Novel Antipsychotics and the Neuroleptic Malignant Syndrome: A Review and Critique

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Objective: The authors' goal was to analyze reported cases of neuroleptic malignant syndrome in patients given clozapine and risperidone. **Method:** They assessed 19 cases of clozapine-induced neuroleptic malignant syndrome and 13 cases of risperidone-induced neuroleptic malignant syndrome against three criteria sets and against extent of exclusionary workup and then designated them as high or low probability of being neuroleptic malignant syndrome. **Results:** Nine of the 19 cases of clozapine-related neuroleptic malignant syndrome and eight of the 13 cases of risperidone-related neuroleptic malignant syndrome were designated as having high probability of being neuroleptic malignant syndrome. The remainder were designated as having low probability because presentations were not linked to treatment or failed to meet criteria for the syndrome. **Conclusions:** Neuroleptic malignant syndrome can occur in patients given atypical antipsychotics and resembles "classical" neuroleptic malignant syndrome. However, side effect profiles overlap considerably with neuroleptic malignant syndrome criteria, and atypical antipsychotics may cause neurotoxicities unrelated to (but misattributed as) neuroleptic malignant syndrome. Insufficient evidence exists for "atypical" neuroleptic malignant syndrome with novel antipsychotics.

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Two reviews (1, 2) found insufficient evidence for neuroleptic malignant syndrome attributable to clozapine. Another (3) proposed a causal relationship, advocating the concept of "atypical" neuroleptic malignant syndrome as well as the disputed spectrum concept (4). Incorrectly diagnosing neuroleptic malignant syndrome during clozapine or risperidone therapy may deprive patients of potentially more efficacious and safer medications; however, clinicians must be alert for neuroleptic malignant syndrome with novel antipsychotics. This review, by critically examining reported cases against established diagnostic criteria, addresses this conundrum.

METHOD

Cases of neuroleptic malignant syndrome related to clozapine or risperidone reported in English were collected (by means of a MEDLINE literature search and contacting pharmaceutical companies as well as authors when necessary) and analyzed against three sets of criteria that represent a continuum of formulations of neuroleptic malignant syndrome: most stringent (Caroff and Mann [5]), intermediary (DSM-IV), and least stringent (Levenson [6]). All criteria sets require adequate workup for exclusion of other etiologies; importantly, the extent of workup is unspecified.

Cases were categorized as high or low probability of being neuroleptic malignant syndrome according to criteria sets, agreement across these criteria, and documentation of adequate, exclusionary workup. For cases designated as having high probability of being neuroleptic malignant syndrome, potential predisposing, precipitating, or contributing factors (use of concomitant medications, rapid titration, age, use of depot neuroleptics, and previous neuroleptic malignant syndrome) were identified.

RESULTS

We identified 19 reports of clozapine-induced neuroleptic malignant syndrome and 13 reports of risperidone-induced neuroleptic malignant syndrome (table 1) with variability in ascribed diagnostic certainty. When we applied the criteria of Caroff and Mann (5), we identified four of the clozapine cases and five of the risperidone cases as being neuroleptic malignant syndrome; when we applied DSM-IV criteria, 10 of the clozapine cases and 10 of the risperidone cases were so identified; when we applied Levenson's criteria (6), 14 of the clozapine cases and 11 of the risperidone cases were so identified. All of the cases identified as being neuroleptic malignant syndrome when we applied Caroff and Mann guidelines were also identified by DSM-IV and Levenson's criteria. All but one (a risperidone case re-

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TABLE 1. Reported Cases of Clozapine- and Risperidone-Induced Neuroleptic Malignant Syndrome[a]

Medication and Author	Patient's Age (years)	Diagnosis	Sex	Criteria Used to Diagnose Syndrome: Caroff and Mann	Criteria Used to Diagnose Syndrome: DSM-IV	Criteria Used to Diagnose Syndrome: Levenson	Probability That Syndrome Was Present	Alternative Diagnosis
Clozapine								
Pope et al. (7)	27	Bipolar disorder	M	No	Yes	Yes	High	
Muller et al. (8)	76	Bipolar disorder	M	No	Yes	Yes	Low	Side effect of polypharmacy
Nopoulos et al. (9)	31	Schizophrenia	M	No	No	Yes	Low	Side effect of clozapine
Miller et al. (10)	50	Schizophrenia	M	Yes	Yes	Yes	High	
Anderson and Powers (11)	26	Schizophrenia; anorexia nervosa; bulimia nervosa	F	No	Yes	Yes	High	
DasGupta and Young (12)	30	Viral encephalitis and mental retardation	M	Yes	Yes	Yes	High	Infection
Goates and Escobar (13)	29	Schizophrenia	M	No	No	Yes	Low	Side effect of clozapine
Reddig et al. (14)	41	Schizophrenia	M	Yes	Yes	Yes	High	Infection
Nemecek et al. (15)	38	Schizophrenia	M	No	Yes	Yes	Low	Caused by haloperidol
Viner and Escobar (16)	40	Schizophrenia	M	No	No	No	Low	Side effect of clozapine
Tsai et al. (17)								
Patient 1	35	Schizoaffective disorder	F	Yes	Yes	Yes	High	Serotonin syndrome; side effect of polypharmacy
Patient 2	42	Schizophrenia and mental retardation	M	No	Yes	Yes	High	Side effect of polypharmacy
Lowy et al. (18)	33	Schizophrenia	M	No	No	No	Low	Infection
Sachdev et al. (3)								
Patient 1	33	Schizophrenia	M	No	No	Yes	Low	Infection
Patient 2	36	Schizophrenia	M	No	No	Yes	High	Infection
Patient 3	15	Psychotic disorder not otherwise specified	M	No	No	No	Low	Side effect of clozapine
Patient 4	36	Schizophrenia	M	No	No	No	Low	Bromocriptine withdrawal; side effect of polypharmacy
Ganelin et al. (19)	42	Schizophrenia	M	No	Yes	Yes	High	
Illing and Ancill (20)	74	Schizophrenia	M	No	No	No	Low	Side effect of polypharmacy
Risperidone								
Tomsic et al. (21)	39	Schizophrenia and mental retardation	F	No	No	Yes	Low	Benzodiazepine withdrawal; side effect
Lee et al. (22)	24	Schizophrenia	M	Yes	Yes	Yes	High	Infection
Webster and Wijeratne (23)								
Patient 1	82	Schizoid personality disorder	M	No	Yes	Yes	High	Infection
Patient 2	81	Vascular dementia	F	No	Yes	Yes	High	
Raitasuo et al. (24)	31	Schizophrenia	M	No	No	No	Low	Side effect of risperidone
Dave (25)	35	Schizoaffective disorder and mental retardation	F	Yes	Yes	Yes	High	Benzodiazepine withdrawal
Singer et al. (26)	70	Schizophrenia and hypertension	M	No	Yes	No	Low	Infection
Murray and Haller (27)	25	Schizoaffective disorder	F	No	No	Yes	Low	Side effect of risperidone
Najara and Enikeev (28)	42	Schizoaffective disorder	F	Yes	Yes	Yes	High	
Meterissian (29)	53	Schizoaffective disorder	F	No	Yes	Yes	High	
Tarsy (30)	43	Schizophrenia and major depressive disorder	F	Yes	Yes	Yes	High	
Kern and Cernek (31)	67	Major depressive disorder and dementia	M	No	Yes	Yes	Low	Side effect of polypharmacy; benzodiazepine withdrawal; serotonin syndrome
Levin et al. (32)	26	Psychotic disorder not otherwise specified and mental retardation	M	Yes	Yes	Yes	High	Infection

[a]Comparison of neuroleptic malignant syndrome in clozapine versus risperidone high-probability cases: mean time to onset was 50 days for clozapine versus 12 days for risperidone; duration of neuroleptic malignant syndrome was 10.6 days versus 11.6 days; fever was 102.6°F versus 101°F; tachycardia was 129 versus 108 bpm; and creatine phosphokinase elevation was 4459 versus 3537 IU/liter. Dantrolene or bromocripine was given in five of nine clozapine cases and one of eight risperidone cases.

ported by Singer et al. [26]) of the cases identified by DSM-IV also met Levenson's criteria. Four clozapine cases (3 [patients 1 and 2], 9, 13) and two risperidone cases (21, 27) met Levenson's criteria alone. There was consensus for nine clozapine cases (3 [patients 3 and 4], 10, 12, 14, 16, 17 [patient 1], 18, 20) and six risperi-

done cases (22, 24, 25, 28, 30, 32); of these, five clozapine cases (3 [patients 3 and 4], 16, 18, 20) and one risperidone case (24) failed to fulfill any criteria.

Clozapine cases were designated as having low probability of being neuroleptic malignant syndrome if 1) presentations were not causally linked to clozapine because important differential diagnoses were not clearly excluded and concomitant medical illness (3 [patient 1], 18), and concomitant psychotropic medications (15) were present or 2) they did not fulfill neuroleptic malignant syndrome criteria but were suggestive of possible neurotoxicity of clozapine alone (9, 13, 16) or with polypharmacy (3 [patient 4], 8, 20). Risperidone cases were designated as having low probability if the presentations were attributable to infection (26), neurotoxicity from polypharmacy (31), benzodiazepine withdrawal (21, 31), serotonin syndrome (31), and risperidone-induced extrapyramidal side effects (24, 27).

Nine of 19 clozapine cases were designated as having a high probability of being neuroleptic malignant syndrome, with consensus across criteria sets for four cases (10, 12, 14, 17 [patient 1]). The remaining five cases were close in presentation to typical neuroleptic malignant syndrome, and this was the most parsimonious diagnosis (2 [patient 2], 7, 11, 17 [patient 2], 19). Diagnostic ambiguity remained for three patients (3 [patient 2], 12, 14) with infections of unclear temporal sequence. Eight of 13 risperidone cases were designated as having high probability of being neuroleptic malignant syndrome, with consensus for five cases (22, 25, 28, 30, 32). Most cases had both fever and rigidity, except two (3 [patient 1], 22) with minimal rigidity and two (7, 29) with fevers around 99°F.

DISCUSSION

Notwithstanding methodological limitations, the following tentative conclusions appear justified: 1) Neuroleptic malignant syndrome can occur during clozapine or risperidone monotherapy. 2) A proportion of published cases of neuroleptic malignant syndrome appear to have implicated clozapine or risperidone inappropriately. 3) The diagnostic conundrum inherent to neuroleptic malignant syndrome is further complicated when atypical antipsychotics are used because side effects are likely to be misattributed to neuroleptic malignant syndrome or because diagnoses of concomitant infection or neurotoxic drug effects may be consistent with the clinical presentation. 4) Insufficient evidence exists currently to support the concept of "atypical" neuroleptic malignant syndrome with novel antipsychotics.

The potential for diagnostic confusion is considerable because of overlap between features of neuroleptic malignant syndrome and adverse effects of atypical antipsychotics. Approximately 3% of patients receiving clozapine develop benign hyperthermia, and approximately 25% have autonomic instability during initial titration of clozapine or risperidone therapy (33). Also, massive creatine phosphokinase elevations with atypical antipsychotics may occur in the absence of other features of neuroleptic malignant syndrome (34). These observations suggest that clinicians should be particularly judicious in ascribing a diagnosis of neuroleptic malignant syndrome (especially early or "incipient" forms) at the initiation of atypical antipsychotic therapy.

Some reports were most likely drug-drug interactions occurring during polypharmacy with lithium, benzodiazepines, antidepressants, or other neuroleptics (8, 15, 21, 31). In several cases (3 [patients 3 and 4], 8, 9, 16, 20, 21, 24, 27), neurotoxicity related to initiation or discontinuation of neuroleptics seemed a more apt explanation. Clarifying risk factors and mechanisms for such adverse reactions and distinguishing these from neuroleptic malignant syndrome is particularly important because treatment of neurotoxicity differs from that of neuroleptic malignant syndrome. Among the high-probability neuroleptic malignant syndrome cases, seven of the nine clozapine-treated patients had schizophrenic or schizoaffective diagnoses and four of the eight risperidone cases had schizoaffective or affective disorders. Concomitant diagnoses of mental retardation were also prominent. This is consistent with findings of high rates of comorbidity and affective disorder in neuroleptic malignant syndrome from typical neuroleptics (35). Three of the nine patients given clozapine (but none given risperidone) had a history of neuroleptic malignant syndrome from typical antipsychotics; there may be a selection bias for clozapine treatment in such patients. Although neuroleptic malignant syndrome patients may tolerate clozapine without recurrence, this clinical practice may over time accrue cases of clozapine-induced neuroleptic malignant syndrome. Four of the clozapine-treated and four of the risperidone-treated patients received concomitant psychotropics; three of the clozapine-treated patients were receiving decanoate preparations before clozapine treatment (with washout periods of 3 weeks to 11 months). Notably, substantial dopamine receptor blockade occurs even at 16 weeks after discontinuation of depot neuroleptics (36). Three of the four patients with clozapine-induced neuroleptic malignant syndrome were rechallenged with clozapine and one with risperidone without subsequent problems. Both patients with risperidone-induced neuroleptic malignant syndrome developed some signs and symptoms short of neuroleptic malignant syndrome when rechallenged with antipsychotics: one had creatine phosphokinase elevation (3293 IU/liter); another had rigidity, fever (99.1°F), and creatine phosphokinase elevation (220 IU/liter). It is important to evaluate carefully whether neuroleptic malignant syndrome can occur with other novel antipsychotics. This process will be advanced by reporting based on recognized diagnostic criteria and by meticulous attention to alternative medical diagnoses and possible neurotoxicities.

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