical heterogeneity. Drug-withdrawal stressors, related to long-term pharmacodynamic adaptations, are implicated. Since the risk was lower after gradually discontinuing oral neuroleptic therapy or stopping depot injections, early relapse may be spared by a slow removal of drugs.

Arch Gen Psychiatry. 1997;54:49-55

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FOLLOWING THEIR introduction in the 1950s, neuroleptic drugs became the cornerstone of pharmacological treatment of psychotic disorders. The findings from many studies support their short-term efficacy and long-term benefits.[1-3] Most studies of neuroleptic maintenance have involved the interruption of treatment to compare a placebo with continued medication. Meta-analyses of such studies have found high rates of relapse in the weeks after the interruption of active treatment.[1,3] Gilbert and colleagues[3] recently concluded that the risk of psychotic relapse within 10 months was only 16% if antipsychotic medication was continued, and 53% after discontinuation.

Late adverse effects (particularly tardive dyskinesia) encourage attempts to minimize the risks without a loss of the benefits of maintenance neuroleptic therapy. Options include individual adjustment to a minimum effective dose,[4-7] as well as the use of very low or intermittent dosing,[8-10] as the search for safer and more effective antipsychotic agents continues.[11,12] Low or intermittent dosing involves the removal of neuroleptic drugs. Such procedures and, indeed, the research that supports long-term neuroleptic treatment, evidently assume that the removal of a drug does not increase the clinical risk above that associated with the natural history of untreated illness. Critical reevaluation of this assumption is encouraged by a recent

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MATERIALS AND METHODS

We searched for studies that involved the abrupt or gradual discontinuation of maintenance treatment with oral antipsychotic agents or stopping injections of long-acting preparations in patients who were diagnosed as having schizophrenia. MEDLINE-computerized searching and references obtained from the resulting reports yielded 11 studies with data on the time to relapse for individuals, or survival analyses of groups, and provided 1006 subjects (795 inpatients and 211 outpatients) who were abruptly withdrawn from oral neuroleptic maintenance.[25-35] Similar new data involved 94 subjects with schizophrenia according to *DSM-III-R* criteria who were rapidly discontinued from oral haloperidol therapy at the Highland Drive Veterans Affairs Medical Center, Pittsburgh, Pa (methodological details have been reported elsewhere[36,37]) and 6 similar subjects from a study at the Massachusetts Mental Health Center, Boston, on removing an average of 85% of the initial medication (A. I. Green, MD, S. V. Faraone, PhD, W. A. Brown, MD, J. Guttierez, MD, and M. T. Tsuang, MD, DSc, PhD, oral and written communications [generously provided by Dr Green to R.J.B.], June 1995). Four studies (n=107 subjects, including 7 from Dr Green) provided additional data on gradual (>3 weeks) withdrawal of oral medication.[28,38,39] Five studies (n=83 cases, including 8 from Dr Green) involved stopping injections of a long-acting neuroleptic drug.[34,40-42] We excluded several studies that involved simultaneous or undefined mixtures of oral and depot neuroleptic medications, intermittent neuroleptic therapy, or imprecisely defined timing of drug discontinuation. Analyses are based on findings from 16 reports plus 2 unpublished data sets, yielding 1210 patients who were diagnosed as having schizophrenia and followed up after discontinuation of maintenance neuroleptic treatment.

Characteristics of the 22 cohorts that were studied[25-42] are summarized (**Table 1**); some studies failed to specify drugs and doses but did indicate when only oral or depot medication was involved. Definitions of relapse or exacerbation of illness varied but usually involved clinical assessment or the use of rating scale scores to indicate the worsening of psychotic symptoms severe enough to warrant hospitalization or reinstitution of antipsychotic treatment. Discontinuation and follow-up assessments were double-blind in 20 of the 22 cohorts (only 2 studies were open). "Abrupt" discontinuation usually involved stopping neuroleptic treatment within 1 day; "gradual" discontinuation included the tapering of oral doses over at least 3 weeks (mean±SD, 3.39±6.00 months), or no further depot neuroleptic therapy after a final injection. Treatment averaged 7.75±6.07 months and postwithdrawal follow-up after the last dose averaged 54±46 weeks (range, 10 weeks to 4 years), or 16, 20, and 17 months after discontinuing oral medication treatment abruptly or gradually, or stopping depot injections, respectively (Table 1).

The relapse risk over time after the discontinuation of neuroleptic therapy was analyzed by Kaplan-Meier and actuarial survival analysis, with variances, and compared statistically by Mantel-Cox nonparametric log rank techniques to provide a χ^2.[20,21,43,44] These values, as well as the time to a defined percent relapse±SE, were calculated with commercially available microcomputer programs (Statview/Survival Tools, Abacus Concepts, Inc, Berkeley, Calif). Unless otherwise stated, data are presented as the means±SD or rates±SE; 2-tailed statistical significance required $P<.05$ (nonsignificance, $P\geq.10$).

reconsideration of the risks involved in experimental protocols that require interruption of maintenance treatments.[13-17]

High early morbid risk follows abrupt interruption of maintenance treatments in several psychiatric disorders. In addition to early withdrawal reactions to the abrupt removal of benzodiazepines in patients with anxiety disorders,[18] and physiological symptoms associated with the removal of some antipsychotic and antidepressant agents,[19] worsening of primary disorders often follows the rapid removal of long-term psychotropic treatments. This response includes recurrence of affective episodes in a majority of patients with bipolar I or II disorders within several months of stopping successful lithium carbonate monotherapy after several years,[20-22] as well as in patients with major depression after interrupting similarly prolonged imipramine hydrochloride maintenance.[23] Moreover, after stopping lithium therapy abruptly in patients with bipolar disorders, the time to a first recurrence was much briefer than the shortest intervals between spontaneous recurrences before starting maintenance treatment.[20] The risk of recurrence of mania or depression in patients with bipolar disorders was reduced markedly by gradual discontinuation of lithium therapy, even during several weeks.[21,22] These[17,21,22] and congruent new findings[24] suggest a period of unusually high relapse risk after the removal of maintenance treatments that can be reduced, and not merely delayed, by gradual removal of medication.

Discontinuing oral neuroleptic medication, particularly abruptly, also carries a high risk of psychotic morbidity.[3,15] The hypothesis that this risk is very high within the first several months after discontinuation and less thereafter is supported by results of a preliminary analysis that indicated a 13-fold increase in relapse within 3 months of discontinuing neuroleptic treatment; this risk fell below 2-fold in the second year.[15] We predicted that slow discontinuation of orally administered neuroleptic drugs or stopping injections of long-acting agents would delay and perhaps even reduce this risk.[15] Survival analysis was used to quantify the risk over time after the interruption of neuroleptic treatment in patients with schizophrenia, based on data from previous reports as well as from studies of new subjects.

RESULTS

The survival function after abrupt discontinuation of oral neuroleptic treatment in 1006 schizophrenic patients (**Figure 1**) indicated a rapid failure of clinical stability within 3 to 6 months, reaching a relapse risk of 25% within

Table 1. Analysis of Schizophrenia Studies*

Source, y	No. of Patients	% Men†	Site‡	Diagnosis	Treated, mo§	Agents Stopped‖	Last Dose, mg/d¶	Study Design	Relapse Criteria#	Follow-up, Wk**
Abruptly Discontinued From Therapy With Oral Medication (n=1006)										
Olson and Peterson,[25] 1960	117		I	Clinical		Various		Open	A	24
Whittaker and Hoy,[26] 1963	19	100	I	Clinical	16	Perphenazine	260	Blind, placebo	B	10
Caffey et al,[27] 1964	171	100	I	Clinical	>12	Chlorpromazine, thioridazine	375	Blind, placebo	A, B	16
Greenberg and Roth,[28] 1966	16	100	I	Clinical	>8	Chlorpromazine	500	Blind, placebo	A	24
Engelhardt et al,[29] 1967	142		O	Clinical		Various		Blind, placebo	C	192
Prien et al,[30] 1969	196	50	I	Clinical	>2	Chlorpromazine	1150	Blind, placebo	A	24
Leff and Wing,[31] 1971	14	(50)	O	Clinical	>1	Various	200	Blind, placebo	A	16
Hogarty et al,[32] 1974	182	(50)	I	Clinical	>2	Chlorpromazine	265	Blind, placebo	C	92
Clark et al,[33] 1975	9	0	O	RDC	>3	Clmozide, thioridazine	225	Blind, placebo	A	24
Levine et al,[34] 1980	27	(50)	O	Clinical	>12	Fluphenazine	1100	Blind, placebo	A, C	15
Cheung,[35] 1981	13	(50)	O	Clinical	>3	Various	185	Blind, placebo	B, C	72
van Kammen et al,[36,37] 1994, 1997††	94	100	I	*DSM-III-R*	>6	Haloperidol	400	Blind, placebo	A	52
Green et al, 1995‡‡	6		O	*DSM-III*	>12	Various		Blind	A	24
Gradually Discontinued From Therapy With Oral Medication (n=113)										
Greenberg and Roth,[28] 1966§§	20	100	I	Clinical	>8	Chlorpromazine	500	Blind, placebo	A	46
Branchey et al,[38] 1981‖‖	20	(50)	I	RDC	>3	Loxapine	890	Blind, placebo	A	247
Crow et al,[39] 1986¶¶	66		O	RDC	>1	Various	175	Blind, placebo	B, C	104
Green et al, 1995‡‡##	7		O	*DSM-III*	>2	Various		Blind	A	24
Discontinued From Therapy With Depot Medication (n=91)										
Denicker et al,[40] 1980	32	75	O	Clinical	>5	Clopenthixol decanoate, clopenthixol palmitate	145, 44.4	Open	A	104
Levine et al,[34] 1980	23	(50)	O	Clinical	>1	Fluphenazine decanoate	30.9	Blind, placebo	A, C	15
Wistedt,[41] 1981	16	(50)	O	Clinical	>12	Fluphenazine decanoate, flupentixol decanoate	24.5, 20.0	Blind, placebo	A, C	24
Sampath et al,[42] 1992	12		O	RDC	>2	Fluphenazine decanoate	33.3	Blind, placebo	A	48
Green et al, 1995‡‡	8		O	*DSM-III*	>2	Fluphenazine or haloperidol decanoate		Blind	A	24

*These studies of cohorts for which neuroleptic maintenance treatment was discontinued involved 1210 psychotic inpatients or outpatients who were receiving long-term maintenance neuroleptic treatment in clinically stable status prior to discontinuation; diagnoses were based on unspecified clinical criteria, Research Diagnostic Criteria (RDC), or the American Psychiatric Association DSM-III or DSM-III-R.

†Gender was defined as the percentage of men; (50%) indicates approximately equal numbers of men and women subjects; approximately 69% were men.

‡Settings of studies were inpatient (I) units (47%) or outpatient (O) clinics (53%).

§Mean duration of treatment prior to discontinuation was 7.75±6.07 months or more.

‖Depot esters (decanoate and palmitate) were injected intramuscularly.

¶Doses are average chlorpromazine-equivalent milligrams per day (oral) or actual milligrams per 3 weeks (depot).

#Relapse criteria: A, clearly worse clinically or by ratings; B, antipsychotic re-treatment required; and C, hospitalization required.

**Weighted (by n) mean follow-up time (months) was 15.6±16.1 (abrupt, oral), 19.5±13.9 (gradual, oral), and 17.4±11.1 (abrupt, depot).

††Data from van Kammen and colleagues were previously unpublished, but their methods were presented elsewhere.[36,37]

‡‡A. I. Green, MD, S. V. Faraone, PhD, W. A. Brown, MD, J. Guttierez, MD, and M. T. Tsuang, MD, DSc, PhD, oral and written communications from Dr Green to R. J. B., June 1995.

§§Gradual discontinuation time was 420 days (weighted average, 3.39±6.39 months).

‖‖Gradual discontinuation time was 23 days (weighted average, 3.39±6.39 months).

¶¶Gradual discontinuation time was 30 days (weighted average, 3.39±6.39 months).

##Gradual discontinuation time was 60 days (weighted average, 3.39±6.39 months).

10.2±0.6 (±SE) weeks and 50% within 30.3±15.4 weeks. There were remarkably few additional relapses after the first 6 months without medication: the computed failure rate reached 46.0% by 6 months, and it increased only another 10.2% in the period from 6 to 24 months (**Table 2**).

Oral neuroleptic drugs were removed rapidly in 795 inpatients and 211 outpatients. Their stability after drug removal differed markedly (Mantel-Cox χ^2=28.4, P<.001 [**Figure 2**]): 25% of inpatients vs outpatients relapsed within 10.0±0.62 vs 18.0±1.65 weeks, and 50% of inpatients relapsed within 18.0±1.65 weeks, while only 40.8% of outpatients relapsed within a maximum of 3.69 years of follow-up (Figure 2). Within 6 months without medication, the relapse risk (±SE) was 49.6%±1.8% for inpatients vs 31.4%±3.2% for outpatients. Differences between hospitalized and ambulatory patients were similar when those who were undergoing gradual removal of neuroleptic drugs were included (data not shown).

The survival over time was very similar after the gradual discontinuation of oral medication over an average of 3.39±6.39 months and stopping depot injections (n=113 and n=91, respectively; χ^2=0.12; P>.10); thus, the data were pooled to provide a group of patients with gradual discontinuation of treatment. There was no significant overall difference in the resulting survival functions for those who discontinued treatment abruptly vs gradually (n=1006 and n=204, respectively; χ^2=1.70; P>.10), although the time to a 25% relapse risk tended to be shorter after abrupt discontinuation (11.0±0.3 vs 15.0±1.0

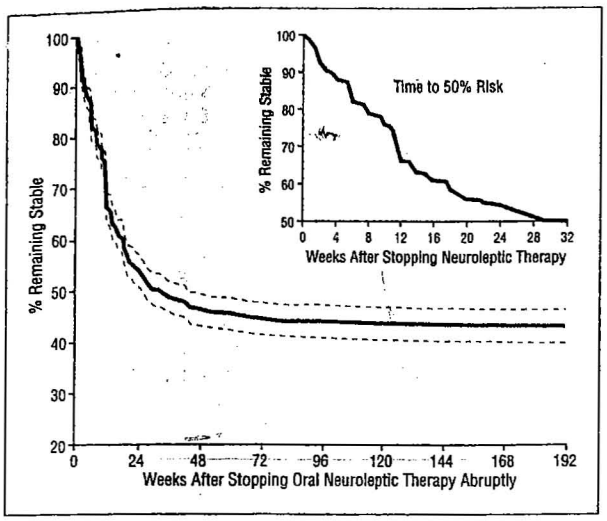

Figure 1. *Computed "survival" functions based on findings from studies that discontinued maintenance oral neuroleptic drugs in patients with schizophrenia (Table 1). Data are the percentage of patients whose conditions remained stable vs the weeks after the abrupt stoppage of treatment (n=1006). Dashed lines indicate 95% confidence intervals. Inset, The time to a 50% relapse risk (7.5 months).*

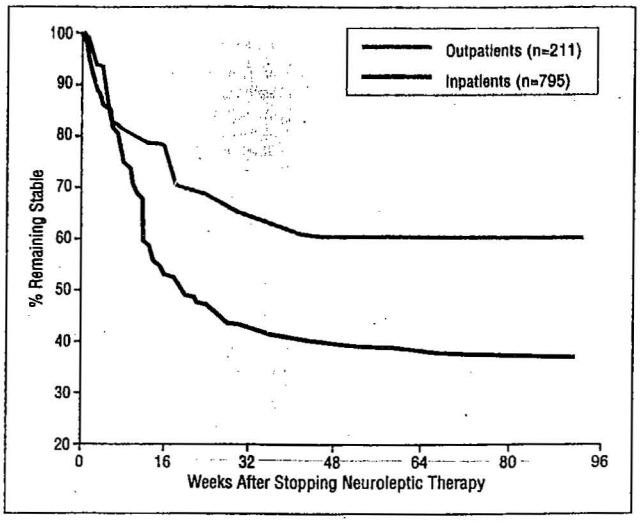

Figure 2. *Percent "survival" of schizophrenic inpatients (n=795) and outpatients (n=211) whose conditions remained stable after abrupt discontinuation of oral neuroleptic therapy. The risk was greater for inpatients (χ^2=28.4, P<.001), of whom 50% relapsed by 5 months; outpatients were followed up to 4 years without reaching a 50% relapse risk (data not shown).*

Table 2. Relapse Risk vs Time After Stopping Oral Neuroleptic Treatment Abruptly*

Follow-up, mo	Cumulative % Relapse (95% CI)
1	12.0 (10.0-14.1)
2	21.6 (19.1-24.2)
3	33.9 (30.9-36.8)
6	45.0 (42.0-49.1)
12	54.4 (51.2-57.5)
24	56.2 (53.1-59.3)

**CI indicates confidence interval. Based on Kaplan-Meier survival analysis, with 95% CIs, as shown in Figure 1.*

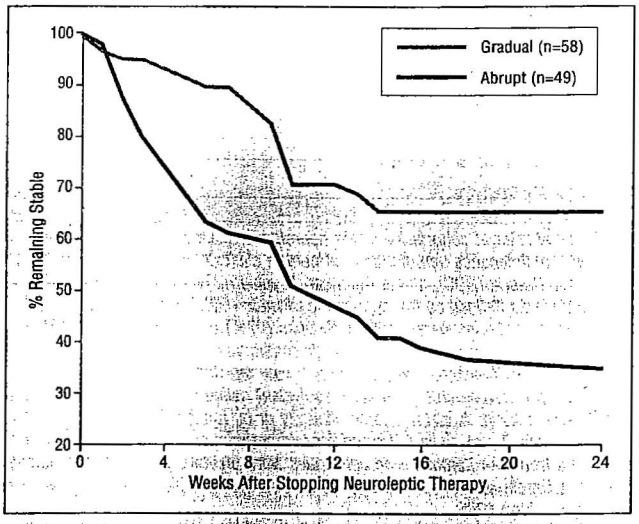

Figure 3. *Percent "survival" of schizophrenic patients whose conditions remained stable after the abrupt discontinuation of neuroleptic therapy (n=49) vs the gradual discontinuation (or stoppage of depot injections [n=58]), based on reports with data for both conditions in the same study[28,34] (A. I. Green, MD, S. V. Faraone, PhD, W. A. Brown, MD, J. Guttierez, MD, and M. T. Tsuang, MD, DSc, PhD, oral and written communications, June 1995). The risk was greater for patients who were withdrawn abruptly (χ^2=11.1, P<.001), of whom 50% relapsed within 2.5 months, while outpatients did not reach that level.*

weeks). Given this suggestive observation and the probable heterogeneity among studies, we further compared results from the 3 studies that were found with abrupt (n=49) and gradual (n=58) removal of neuroleptic agents within the same trial[28,34] (A.I. Green et al, oral and written communications, June 1995) (Table 1). With data pooled from these better-matched cohorts, there was a significant difference in survival functions (χ^2=11.1, P<.001 [**Figure 3**]). After abrupt vs gradual discontinuation, respectively, the computed time to a 25% relapse risk was 6.00±1.50 vs 10.0±1.73 weeks, and the computed probability of relapsing within 6 months was 32.5%±3.0% vs 64.9%±6.5% (a 2-fold difference).

COMMENT

The present findings from 1960 to 1995 should be interpreted cautiously owing to the variability in diagnostic criteria, lengths and methods of follow-up, and definitions of relapse, as well as the types, duration, and doses of neuroleptic drugs (Table 1). Most reports also provided little information about possibly relevant aspects of clinical history, current state, and nonpharmacological variables in aftercare. Since most data were derived from the randomized placebo cohorts of controlled trials, following substantial periods of stabilization with drug treatment, it is probable that acutely ill patients were excluded from drug withdrawal. Despite these caveats, the present analyses yield interesting information about the relapse risk over time, especially its relation to hospitalization and to the rate of drug removal.

There was a high early risk of exacerbation of psychotic symptoms soon after the abrupt interruption of ongoing oral neuroleptic maintenance. The initial re-

symptomatic differences between hospitalized and ambulatory psychotic patients.[2,45,47]

The full implications of the present findings are limited by the typically complex and irregular course of untreated schizophrenia[46,47] to be compared with the course following discontinuation of treatment. Although clinical and possible ethical considerations now severely constrain observations of untreated psychotic patients for prolonged periods,[13,14] treatment noncompliance as well as elective clinical practice often interrupt antipsychotic treatment for varying periods. In psychotic affective disorders, intermittent-interrupted exposure to neuroleptic drugs is particularly common, and its potential contribution to clinical instability is unknown.[1,2,54,55] In addition, most experimental protocols that evaluate the long-term efficacy of neuroleptic agents and many other drugs have compared continued vs withdrawn treatment.[1-3,15-17] The results of such studies that support a therapeutic effect usually have not considered contributions of drug withdrawal to observed drug-placebo contrasts. Moreover, protocols that have been designed to study patients in a presumed drug-free state often have employed a drug "washout" that was probably too short to provide a drug-free and physiologically basal state.[1,2,48]

In conclusion, rapid discontinuation of maintenance treatment with short-acting oral neuroleptic agents in schizophrenia carried a 50% risk of relapse within 30 weeks; pharmacodynamic stress factors contributing to this risk may include supersensitivity of central dopamine receptors. Further study is required to clarify whether (1) the high morbid risk following abrupt interruption of maintenance treatment exceeds that in untreated psychotic illness and (2) gradual drug removal can reduce, and not merely postpone, relapse. In general, the present findings add to growing evidence that abrupt discontinuation of maintenance treatment with psychotropic agents is followed by a high rate of early relapses in several major psychiatric disorders. This phenomenon should be considered in the design and interpretation of research protocols as well as in clinical management, and the rates reported here should help in planning research and in counseling patients. Gradual dose reduction (with close clinical follow-up) may limit relapse risk associated with interruption of maintenance treatment, and is recommended.[1]

Accepted for publication January 3, 1996.

This study was supported in part by grants MH-31154 and MH-47370 from the National Institute of Mental Health, Rockville, Md, and by awards from the Bruce J. Anderson Foundation and the Adam Corneel, Anonymous Donor, Vivian Temte, and Richard Whalin Psychiatric Research Funds, Boston, Mass.

Alan Green, MD, generously provided data from his studies. Mary Kelley, MS, Silvina Zarate, and Michelle Weiss, MS, assisted with data analyses.

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