Eur Arch Psychiatry Clin Neurosci (1998) 248 : 231–239

ORIGINAL PAPER

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Neuroleptic malignant syndrome under treatment with antidepressants? A critical review

Received: 7 August 1997 / Accepted: 5 May 1998

Abstract Neuroleptic malignant syndrome (NMS) is a rare complication of treatment with neuroleptics. The pathophysiology is not fully known. A dopaminergic transmission block in the basal ganglia and hypothalamus is thought to be the pathophysiological mechanism of NMS. Several cases of NMS have been reported, precipitated by medication without a direct effect on the dopaminergic system. This Medline analysis concerns 23 cases of antidepressant-induced NMS reported in the literature with the differing pathophysiological hypotheses on the precipitation of NMS. The results indicate no hard evidence of an antidepressant-evoked NMS. However, various hypotheses assuming an disturbed balance of the dopaminergic and non-dopaminergic system may be relevant in animal studies, but are without clinically relevant proof presently. An antidepressant-induced NMS is a very rare complication on the basis of pretreatment with neuroleptics causing chronic dopamine blockade and elevated plasma level of neuroleptics due to comedicated antidepressants.

Key words Neuroleptic malignant syndrome · Antidepressants

Introduction

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal idiosyncratic complication of neuroleptic medication. Its pathophysiology is not fully known [1, 6, 43]. A dopaminergic transmission block in the basal ganglia and the hypothalamus is thought to be the pathophysiological mechanism of NMS [24, 33]. The prevalence of NMS among admissions to acute psychiatric wards has been estimated to vary from 0.07 to 2.0% [15, 21, 33, 45]. Neuroleptic malignant syndrome is characterized by muscular rigidity, fever, autonomic dysfunction, and altered consciousness [36]. Although classically only neuroleptics were considered to induce NMS, several other drugs have been associated with NMS, e.g. carbamazepine, lithium and tetrabenazine [21]. Particularly antidepressants have been ascribed to evoke NMS.

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Methods

This review was carried out to summarize all cases with NMS associated with antidepressants reported in Medline during 1980 to 1996. All cases were briefly described together with the pathophysiological hypotheses given by the authors. The diagnostic criteria of each case were evaluated according to the DMS-IV criteria for NMS.

Cases of NMS associated with antidepressants

Cases 1 and 2

Eiser et al. [12] described three cases of acute myoglobinuric renal failure. Two patients developed NMS shortly after receiving a neuroleptic and an antidepressant. The other patient was receiving only haloperidol and is not reported.

In case 1, a 60-year-old woman received 15 mg/day of haloperidol and amitriptyline 200 mg/day. Her temperature rose to 41.2 °C with elevated pulse and normal blood pressure. Initially, she was agitated and disoriented and became progressively obtunded. Creatine kinase was found to be 1530 U/l and white cell count was 20,000/µl. The patient died after 23 days.

In case 2, a 43-year-old man with depression received 100 mg/day of chlorpromazine and 200 mg/day of imipramine. He was noted to have increased tremor and profuse diaphoresis. Temperature was 39.2 °C, pulse 140 bpm and blood pressure 140/80 mm Hg. Creatine kinase was 1590 U/l leucocyte count 17,000/µl. He underwent peritoneal dialysis for oliguric renal failure and suffered from generalized seizures. The clinical outcome was not reported.

Cases 3 and 4

Sumiyoshi et al. [40] described a 24-year-old female with depression. She was treated with amitriptyline 75 mg, cloxazolam 6 mg and lithium-carbonate 400 mg daily, and was additionally given intravenous administration of clomipramine 25 mg.

The second case, a 57-year-old female with depression, was given daily nortriptyline 30 mg, amitriptyline 25 mg, cloxazolam 6 mg and promethazine 75 mg, and also a shot of levomepromazine 25 mg. These two cases gradually showed signs of tremor, muscular rigidity and, after a short time development of akinesia, mutism and various autonomic symptoms. Fever, elevated creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) were reported.

Case 5

Steele [39] described a 45-year-old patient with major depression. He was treated over 5 days with haloperidol 15 mg/day. The haloperidol was discontinued and amoxapine was started up to 300 mg/day. Eight days after haloperidol was discontinued and 7 days after amoxapine was begun, he developed parkinsonian gait and posture. He resumed taking 10 mg/day of haloperidol. Amoxapine was increased to 400 mg/day. The following day he developed fever up to 39.8 °C, an increase in parkinsonian signs with rigidity, cogwheeling of his arms and mask-like faces. Over the next days he developed fever up to 40.4 °C, leucocytosis and elevation of S-GPT, S-GOT and LDH. Although psychotropic medication was discontinued when his fever developed, he had a degree of bradykinesia, shuffling gait and masked faces that persisted for 2 weeks.

Case 6

Grant [14] described the first case of NMS occurring in a patient receiving only an antidepressant. He reported on dothiepin, a thioanalogue of amitriptyline, without mentioning the dosage. A 68-year-old woman presented 2 weeks after starting dothiepin with rigidity, akinesia, mutism, waxy flexibility, pyrexia, dehydration, tachycardia and retention of urine. Creatine kinase activity and white cell count was raised. Dothiepin was discontinued. During the next 48 h her pyrexia settled but she became agitated and confused. Symptoms remitted after 5 days.

Case 7

Ansseau et al. [2] described a 54-year-old woman with a major depressive disorder. Treatment with amitriptyline and imipramine was without effect. She was put on haloperidol 2–6 mg/day orally. Clomipramine 25–100 mg/day was instituted intravenously with some clinical improvement. After 4 weeks of therapy with haloperidol 6 mg and 150 mg of clomipramine orally, she developed rigidity, mutism and hyperthermia with a maximum of 40.4 °C. Creatine kinase and leucocyte count were found to be normal. She died 45 days after the onset of symptoms.

Case 8

Merriam [29] reported on a 36-year-old woman with multiple sclerosis and severe depression, paranoid delusions and auditory hallucination. She was treated with haloperidol 60 mg/day and imipramine 300 mg/day. Imipramine was lowered to 100 mg/day and she exhibited muscular rigidity and was obtunded and febrile. The patient died.

Case 9

Lesaca [23] described a 69-year-old woman with a history of early primary degenerative disorder. On admission she had depression and the only psychotropic medicine (trifluoperazine 6 mg/day) during the previous 4 months was discontinued. She was put on trazodone 200 mg/day and clonazepam for 1 night. On the fifth hospital day lithium carbonate (600 mg/day) and amoxapine (75 mg/day) were begun. By day 7 amoxapine had been increased to 150 mg/day and clonazepam (1.5 mg/day) was added 3 days later. She developed dyspnoea, dysphagia, confusion, dysarthria, spastic movements and tremor of the extremities. Temperature was 40.4° C, heart rate was 120 bpm, blood pressure 170/100 mm Hg, white cell count was 29,900/µl, creatinine phosphokinase was 3235 U/l, and kreatinine and blood urea were elevated. All medication was stopped. Fifteen days after diagnosis of NMS, symptoms normalized without further specific treatment.

Case 10

Burch and Downs [7] described a 59-year-old man with depression and a multitude of somatic complaints. He was treated with doxepine up to 250 mg/day and alprazolam up to 2 mg/day. Because of an exacerbation of the depression, his medication was changed and he was put on a combination of imipramine, alprazolam (4 mg/day) and thiothixene (20 mg/day) for 6 weeks. Because of no significant lasting improvement, imipramine was discontinued in favour of amoxapine 100 mg/day. Diphenhydramine and benzotropinemesylate were required prior to this change to control drooling, shuffling gait. tremors and cogwheel regidity. Thiothixene and alprazolam were discontinued, and amoxapine was raised to 300 mg/day over 2 weeks. Sixteen days after amoxapine was started and 3 days after discontinuation of alprazolam, the patient developed altered mental status, lethargy, generalized tremors, later fluctuating stiffness, rigidity, fever, tachycardia, altered consciousness, diaphoresis and elevated CPK (739 U/l), myoglobinuria and leucocytosis (22,500/µl). The patient died.

Case 11

Corrigan and Coulter [10] presented a case of a 51-year-old male with psychotic depression. Under the medication thioridazine (150 mg/day) over 13 days and amitriptyline (50 mg/days) over 2 days he developed NMS. In the course of NMS he was noted to be rigid and stiff with definite cogwheel rigidity, and there was a tremor in his limbs. His temperature rose to 39.4 °C and his respiratory rate was 38/min. His pulse was 110/min. He was described as sweating profusely and tremulous. Creatine kinase was found to be 4260 U/l and white cell count had risen to 15,800/µl. The patient died after 9 days having clearly developed a chest infection.

Case 12

Taylor and Schwartz [41] described a 37-year-old woman with a history of schizoaffective disorder who ingested an intentional overdose of amoxapine 875 mg as well as an unknown amount of triazolam and alprazolam. She developed rigidity in all extremities, she was diaphoretic, temperature was 38.1 °C, pulse 110 bpm and CPK 246 U/l. During the subsequent days her mental status fluctuated from stupor to agitation. Over the second and third hospital days she received a total of 13 mg haloperidol to control her delusions and her violent behaviour. The diagnosis of catatonia was assumed. Another 2 mg of haloperidol was administered. Symptoms worsened with profuse diaphoresis, tremor, lead-pipe rigidity in her legs, cogwheeling in her arms, trismus, temperature 38.8 °C, pulse 150 bpm. blood pressure 200/120 mm Hg, leucocytes 15,000/µl and CPK 10,650 U/l. Treatment consisted of acetominophen, clonidine, ice packs and intravenous hydration. She improved within 13 days.

Case 13

Washington et al. [44] described a 75-year-old man with depression. He had a history of psychotic depression and was treated with

thiothixene, imipramine, alprazolam and diphenhydramine. Because he was not responding to previous combination therapy, his drug regimen was changed to alprazolam, benztropine and amoxapine. Alprazolam was tapered and amoxapine was gradually increased to 300 mg/day. Two days after the alprazolam was discontinued and 5 days after the amoxapine had been increased, the patient became lethargic and incoherent, and developed generalized tremors of the extremities, fever and rigidity. Amoxapine was discontinued and 2 mg of lorazepam was administered intramuscularly for seizure control. Creatine kinase was 739 U/l, urine myoglobin 10,380 ng/ml and leucocytosis 22,500/μl. The patient appeared to be a status epilepticus. Intravenous dantrolene sodium was administered. Seizure activity continued and he was given diazepam, phenytoin and phenobarbital. His temperature had risen to 42.0 °C, and he died shortly thereafter.

Case 14

Langlow and Alarcon [22] described a 47-year-old woman with obsessive – compulsive disorder and major depression. She had been treated previously with amoxapine, amitriptyline, thiothixene and haloperidol to no avail. She was started on a regimen of clomipramine for 2 weeks. The medication was discontinued and ECT was started because of psychotic depression. After responding to ECT she was put on a regimen of trimipramine up to 250 mg/d. Approximately 1 month later, she developed polyuria, diarrhoe, lead-pipe rigidity without cogwheeling. She was mute. White blood cell count was 15,200/μl, and CPK 1846 U/l. Shortly after admission, the patient became febrile (38.3 °C). Alprazolam was given 3 mg/day during the 4 weeks prior to the hospitalization. Her NMS symptoms were associated with a brief episode of polydipsia and polyuria. Twenty-four hours after admission, she developed pneumonia. The patient improved with dantrolene and bromocriptine.

Case 15

Madakasira [26] described a case of a 62-year-old woman with depression who was treated with amitriptyline 150 mg/day. Lithium carbonate was added to 900 mg/day to augment the antidepressant effect. Perphenazine was started; however, perphenazine and lithium were discontinued because of side-effects. One month later, amitriptyline was replaced with amoxapine to 200 mg/day. The patient's depressive symptoms improved. Approximately 1 month after starting amoxapine, she developed bradykinesia, mask-like facies, left-sided cogwheel rigidity and smaking-lip movements. Benztropine-mesilat was begun to counter the extrapyramidal symptoms. Approximately 17 weeks after the amoxapine treatment began, the patient developed confusion, incoherence, tremoulosness, fever up to 37.8 °C, mild rigidity, stupor, hypertension (170/100 mm Hg), tachycardia (130 bpm), diaphoresis, elevated CPK level (20,020 U/l), LDH 2805 U/l and leucocytosis (15,800/μl). A diagnosis of NMS was made and amoxapine was discontinued. The total amoxapine blood concentration was 440 μg/l (therapeutic upper level: 500 μg/l). She improved without specific treatment.

Case 16

Baca and Martinelli [4] reported on a case of NMS receiving an antidepressant with no exposure to neuroleptics. A 58-year-old woman with a long-standing history of depression was treated with desipramine 50 mg/day over 7 months. She was agitated, confused, making buccolingual movements and was brought to hospital. She developed lead-pipe rigidity and temperature rose to 39.4 °C with a respiratory rate of 32/min. Her pulse was 130 bpm and blood pressure was 160/90 mm Hg. There was an extreme diaphoresis. Creatine kinase was found to be 5400 U/l and white cell count was 16,500/μl. She was treated intravenously with dantrolene 400 mg/day and bromocriptine was increased to a maximum of 60 mg/day. Her hospital course was complicated, but gradually she remitted.

Case 17

Halman and Goldbloom [16] reported on a case of a 53-year-old man with a history of a recurrent major depression. He first presented with an overdose of carbamazepine (2000 mg), methotrimeprazine (250 mg), and tryptophan (5000 mg). On the ninth day following the overdose, fluoxetine was initiated at a dose of 20 mg/day. On day 5 of fluoxetine, he was rigid, frightened and mute. In the course he displayed tremor of his hand and cogwheel rigidity. His temperature elevated to 38.8 °C with tachycardia and tachypnoea and blood pressure was 170/110 mm Hg. He was diaphoretic and dehydrated and became incontinent of urine and feces. He had an elevated creatine phosphokinase of 736 U/l and a leucocytosis level of 23,500/μl. Neuroleptic malignant syndrome was diagnosed on day 9. After 12 days there was a resolution of the extrapyramidal symptoms with full recovery, although he remained depressive.

Case 18

Heyland and Sauvé [20] presented a 56-year-old woman with a history of recurrent depression. She was treated with 45 mg/day of phenelzine and 25 mg/day of amitriptyline, gradually increased to 125 mg/day. The patient was not receiving any neuroleptic therapy. She developed increasing delirium and was disoriented and agitated. The heart rate was 158 bpm and the temperature 41.4 °C. Her pupils were dilated, and she was diaphoretic, tremulous and rigid. All medications were stopped. Dantrolene and bromocriptine were given. The serum creatine kinase level rose from 6715 to 18750 U/l. The serum amitriptyline level was 450 nmol/l and the serum nortriptyline level 490 nmol/l. The phenelzine level was not available. On the fourth day the patient was afebrile and awake. She remained somewhat confused and agitated, and her muscle tone was normal.

Case 19

Otani et al. [32] described a 68-year-old woman suffering from major depression. She had a history of NMS with typical symptoms under haloperidol. Fourteen months later, amoxapine 25 mg/day was introduced. Twenty-one days after treatment, the patient developed stupor, rigidity, fever (39.0 °C), autonomic disturbances and elevated CPK (1090 IU/l). Amoxapine was withdrawn and all symptoms disappeared with levodopa treatment.

Case 20

Fava and Galizia [13] reported on a 61-year-old male with a history of bipolar affective disorder who presented with an acute manic relapse. He was started on chlorpromazine over 7 days for treatment of hypomania. After remission, neuroleptic treatment was discontinued and changed to amitriptyline in a dosage of 25 mg/day and lithium carbonate of 300 mg/day. One week later, he developed pyrexia of 39.5° C, tachycardia, impaired consciousness, rigidity of the limbs, neck and abdominal muscles, and elevation of creatine kinase to 715 U/l. Serum levels of chlorpromazine was undetectable at admission. The patient was started on bromocriptine and a levodopa–carbidopa combination. The level of consciousness returned to normal within 24 h and fever normalized within 30 h.

Case 21

Miyaoka and Kamijima [30] reported on a 46-year-old man suffering from depression. He was treated with amitriptyline 300 mg/

Table 1 NMS and antidepressants

Author(s)	Year	Age	Sex	Diagnosis	Antidepressant	Dose	Comedication	Dose	Premedication	Dose	Discontinuation before NMS
1. Eiser et al. Case 1	1982	60	F	?	Amitriptyline	200 mg/day	Haloperidol diazepam	15 mg/day 20 mg/day	Thioridazine	100 mg/day	1 day
2. Case 2		43	M	Depression	Imipramine	200 mg/day	Chlorpromazine	Once 100 mg	Haloperidol amitriptyline benztropine mesylate	30 mg/day 100 mg/day 2 mg/day	3 weeks 1 month 3 weeks
3. Sumiyoshi et al. Case 1	1982	24	F	Depression	Amitriptyline	75 mg/day	Cloxazolam lithium clomipramine	6 mg/day 400 mg/day 25 mg/day	Not mentioned	No	No
4. Case 2		57	F	Depression	Nortriptyline Amitriptyline	30 mg/day 25 mg/day	Cloxazolam promethazine levomepromazine	6 mg/day 75 mg/day Once 25 mg	Not mentioned	No	No
5. Steele	1982	45	M	Depression	Amoxapine	400 mg/day	Haloperidol	10 mg/day	Haloperidol	15 mg–5 days	15 days
6. Grant	1984	68	F	?	Dothiepin	?	No	No	No	No	No
7. Ansseau et al.	1986	54	F	Depression	Clomipramine	25–100 mg/day	Haloperidol	6 mg	Amitriptyline imipramine haloperidol clomipramine	? ? 6 mg/day 150 mg/day	? ? 0 0
8. Merriam	1987	34	F	Depression	Imipramine	300 mg/day; 100 mg/day	Benzotropine haloperidol	4 mg/day 60 mg/day	?	?	?
9. Lesaca	1987	69	F	Depression/ dementia	Amoxapine	150 mg/day	Clonazepam lithium	1.5 mg/day 600 mg/day	Trifluoperazine trazodone	6 mg/day once 200 mg	10 days 9 days
10. Burch and Downs	1987	59	M	Depression	Amoxapine	300 mg/day	No	No	Alprazolam thiothixene	0.5 mg/day 20 mg/day	3 days 16 days
11. Corrigan and Coulter	1988	51	M	Depression	Amitriptyline	50 mg/day	Temazepam thioridazine	10 mg/day 150 mg/day	Lentizol thioridazine	50 mg/day 150 mg/day	13 days 4 days
12. Taylor and Schwartz	1988	37	F	Schizo-affective	Amoxapine overdose	once 875 mg 4 days before NMS	Triazolam/ alprazolam haloperidol 2 days before NMS	? 13 mg total over 2 days	? ?	? ?	?
13. Washington et al.	1989	75	M	Depression	Amoxapine	300 mg/day	Benzotropine	?	Alprazolam	?	2 days
14. Langlow and Alarcon	1989	47	F	OCD, depression	Trimipramine	250 mg/day	No	No	Clomipramine amoxapine/halop.	? ?	4 weeks > 4 weeks
15. Madakasira	1989	62	F	Depression	Amoxapine	200 mg/day	Benzotropine mesilate	?	Perphenazine amitriptyline	? 150 mg/day	> 8 weeks 4 weeks
16. Baca and Martinelli	1990	58	F	Depression	Desipramine	50 mg/day	No	No	Diazepam midazolam	? 3 mg once	2 days 1 day
17. Halman and Goldbloom	1990	53	M	Depression	Fluoxetine	20 mg/day	No	No	Carbamazepine overdose tryptophan overdose methotrimeprazine overdose	2000 mg 5000 mg 250 mg	13 days 13 days 13 days
18. Heyland and Sauve	1991	56	F	Depression	Amitriptyline	125 mg/day	Phenelzine	15 mg/day	Desipramine	?	6 weeks

Table 1 (continued)

Author(s)	Year	Age	Sex	Diagnosis	Antidepressant	Dose	Comedication	Dose	Premedication	Dose	Discontinuation before NMS
19. Otani et al.	1991	68	F	Depression	Amoxapine	25 mg/day	No	No	Mianserin maprotiline clomipramine	10–20 mg/day 10–30 mg/day 10–50 mg/day	? ? ?
20. Fava and Galizia	1995	61	M	Bipolar disorder	Amitripyline	25 mg/day	Lithium	300 mg/day	Chlorpromazine	25 mg/day	1 weeks
21. Miyaoka and Kamijima	1995	46	M	Depression	Amitriptyline	300 mg/day	Diazepam nitrazepam/flunitrazep.	18 mg/day 10 mg/day; 1 mg/day	?	?	?
22. Mancias et al.	1995	14	M	Depression/ abuse	Amoxapine overdose	once 1900 mg	No	No	No	No	
23. Heinemann and Assion	1995	22	M	Schizophrenia	Paroxetine	20 mg/day	Promethazine	30 mg/day	Haloperidol decanoate thioridazine lorazepam chlorprotixen	3 ml/14 days 100 mg/day 2 mg/day ?	> 1 month 3 weeks 3 weeks 3 weeks

day, diazepam 18 mg/day, nitrazepam and flunitrazepam. He developed tremor, myoclonus, mild muscular rigidity, diaphoresis, tachycardia, fever of 38.8 °C and CPK 2196 U/l. Neuroleptic malignant syndrome was diagnosed and bromocriptine therapy was begun. The patient fully remitted.

Case 22

Mancias et al. [27] described a 14-year-old boy with a history of depression, drug and alcohol abuse who attempted suicide by ingesting 1900 mg of amoxapine. The boy developed seizures, hypertension, transient bilateral visual loss, fever (40.1 °C), altered mental status with agitation, confusion and incoherent speech, and transient parkinsonian features with mild cogwheel rigidity; but muscular rigidity was not present. The CPK level was 1091 U/l and he developed renal failure. A computed tomography (CT) scan showed vague area hypodensity in the left parieto-occipital region, and magnetic resonance imaging showed increased intensity bilaterally in parieto-occipital lobes.

Case 23

Heinemann and Assion [17, 19] reported on a 22-year-old patient with paranoid schizophrenia. One year prior he had been put on neuroleptics. A depressive episode was treated with paroxetine. Some months before hospitalization, paroxetine, haloperidol and promethazine were stopped and changed to thioridazine and lorazepam. He attempted suicide and suffered from polytrauma. A CT scan revealed an epidural haematoma that led to neurosurgical trepanation and exstirpation. The postoperative medication of promethazine 60 mg/day was reduced to 30 mg/day. Neurological exam and laboratory testing were normal except for presence of leucocytosis (12,000/µl). Paroxetine (20 mg/day) was initiated 16 days after operation. One day after this medication, he was rigid with tremor of the limbs, had clouded consciousness and was sweating profusely. His temperature was 38.9° C with tachycardia to a maximum of 180 bpm. His blood pressure was 180/110 mm Hg. He had leucocytosis of 21,000/µl and elevated transaminases of the liver. Creatine kinase was elevated to a maximum of 680 U/l after 4 days. Paroxetine and promethazine were put off and CK normalized within 8 days. He was treated with dantrolene and amantadine. After 16 days, there was a resolution of symptoms.

Results

From 1982 to 1996, 23 cases of NMS associated with antidepressants were described in the literature. These cases comprised 13 female and 10 male patients with a mean age of 50.6 years (range 14–75 years).

The diagnosis of depression was made in 18 patients. Schizoaffective psychosis, bipolar disorder and schizophrenic disorder were diagnosed in 1 patient each. No diagnosis was given in 2 patients.

Especially tricylics were associated with NMS. Eight patients had received amoxapine including two with signs of intoxications. Another 6 patients were treated with amitriptyline, 2 with imipramine and only 1 patient each with dothiepin, clomipramine, trimipramine and desipramine. SSRI were associated in 2 cases (fluoxetine, paroxetine). In only one case was a combination of the antidepressants nortriptyline and amitriptyline administered.

A comedication of neuroleptics was given in 9 cases: haloperidol in 5 cases, and chlorpromazine, promethazine, levomepromazine and thioridazine in 1 case each. Three

patients were comedicated with lithium and 7 with benzodiazepines. Neuroleptic premedication was haloperidol in 5 cases, thioridazine in 3, and chlorpromazine, perphenazine and trifluoperazine in 1 case each.

Eight cases were found neither with a neuroleptic comedication nor a neuroleptic premedication, although two of these cases were without data on neuroleptic premedication.

According to DSM-IV criteria for neuroleptic malignant syndrome, 2 cases did not fullfil the criteria A (rigidity and elevated temperature). One of these cases did not mention muscle rigidity, and the other did not describe febrile temperature [23, 26]. All cases fulfilled two or more of criteria B. Elevated CPK was found in 20 cases, ranging from 680 to 20,020 U/l, whereas in two case reports a CPK level was not mentioned. Creatine phosphokinase was normal only in 1 case.

In 17 cases a duration of NMS lasting from 1 to 45 days was reported. Specific therapy was administered in 9 cases with either dantrolene, bromocriptine, amantadine or levodopa. Complications were described in 15 cases; 6 patients died.

Discussion

We found 23 cases of NMS reported in the literature with antidepressants having triggered the disorder. Analysis of these case reports presents difficulty due to the lack of generally accepted diagnostic criteria. Even ICD-10 does not include diagnostic standards for NMS. Only the recently developed DSM-IV has made operational diagnostics possible [11]. Therefore, the best approach to such case reports is an analysis according to these criteria.

Additional difficulties are encountered when attempting to differentiate NMS from other disorders such as the serotonin syndrome or febrile catatonia, the so-called catatonic dilemma. As is seen in Tables 1–3, the cases were

Table 2 Cases of NMS according to DSM-IV criteria

Author(s)	Rigidity	Body temperature (°C)	Consciousness	Tremor	Tachycardia	Blood pressure (mm Hg)	CPK	Leucocytosis	Diaphoresis
1. Eiser et al. Case 1	Yes	41.2	Obtunded, disoriented	?	130 bpm	140/90	1530 U/l	20000	?
2. Case 2	Cogwheel	39.2	?	Yes	140 bpm	140/80	1590 U/l	17000	Yes
Sumiyoshi et al.									
3. Case 1	Yes	Fever	?	Yes	?	?	Elevated	?	?
4. Case 2	Yes	Fever	?	Yes	?	?	Elevated	?	?
5. Steele	Cogwheel	40.4	?	?	?	?	?	Yes	?
6. Grant	Yes waxy flexibility	Elevated	?	?	Yes	?	Elevated	Elevated	?
7. Ansseau et al.	Lead pipe	40.4	?	?	?	?	Normal	Normal	?
8. Meriam	Yes	40.3	Obtunded	?	?	?	?	?	?
9. Lesaca	?	40.4	Confusion	Yes	120 bpm	170/100	3235 U/l	29900	?
10. Burch and Downs	Cogwheel	Fever	Altered mental status	Yes	Yes	?	739 U/l	22500	Yes
11. Corrigan and Coulter	Cogwheel	39.4	?	Yes	110 bpm	?	4260 U/l	15800	Yes
12. Taylor and Schwartz et al.	Lead pipe, cogwheel	38.8	Stupor	Yes	150 bpm	220/120	10650 U/l	15000	Yes
13. Washington et al.	Yes	42	?	Yes	Yes	No	739 U/l	22500	?
14. Langlow and Alarcon	Lead pipe	38.3	Awake	?	?	?	1846 U/l	15200	?
15. Madakasira	Cogwheel	37.8	Confusion	Yes	130 bpm	170/100	20020 U/l	15800	Yes
16. Baca and Martinelli	Lead pipe	39.4	Changed	?	130 bpm	160/90	5400 U/l	16500	Yes
17. Halman and Goldbloom	Cogwheel	38.8	?	Yes	Yes	170/110	736 U/l	23500	Yes
18. Heyland and Sauve	Rigid	41.4	Delirium	Yes	158 bpm	?	18750 U/l	No	Yes
19. Otani et al.	Lead pipe	39	Stupor	?	?	?	1090 U/l	?	Yes
20. Fava and Gallzia	Yes	39.5	Obtunded	?	?	?	715 U/l	?	?
21. Miyaoka and Kamijima	Yes	38.8	Dazed	Yes	Yes	159/90	2196 U/l	?	Yes
22. Mancias et al.	Cogwheel	40.1	Confusion	?	?	220/120	1091 U/l	?	?
23. Heinemann and Assion	Yes	38.9	Obtunded	Yes	180 bpm	180/110	680 U/l	21000	Yes

Table 3 Cases of NMS, continued

Author(s)	Duration (Days)	Therapy (Specific medication)	Complications	Outcome
1. Eiser et al. Case 1	23	No	Renal failure, pneumonia, septic shock	Death
2. Case 2	?	No	Renal failure, seizures	Remission
3. Sumiyoshi et al. Case 1	?	?	?	?
4. Case 2	?	?	?	?
5. Steele	?	?	No	Remission
6. Grant	ca. 5	?	No	Remission
7. Ansseau et al.	45	No	Pneumothorax, cerebral edema, nonspecific meningeal inflammatory reaction	Death
8. Merriam	?	No	Arrythmia	Death
9. Lesaca	15	No	No	Remission
10. Burch and Downs	1	Dantrolene	Cerebral edema, pulmonary and visceral congestion	Death
11. Corrigan and Coulter	6	No	Chest infection	Death
12. Taylor and Schwartz	13	No	No	Remission
13. Washington et al.	1	Dantrolene, lorazepam	Status epilepticus	Death
14. Langlow and Alarcon	ca. 3 weeks	Dantrolene, bromocriptine	Aspiration, pneumonia	Remission
15. Madakasira	ca. 5	No	Urinary tract infection	Remission
16. Baca and Martinelli	25	Dantrolene, bromocriptine	Apnea, sepsis, thrombosis	Remission
17. Halman and Goldbloom	ca. 10	Lorazepam	Dehydration	Remission
18. Heyland and Sauve	4	Dantrolene, Bromocriptine	Ventilation	Remission
19. Otani et al.	?	Levodopa	No	Remission
20. Fava and Galizia	ca. 1–2	Levodopa/carbidopa	Intestinal pseudoobstruction	Remission
21. Miyaoka and Kamijima	11	Bromocriptine	Subileus	Remission
22. Mancias et al.	14	No	Renal failure, pulmonary edema, transient visual loss	Remission
23. Heinemann and Assion	ca. 16	Dantrolene, amantadine	No	Remission

frequently represented without sufficiently considering the presence or absence of symptoms important for the valid diagnosis of NMS. Thus, two of the reported cases did not even include such standard symptoms as rigidity or elevated temperature (criteria A) [23, 26].

Moreover, only few reports consider and discuss relevant differential diagnosis. Therefore, there is reason to doubt whether all reports are actually based on NMS cases. For example, a differential diagnosis of the case described by Halman and Goldbloom [16] could lead to the conclusion that the symptoms described might also be interpreted as an occurrence of the serotonin syndrome. Regarding the pharmacological triggering of the postulated malignant neuroleptic symptoms, it is necessary to point out that in 9 cases the patients were given not only antidepressants, but also neuroleptics, which could have triggered NMS.

Apart from the question of comedication, it is essential to consider all neuroleptic premedications with respect to their duration of efficacy and bioavailability. Thus, neuroleptic premedication was administered in 12 cases. A total of 15 cases in which patients received either neuroleptic premedication or comedication previously or simultaneously is remarkable.

No neuroleptics were prescribed in five of the reported cases. However, two case reports contain insufficient information about the possibly administered premedication [30, 40]. Another case is not well documented [14]. Only two cases are conclusively reported to demonstrate that neuroleptics cannot be responsible for the development of the symptoms [4, 20]. In these cases one might justly see antidepressants as having triggered the disorder. However, whether the symptoms unequivocally allow for diagnosis of NMS or whether they could also be considered for febrile catatonia cannot be definitely established retrospectively.

In the previously mentioned cases the authors had various explanations for the aetiopathogenesis of NMS associated with antidepressants. They can be summarized into four broader concepts.

1. Tricyclic antidepressants and neuroleptics are metabolized by common pathways. Both drugs are supposed to inhibit competitively each other's degradation. This may increase the serum level and thus the likelihood of producing NMS when used concurrently [14]. Unfortunately, the serum levels of both neuroleptics and antidepressants were rarely determined in the described cases.

2. Antidepressants such as dothiepin, amoxapine and trimipramine, have a similar chemical structure to neuroleptics with possible postsynaptic dopaminergic receptor blocking activity [2, 7, 22, 23, 26, 27, 39, 40, 41]. In eight cases amoxapine was considered responsible for the occurrence of NMS. Three of the eight patients had received neither neuroleptic premedication nor any such comedication. Amoxapine belongs to the group of tricyclics but occupies a special position particularly in view of its pharmacodynamic characteristics. The substance is known to have dopamine antagonistic effects and therefore neuroleptic properties [9, 42]. According to results from receptor-binding studies, 100 mg of amoxapine is supposed to be equivalent to 1 mg of haloperidol. Due to its particular pharmacological properties, amoxapine might conceivably trigger NMS, a process which would be in accordance with well-known pathophysiological concepts [25].

3. Serotonin- or norepinephrine reuptake inhibitors may increase central serotonin or norepinephrine levels leading to an imbalance of the ratio to dopamine. This may cause a relative central hypodopaminergic state [4, 16, 30]. This hypothesis is supported by some results from animal studies on various extrapyramidal motor disturbances [5, 8]. To date, however, sufficient clinical data is missing to transfer this pathophysiological explanation to the development of NMS.

4. Long-term treatment with antidepressants may result in a cholinergic receptor supersensitivity evoking a hypodopaminergic state [10].

In conclusion, there is no hard evidence of antidepressants to have solely triggered NMS. Amoxapine must be regarded separately for its dopamine antagonistic properties on a level similar to neuroleptics. Since antidepressive treatment is frequently in combination with neuroleptics, and assuming NMS-inducing properties of antidepressants, one would expect a higher frequency of antidepressant-induced NMS. On the basis of chronic dopamine blocking activity of premedicated neuroleptics, together with elevated serum levels of neuroleptics due to comedicated antidepressants, one may attribute the development of NMS in rare cases strictly to antidepressants. Finally, from our point of view, there is no sufficient clinical evidence of an imbalance between the dopaminergic system and other transmitter systems to explain antidepressant-triggered NMS.

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