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Expert Opinion

Movement Disorders From the Use of Metoclopramide and Other Antiemetics in the Treatment of Migraine

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Nausea and vomiting are a frequent accompaniment of migraine and anti-nausea medications are frequently used in its management. The majority of anti-nausea medications that are used in migraine are dopamine receptor blocking agents and therefore have the potential to cause drug-induced movement disorders. This article explores the risk of such drug-induced movement disorders in migraineurs who were treated with these medications.

Key words: migraine, acute dystonic reaction, tardive dyskinesia, akathisia, metoclopramide, prochlorperazine, promethazine

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Antinausea medications are often used to control nausea and vomiting, frequent accompaniments of migraine headaches. In addition to reducing the gastrointestinal symptoms, these medications also help to reduce the headache pain itself and therefore are frequently used in the management of acute migraine.[1] Metoclopramide, prochlorperazine, and promethazine are among the most frequently used antinausea medications[2] and their efficacy in acute migraine has been established in multiple studies.[1,3–6] All 3 medications are dopamine receptor blocking agents (DRBA), also referred to as neuroleptics, and, therefore, have the potential to cause drug-induced movement disorders (DIMD) that can be disabling and permanent.[7] However, the risk of DIMD in migraine patients exposed to these drugs is not known. This article discusses the potential DIMD caused by these medications, their frequency and occurrence in migraine patients, and potential preventive and treatment approaches.

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CASE HISTORY

A 28-year-old woman with a history of chronic migraine was hospitalized to receive a 5 day regimen of intravenous dihydroergotamine for an acute exacerbation of her migraine. Each dose of intravenous dihydroergotamine (DHE) was preceded by an infusion of 10 mg of metochlorpromide which was given 30 minutes prior to the DHE infusion. After the second administration of metoclopramide, she developed abnormal posturing of the neck consistent with acute cervical dystonia that resolved with intravenous diphenhydramine.

EXPERT OPINION

What Are the Potential Drug-Induced Movement Disorders That Can Occur Following Exposure to Dopamine Receptor Blocking Agents?—A wide range of hyperkinetic and hypokinetic movements

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can occur following exposure to DRBA. Acute dystonia and acute akathisia are some of the earliest DIMD that can occur following exposure to these medications.

The term *tardive dyskinesia* (TD) is used to describe multiple phenomenologies that include *classic tardive dyskinesia* (CTD), as well as *tardive dystonia*, *tardive akathisia*, *tardive tremor,* and *tardive tics* among others.[7] These are phenomenologically distinct movement disorders but share the same etiological background, namely recent exposure to DRBA. To make a diagnosis of TD there has to be a history of at least 3 months' total cumulative neuroleptic exposure during which the exposure can be continuous or discontinuous, and must have the presence of at least "moderate" abnormal involuntary movements in one or more body areas or at least "mild" movements in 2 or more body areas, and absence of other conditions that might produce abnormal involuntary movements.[8] However, short-term use can also result in persistent TD.[9,10] According to the diagnostic criteria, to make diagnosis of TD, symptoms have to occur within a period of 3 months from the time the medication was discontinued.

Acute akathisia is one of the most common DIMD seen following exposure to DRBA. This has two clinical components: (1) sensory component, subjective feeling of restlessness, and discomfort (such as pain in the mouth or vagina); and (2) motor component manifested by involuntary or unvoluntary (in response to an inner urge) movement and inability to keep still accompanied by stereotypic, seemingly purposeless movements of the limbs, body rocking or rubbing of the face or scalp, and other restless movements. Akathisia frequently goes unrecognized or is mistaken for anxiety or depression.[11,12] The term *acute akathisia* is used when symptoms occur within minutes, hours, or days following exposure to a DRBA. This is often transient and resolves when the medication is discontinued.

Another DIMD that is seen very early on is *acute dystonia* or *acute dystonic reaction*. This is characterized by relatively abrupt onset of dystonia: 50% of patients experience these symptoms within 48 hours and 90% occurs within 5 days of initiating a DRBA.[13] These symptoms can be painful and very alarming to the patient and family. Acute dystonic reaction is typically manifested by oculo-gyric deviations, which consist of extreme and sustained deviations of the eyes upwards, laterally, downwards, or sustained convergence that can last minutes to hours. Acute dystonic reactions can also result in abnormal posturing of the neck (cervical dystonia) such as retrocollis, lateralcollis, torticollis, or a combination. Other abnormal movements include oromandibular dystonia presenting as jaw opening dystonia and lingual dystonia. Overactive cholinergic transmission is one of the suggested hypotheses for this syndrome which is supported by relatively consistent relief of symptoms with anticholinergic drugs (discussed below).[14]

The term CTD refers to the patterned, repetitive, stereotypic movements of the bucco-oro-lingual region manifesting as complex chewing, blowing, licking, lip smacking, pursing, tongue protruding ("fly-catcher's tongue") and facial grimacing movements. CTD can also manifest as repetitive rhythmic writhing movements of the hands, feet, trunk as well as body rocking, shallow and rapid breathing (respiratory dyskinesia), pelvic thrusting (copulatory dyskinesia), crossing and uncrossing of legs, shifting of body weight from one leg to the other, pacing or marching in place, and a variety of vocalizations and noises, such as humming and moaning noises. The risk of CTD depends on the duration of use and the cumulative dose and symptoms can occur during the treatment period or shortly after the dose is tapered off.

Tardive dystonia is characterized by focal dystonia involving jaw, tongue and facial muscles, as well as segmental dystonia involving the neck or paraspinal muscles which can be indistinguishable from idiopathic dystonia. Retrocollis or opisthotonus posturing (arching) accompanied by adduction of arms and extension of elbows is a classic presentation of tardive dystonia. Unlike CTD, which tends to occur predominantly in older females, tardive dystonia tends to occur in males and younger age groups. *Tardive tremor* has been reported with metoclopramide[15] and with other DRBAs.[16] Another DIMD is tardive akathisia which, in contrast to acute

akathisia, follows after chronic exposure and can be permanent.

Drug-induced parkinsonism, manifested by loss of facial expression (hypomimia), slowness of movement (bradykinesia), rest tremor, rigidity, and shuffling gait is another DIMD that can occur after relatively short exposure to DRBA (days or weeks) or following chronic treatment with high doses of DRBA. While two-thirds of all patients with drug-induced parkinsonism recover within 7 weeks of stopping the offending drug, the symptoms can persist for more than 18 months.[17] In some cases, it may persist indefinitely and underlying idiopathic Parkinson's disease is suspected in such cases.[18] Drug-induced parkinsonism has been reported with metoclopramide[19] and essentially all DRBAs. Other, much less common, DIMD seen following exposure to DRBDs include tardive chorea, tardive tics, and tardive myoclonus.

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction that can sometimes be life threatening can occur with metoclopramide[20] and other DRBAs.[21] The clinical triad consists of hyperthermia, rigidity, and alteration of mental status. Symptoms usually begin suddenly and can appear following a single exposure.

What Are the Risk Factors for Development of Drug-Induced Movement Disorders?—Based on epidemiological studies, multiple risk factors have been identified.[22] For acute dystonic reaction, male gender and younger age appears to be a risk factor. For TD, women are at a higher risk than men[23,24] and age is also factor; elderly women carry the greatest risk for CTD.[19,24] The presence of diabetes also increases the risk of CTD.[25] Younger patients are more susceptible to dystonias, whereas the elderly are more likely to develop CTD or drug-induced parkinsonism.[26] The development of TD is directly related to duration of exposure and the cumulative dose. The sooner the offending drug is withdrawn the more likely that the symptoms will resolve over time. The withdrawal of the offending drug, however, must be done gradually as an abrupt discontinuation can actually increase the risk of TD.

What is the Pathophysiology of Abnormal Movements?—Pathophysiology of TD remains poorly understood. It is believed to be the result of chronic blockade of dopamine receptors, particularly D2 and possibly D3 by DRBAs. In addition to dopamine, other neurotransmitter receptors may be important in determining a drug's propensity to facilitate TD, especially 5-hydroxytryptamine 2 (5-HT2) receptors that are widely distributed in the striatum and are thought to be involved in modulating motor activity by interaction with dopaminergic neurotransmission.[27]

One theory for the pathophysiology of TD is that chronic exposure to a DRBA causes postsynaptic dopamine receptor super-sensitivity due to D2 receptor upregulation.[28] By blocking D2 receptors in the nigrostriatal and striatopallidal pathways, metoclopramide and other DRBAs may eventually cause upregulation of D2 receptors and increase the risk for development of TD. This may explain why there is temporary improvement in symptoms of CTD when the dose is increased and exacerbation of symptoms when the medication is suddenly withdrawn. Another hypothesis is that TD is caused by maladaptive synaptic plasticity.[29] This is based on the observation that D2 receptors are inhibitory receptors expressed on medium-spiny neurons that project onto the indirect pathway. Their hypersensitivity can result in disinhibition of the globus pallidus internus and subthalamic nucleus, producing a variety of hyperkinetic movement disorders.[29] Another possibility is that long-term use of DRBAs leads to drug accumulation in the neuromelanin in DA neurons in the substantia nigra with internalization of the cell membranes and cell loss, eventually leading to persistent supersensitivity of postsynaptic dopamine receptors.[30]

What is the Risk of Drug-Induced Movement Disorders With the Use of Metoclopramide, Promethazine, and Prochlorperazine in Migraine Patients?—*Metoclopramide.*—Metoclopramide is a benzamide antiemetic with dopamine type-2 (D2) receptor blocking action. It reduces nausea and vomiting by antagonizing D2 receptors in the chemoreceptor trigger zone. Multiple studies have shown the effectiveness of metoclopramide in acute migraine.[1,3,31,32]

It is commonly used not only as an intravenous drug in the emergency room (ER) setting in

migraine patients but also as one of the most widely used drugs for the treatment of gastroenterologic motility disorders. Metoclopramide accounts for nearly a third of all DIMD, and the entire spectrum of DIMD can be seen in relation to this medication.[33] The Food and Drug Administration (FDA) recommendation is that metoclopramide should be used on a short-term basis, and preferably less than 12 weeks. Because some patients develop DIMD, particularly after chronic use, metoclopramide is frequently implicated in malpractice law suits.[33]

Acute akathisia is one of the most common DIMD seen with metoclopramide in migraineurs, which can range from 4–32%.[1,34–36] Another study showed that acute dystonic reaction or acute akathisia due to metochlorpromide is seen in about 6% of cases, which can occur after a single dose.[9] One study involving 205 patients with acute migraine in the ER setting was evaluated for the incidence and severity of akathisia due to metoclopramide infusion vs bolus dose.[36] Akathisia occurred in 26 of 205 (12.7%) participants, and there was no difference in the rate of akathisia between patients receiving metoclopramide 20 mg as a bolus vs infusion. The median age of participants who developed akathisia was significantly ($P = .04$) younger among those who did (34 years; range: 29–40) compared with those who did not develop akathisia (42 years; range: 40–45). Two other studies showed a higher rate of akathisia, 24.7% (in 146 patients)[35] and 29.3% (in 58 patients),[37] respectively, and akathisia was less when metoclopramide was given as a slow infusion compared with a bolus dose, 5.8% and 6.5%, respectively. Akathisia due to metoclopramide can be a very distressing condition and has been associated with refusal of treatment by the patient and self-discharge,[38] medical litigation,[33] and suicide attempts.[39]

Acute dystonic reactions are also occasionally encountered in patients with acute migraines treated with metoclopramide. In one study, one patient out of 37 (3%) who received 10 mg IV metoclopramide developed an acute dystonic reaction.[40] These can be very uncomfortable and alarming to the patient and can potentially prolong the ER stay or require the patient to return for further evaluation and management.

Outside the migraine population, metoclopramide is commonly used in patients with gastrointestinal disorders and it is a major cause of tardive syndrome in this group. The frequency of TD in patients treated with metoclopramide for gastroparesis was reported to be 1–15%.[41,42] In a retrospective analysis of 434 patients referred for tardive syndrome to a tertiary care center movement disorder clinic, overall metoclopramide was the second most common medication to induce tardive syndrome, after haloperidol, and was responsible for 39.4% of cases in this series.[9] By the year 2000, metoclopramide surpassed haloperidol as the most common medication to induce tardive syndrome.[9] Recent data show that the risk of tardive syndrome due to metoclopramide is likely to be <1%, much less than the estimated 1–10% risk previously suggested in national guidelines.[43] The risk of DIMD is related to the duration of treatment and the total cumulative dose.[34] The risk is highest when taken regularly for longer than three months. NMS, a potentially fatal condition, has been previously reported to be associated with exposure to metoclopramide.[20,44,45]

Although the risk of tardive syndrome related to metoclopramide is well known in patients with gastrointestinal disorders, the incidence in migraineurs is not known as there are no well-conducted studies in migraine patients evaluating this risk. The incidence of other DIMD such as acute akathisia and acute dystonic reactions are reported.[35,37,40,46]

Prochlorperazine.—Prochlorperazine is a dopamine (D2) receptor antagonist that belongs to the phenothiazine class of highly potent antipsychotic agents. It is another commonly used medication in migraineurs and intravenous administration is used in status migrainosus.[5,6,47] In adult studies, as many as 36–44% of patients receiving prochlorperazine developed akathisia,[48–50] a higher frequency than that reported with metoclopramide (4–32%).[1] A randomized controlled trial comparing prochlorperazine to metoclopramide in the treatment of acute migraine, found the rate of akathisia to be 46% for prochlorperazine vs 32% for metoclopramide.[51]

A single case of *tardive dystonia* with prochlorperazine was reported in a 32-year-old male with a

2-year history of migraine[52] who self-medicated with prochlorperazine 10 mg/day for 12 months followed by the same dose for at least 10 days per month over the next 6 months. After 18 months of prochlorperazine use, he developed jaw dystonia characterized by a spasmodic, wide opening of the mouth. During the dystonic periods, he was unable to eat or speak. There was no history of exposure to other medications.[52]

Promethazine.—Promethazine is a neuroleptic and a first-generation antihistamine of the phenothiazine family. It acts primarily as a strong antagonist of the H_1 receptor (antihistamine) and a moderate acetyl choline receptor antagonist, weak to moderate affinity for the 5-HT_{2A}, 5-HT_{2C}, D_2, and α_1-adrenergic receptors, where it acts as an antagonist at all sites. It is usually administered orally or as a rectal suppository. The drug has strong sedative and weak antipsychotic effects. Besides its antiemetic use, promethazine reduces motion sickness.

A randomized clinical trial found that the combination of sumatriptan with promethazine was better than sumatriptan and placebo in patients with acute migraine.[53] In this study, 4.3% of patients experienced "extrapyramidal" symptoms but further details are not available.

What Treatment Do You Recommend for the TD and Other Drug-Induced Movement Disorders?—TD is a rare potential complication with any DRBA used for migraine, especially metoclopramide, which might be discussed with the patient prior to starting treatment. Once a decision is made to use either metoclopramide, prochlorperazine, or promethazine, the lowest effective dose should be used. When providing a prescription for the oral antinausea medication, a limited prescription is recommended, which will prevent the patient from using the medication frequently for a prolonged period of time without any supervision from a physician. The FDA recommends that treatment with metoclopramide for more than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing TD.[54]

Studies have shown that the incidence of akathisia can be reduced by slowing down the infusion rate. With metoclopramide, the frequency of akathisia was significantly ($P < .001$) reduced from 24.7% to 5.8% when the infusion was given at a slower rate, 2 minutes vs 15 minutes, respectively.[35] With prochlorperazine, the incidence of akathisia was also reduced when the infusion rate was slowed down but this was not statistically significant.[50] Combining the antinausea medication with diphenhydramine, which is an antihistamine with anticholinergic prosperities, reduced the incidence of acute akathisia.[2] A randomized trial involving 289 patients who presented to the ER with nausea was evaluated with 2 doses of metoclopramide with diphenhydramine or placebo and concluded that diphenhydramine may decrease subjective restlessness when combined with 20 mg of metoclopramide, but routine prophylaxis with diphenhydramine to prevent akathisia is unwarranted when intravenous metoclopramide is administered over 15 minutes.[55] Combining prochlorperazine with diphenhydramine reduces signs and symptoms of acute akathisia.[56]

In the management of acute dystonic reaction, the first step is to discontinue the offending medication immediately followed by injectable anticholinergic medication such as diphenhydramine. Diphenhydramine may need to be continued for a longer period to reduce relapses. If the dystonia is mild then oral anticholinergics such as benztropine or trihexyphenidyl, or diazepam can be used.

If a tardive syndrome is suspected, then the antinausea medication has to be discontinued but other antiemetics that do not carry the risk of DIMD, such as trimethobenzamide, ondansetron, or domperidone can be helpful (see below). If the patient has been taking the medication on a regular basis, a slow taper is preferred compared with sudden discontinuation as it can exacerbate symptoms. The best medication, available off label, for the treatment of TD is tetrabenazine, approved by the FDA for the treatment of chorea related to Huntington's disease.[57] Tetrabenazine, a dopamine-depleting drug that acts by inhibiting incorporation of dopamine into presynaptic vesicles by blocking the vesicular monoamine transporter 2 (VMAT2), has been found to be the most helpful medication for the various forms of TD.[58] Other VMAT2

inhibitors, such as NBI-9884 and SD-809, are currently in development, and these may have fewer adverse effects and longer duration of action.[59]

Amantadine, although not as effective as tetrabenazine, is an alternative medication, but its efficacy in the treatment of TD has not been established. One should avoid anticholinergics such as benztropine and trihexyphenidyl as these drugs can potentially worsen CTD. Deep brain stimulation surgery may be an option for those with TD that is disabling despite optimal medical therapy.[60] Repeat botulinum toxin injections into the affected muscles in patients with oromandibular, cervical, or other focal or segmental tardive stereotypy or tardive dystonia can provide meaningful improvement lasting about 3–4 months.

Unfortunately, in patients with TD, the rate of complete remission is as low as 2%, although some improvement is likely to occur in 30–50% of patients, particularly children or young adults.[25,61] Overall, 36–55% of patients improve within 3 months after withdrawal of a DRBD.[62]

What Treatment Do You Recommend for Nausea and Vomiting in Migraineurs?—Metoclopramide, promethazine, and prochlorperazine are among the most studied antinausea medications in migraine. Although there are other antinausea medications that do not block dopamine, their efficacy in migraine is not systematically studied. Ondansetron is an antinausea medication that acts as a selective serotonin 5-HT3 receptor antagonist located in the vagus nerve terminals and the chemoreceptor trigger zone in the central nervous system. There are several case reports of showing benefit of ondansetron in migraine[63] and to the contrary there are also several case reports showing ondansetron triggering migraine like headaches.[64,65] Formal studies are clearly needed to evaluate its efficacy in migraine.

Domperidone is a peripheral dopamine (D2) and (D3) receptor antagonist. It provides relief from nausea by blocking receptors at the chemoreceptor trigger zone at the floor of the fourth ventricle. Currently domperidone is not available in the US but it is available in Canada and Europe. A randomized, double-blind, three-way cross-over study compared 1 g of acetaminophen with either domperidone 30 mg, domperidone 20 mg, or placebo, taken at the onset of headache. Forty-six patients completed the study. A significant difference was observed in the duration of the migraine attack: a median of 17.5 hours with acetaminophen alone was reduced to 12.0 hours with the addition of domperidone 20 mg, and to 12.0 hours with domperidone 30 mg. No significant adverse events were reported. A reduction in pain intensity and nausea was noted but this was not statistically significant. It was concluded that domperidone shortens the duration of a migraine attack and may help reduce headache and associated symptoms.[66] Another study also showed effectiveness of domperidone in migraine patients.[67] Currently domperidone is included in the Canadian Headache Society's guidelines for treatment of nausea associated with acute migraine.[68]

There is a need for alternative options to manage nausea and vomiting in migraineurs and further studies with existing non DRBA or newer medications are clearly needed that cause less side effects and no DIMD.

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