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Emil Ștefănescu

*Carol Davila University of Medicine and Pharmacy, [emil\\_e\\_stefanescu@yahoo.com](mailto:emil_e_stefanescu@yahoo.com)*

Mihaela Pleșu

*Nicolae Testemițanu State University of Medicine and Pharmacy*

Corina Scutari

*Nicolae Testemițanu State University of Medicine and Pharmacy*

Adrian Junghină

*Medico Farmaceutic Denyro Ltd*

Horațiu Mireșan

*Ovidius University of Medicine and Pharmacy*

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# Metoclopramide neurological side effects screening; a pharmacovigilance study in Romanian community pharmacies

**Emil Ștefănescu<sup>1</sup>, Mihaela Pleșu<sup>2</sup>, Corina Scutari<sup>3</sup>, Adrian Junghină<sup>4</sup>, Horațiu Mireșan<sup>5</sup>**

<sup>1</sup> Carol Davila University of Medicine and Pharmacy, Department of Pharmacology and Clinical Pharmacy

<sup>2</sup> Emergency Clinical Hospital of Constanța, Department of Pharmacy

<sup>3</sup> Nicolae Testemițanu State University of Medicine and Pharmacy, Department of Pharmacology and Clinical Pharmacy

<sup>4</sup> Medico Farmaceutic Denyro Ltd – Bucharest

<sup>5</sup> Ovidius University of Medicine and Pharmacy, Department of Toxicology

Corresponding author: Emil Ștefănescu, email: [emil\\_e\\_stefanescu@yahoo.com](mailto:emil_e_stefanescu@yahoo.com)

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## Abstract

*Background.* Metoclopramide is a pharmacological agent frequently used in therapy against nausea and vomiting that can occur in indigestion, motion sickness, gastric ulcer, pyloric spasm and after surgery as a side effect of some anesthetics. Knowing the frequency and intensity of metoclopramide neurological side effects is essential for an efficient management of the dysfunctions it addresses.

*Material and method.* Based on a standard questionnaire containing questions regarding metoclopramide therapy, we analyzed the answers given by 1000 patients or patient tutors in 20 open circuit pharmacies situated all over Bucharest. All subjects freely consented to participate in this study that was coordinated only by pharmacists.

*Results.* Our study highlights the fact that in certain situations having to do with the age of patients, with the use of multiple drugs or with the tendency to self medicate, the neurological side

effects of metoclopramide can reach dangerous levels. In some cases it might even be necessary to immediately interrupt metoclopramide therapy, despite its positive benefit/ risk ratio.

*Conclusions.* Respecting the physician's recommendations, avoiding self medication and reporting side effects as quickly as possible, are essential elements for minimizing the consequences of metoclopramide side effects.

## **Introduction**

Metoclopramide is an antiemetic and gastro-prokinetic agent working as a dopaminergic antagonist, currently under close survey by the European Medicines Agency due to its acute and chronic neurological side effects. The Metoclopramide molecule was first described by Besancon and Laville in 1964 and by the end of 1982 it was already available in generic form (1). Since then, the scientific literature has recorded extrapyramidal phenomena as the main side effects of metoclopramide. They consist in dystonia (opisthotonus, torticollis, trismus, dysarthria, oculogyric crisis), akathisia, parkinsonism, tardive dyskinesia and can occur both in high and in usual doses. The incidence of extrapyramidal side effects after metoclopramide use is generally 0.2%, but it can reach up to 25% in elderly patients and teenagers. In children, the risk of this type of side effect occurring is 6 times higher than it is in adults. Tardive dyskinesia and parkinsonism are known to appear only after chronic use while dystonia and akathisia can occur even after a single dose of metoclopramide. The main predisposing factors that favor neurological side effects are: high doses, long term treatment and use of metoclopramide in children and elderly patients. A detailed anamnesis before initiating metoclopramide therapy is necessary in order to avoid wrong diagnostics and inappropriate management of neurological side effects (2, 3).

The clinical manifestations of extrapyramidal symptoms such as dystonia, akathisia, parkinsonism and dyskinesia include an atypical number of involuntary muscle contractions that affect posture, movement and walking (4). The cause of this type of phenomena is most likely the blockage of

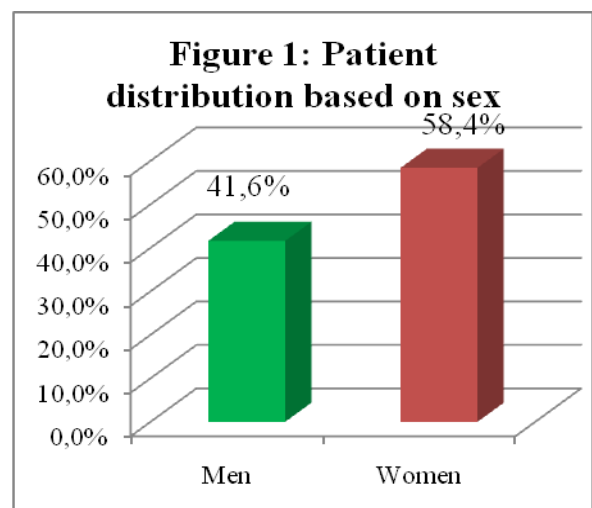
dopamine transmission in various CNS structures. Extrapyramidal symptoms generated by some antipsychotic drugs may also be associated with some other pharmacological agents such as antiemetics, antidepressants, oral antidiabetics, lithium, antiepileptics, and contraceptives (5). The goal of the current study is on one hand to underline the importance of pharmacovigilance in identifying and quantifying foreseeable (dose dependent) side effects and unforeseeable (dose independent) side effects (6) and on the other hand to compare our results to what medical literature describes regarding the neurological side effects of metoclopramide.

## Materials and Methods

1000 patients or tutors of patients were questioned regarding the pathological context that prompted the initiation of metoclopramide therapy and the neurological side effects experienced under these circumstances. The study was conducted in 20 open circuit pharmacies between March of 2014 and June of the same year. Only pharmacists asked the questions, noted the answers and explained the medical terminology to the patients.

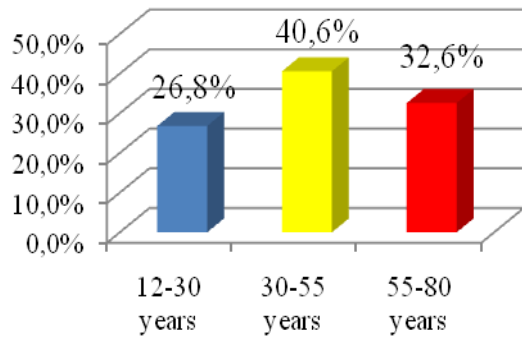
Inclusion criteria were as follow: Age of patients between 12 and 80 years old, maximum 2 additional illnesses or associated co-morbidities (patients with major decompensated neurological conditions were not enlisted in this study), absence of known conditions that reduce the activity of organs involved in drug biotransformation and elimination (liver and/or kidney)

*Statistics.* The statistical calculus of the percentages expressing the results of our study was done using Microsoft Excel 2003 software.

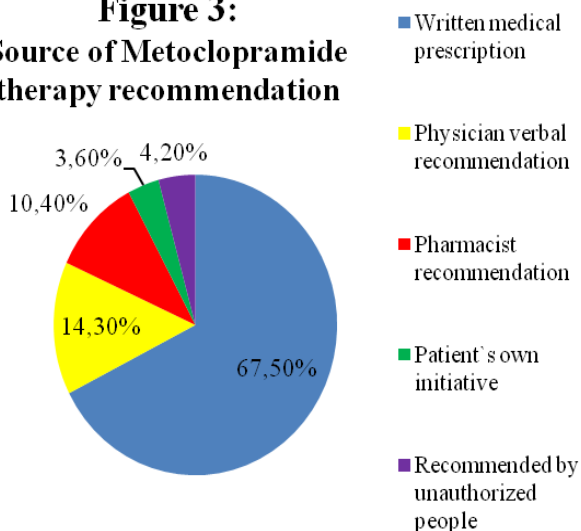


## Results

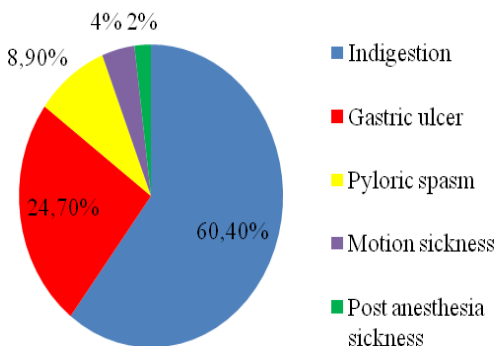
**Figure 2: Patient distribution in age groups**



**Figure 3: Source of Metoclopramide therapy recommendation**



**Figure 4: Diagnostic that prompted Metoclopramide therapy**

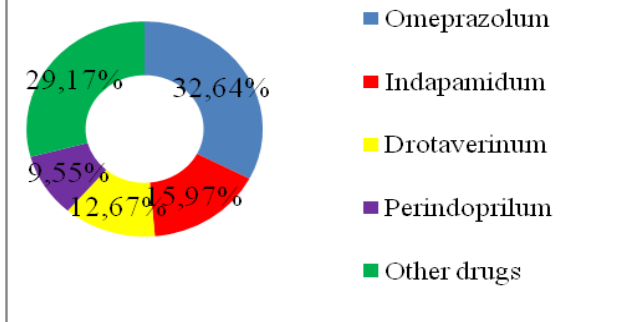


After the centralization of all data we report the following results: the sex distribution of the subjects showed that 58.4% of the patients were female and 41.6% were male. Taking into account the age criteria, 26.8% were between 12 and 30 years old, 40.6% between 30 and 55 years old and 32.6% between 55 and 80 years old. Metoclopramide therapy was initiated based on a written medical prescription in 67.5% of cases, based on the physician's verbal recommendation in 14.3% of cases, based on the pharmacist's recommendation in 10.4% of cases, based on patient's own initiative in 3.6% of cases and based on the recommendation of unauthorized persons in 4.2% of cases.

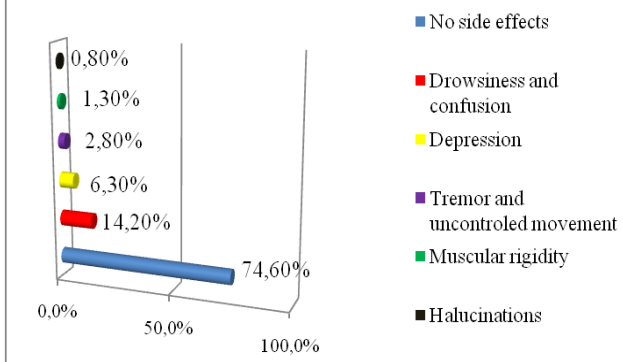
The diagnostic that prompted the initiation of metoclopramide therapy was indigestion in 60.4% of cases, gastric ulcer in 24.7% of cases, pyloric spasm in 8.9% of cases, motion sickness in 4% of cases and post anesthetic sickness in 2% of cases. 57.6% of all patients reported using other drugs while being under metoclopramide therapy. 32.64% of them (188 individuals) reported using omeprazole, 15.97% (92 individuals) reported using indapamide, 12.67% (73

individuals) reported using drotaverine, and 9.55% (55 individuals) reported using perindopril and 29.17% (168 individuals) reported using other drugs.

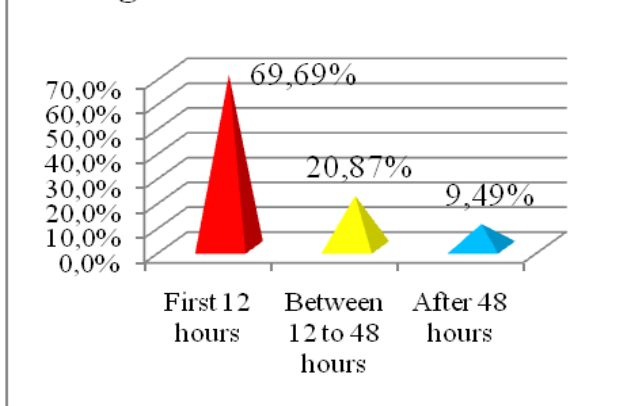
**Figure 5: Drugs used by some patients alongside with Metoclopramide therapy**



**Figure 6: Incidence and nature of reported side effects**



**Figure 7: Side effect debut**

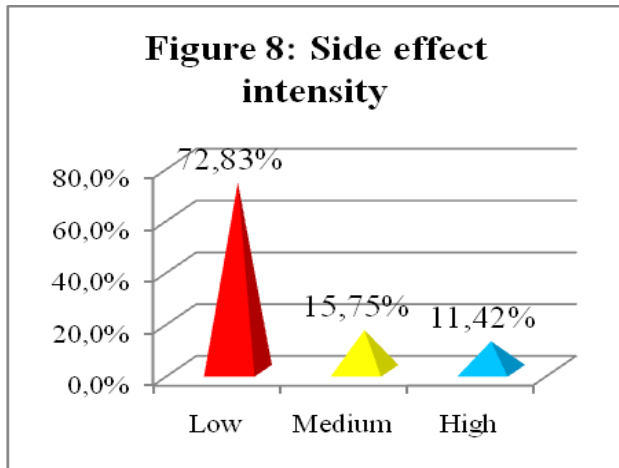


Regarding side effects, 74.6% of patients reported no side effects what so ever, 14.2% reported sleepiness and confusion, 6.3% reported depression, 2.8% reported tremors and uncontrolled movements, 1.3% reported muscle rigidity and 0.8% reported hallucinations and altered states of conscience. Out of the 254 patients that did report side effects, 69.69% reported experiencing them in the first 12 hours, 20.87% felt them between 12 and 48 hours after initiating metoclopramide therapy and in 9.49% of cases, the side effects occurred more than 48 hours after the first dose of metoclopramide. Regarding side effect intensity, 72.83% of patients (185 individuals) considered them as having a low intensity, 15.75% (40 individuals) rated the side effects as being moderate and 11.42% (29 individuals) felt them with severe intensity.

Analyzing the age of patients that reported side effects we observed that 42.51% (108 individuals) were between 12 and 30 years old, 25.98% (66 individuals) were between 30 and 55

years old and 31.51% (80 individuals) were between 55 and 80 years old.

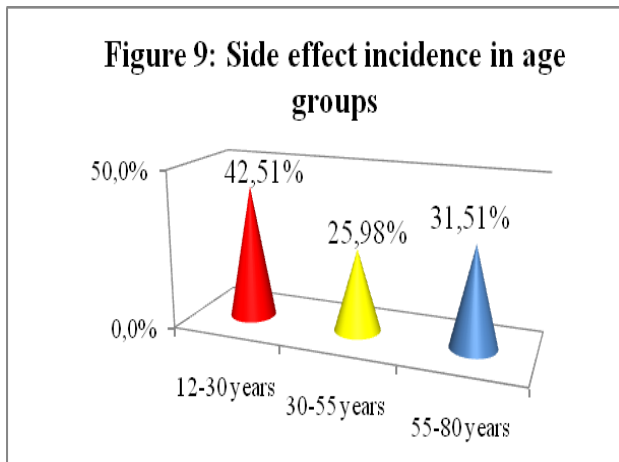
Out of the 254 patients that reported side effects after using metoclopramide, 38.98% (99 individuals) were also under treatment with omeprazole. Analyzing compliance, we observed a higher



tendency to noncompliance, especially by reducing the interval between doses and by increasing prescribed doses in patients below the age of 30. This observation can be correlated with the higher incidence of side effects reported by this age group.

Analyzing the individual cases of patients that reported moderate and severe side effects we noted

the following particular situations:



5 patients were under treatment with selective inhibitors of serotonin recapture (2 with fluoxetine 100mg/day and 3 with paroxetine 20mg/day) when they started administering metoclopramide and reported agitation, hyperexcitability, tremors,

hyperthermia and intense sweating

- 7 patients were under treatment with first generation antihistaminic drugs (5 with cyproheptadine 4mg/day and 2 with chlorpheniramine 8mg/day) when they started administering metoclopramide and reported intense daytime sleepiness, lack of motor coordination and inability to perform precision requiring activities
- 4 patients were under treatment with antidopaminergic neuroleptics (2 with haloperidol 2mg/day and 2 with chlorpromazine 10mg/day) when they started administering metoclopramide and reported involuntary movement of neck and tongue muscles, rigidity in extremities, hyperthermia and hallucinations

- 2 epileptic patients under treatment with carbamazepine (400mg/day) reported an epileptic seizure more intense than usual in the first 12 to 36 hours after initiating metoclopramide therapy

## Discussion

Metoclopramide is the first choice antiemetic for treating nausea due to intestinal disorders, hepatic or gall dysfunctions, but it can also be used to some extent in nausea and vomiting induced by radiotherapy, chemotherapy, Ménière syndrome and motion sickness. Metoclopramide is also a gastroprokinetic drug due to its peripheral cholinergic mechanism and is used in gastrointestinal reflux and pyloric spasm because it increases the tonus of the Cardia sphincter, it relaxes the pyloric sphincter, it speeds up the emptying of the stomach, it improves intestinal transit and it enhances the peristaltic movement of the esophagus, the stomach and intestines (6, 7). Metoclopramide has two main types of mechanisms that explain on one hand the therapeutic effects (antiemetic, gastroprokinetic) and on the other hand, the neurological side effects (sleepiness, anxiety, depression, dystonia, akathisia, parkinsonism, dyskinesia) and the abdominal side effects (diarrhea, constipation, flatulence):

- D2 dopaminergic receptors antagonist both on a central level in the rachidian bulb and in the triggering chemoreceptor area and on a peripheral level in the gastrointestinal tract; by exacerbating the D2 blockage, extrapyramidal effects manifest themselves especially in children, teenagers and elderly patients. They consist in dystonic movements of the face, tongue and limbs, tetanic spasm, torticollis, trismus, tardive dyskinesia and akathisia. Another antidopaminergic related side effect is hyperprolactinemia often associated with diminished libido, gynecomastia, galactorrhea and amenorrhea.
- Cholinergic effect by releasing acetylcholine in the digestive neuroeffector junctions, thus accelerating the emptying of the stomach and improving intestinal transit; exacerbating the cholinergic mechanisms leads to symptoms such as diarrhea and abdominal pain (6, 8).

Medical literature describes the following neurological side effects of metoclopramide:



Dyskinesia consists in rapid, involuntary and repetitive movements of the face, torso, limbs and respiratory muscles. This is an extrapyramidal side effect that can have an early or a late onset (tardive dyskinesia) and is irreversible in about 6% of cases (4). Metoclopramide induced tardive dyskinesia has an incidence lower than 1%. The favoring factors for this condition are the long term use, old age, female gender, diabetes, preexisting abnormal movements, organic cerebral lesions and psychic disorders (3).

A study on a group of 51 hospitalized patients, all under metoclopramide therapy for at least 30 days, demonstrated that 27% of them developed tardive dyskinesia symptoms, compared to only 12% that developed the same symptoms in the control group (9).

Dystonia consists in involuntary muscle contractions of the torso and neck (torticollis, opisthotonus), limbs, tongue, face, eyes, laryngeal spasm, pharyngeal dysphagia, hoarseness and oculogyric crisis. The incidence of metoclopramide induced acute dystonia is between 0.2% and 6%, especially occurring in women after intravenous administration of relative high doses. These manifestations usually can be observed in the first 24-48 hours after the initiation of metoclopramide therapy (3, 4, 10).

Akathisia is an extrapyramidal disorder characterized by a feeling of unease, anxiety, permanent and meaningless movements of the extremities or of the entire body. The incidence of metoclopramide induced akathisia is between 10% and 25%, it can have various levels of severity and it can be prevented by reducing the speed of metoclopramide intravenous injection. Benzodiazepines,  $\beta$ -blockers, opioids,  $\alpha_2$  presynaptic agonists and anticholinergic drugs can be used for treating this disorder (3, 4, 11).

Parkinsonism is characterized by tremors, bradykinesia, muscle rigidity and posture instability. Long term use of metoclopramide, old age, female gender, diabetes and multiple drug abuse are favoring factors for metoclopramide induced parkinsonism. Patients using metoclopramide are 3 times more likely to require antiparkinson treatment than patients that are not using this antiemetic (12).

Out of 479 reported cases of metoclopramide induced extrapyramidal effects in the UK over a period of 15 years, 455 were acute dystonia reports, 20 were parkinsonism reports, and 4 were tardive dyskinesia reports (10).

Constant reports regarding metoclopramide extrapyramidal side effects were registered all over the world ever since this drug was first introduced in therapy up to the present day. This fact prompted the development of a standardized quantification system in order to better understand the clinical manifestations of extrapyramidal side effects. Thus the Abnormal Involuntary Movement Scale (AIMS) was created as a tool for cataloging this type of manifestations both from a qualitative and a quantitative point of view. With the help of AIMS, several irregular movements were characterized in 7 distinct areas of the body, especially the face, mouth, extremities and torso. The AIMS score is now a useful tool that allows a better management of extrapyramidal disorders (4).

The results of our study, generally confirm the known data described by medical literature regarding metoclopramide neurological side effects, but also reveal some elements that are characteristic to Romanian patients. Thus, the study shows that metoclopramide therapy was initiated based on a written medical prescription in only 67.5% of cases. This is a relatively low percentage compared to the one observed in western countries where more than 90% of patients start administering drugs only after getting a written medical prescription. Our study also highlights the fact that 7.8% of patients have chosen to self administer metoclopramide based on their own knowledge about the drug or on the recommendation of unauthorized persons. In other countries less than 2% of patients do the same (13).

Regarding side effects, a little over a quarter of all patients (25.4%) reported experiencing them. 72.83% of these patients rated the side effect intensity as being low or moderate.

Analyzing the use of multiple drugs at the same time, we noted that more than half of all patients (57.6%) reported using at least one other drug while under treatment with metoclopramide. 32.64% indicated omeprazole as being that drug. When correlating the side effect reports with multiple drug use

reports, we calculated that 38.98% of patients that reported side effects had taken metoclopramide at the same time with omeprazole. This situation can be explained by the fact that omeprazole is a known CYP2C19 and CYP3A4 inhibitor, thus determining a relative overdosing of metoclopramide, when the 2 drugs are used at the same time. A similar phenomenon occurs when metoclopramide is used simultaneously with fluoxetine or paroxetine, as the 2 antidepressants are strong CYP2D6 inhibitors and can also determine a relative overdosing of metoclopramide (14), which explains why these patients reported more intense side effects. An additional explanation for a higher intensity of side effects in this particular case may also be related to a 5HT<sub>4</sub> receptors agonist mechanism that metoclopramide is reported to have, thus favoring the onset of a serotonergic syndrome (15).

The sedation induced by 1<sup>st</sup> generation antihistaminic drugs (H<sub>1</sub>-blockers) was significantly enhanced during metoclopramide therapy in 7 patients. They reported intense daytime sleepiness and increased time reaction to external stimuli, which confirm the CNS inhibition effect of metoclopramide, especially when the nervous tonus is already depressed.

Symptoms more or less intense, characteristic to the malignant neuroleptic syndrome were described by a patient under treatment with the incisive neuroleptic drug haloperidol and by another one under treatment with the sedative neuroleptic agent chlorpromazine. These symptoms manifested themselves 12 hours or more after initiating metoclopramide therapy and can be explained by the synergism of addition that occurs between the antiemetic and the antipsychotic drugs, both having an antidopaminergic mechanism.

The onset of a convulsive episode more intense than usual, reported by 2 epileptic patients under treatment with carbamazepine, while taking metoclopramide at the same time, can be explained by the gastroprokinetic effect of this drug that accelerates the intestinal transit, thus reducing the absorption rate of the antiepileptic.

## Conclusions

The current study underlines the importance of pharmacovigilance in identifying drug side effects and their favoring factors (multiple drug use, noncompliance, self medication). Our results confirm the data described by medical literature regarding metoclopramide neurological side effects. The relatively low incidence of side effects we observed proves that the benefit/risk ratio of metoclopramide continues to be a positive one. However closer monitoring of pharmacokinetic and pharmacodynamic interactions is absolutely necessary in order to prevent the onset of unwanted effects, especially in a complex pathological context that requires multiple drug use.

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