Brief Communications

Symptoms of Neuroleptic Malignant Syndrome in 82 Consecutive Inpatients

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This study, a retrospective chart review of 82 consecutive male inpatients, assessed the spectrum and prevalence of neuroleptic malignant syndrome. The prevalence of diagnosed neuroleptic malignant syndrome (2.4%) was greater than that generally reported. Eight additional patients manifested symptoms that abated without cessation of neuroleptic treatment. This suggests that neuroleptic malignant syndrome is a spectrum disorder that has milder variants. Affective illness may be a risk factor for its development.

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N euroleptic malignant syndrome remains underdiagnosed, and the literature to date includes a series of review articles and numerous case reports that focus primarily on management and treatment. Prompted by seeing several cases of neuroleptic malignant syndrome and believing that we had aborted others through early recognition of the evolving syndrome and discontinuation of neuroleptic treatment, we undertook a retrospective chart review. Our goals for the review were to ascertain the actual prevalence of neuroleptic malignant syndrome, to determine whether a predictable prodrome exists, and to determine whether early discontinuation of the neuroleptic

could circumvent development of the full-blown syndrome.

METHOD

We examined the hospital records of 82 men between the ages of 18 and 35 who had been consecutively admitted to two acute inpatient units at New York Hospital, Westchester Division. Young men are believed to be at high risk for neuroleptic malignant syndrome (1). These subjects had *DSM-III* diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, brief reactive psychosis, and atypical psychosis. All had been treated with neuroleptic medication. Their hospital records were reviewed to collect data on 20 variables. These covered signs and symptoms of autonomic dysfunction, behavioral disturbance, extrapyramidal symptoms, concomitant medications, lithium levels, laboratory abnormalities, and treatment with ECT. Of these 20 items, 10 were signs and symptoms used to identify neuroleptic malignant syndrome, variables that we felt were central to its diagnosis: elevated temperature ($\geq$99° F) in the absence of other systemic illness, extrapyramidal symptoms (rigidity, tremor), tachycardia ($\geq$100 beats/minute), elevated blood pressure ($\geq$150/100 mm Hg), diaphoresis, incontinence, leukocytosis (>10,800 cells/mm^3), confusion, and elevated creatine phosphokinase level (>83 U/liter). The absence of elevated temperature or extrapyramidal symptoms precluded the diagnosis of neuroleptic malignant syndrome. The symptoms were then analyzed for a temporal relationship; the occurrence of five symptoms (including elevated temperature and extrapyramidal symptoms) within the same 48-hour period was used to identify an episode. The data were analyzed for possible associations between symptoms of neuroleptic malignant syndrome, affective illness, and concomitant lithium treatment.

RESULTS

Two patients (2.4%) with a previous history of neuroleptic malignant syndrome had been diagnosed as having recurrences of the syndrome, and their neuroleptic medication had been discontinued. One patient had improved immediately, and the other had continued to be symptomatic. An additional eight patients (9.8%) had had a minimum of five symptoms of neuroleptic malignant syndrome. Their symptom profiles are shown in table 1. Their symptoms had resolved without cessation of neuroleptic treatment.

Of our 82 patients, 25 (30%) had affective diagnoses (bipolar disorder or schizoaffective disorder) and 20 (24%) were receiving lithium along with a neuroleptic. Of the 10 patients with diagnosed neuroleptic malignant syndrome or mild symptoms of it, seven (70%) had an affective diagnosis ($\chi^2=5.83$, df=1, p<.03) and five (50%) were treated with lithium along with neuroleptics ($\chi^2=2.42$, df=1, n.s.). This suggests that patients with affective diagnoses may be at higher risk for the development of neuroleptic malignant syndrome or a milder form of this disorder.

DISCUSSION

This review indicates that symptoms of neuroleptic malignant syndrome, often without marked temperature elevation, can stop without cessation of neuroleptic treatment. It suggests that neuroleptic malignant syndrome is a continuous spectrum of physiologic reactions to neuroleptics that, in some patients, takes a severe, potentially lethal form. Although Caroff's often-referred-to review (1) describes neuroleptic malignant syndrome as having an abrupt, fulminant onset extending over 24–72 hours, several investigators (2–6) have described a more insidious evolution of symptoms. Dramatic cases with extreme hyperthermia have been frequently reported, but a number of patients who have temperatures of 101° F or less and other typical signs of neuroleptic malignant syndrome have also been described (7–11). Kirkpatrick and Edelsohn (12) also identified a variant of neuroleptic malignant syndrome with lower temperature in their recent review. In a similar vein, others (13, 14) proposed that catatonic reactions to neuroleptics might be the first step in a process potentially leading to neuroleptic malignant syndrome.

Because of the limitations imposed by a retrospective design and the fact that none of our patients with a milder variant of neuroleptic malignant syndrome had gone on to develop the full-blown syndrome, it is unclear which factors predispose a patient to a reaction of a given intensity or duration. We arbitrarily defined an episode as a cluster of five symptoms occurring within 48 hours; however, one patient had had an episode lasting several weeks while others had had symptoms for a number of days. The prevalence of diagnosed neuroleptic malignant syndrome in our

TABLE 1. Neuroleptic Malignant Syndrome Symptoms in Eight Patients

Patient	Diagnosis	Medication (mg/day)	Syndrome Duration (days)
1	Bipolar disorder	Haloperidol, 20; lithium, 600	23
2	Schizophrenia	Molindone, 300	2
3	Schizoaffective disorder	Thioridazine, 400; lithium, 1200	2
4	Schizophrenia	Fluphenazine hydrochloride, 15; haloperidol, 5	3
5	Bipolar disorder	Thiothixene, 55; lithium, 1800	2
6	Bipolar disorder	Chlorpromazine, 800; lithium, 1200	14
7	Schizophrenia	Thiothixene, 15	1
8	Bipolar disorder	Fluphenazine hydrochloride, 5	11

study (2.4%) is much higher than the frequently quoted 0.5%–1.0%. If we consider neuroleptic malignant syndrome as a spectrum disorder, as supported by our identification of eight patients (9.8%) with a milder variant, then the prevalence of these disorders may be higher than previously suspected. While this difference may be related to a sampling bias, it is worth noting that the generally accepted prevalence is based on only one report of five cases of neuroleptic malignant syndrome found among several hundred treated patients (15). Our results and the remarkable increase of reported cases in recent years suggest that the prevalence needs to be reevaluated.

Our data also indicate that affective illness may be a risk factor for the development of neuroleptic malignant syndrome. This finding may be related to West and Meltzer's proposal (16) that the acute manic state fosters the development of lithium neurotoxicity. Alternatively, this effect may be explained simply by the manic patient's agitation and tendency to become exhausted and dehydrated, generally accepted risk factors (1, 17).

We expected that lithium would be significantly associated with the development of neuroleptic malignant syndrome, but our data did not support this. That lithium may be a predisposing factor has been proposed by other investigators (18) and has several possible pharmacodynamic bases. Lithium has been reported to increase RBC levels of haloperidol (Z.C. Nemes et al., unpublished paper), inhibit striatal dopamine synthesis (19), and prevent neuroleptic-induced functional supersensitivity of brain dopamine systems (20), thereby further impairing dopaminergic function, the putative mechanism leading to neuroleptic malignant syndrome.

Several constraints on this study render our conclusions tentative pending further corroborating evidence. Inadequate documentation is a limitation in retrospec-

				Symptoms				
Temperature (°F)	Rigidity or Tremor	Hypertension (≥150/100 mm Hg)	Rapid Pulse (≥100 beats minute)	Diaphoresis	Incontinence	Confusion	Elevated WBC (cells/mm³)	Elevated Creatine Phosphokinase (U/liter)
101.8	Yes	Yes	Yes	Yes	Yes	Yes		
100.4	Yes	Yes	Yes	Yes				
100.3	Yes		Yes			Yes	11.9	241
99.0	Yes		Yes				12.8	553
99.2	Yes	Yes		Yes		Yes	14.8	
99.8	Yes		Yes		Yes	Yes		
99.0	Yes		Yes				15.0	102
99.2	Yes	Yes	Yes	Yes			13.0	

tive designs that was particularly problematic in this study because the signs of neuroleptic malignant syndrome have only recently been widely recognized. Yet, since it is most likely that the clinical and laboratory data on our sample were underreported, it can be assumed that better documentation would only provide further support for our conclusions. Our sample was limited to young men, and therefore our results might not necessarily be generalizable; however, our clinical experience indicates that the same results would be found with women. Catatonia (13, 14), elevated creatine phosphokinase level (21), and autonomic changes may be seen in untreated patients. As most of our patients were placed on neuroleptic treatment early in their hospital course, it is not possible to determine which signs of neuroleptic malignant syndrome occurred before initiation of treatment. Also, since we treat most actively psychotic patients with neuroleptics, we do not have an appropriate control group.

Despite the variety of factors that limit our conclusions, we feel our results dictate a need for further well-controlled prospective studies of this potentially lethal syndrome. Also, although some patients develop symptoms of neuroleptic malignant syndrome that abate with continued use of neuroleptics, on the basis of our findings it is not yet possible to determine who will go on to manifest the full-blown syndrome. In addition, it is premature to recommend treatment guidelines. We do, however, concur with other investigators that the development of marked symptoms of neuroleptic malignant syndrome demands immediate cessation of all neuroleptic medications.

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Failure of Buspirone to Manage Benzodiazepine Withdrawal

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Fifteen patients with 146 cumulative years of tranquilizer use were withdrawn from their benzodiazepine (nine gradually and six abruptly), and buspirone, a new nonbenzodiazepine anxiolytic, was substituted. The addition of buspirone did not appear to lessen the intensity of the withdrawal state. This finding supports preclinical studies indicating that buspirone has no clinically significant benzodiazepine receptor activity.
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The introduction of benzodiazepines in the 1960s heralded a new era of safe and effective anxiolysis. Tolerated well and with a wide therapeutic window, benzodiazepines rapidly supplanted barbiturate and nonbarbiturate agents as the treatment of choice for anxiety and minor depression. The ubiquity of benzodiazepines has, in the past decade, raised questions about their overuse or misuse, although community surveys of drug-taking behavior suggest an actual rate of use much lower than previously estimated (1). Coupled with concern about overuse has been the issue of benzodiazepine dependence and withdrawal.

The past two decades have seen the introduction of numerous anxiolytic compounds chemically related to the first benzodiazepine, chlordiazepoxide. More than 30 benzodiazepines are available worldwide. All appear to share a similar liability toward dependence and all generally counteract the withdrawal syndrome pro-

duced by other benzodiazepines, although it recently has been suggested that alprazolam and diazepam might not be fully cross-tolerant (2).

Multiple clinical trials (3, 4) have demonstrated that buspirone, a novel heterocyclic compound, has anxiolytic properties comparable to those of other benzodiazepines. It is a structurally unique psychotropic that possesses an as-yet undefined mechanism of action (5), although it appears to be inactive at the benzodiazepine and GABA receptor sites (6). Furthermore, preclinical studies (5, 6) suggest that chronic buspirone administration does not result in physical dependence or withdrawal symptoms. This favorable anxiolytic profile and low addiction potential led us to investigate the role of buspirone in withdrawing patients from chronic benzodiazepine treatment. We report here on an open-label pilot study in which buspirone was administered to 15 patients being withdrawn from benzodiazepines.

METHOD

Fifteen patients were selected from a larger study of withdrawal from chronic benzodiazepine treatment. The patients in the current study were evaluated and treated at the Psychopharmacology Research Unit at the University of Pennsylvania, and all gave written informed consent. All patients had failed previous attempts at both abrupt and gradual withdrawal in our clinic, but most had managed a substantial benzodiazepine dose reduction—often over a period of many months.

After at least a 2-week stabilization of their current benzodiazepine dose, the patients were assigned to either abrupt or gradual buspirone substitution. Allocation of patients into the abrupt (N=6) or gradual (N=9) group was made on clinical grounds in light of such factors as dose of benzodiazepine, age of patient, and concomitant medical problems. The mean±SD