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Review Article

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PHARMACOVIGILANCE STUDY ON PROTON PUMP INHIBITORS

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ABSTRACT

Pharmacovigilance is the science that deals with the study of adverse effects associated with a particular drug. Proton pump inhibitors (PPI) are drugs that are used in the management of gastric acid-related disorders, seeing as how their introduction to the market in 1999. These drugs have a mechanism of action based on the last step of gastric acid secretion by a peripheral cell and very few, mostly tolerable adverse effects. However, the use of PPI may lead to long-term adverse effects, including liver infection, an increased risk of kidney disease, dementia, cardiovascular disease, enteroendocrine tumors of the GIT, and respiratory, gastrointestinal, and respiratory infections. It is very important to raise new questions about PPI safety profiles and their clinical indications. Thus, the main aim of this review is to assess the worth of the concern about the association between the use of PPI and the risk of serious adverse effects.

KEYWORDS: Proton pump inhibitors, Gastrointestinal reflux diseases, chronic kidney disease, cardiovascular disease, omeprazole-induced galactorrhea, carcinogenic effects of omeprazole.

INTRODUCTION

Pharmacovigilance: The clinical research starting from drug discovery to post-marketing surveillance is known as pharmacovigilance. According to the WHO, pharmacovigilance may be defined as the science in which we can detect, assess, understand, and prevent adverse effects or any other possible drug-related problems. It is most important to identify the adverse drug reactions of patients taking medications. Identification of an adverse drug reaction is important for the safety of patients. This information is received from healthcare professionals, pharmaceutical companies, and patients.

According to the National Library of Medicine, "Pharmacovigilance of drugs is important to promote the safe use of drugs.

Need of Pharmacovigilance

- To promote the safe use of drugs
- Early detection of adverse drug reactions.

Objectives of pharmacovigilance

- To improve patient care
- To promote understanding, clinical training, and education in pharmacovigilance
- To improve the safety of patient
- To improve public health services
- To provide medicines and all medical and paramedical services safe.
- To understand the risks, benefits, and effectiveness of medicines.
- To support effective communication to health care professionals and the public.

Pharmacovigilance Program of India (PvPI): It was launched on July 14, 2010. India joined WHO PIDM (the WHO program for international drug monitoring) in 1998. PvPI is generally managed by the IPC (Indian Pharmacopeial Commission). The PvPI works as a safeguard for India. The main aim of this program is to build trust between physicians and patients by increasing patient safety. The various challenges are faced by PvPI, like monitoring generic drugs, biosimilar drugs, and disease-specific ADR of cardiovascular, antidiabetic, etc., and creating awareness, which is a continuous process.

UPPSALA Monitoring Centre (WHO Collaborative Centre): It was established in 1978. It is present in Sweden. This centre is operated by the WHO, and 124 countries have joined it till now.

ADR: ADR may be defined as the unintended, unwanted reactions that occur in our body during the period of medication.

Unwanted and harmful reactions are experienced after the administration of a drug or combination of drugs under normal conditions of use. e.g., thalidomide birth defects.

Classification of ADRs

1. **Depending on the onset of the event**

- Acute ADR (quick action)
- Subacute ADR
- Latent ADR

2. **Types of reaction**

- **Type A (augmented effect):** The reaction is predicted from the known pharmacology of the drug. ADRs are minimized by adjusting the dose. E.g., Bradycardia is caused by beta blockers.
- **Type B (Bizarre Effect):** This type of reaction occurs suddenly for an unknown reason. E.g., allergy due to hypersensitivity.
- **Type C (chronic effect):** This type of ADR occurs due to the prolonged use of drugs. E.g., NSAIDS causes nephrotoxicity.
- **Type D (delay effect):** This type of reaction occurs when the effect of a drug is delayed after prolonged use of the drug. E.g., carcinogens cause cancer.
- **Type E (end of use):** This type of ADR occurs when we suddenly stop the use of a drug that we have been taking for a long time., E.g hypertension after beta blockers.
- **Type F (failure):** This type of ADR occurs when drugs fail to show their efficacy. This does not show their effect. E.g., the use of oral contraceptives

1.1 Proton Pump Inhibitors

The stomach secretes acidic fluid at a low pH, i.e., 2. Gastric secretion is important for the sterilization of bacteria that are present in the ingested food, and this gastric secretion is also used for the absorption of various nutrients (such as vitamins, proteins, etc.) and the digestion of food. From that point, this gastric acidic fluid may damage the gastrointestinal tract and mucosal secretion.[1] This secretion of acid conquers these protective mechanisms; after that, the gastrointestinal mucosa becomes damaged and irritated. That results in unnecessary symptoms or diseases. These conditions may cause acid-related diseases such as gastric-duodenal ulcers, gastroesophageal reflux disease (GERD), Barrett's esophagus, etc. For the treatment of acid-related diseases, various inhibitors of gastric fluid have been developed.[1,2]

PPIs are generally used for the treatment of gastrointestinal disorders worldwide. Focusing on GERD, 25% of people in developed countries experience dyspepsia (indigestion) at least per month.[3,4]

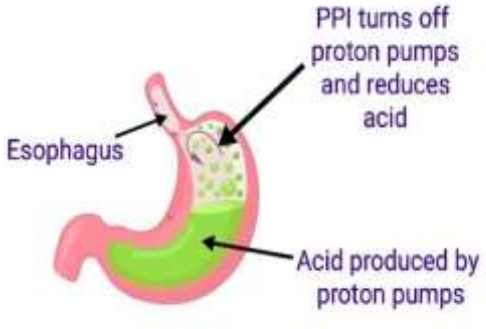


Figure 1: Effect Of PPI On Gastric Acid.

Proton pump inhibitors are broadly used to reduce the production of gastric acid in the stomach. The proton pump inhibitors work on the fact that they irreversibly block an enzyme called H+/K+ ATPase, which controls acid production in the stomach. This enzyme is found in parietal cells, and this enzyme is also known as the proton pump.

Proton pump inhibitors have largely replaced the H_2-receptor antagonists (a group of medications with similar effects but different modes of action) and antacids.[5]

PPIs are the most widely sold drug in the world. The PPIs are the medications that are on the World Health Organization's list of essential medicines.

Medical Uses of PPI

These medications are used to treat many conditions, like

- Dyspepsia
- Peptic ulcer
- Zollinger-Ellison syndrome
- Non-erosive reflux disease
- *Helicobacter pylori* infections
- Gastroesophageal reflux disease

Classification of PPI

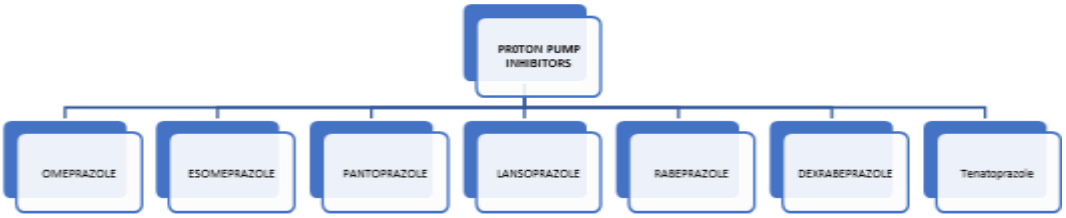
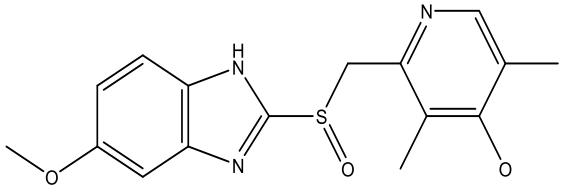
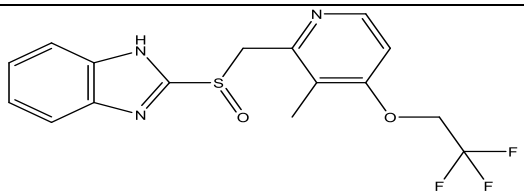
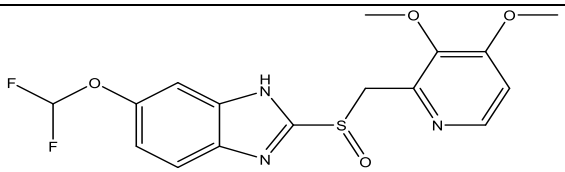
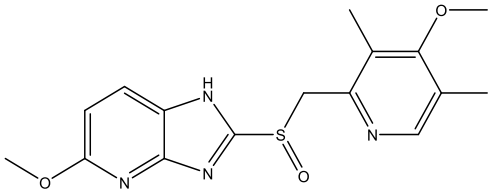


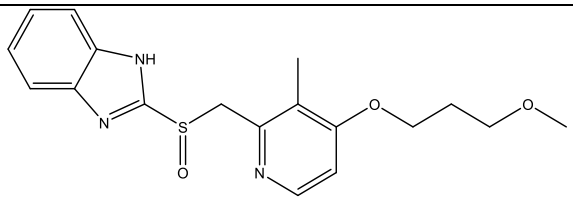
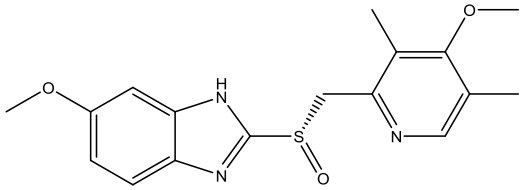
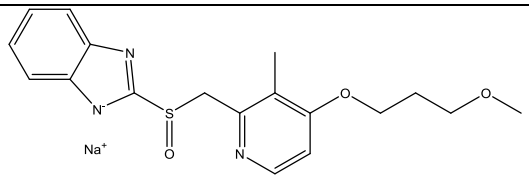
Figure 2: Proton pump classification.

Omeprazole was the first class of PPI that is a useful compound and was introduced in the market in 1989.[6] The structure of omeprazole is,5-methoxy-2-[(4-mehoxy-3,5-dimethyl-2-pyridinyl) methylsulphinyl]-1H-benzimidazole is shown in figure 3, and the structures of the other commonly used PPI's, lansoprazole, pantoprazole, tenatoprazole (newer PPI discovered) and rabeprazole which have benzimidazole. 2(pyridinylmethylsulfinyl) benzimidazole.

Esomeprazole is the isomer of omeprazole which shows therapeutic effects. Esomeprazole is the racemic mixture of (R)- and (S)-isomers. In comparison with omeprazole, esomeprazole shows less dose-related adverse effects.[7,8] Dex rabeprazole is an isomeric form of rabeprazole used in the treatment of gastroesophageal reflux diseases by decreasing gastric acid secretion.

Table 1: Classification of drugs along with their chemical structures, generic name, and their mechanism of action.

Sr. no.	Name of Drug	Structure	Generic Name	Mechanism of action
1.	Omeprazole	 omeprazole	Prilosec	It blocks the enzyme ATPase and inhibits the secretion of gastric acid.
2.	Lansoprazole	 lansoprazole	Prevacid	It inhibits H+/K+ ATPase enzyme in gastric parietal cells.
3.	Pantoprazole	 Pantaprazole	Protonix	It blocks the enzyme ATPase and inhibits the secretion of gastric acid.
4.	Tenatoprazole	 Tenatoprazole	Benatoprazole	It blocks the enzyme ATPase and inhibits the secretion of gastric acid.

5.	Rabeprazole	 Rabeprazole	Aciphex	It generally inactivates the gastric parietal cell H+/K+ ATPase.
6.	Esomeprazole	 Esomeprazole	Nexium	It decreases gastric acid secretion by inhibition of H+K+-ATPase in the parietal cell in the stomach.
7.	Dex rabeprazole	 Dexarabeprazole	Aciphex	inactivates the gastric parietal cell H+/K+ ATPase.

SIDE EFFECTS ASSOCIATED WITH THE USE OF PPI

In general, PPI shows few side effects, but they are preventable. People have experienced side effects after the use of short-term PPI, such as headaches, dizziness, rashes, and gastrointestinal symptoms, i.e., nausea, constipation, fatigue, and diarrhea. If these side effects are not cured within 2 weeks, then physicians and doctors will be concerned about these side effects. If the use of these drugs increases, then the side effects will also increase with long-term use.[9]

Recent studies show that PPIs should be used for the shortest period of time at the smallest effective dose,[10] such as infections, dementia, kidney disease, and hypergastrinemia-related side effects are associated with the long-term use of PPIs.[9]

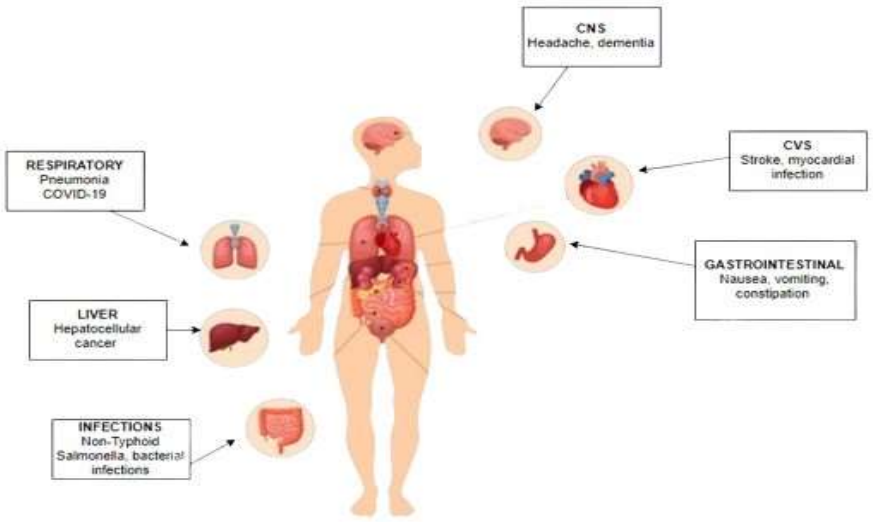


Figure 2: Side effects shown with the use of PPIs.

1. Kidney disease

After 1992, many cases of acute kidney injury were shown with the use of PPI.[9] and after that, two studies were linked with the risk of chronic kidney disease (CKD), which was not exclusively caused by the risk of acute kidney injury. The patients who used PPIs for the long term had an inflated risk of CKD.[11]

The main mechanism contributing to renal pathology due to the use of PPI could be acute interstitial nephritis. 50% of the patients who suffered from PPI-induced acute

interstitial nephritis.[12] did not fully recover. It led to the belief that PPI-induced CKD is due to the succession of acute interstitial nephritis with hydropsy to chronic interstitial scarring and tubular atrophy. These discoveries show good substantiation that PPIs cause acute interstitial nephritis, and some other evidence shows that they also increase the risk of CKD.[13,14]

2. Infections

Gastrointestinal infections

PPI has been associated with a major risk of both incidental and recurrent Clostridium difficile infection.[15,18] Acid secretion in the gastrointestinal tract by parietal cells is a major immunological barrier that results in a deficiency of stomach acid. The inhibition of gastric acid secretion is associated with an increased risk of Clostridium difficile infections.[9] Studies have indicated that intense inhibition of gastric acid secretion is linked with an increase in the risk of Clostridium difficile infection. Researchers have reported other enteric infections, such as non-typhoid Salmonella and Campylobacter infections.[15]

Gastrointestinal malignancies

With the ingestion of PPIs, gastric acid secretion decreases, and the remunerative raising of gastric acid levels in patients has had a bursting effect on the growth of the cells, indicating the linkage of PPIs with the development of neuroendocrine tumors and cancer of the gastrointestinal tract.[19-21]

Its other mechanism is that it facilitates gastric colonization by the bacteria *Helicobacter pylori* because of the decrease in the normal stomach acidic secretion.[22]

In recent studies, it has been observed that reducing the level of acidity and hypergastrinemia may be the cause of gastric cancer in the fundus region of the stomach.

3. Respiratory infection

Pneumonia

The intake of PPIs is associated with pneumonia (short-term effect), that is, fewer than 30–90 days, regardless of how, in recent studies, it has been shown that this association may be overestimated.[23] With the increased PPI intake, there is an increased risk of respiratory infections, including hypochlorhydria, which increases the microaspiration of gastric acid, which generally increases lung colonization and pneumonia.[9]

COVID- 19

The coronavirus disease (COVID-19) is also associated with the use of PPI. As researchers have shown in their recent studies, these drugs have shown a positive risk of COVID-19.[24] The impact of acid suppression is unclear, as coronaviruses are easily destroyed by an acidic gastric pH. Past studies say that individuals with a gastric pH of up to 3 have fewer chances of developing a severe acute respiratory syndrome coronavirus 1.[24] Moreover, researchers have shown that patients with a basic gastric pH (who use drugs like omeprazole and esomeprazole) have larger chances of surviving the coronavirus.[24] Hence, it is shown that current and past use of PPI was linked with poor aftereffects of COVID-19. However, the use of PPIs did not increase the vulnerability to a severe acute respiratory syndrome coronavirus 2 infection.[24]

4. Liver infection

The use of PPI is also associated with liver complications like liver cancer and hepatic encephalopathy.[21-24] These effects are seen with the chronic use of PPI. Any patient who takes PPI for more than one year has the risk of developing hepatocellular carcinoma.[9] The scientific researcher observed that H+/K+ ATPase inhibition may cause intestinal bacterial growth, but the mechanism of liver injury caused by using PPI is not properly understood.[25] Most of the PPIs are metabolized in the liver. Still, those who have liver disease may increase their risk of hepatotoxicity, which can have an effect on the liver cells and cause hypergastrinemia-induced carcinogenic effects.[26-27] The researcher reported that the use of PPI may cause carcinogens in the liver (liver cell gene expression inhibition).[28]

5. Cardiovascular Disease

During the past decade, the use of PPIs has been linked with cardiovascular illness and mortality.[29] The use of a high dose of PPI shows that it is linked to cardiovascular diseases like acute myocardial infarction and stroke.[30-31] The use of PPI is also concerned with the risk of malignant ventricular arrhythmias due to the development of hypomagnesemia (an electrolyte disorder caused by a low serum magnesium level in the blood).[32] PPI inhibits the dimethylarginine dimethylaminohydrolase enzyme, which reduces nitrous oxide synthesis.[33] The use of PPI also increases the level of chromogranin A (which is an important marker of neuroendocrine tumors and also a biomarker of cardiovascular disease).[34]

6. Risk of Fracture

The use of PPI may increase the risk of fracture.[35] Re-evaluation studies indicate that the relationship between PPI and low bone mineral density is dose-dependent, leading to a higher risk of fracture, mainly hip fractures. This risk factor may be seen in patients with a higher risk of osteoporosis (weakness of the bones). Regular treatment for osteoporosis is recommended for PPI users to prevent osteoporotic fractures.[35-37] According to recent studies, researchers show that the short- to medium-term use of PPI may not lead to fracture risk.[38-39] This is mainly linked with long-term PPI-based theory and decreased fracture risk, including hypochlorhydria associated with malabsorption of calcium and inhibition of bone reabsorption by inhibiting H+/K+ATPase.[40,42]

7. Dementia

The risk of PPI use includes dementia. Researchers have yet to come to terms with the risk of dementia due to the

use of PPI. Chronic administration of proton pump inhibitors is associated with brain dysfunction.[43] Some neurological side effects, such as dizziness and headaches, are also associated with the increased use of PPI. Short-term side effects with the use of PPI include drowsiness, depression, nervousness, insomnia, hallucinations, etc.[44] Even though the mechanism of action is not clear, neurological effects are caused by ionic pumps that sway the membrane potential of nerve cells.[43] The lysosomes of the patient are less acidic when they use PPI as compared to those who do not, which may decrease the accumulation in the brain in patients suffering from Alzheimer's disease.[45–46] Other causes include magnesium and vitamin B12 deficiency.

8. Other ADR includes

8.1 Case report of omeprazole causing Galactorrhea in kidney transplant patients

The use of PPI, including omeprazole, may cause Galactorrhea in kidney transplant patients. Omeprazole generally affects a metabolic process that includes tacrolimus levels *(a* macrolide immunosuppressant agent is indicated for the prophylaxis of organ rejection in patients) that requires therapeutic drug monitoring of tacrolimus in the patient of a kidney transplant to avoid acute graft rejection. The ingestion of omeprazole causes galactorrhea, a rare reaction that is based on the omeprazole metabolic process. The seven cases of Galactorrhea caused by the ingestion of omeprazole were reported in the VigiBase system maintained by the UPSALA Monitoring Centre on July 13, 2021. Through these, two cases were reported by the ICSR (individual case safety reports) from Germany, France, Spain, and the Netherlands. It is very important to report rare drug reactions to health professionals and become aware of these drug reactions.

8.1.1 Galactorrhea (hyperprolectemina)

It is defined as non-lactational milk production after pregnancy and the termination of breastfeeding. It may occur in women who have never given birth to offspring, in postmenopausal women, and even in men. Even though this is a very rare reaction, it can occur in 90% of women with hyperprolectemina (an elevated blood lactate concentration). The main hormones that are responsible for lactation and breast development are estrogen, progesterone, and prolactin (PRL). Due to the lack of morphological symptoms, lack of awareness among doctors and patients, and mainly due to embarrassment, drug-induced hyperprolactinemia is a concern due to the insufficient reporting of these drug reactions.

As per Franch pharmacovigilance databases, it is observed that from 1985–2000, there were 182,836 concurrent adverse drug reaction reactions, of which 159 (0.08%) were linked with hyperprolactinemia.[47] The male-to-female sex ratio was 5.9, i.e., 136 women and 29 men, and their mean age was 40 (18–85) years. It includes neuroleptics (31%), neuroleptic-like drugs (28%), antidepressants (26%), H2 receptor antagonists (5%), and others (10%), as per the same report.[48] The main mechanism includes neuroleptic drugs that induce galactorrhea and regulate dopamine and PRL in the brain. The regulation of dopamine includes four pathways: 1. Mesolimbic tract; 2. Mesocortical tract; 3. Tuberoinfundibular dopaminergic (TIDA) tract; 4. Nigrostriatal tract. Higher activity of TIDA neurons is affected by an increased level of PRL, and vice versa. Dopamine, which is generally released from the hypothalamus, travels down to the pituitary, and PRL alters their release by " short loop feedback regulation". Dopamine is the main inhibitor of PRL secretion.[49-50]

Recent studies show that if the level of PRL increases, that results in a higher risk of hyperprolactinemia. A case report study from 2013 shows that a girl suffering from galactorrhea has undergone a kidney transplant after discontinuing omeprazole. Omeprazole is a prodrug that generally shows a metabolic process for inhibiting acid secretion in the stomach. The two metabolites are hydroxy-omeprazole and omeprazole sulfone, which are generally formed by CYP2C19 and CYP3A4 enzymes.[51–52] The sensitive drugs include omeprazole, lansoprazole, and pantoprazole used in degradation in the stomach acidic medium. Hence, they adopt a modified formulation to overcome this problem. Omeprazole and Lansoprazole are formulated as hard gelatin capsules, i.e., enteric-coated granules, and pantoprazole is formulated as an enteric-coated tablet.[51]

8.2 *Carcinogenic Effects of Omeprazole*

In recent studies, gastric cancer has been identified as the 15th leading cause of death. It is more common in many people and is mainly affected by age, diet, and stomach diseases such as H. pylori *infection.*[52] The isotope of omeprazole, i.e., esomeprazole, can cause acid suppression that leads to indigestion and increases the risk of bacterial infections that are generated in the stomach.[53] The long-term ingestion of omeprazole may cause cell proliferation and cancer.[52] Recent studies show that acid-suppressing drugs increase the risk of gastric cancer through nitrosamine production and high gastric acid levels.

CONCLUSION

The pharmacovigilance study of proton pump inhibitors is an important factor in understanding their safety and efficacy. It is used to treat acid-related disorders like gastroesophageal reflux disease (GERD) and peptic ulcer disease, although they are linked with several adverse effects. Our study found an increased risk of gastrointestinal infection with long-term or high-dose PPI use. A lot of studies have look over the adverse effects of proton pump inhibitors. The use of PPI is also linked with an increased risk of bone fractures, cardiovascular disease, dementia, liver infections, etc. Healthcare professionals such as doctors, physicians, and pharmacists should regularly evaluate the importance of continued PPI therapy and consider alternate treatment

options such as less potent acid-suppressing medication and lifestyle modification including daily exercise, eat balanced diet such as fruits, vegetables, Calcium rich diet, avoid junk food. The long-term PPIs risk and benefits should be carefully evaluated specially in young age patients who treatment with proton pump inhibitors drugs could last many years. There are many reported related with adverse effect of these drugs, in most patients with short term risk are evaluated. Pharmacovigilance is necessary to monitor and evaluate the risks linked with the use of PPI, optimizing the safety of patients and outcomes.

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