Brief Report
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Risk of Neuroleptic Malignant Syndrome with Vesicular Monoamine Transporter Inhibitors

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Objective: Vesicular monoamine transporter-2 (VMAT2) inhibitors have been proven to be effective for the treatment of tardive dyskinesia and their use is likely to increase. The evidence base of published clinical reports was reviewed to evaluate the possible risk of neuroleptic malignant syndrome (NMS) with these drugs.
Methods: Pubmed, Embase, Web of Science and PsycINFO databases were queried for all years using terms for "neuroleptic malignant syndrome", "hyperthermia" AND "vesicular monoamine transporter inhibitors", "reserpine", "tetrabenazine", "valbenazine" or "deutetrabenazine"
Results: Thirteen clinical cases, ten of which involved tetrabenazine, were identified in which VMAT2 inhibitors were prescribed in patients with current or past NMS episodes. In most cases, the association was confounded by limited reporting of clinical data, variable temporal correlation with VMAT2 inhibitors, polypharmacy with antipsychotics, and uncertain differential diagnoses.
Conclusion: While rare cases of NMS meeting consensus criteria have been reported primarily with tetrabenazine, the risk with recently developed VMAT2 inhibitors may be even less. Evidence of causality of NMS with VMAT2 inhibitors is confounded by concomitant treatment with antipsychotics and diagnostic uncertainties in patients susceptible to basal ganglia dysfunction. Nevertheless, clinicians should remain vigilant for early signs of NMS in all patients treated with any drugs that affect brain dopamine activity.

KEY WORDS: Neuroleptic malignant syndrome; Tardive dyskinesia; Antipsychotic agents; Tetrabenazine; Valbenazine; Deutetrabenazine; Huntington's disease.

INTRODUCTION

Dopamine depletion achieved by inhibition of vesicular monoamine transporter-2 (VMAT2) has been a recognized intervention for reducing abnormal movements associated with Huntington's disease, tardive dyskinesia (TD) and other movement disorders [1]. Recent approval by the United States Food and Drug Administration (FDA) of two new, selective VMAT2 inhibitors, valbenazine and deutetrabenazine, for the treatment of TD in adults promises to transform evidence-based treatment of this disorder. These drugs were proven to be effective and safe in suppressing movements of TD in randomized, controlled trials [2]. However, research trials of selected patient samples may not always reveal rare adverse effects that are often recognized only after marketing, when drugs are prescribed to larger segments of the population in real-world settings. For example, neuroleptic malignant syndrome (NMS) is a rare but serious neurological side effect that was first recognized many years after antipsychotic drugs were first introduced [3-7]. NMS has been reported in 0.02% of patients who are treated with antipsychotics [3], but other drugs that affect dopamine neurotransmission have been implicated as well, including VMAT2 inhibitors. In fact, the package labeling for two of the VMAT2 inhibitors (tetrabenazine, deutetrabenazine) include warnings mandated by the FDA concerning the risk of NMS with these agents.

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In view of the likelihood that the new VMAT2 inhibitors will be increasingly prescribed for more patients with TD, and the fact that the number of patients enrolled in research trials of VMAT2 inhibitors may have been too small to detect NMS, it is important to evaluate the accumulated evidence base of published case reports to substantiate or refute the risk of NMS that may occur during treatment with VMAT2 inhibitors.

METHODS

Pubmed, Embase, Web of Science and PsycINFO databases were queried for all years using terms for "neuroleptic malignant syndrome", "hyperthermia" AND "vesicular monoamine transporter inhibitors", "reserpine", "tetrabenazine", "valbenazine" or "deutetrabenazine", yielding 13 case reports of patients with possible NMS episodes who also received treatment with VMAT2 inhibitors [8-19]. This study is a literature review without use of any patient or subject identifying information requiring institutional review.

RESULTS

Thirteen case reports were identified in which NMS-like episodes were described in patients who had been or were receiving VMAT2 inhibitors (Table 1). Ages ranged from seven to 81 years old, with four women and nine men. Twelve patients had evidence of underlying basal ganglia disorders which may increase risk of NMS, with VMAT2 inhibitors used for Huntington's disease in six patients, TD in four (1 case of tardive dystonia), and idiopathic dystonia and catatonia in one each.

Tetrabenazine (12.5−350 mg/day) was implicated in 10 cases, reserpine (1.25−4.5 mg/day) in two and valbenazine in one. Duration of treatment with VMAT2 inhibitors ranged from two weeks to 10 years while only four cases fell within the initial 30 day exposure period typical for the acute onset of nearly all NMS episodes in temporal association with antipsychotics [5]. Polypharmacy existed in all cases; concomitant treatment with adjunctive drugs, such as lithium, has been proposed as possible risk factors for NMS, although this effect has not been confirmed in controlled studies [5]. However, eight cases occurred in combination with antipsychotics. In four of these, NMS symptoms occurred or worsened after the VMAT2 inhibitor was discontinued and antipsychotics were administered [8,9,14,15]. In one case, NMS occurred on tetrabenazine alone after haloperidol was discontinued [10], and in three cases it occurred during concurrent treatment with an antipsychotic and a VMAT2 inhibitor [17-19]. Using International Expert Consensus Criteria that were developed to standardized and reliably define NMS [4], all but one case were near or exceeded the cutoff score for consensus agreement on the diagnosis of NMS (Table 1). In the one case that did not meet criteria for a current diagnosis of NMS [14], the authors describe a patient who had a definite past episode of NMS associated with haloperidol, and years later developed catatonic stupor, extreme rigidity, and rhabdomyolysis while receiving reserpine which then worsened after loxapine was administered. Although there is a known risk of recurrence of NMS on re-challenge with antipsychotics, the less severe or partial symptoms of the second episode in this case associated with reserpine and loxapine may reflect the less potent effects of these drugs on dopaminergic activity compared with haloperidol implicated in the earlier episode [5]. More likely, as the authors opine, the role of reserpine is "problematic" and "incidental" to the reported episode. This case is included in the review for completeness due to the history of both a past episode of NMS and a current episode of malignant catatonia probably due to the underlying psychiatric disorder during VMAT2 treatment in the same patient.

Since NMS is a diagnosis of exclusion, alternative conditions that could be the primary diagnosis in these case reports included heatstroke or serotonin syndrome [13], malignant catatonia due to schizophrenia [14], and intercurrent systemic infection or baclofen withdrawal [16]. Given the limited data in some reports, variable temporal correlation with VMAT2 inhibitors, concurrent treatment with antipsychotics, and possible alternative differential diagnoses, perhaps only five cases, all associated with tetrabenazine, provided persuasive evidence implicating VMAT2 inhibitors as a principal cause of possible NMS [8,10,11,15,17].

Regarding risks of recurrence of NMS following re-challenge with VMAT2 inhibitors, one patient recovered from a past episode of NMS with haloperidol and developed malignant catatonia during or unrelated to long-term treatment with reserpine as described above [14]. Three patients received tetrabenazine after recovery from

Table 1. Cases of NMS-like episodes associated with vesicular monoamine transporter inhibitors

Reference	Age (yr)	Sex	Diagnosis	VMAT inhibitor	Other medications	Clinical features	IEC[a]	Outcome
Burke *et al.* [8]	32	M	HD	Tetrabenazine 350 mg/d (7 months)	α-methyltyrosine 250 mg/d, haloperidol 2 mg	T40°C, dystonia, delirium, diaphoresis,dyspnea, CPK 3,375 U/L	90	Recovered, rechallenged/ tetrabenazine
Haggerty *et al.* [9]	30	M	Psychosis, TD	Reserpine 1.25 mg/d (2 weeks)	Lithium 900 mg/d, diazepam 30 mg/d, haloperidol 5 mg/d, thioridazine 100 mg/d	T40°C, rigidity, hallucinosis, diaphoresis, tachycardia, CPK > 99,999 U/L	100	Recovered
Mateo *et al.* [10]	53	F	HD	Tetrabenazine 100 mg/d (3 weeks)	Haloperidol 2 mg/d (tapered)	T41°C, rigidity, unresponsive, diaphoretic, autonomic Δs, dyspnea, CPK 2,850 U/L	100	Recovered, rechallenged/ tetrabenazine
Ossemann *et al.* [11]	52	M	HD	Tetrabenazine 131 mg/d (2 weeks: ↑dose)	Clonazepam 4.5 mg/d	T41°C, rigidity, CPK 42,350 U/L	72	Recovered, died 2 months later
Petzinger and Bressman [12]	33	F	Depression, tardive dystonia	Tetrabenazine 175 mg/d (4 years)	Benztropine 4 mg/d	T39.2°C, rigidity, delirium/stupor, diaphoresis, autonomic Δs, CPK 5,700 U/L	100	Recovered
Stevens *et al.* [13]	45	M	Depression, TD, heatstroke	Tetrabenazine 75 mg/d (6 months)	Clomipramine 110 mg/d, mianserin 30 mg/d, lorazepam 2.5 mg/d	T41.3°C, delirium, autonomic Δs, dyskinesia, myoclonus, CPK 67,000 U/L	76	Recovered
Boyarsky *et al.* [14]	47	M	Schizophrenia, history of NMS, catatonia	Reserpine 4.5 mg/d (10 years)	Benztropine 1.5 mg/d, clonazepam 1.0 mg/d, loxapine 10 mg	Stupor, rigidity, dyspnea, CPK 1,927 U/L	60	Recovered
Gaasbeek *et al.* [15]	30	M	HD	Tetrabenazine 150 mg/d (17 days: ↑dose)	Benzodiazepines	T41.0°C, agitation, tachycardia, diaphoresis, CPK 14,000 U/L	83	Recovered
	44	F	HD	Tetrabenazine 100 mg/d (tapered over 4 months)	Haloperidol 10 mg/d, clorazepate 15 mg/d	T38.6°C, agitation, mute, tachycardia diaphoresis, CPK 2,779 U/L	73	Recovered
Perret *et al.* [16]	7	M	Dystonia, pneumonia	Tetrabenazine (>12 months)	Baclofen (intrathecal)	T↑, somnolence, dystonia, hypernatremia, metabolic acidosis, CPK ↑, renal failure	78	Recovered
Nozaki *et al.* [17]	81	F	HD, breast cancer	Tetrabenazine 12.5 mg/d (36 days)	Tiapride 75 mg/d, anastrozole, alendronate	T38.5°C, rigidity, drowsiness, autonomic Δs, CPK 999 U/L	100	Recovered, rechallenged/ tetrabenazine
Noori *et al.* [18]	21	M	Schizophrenia, TD	Valbenazine (3 months)	Aripiprazole LAI	T41°C, rigidity, altered mentation, CPK 107,464 U/L	90	Recovered
Illing and Ancill [19]	74	M	Schizophrenia	Tetrabenazine ("several weeks")	Risperidone, triheyphenidyl	T↑, rigidity, tremors, diaphoretic, dyspnea, delirium, CPK 1,606 U/L	100	Recovered

NMS, neuroleptic malignant syndrome; VMAT, vesicular monoamine transporter; IEC, International Expert Consensus; HD, Huntington's disease; TD, tardive dyskinesia; CPK, creatine phosphokinase.
[a]IEC diagnostic criteria score for NMS [4].

NMS without recurrence of symptoms (Table 1).

DISCUSSION

NMS as defined by established consensus criteria has been reported with tetrabenazine treatment but in relatively few cases, considering that it has been available for many years. The risk of NMS with recently developed VMAT2 inhibitors may be even less. Even though there have been no head-to-head comparisons, the idea that

the risk of NMS is reduced with newer VMAT2 inhibitors is consistent with evidence from clinical trials suggesting a decreased risk of other neurological side effects with valbenazine and deutetrabenazine [2,20].

While the association of tetrabenazine with NMS could result from its D2-receptor blocking properties apart from VMAT2 inhibition, the risk may be less than with antipsychotics which in general are more potent D2-receptor antagonists than tetrabenazine and are often titrated more rapidly in parenteral forms [5,21]. The risk should be diminished even further with valbenazine, which lacks significant D2-receptor binding, and with deutetrabenazine, which is effective at lower doses compared to tetrabenazine [2,22]. However, acute interruption of dopamine activity per se by any mechanism, e.g., pre-synaptic dopamine depletion as well as post-synaptic D2-receptor blockade, may be sufficient to produce NMS. For example, an NMS-like syndrome following abrupt cessation of dopamine agonist therapy in Parkinson's disease is well-known [23]. Similarly, pre-synaptic dopamine depletion by VMAT2 inhibitors may raise the risk of NMS, especially when combined with D2-receptor blocking antipsychotics. But whether the property of pre-synaptic dopamine depletion that occurs with VMAT2 inhibitors can be linked to NMS is uncertain; on the contrary, it remains puzzling that striatal dopamine depletion by injections of the neurotoxin 6-hydroxydopamine in animal models of Parkinson's disease has not been associated with life-threatening features of NMS [24].

Although theoretically plausible, credible published reports of the association between VMAT2 inhibitors, primarily tetrabenazine, and NMS are exceedingly rare. While it is possible that NMS may be underdiagnosed or unreported in relation to VMAT2 inhibitors, studies of large, post-marketing regulatory or prescription claims databases may provide a clearer picture of the relative risk of NMS with these drugs. Even if VMAT2 inhibitors have a real but minimal risk of rare NMS episodes in susceptible patients, this does not outweigh the proven benefits of these drugs in reducing abnormal movements that may significantly impact the functioning of large numbers of patients with TD and other movement disorders. However, VMAT2 inhibitors should be prescribed with caution in patients with a history of NMS, which has been shown to recur after re-challenge with antipsychotics [5]. Regarding recognition and reporting of cases of NMS in the future, it may be difficult to tease apart the relative influence of VMAT2 inhibitors versus the more accepted role of antipsychotics in causing NMS when prescribed concurrently. Cases of NMS occurring in the course of antipsychotic treatment instead may be wrongly attributed entirely to VMAT2 inhibitors that are prescribed in combination for coincidental TD. The new VMAT2 inhibitors, which have been proven to be effective and well-tolerated when used alone or in combination with antipsychotics, are a welcome addition to the treatment of TD. Nevertheless, clinicians should remain vigilant for early signs of NMS in all patients treated with any drugs that affect brain dopamine activity.

■ Conflicts of Interest

Dr. Caroff served as a consultant to Neurocrine Biosciences, Inc., TEVA Pharmaceuticals, Osmotica Pharmaceuticals, Dispersol Technologies and received a research grant from Neurocrine Biosciences, Inc.

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