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Review Article

Proton pump inhibitors in Iranian population: from clinical regimens to pharmacogenomics

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Abstract

Proton pump inhibitors (PPIs) are one of the highly prescribed or over-the-counter available medications among Iranians, mainly to treat conditions such as helicobacter pylori infection, gastroesophageal reflux disease or frequent heartburn. In recent years, several reports have shown potential adverse effects of PPI administration among which cardiovascular adverse events, myocardial infarction and chronic kidney disease are considered as the greatest risks. Recent addition of proton pump inhibitors to the list of medications on Beers Criteria of Potentially Inappropriate Drugs has arisen significant concerns about their safety. This review aims at providing an up-to date overview of PPIs indications and their pharmacogenomics and pharmacokinetics in Iranian population. The focus of this review is on PPIs regimens in Iranian population and then it is compared with the reported studies performed on other ethnic groups around the world. An extensive review of the literature was carried out and data under various sections were identified using a computerized literature search via Pubmed, Web of Science, Google Scholar and some local search engines. All abstracts and full text articles were examined and most relevant papers were selected for inclusion in this review. Also several expert internalists were interviewed for their clinical experiences in this field.

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Introduction

The H^+-K^+-ATPases, classified as P-type ATPases, hydrolyse ATP to pump hydrogen (H^+) and potassium (K^+) ions against their concentration gradients. The H^+-K^+ ATPases are mainly found in stomach and parietal cells. A few number of H^+/K^+ ATPase are also found in the renal medulla. During its activation, the enzyme exchanges potassium from the intestinal lumen with cytoplasmic hydronium to acidify the stomach content (Andersson and Carlsson, 2005; Gumz et al., 2010; Shin et al., 2009). Meanwhile, the renal H^+-K^+ ATPase is responsible for K^+ reabsorption during hypokalemia (Gumz et al., 2010). Proton pump inhibitors (PPIs) cause a rapid and sustainable gastric acid suppression without the tachyphylaxis accompanied by histamine receptor antagonists (Wang et al., 2005; Zhang et al., 2015). Proton pump

inhibitors have been routinely prescribed to treat various acid-peptic disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease and gastropathy induced by nonsteroidal anti-inflammatory drugs for near 30 years (considering omeprazole first being launched in 1988) (Sachs et al., 2006).

PPIs are substituted benzimidazoles with a relatively short plasma half-life. Protonation of these lipophilic weak bases in the acidic parietal cell canaliculus will result in an activated sulphenamide form of the drug that covalently binds to the H^+/K^+ ATPase enzyme. Consequently, the pump-drug interaction leads an irreversible inhibition of acid secretion. Besides the established efficacy of PPIs in the treatment of acid-related diseases, their safety has arisen serious worries (Strand et al., 2017). Several studies have reported potential adverse effects associated with PPIs consumption, including hypomagnesaemia (Choi et al., 2012; Florentin and Elisaf, 2012; Janett et al., 2015; Rafiei et al., 2015), hypocalcemia (Choi et al., 2012; Galdo, 2013; Shirazi et al., 2014), clostridium difficile infection (Bernal et al., 2019; McDonald et al., 2015; Patil and Blankenship, 2013), pneumonia (Bashar et al., 2013; Giuliano et al., 2012; Khorvash et al., 2014) and more serious cardiovascular adverse events (Cardoso et al., 2015; Charlot et al., 2010; Ghebremariam et al., 2013; Ho et al., 2009; Shah et al., 2015; Shih et al., 2014; Simon et al., 2011; Yan et al., 2016). There are still competing theories about on whether/how PPIs enhance the risk of major cardiovascular adverse events amongst individuals with a history of adverse cardiovascular syndrome. While PPIs may reduce the absorption of cardiovascular drugs (a controversial hypothesis given that PPIs have been shown not to diminish the anti-platelet aggregation properties of aspirin), a similar reduction in gastric pH is achieved with H_2 receptor blockers, which are believed not to increase cardiovascular risks (Cardoso et al., 2015; Charlot et al., 2010; Simon et al., 2011; Yan et al., 2016). A shocking hypothesis was given in 2013 by Ghebremariam et al. trying to explain the association of PPIs with increased major cardiovascular adverse events in patients with unstable coronary syndromes. They have claimed that this adverse mechanism is concerning especially when population using PPIs extend to the general. This study suggested that PPIs' cardiovascular-adverse effects had no relation to clopidogrel consumption, but was instead a direct effect on blood vessels which means everybody on PPIs, not just people with coronary disease, is at increased risk of cardiovascular events occurrence (Ghebremariam et al., 2013). In 2014, a research by Shih et al. demonstrated that PPI use alone is associated with a greater risk of myocardial infarction in patients with normal cardiovascular risk that reinforced existing concern of FDA about the potential cardiovascular events during PPI use, even in patients without traditional cardiovascular risk factors. In 2015 study by Shah et al. the association of PPI exposure with risk of myocardial infarction in the general population was further highlighted. Lazarus et.al., have performed two observational studies looking at a combined 259,233 patients and the possible relationship between PPI use and chronic kidney disease in which the obtained results statistically confirmed increased risk for chronic kidney disease incident in patients who had taken PPI medication (Lazarus et al., 2016). They have also showed that histamine-2 receptor antagonists are better alternatives that are not associated with increased kidney disease. Further, long-term use of PPIs have been reported to enhance risk of gastric cancers (Ko et al., 2016; Tran-Duy et al., 2016). Gastric cancer alone constitutes 20% of cancer mortality in Iran (Sadjadi et al., 2005). The H. pylori infection rate, as an excess cancer risk factor, is very high in Iranian population (Ghadimi et al., 2007; Jafarzadeh et al., 2007; Malekzadeh et al., 2009; Nouraie et al., 2009; Sotoudeh et al., 2008). The life style in the developing cities and the daily dietary including, high intake of salt, frequent consumption of red meat, insufficient intake of sea foods, fresh fruits and vegetables as well as inadequate exercise are additional factors to trigger gastrointestinal disease in Iranian population (González et al., 2006; Kypridemos et al., 2017; Nemati et al., 2012; Pourfarzi et al., 2009; Sepanlou et al., 2015; Zarea et al., 2017). Also, a wide variation of gastrointestinal incidences are observed in different geographical regions and ethnic groups. Mazandaran and Golestan, the two states located on the Caspian Sea shore line, have demonstrated the highest rate of gastric cancer occurrence among Iranians, followed by Ardabil, a northwestern province (Malekzadeh et al., 2009). Since changing a whole life and dietary styles is much harder than taking a proton pump

inhibitor for long time, proton pump inhibitors are among frequently prescribed medications in Iran. Recent addition of proton pump inhibitors to the list of medications on Beers Criteria of Potentially Inappropriate Drugs should be considered as an alarm for PPI administration (Panel et al., 2015). Herein, we describe and discuss the drug regimens of PPIs in Iranian population followed by the studies done on pharmacokinetic and pharmacogenomic of the drugs and compare the reported results with studies performed on other nations.

PPI Pharmacodynamics

Control of the gastric acid secretion and gastric pH is very important in managing the acid related diseases, eradication of helicobacter pylori, and healing of duodenal ulcers. It is important that for a period of time keep the pH at desired level (Boomgaard, 1998; Varannes et al., 1994). This pH also can help to evaluate the drugs efficacy. However, the degree of acid suppression shown by intragastric pH profile would be the best *in vivo* parameter with which to compare the potency of PPIs (Bell et al., 1992; Furuta et al., 1999). PPIs block the gastric enzyme H,K-ATPase, therefore, inhibiting gastric acid secretion. This effect causes healing of gastric and deudenal ulcers, GERD, Zollinger-Ellison syndrome and Barrett's esophagus as well as the eradication of helicobacter pylori in combination with other drugs. PPIs have shown superiority compared to histamine antagonists at H_2 receptors. Since their introduction, a significant improvement has been observed in management of acid-related diseases with holding the pH about 3-4.

The prototype drug, omeprazole has proved to be effective clinically by 20mg dose. Other frequently prescribed PPIs are Lansoprazole (30 mg/day), and pantoprazole (40 mg/day). Generally speaking, omeprazole, lansoprazole, pantoprazole and rabeprazole have similar efficacy for healing the acid-related diseases (Varannes et al., 1994). S-omeprazole (esomeprazole) gave improved gastric pH compared to omeprazole (Boomgaard, 1998; Timmer et al., 1995). The previous studies with esomeprazole have shown that esomeprazole 40mg once daily is superior to all other PPIs at standard doses in achieving higher intra-gastric pH and the number of patients achieving intra-gastric pH = 4 for at least 12 hours per day; therefore a better healing rate was observed in acid-related diseases. About some interactions between omeprazole and other drugs used by patients, there are some concern about cardiovascular outcomes in combination therapy (Chen et al., 2012).

PPI drug regimens in Iranian patients

Helicobacter pylori infection

There are several therapeutic regimens for therapy of H. pylori, including triple, quadruple, sequential and hybrid therapies. Graham et al. (2007) classified the efficacy of H. pylori eradication regimens based on per-protocol success as follows: (A) excellent (>95%); (B) good (90–95%); (C) fair (85–89%); (D) bad (81–84%) and (F) unacceptable (<80%). Table 1 compares different drug regimens used in Iranian population from 2004 to 2016 (earlier therapeutic regimens have already been reviewed by Malekzadeh et al. (2004). According to per-protocol success and intention-to-treat eradication rates, hybrid therapy with %per-protocol success of 92.9 and intention-to-treat of 89.5, seems to be the best treatment schedule for eradication of H. pylori in Iran. These results are in agreement with the study done by Sardarian et al. (2013), where hybrid therapy shows to be more effective than sequential regimens and quadruple therapy (Saberi-Firoozi and Nejabat, 2015). Additionally, as it has already been reported that triple therapies have shown not to be as successful as hybrid therapy but is still better than other therapeutic regimens including Quadruple Therapy and Sequential Therapy (Maledzadeh et al., 2004). It should also be mentioned that not many studies have monitored sequential and hybrid therapies and further studies are needed. Additionally, no precise study has been conducted to monitor the efficacy of different types of PPI in treatment of H. Pylori infection in Iran. Omeprazole and pantoprazole are the most commonly prescribed PPIs which is probably due to their manufacture and availability in Iran. It should also be mentioned that the growing need for finding new anti-H. pylori agents have driven scientists attentions toward herbal therapy. The vast diversity of medicinal plants available in Iran have been always considered as a source of plant-derived substances. As a matter, traditional Iranian herbal medicines that are routinely consumed as remedies and sold as medicines to manage different diseases are screened for their anti-

Table 1: The comparison of drug regimens used in Iranian population from 2004 to 2018 for H. pylori treatment

Therapy Method	Regimen	Detection Method	Num. of patients	Duration	PP%	ITT%	Year	Ref.
Triple Therapy								
Method 1	• Omeprazole (20 mg bd) • Clarithromycin (500 md bd) • Amoxicillin (1 g bd)	C-urea BT	50	10 days	92.0	75.0	2006	(Bahremand et al., 2006)
		C-urea BT	80	14 days	89.0	83.8	2007	(Keshavarz et al., 2007)
		RUT-HIS	50	14 days	70.0	66.0	2009	(Taghavi et al., 2009)
		C-urea BT	49	14 days	87.7	-	2013	(Vafaeimanesh et al., 2013)
		UBT	98	14 days	90.8	-	2013	(Seyedmajidi et al., 2013)
Method 2	• Omeprazole (20 mg bd) • Pentabactam (750 mg bd) • Clarithromycin (500 md bd)	UBT	100	14 days	87.0	-	2013	(Seyedmajidi et al., 2013)
Method 3	• Omeprazole (20 md bd) • Doxycycline (100 mg bd) • Co-amoxiclave (625 mg td)	RUT-HIS	61	14 days	68.0	61.0	2009	(Taghavi et al., 2009)
Quadruple Therapy								
Method 1	• Omeprazole (20 mg bd) • Metronidazole (500 mg bd) • Amoxicillin (1g bd) • Bismuth (240 md bd)	C-urea BT	50	10 days	84.0	68.8	2006	(Bahremand et al., 2006)
		C-urea BT	49	14 days	55.1	-	2013	(Vafaeimanesh et al., 2013)
		UBT	100	14 days	56.0	-	2013	(Seyedmajidi et al., 2013)
Method 2	• Pantoprazole (40 mg bd) • Amoxicillin (1g bd) • Bismuth (240 mg bd) • Furazolidone (100/200 mg bd for the first 7 days)	C-urea BT	148	14 days	88.7	80.4	2011	(Fakheri et al., 2012)
Method 3	• Omeprazole (20 mg bd) • Amoxicillin (1g bd) • Bismuth (240 mg bd) • Furazolidone (100/200 mg bd)	RUT-HIS	60	14 days	56.0	49.0	2009	(Taghavi et al., 2009)
Method 4	• Omeprazole (20 mg bd) • Amoxicillin (1g bd) • Bismuth (240 mg bd) • Clarithromycin (500 mg bd)	UBT	110	14 days	74.7	64.5	2010	(Minakari et al., 2010)
		C-urea BT	61	10 days	84.4	87.1	2016	(Fakheri et al., 2016)
Method 5	• Omeprazole (20 mg bd) • Azithromycin (250 mg bd) • Bismuth (240 mg bd) • Ofloxacin (200 mg bd)	UBT	110	14 days	86.7	77.3	2010	(Minakari et al., 2010)
Sequential Therapy								
Method 1	• Pantoprazole (40 mg bd) • Amoxicillin (1g bd for 1st 5 days) • Clarithromycin (500 mg bd for 2nd 5days) • Tinidazole (500 mg bd for 2nd 5 days)	C-urea BT	148	10 days	89.1	83.7	2011	(Fakheri et al., 2012)
		C-urea BT	120	14 days	79.9	76.7	2012	(Sardarian et al., 2013)
Hybrid Therapy								
Method 1	• Pantoprazole (40 mg bd) • Amoxicillin (1g bd for 2nd 7 days) • Clarithromycin (500 mg bd) • Tinidazole (500 mg bd for 2nd 7 days)	C-urea BT	210	14 days	92.9	89.5	2012	(Sardarian et al., 2013)

H. pylori activity which is commonly induced through urease enzyme inhibition (Biglar et al., 2014; Nabati et al., 2012).

Gastro-esophageal reflux disease

GERD, also known as gastro-oesophageal reflux disease or acid reflux disease, is a common and chronic problem which is usually characterized by

heartburn and acid regurgitation, although the symptoms vary in different populations (Dent et al., 2005; Pourhoseingholi et al., 2012). The disease is prevalent gastrointestinal conditions in which reflux of the stomach contents into the oesophagus results in heart burn and a bad taste in back of the mouth. A trial of a PPI for 4–8 weeks is often useful. In 2012, Fazel et al. have published a review on the increasing trend of GERD prevalence from 1.9% to 52% in Iran and they have predicted that the prevalence of GERD would increase due to westernization as it is observed in Iran and many other Asian Countries. Lifestyle modification and dietary change are the first step toward decreasing GERD symptoms (Malekzadeh et al., 2003). Histamine H2 blockers proved to be effective in about 50–60% of GERD cases. Proton pump inhibitors are the most effective medical treatment with fast symptom relief and longer duration of action at adequate dosage, in about at least 85–90% of cases (Malekzadeh et al., 2003; Vela, 2014). In case of significant erosive esophagitis, PPI therapy is maintained even if it is asymptomatic (Badillo and Francis, 2014). Although, some recent studies demonstrated an increased risk of esophageal adeno carcinogenesis for patients taking PPIs especially for a long time (Cheung et al., 2018; Duan et al., 2009; Erridge et al., 2018; Kinoshita et al., 2018), not enough studies are performed on the side effects of long term consumption of PPIs on GERD in Iranian population. Consequently, precise studies must be conducted to monitor the efficacy of different types of PPI in treatment of GERD in Iran and their probable side effects.

PPI pharmacogenomics (with emphasize on Iran)

Drugs can be classified as ethnically sensitive or insensitive during the development process. It has been proven that each population has characteristic specific pattern of gene polymorphism that extremely affect drug metabolism in that population. The guidelines proposed by the International Conference on Harmonization (1998), suggest the presence of several factors associated with a drug pharmacokinetic to be ethnically sensitive (Committee, 1998; Noubarani et al., 2012). There are large number of reports in the literature speculating the ability of genotyping as an essential tool for safe and wise drug prescribing (Azarpira et al., 2010; Thaker et al., 2017; Vogl et al., 2015). A well-known polymorphism that affect drug metabolism involve oxidation by cytochrome P450 enzymes (CYP). CYP2C subfamily are encoded by genes located on chromosome 10 and alternations in the amino acid sequence of these target enzymes metamorphose enzymatic activity, with high, low or no activity along with substrate specificity. The CYP2C enzymes are responsible for the metabolism of 20% of drugs widely prescribed in clinic (Vogl et al., 2015). CYP2C9 is one of the highly populated subcategories of CYP2C which actively involves many drugs metabolism (like S-warfarin, losartan, diazepam, phenytoin and nonsteroidal anti-inflammatory drugs). Normal enzymatic function is dictated through the wild type CYP2C9*1 allele while the other two widely spread allelic variants, CYP2C9*2, with single nucleotide polymorphisms (SNP) ID: rs1799853 and 430C>T mutation and CYP2C9*3 with SNP ID: rs1057910 and 1075A>C mutation, result in enzyme activity reduction up to 30% and 80%, respectively (Sausville et al., 2018). Consequently, individuals carrying the homozygous wild type allele of CYP2C9 (CYP2C9*1/*1) are extensive metabolizers while those with one copy of a non-functional allele (CYP2C9*1/*2, CYP2C9*1/*3) are intermediate metabolizer. According to the literature, CYP2C9*2 and CYP2C9*3 are the widely spread variants and CYP2C9*2/*3 and CYP2C9*3/*3 comprise up to 40% and 15% of the population worldwide, respectively (Scordo et al., 2004).

Another key enzyme regarding metabolic capacity of many drugs (like S-mephenytoin, R-warfarin, proguanil, citalopram, omeprazole and antidipressants) is CYP2C19, which is highly polymorphic with 35 variant star (*) alleles among which allelic variants of CYP2C19*1 (wild type allele when no variants), CYP2C19*2 (SNP ID: rs4244285, 681G>A mutation), CYP2C19*3 (SNP ID: rs4986893, 636G>A mutation) and CYP2C19*17 (SNP ID: rs12248560, −806C>T & −340C>T) are the most frequent. CYP2C19*2 and CYP2C19*3 are the most common allelic mutants in caucasians and chinese population that are associated with impaired drug metabolism, known as poor metabolizers. CYP2C19*17 is a common novel variant that causes ultrarapid drug metabolism with an increased activity, known as ultrarapid metabolizers. (Hunfeld et al., 2008; Sim et al., 2006). Further, individuals carrying

Table 2: Allele frequencies of CYP2C9 among Iranians

Study groups	Year	Ethnicity	Sample size	CYP2C9 Allele Frequency *1	*2	*3	Reference
Healthy Volunteers	2006	Unrelated	200	87.25	12.75	0.00	(Zand et al., 2007)
Healthy Volunteers	2010	Fars	150	64.88	24.34	9.80	(Azarpira et al., 2010)
Patients under WT[1]	2010	Fars	99	64.00	27.00	9.00	(Namazi et al., 2010)
Healthy Volunteers	2013	Turkman	110	88.00	8.00	4.00	(Ataby et al., 2013)
Healthy Volunteers	2013	Unrelated	110	83.00	11.00	6.00	(Ataby et al., 2013)
Healthy Volunteers	2015	Baluch	110	80.90	11.82	7.27	(Tabari et al., 2015)
Healthy Individuals	2017	Southern Khorasan	120	80.08	9.10	10.00	(Razavi et al., 2017)
Patients under WT	2018	Kurdish	110	80.40	14.00	5.40	(Hosseinkhani et al., 2018)
Healthy Individuals	2018	Sistani	140	76.10	16.10	7.80	(Marjani and Gharanjik, 2018)
Phenotype	-	-	-	**EM**	**PM**	**PM**	-

[1]Warfarin Therapy

Table 3: Genotype frequencies of CYP2C9 among Iranians

Study groups	Year	Ethnicity	Sample size	Genotype Frequency % *1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	Reference
Healthy Volunteers	2010	Fars	150	41.21	37.83	9.46	1.35	10.13	-	(Azarpira et al., 2010)
Healthy Volunteers	2015	Baluch	110	70.90	11.82	8.18	4.55	2.73	1.82	(Tabari et al., 2015)
Patients in WT[1]	2010	Fars	100	39.00	41.00	9.00	2.00	9.00	0.00	(Namazi et al., 2010)
Patients in WT	2015	Unrelated	115	61.70	20.00	14.80	-	2.60	0.90	(Poopak et al., 2015)
Healthy Volunteers	2013	Turkman	110	76.36	15.45	7.27	0.00	0.90	0.00	(Ataby et al., 2013)
Healthy Volunteers	2013	Fars	110	70.00	14.55	10.91	2.73	1.82	0.00	(Ataby et al., 2013)
Healthy Volunteers	2006	Unrelated	200	82.00	10.5	0.00	7.5	0.00	0.00	(Zand et al., 2007)
Healthy Individuals	2017	Southern Khorasan	120	64.10	15.80	17.50	0.00	2.5.00	0.00	(Razavi et al., 2017)
Patients under WT	2018	Kurdish	110	71.00	17.2	1.80	5.40	-	4.50	(Hosseinkhani et al., 2018)
Healthy Individuals	2018	Sistani	140	53.90	22.10	11.40	2.90	4.30	0.00	(Marjani and Gharanjik, 2018)
				EM	**IM**	**IM**	**PM**	**PM**	**PM**	

[1]Warfarin Therapy

the homozygous wild type allele of CYP2C19 (CYP2C19*1/*1) are extensive metabolizers and those with the heterozygous wild type or CYP2C19*17 alleles that carry one copy of a non-functional allele (CYP2C19*1/*2, CYP2C19*1/*3 and CYP2C19*2/*17) are considered as intermediate metabolizer. In contrast, CYP2C19*1/*17 heterozygotes are rapid metabolizers and individuals with homozygous allele CYP2C19*17 (CYP2C19*17/*17) are ultrarapid metabolizers. Poor metabolizers carry two non-functional alleles (CYP2C19*2/*2, CYP2C19*2/*3 and CYP2C19*3/*3).

Individuals with different phenotype/ genotype heredity show diverse clinical responses, including detrimental drug metabolism upon consumption (El Rouby et al., 2018). Further, CYP2C19 genetic polymorphism alters endogenous compounds equilibrium (Fricke-Galindo et al., 2016). A recent observation has shown that PPI therapy is associated with higher respiratory tract and gastrointestinal tract infection rates in children with normal CYP2C19 function than in those with increased CYP2C19 function (Bernal et al., 2019; Franciosi et al., 2018). Hence, acquiring precise information on the

Table 4. Genotype frequencies of CYP2C9 in different ethnic groups

			CYP2C9 Allele Frequency (%)			CYP2C9 Genotype Frequency (%)						
Ethnicity	**Year**	**Sample size**	***1**	***2**	***3**	***1/*1**	***1/*2**	***1/*3**	***2/*2**	***2/*3**	***3/*3**	**Ref.**
Bolivian	2005	778	92.2	4.8	3	84.7	9.3	5.7	0	0.4	0	(Bravo-Villalta et al., 2005)
British	2005	561	84.1	10.6	5.2	69.9	19	0.06	0.003	0	0	(Sconce et al., 2005)
Chinese	1995	115	98.3	0	1.7	97	0	3	0	0	0	(Wang et al., 1995)
German	2002	734	81.6	10.6	7.8	-	-	-	-	-	-	(Xie et al., 2002)
Greek	2007	283	79	12.8	8.1	62	20	13.5	1.5	2.8	0	(Arvanitidis et al., 2007)
Hungarian	2009	535	78.7	12.5	8.8	62	19.5	13.9	2.1	1.5	1.1	(Sipeky et al., 2009)
Iranians	2006	200	87.3	12.8	0	82	10.5	0	7.5	0	0	(Zand et al., 2007)
Italians	2004	360	77.7	12.5	9.7	62	17.2	14.5	2.7	2.2	1.3	(Scordo et al., 2004)
Japanese	2006	828	97.6	0	2.3	95	0	4	0	0	1	(Mushiroda et al., 2006)
Kerala	2005	120	90	2	8	81	4	14	0	0	1	(Jose et al., 2005)
Koreans	2006	574	98.9	0	1.1	97.7	0	2.3	0	0	0	(Moridani et al., 2006)
North Indians	2016	89	85.4	4.5	10.1	71.9	7.9	19.1	1.1	0	0	(Chaudhary et al., 2016)
Pakistan	2010	120	91.6	0.8	7.5	85.8	0	11.7	0.8	0	1.7	(Siddiqi et al., 2010)
Roma	2009	465	72.7	11.8	15.5	53.3	16.8	21.9	1.1	4.7	2.2	(Sipeky et al., 2009)
Russians	2003	290	82.7	10.5	6.7	68	18.2	10.3	0.6	1.2	0.3	(Gaikovitch et al., 2003)
Slovenians	2003	129	81.7	12	6.2	86.6	19.3	10.8	1.5	1.5	0	(Herman et al., 2003)
Swedish	1999	430	81.9	10.6	7.4	66.7	18.6	11.6	0.4	1.6	0.6	(Yasar et al., 1999)
Spanish	2001	150	64	16	20	50	16	23.3	2	8.7	0	(Martínez et al., 2001)
Tamilians	2003	135	90.7	2.6	6.7	82.3	4.4	12.7	0	0.7	0	(Adithan et al., 2003b)
Genotype	-	-	**EM**	**PM**	**PM**	**EM**	**IM**	**IM**	**PM**	**PM**	**PM**	-

pharmacogenetic characteristics of these polymorphisms' geographic distribution, popularization and variability will definitely enhance public health care by preventing adverse drug reactions as well as therapeutic failure.

Previous studies have focused on genotype as well as allelic frequencies of CYP2C9 and CYP2C19 in Iranian populations. According to Table 2, CYP2C9*1 (wild type) is the most frequent allele among Iranians, vary from 64% to 88%, where Turkman have the highest and Fars people have the lowest frequencies (Ataby et al., 2013; Azarpira et al., 2010; Hosseinkhani et al., 2018; Marjani and Gharanjik, 2018; Namazi et al., 2010; Razavi et al., 2017; Tabari et al., 2015; Zand et al., 2007). Ultimately, Fars people possess highest CYP2C9*2 and CYP2C9*3 allele frequencies of 24.34% and 9.8%, respectively. Considering Table 3, the prevalence of CYP2C9*1/*1 is the highest, except for that reported by Namazi et al. (2010), where CYP2C9*1/*2 have the highest genotype frequency of 41% (Ataby et al., 2013; Azarpira et al., 2010; Hosseinkhani et al., 2018; Marjani and Gharanjik, 2018; Namazi et al., 2010; Poopak et al., 2015; Razavi et al., 2017; Tabari et al., 2015; Zand et al., 2007). While Fars population reveals the lowest CYP2C9*1 allelic frequency among the studied Iranian populations, frequencies of CYP2C9*2 and CYP2C9*3 variants are the highest. Comparing CYP2C9*2 allele holders as well as high prevalence of CYP2C9*1/*2, CYP2C9*1/*3 and CYP2C9*2/*3 genotypes, it is concluded that Fars are the poorest PPI metabolizers among Iranians. Considering CYP2C9 allele frequency reports across the world (Table 4), CYP2C9*1 (wild types) is the most distributed among Iranian populations, that is close to those reported for British (Sconce et al., 2005) and North Indians (Chaudhary et al., 2016) but higher than those of Greek (Arvanitidis et al., 2007), Hungarian (Sipeky et al., 2009), Italians (Scordo et al., 2004), Roma (Sipeky et al., 2009), Russians (Gaikovitch et al., 2003), Slovenian (Herman et al., 2003), Swedish (Yasar et al., 1999) and German (Xie et al., 2002). Also the allelic frequency of CYP2C9*1 in Bolivians (Bravo-Villalta et al., 2005), Chinese (Wang et al., 1995), Japanese (Mushiroda et al., 2006), Kelara (Jose et al., 2005), Koreans (Moridani et al., 2006), Pakis (Siddiqi et al., 2010) and Tamilians (Adithan et al., 2003a) are higher than that

of Iran. The prevalence of CYP2C9*2 phenotype frequency of Iranians is similar to those of Greek, Hungarians, Italians, Roma and Slovenians, that are significantly higher than those of Chinese, Japanese, Kelara, Koreans and Tamilians. Also, no CYP2C9*3 is observed in Iranians. It is noteworthy to mention that Spanish have the lowest prevalence of CYP2C9*1 and the highest prevalence of CYP2C9*2 and CYP2C9*3 among the studied nations (Martínez et al., 2001).

Significant differences are observed in the genotype frequencies in different ethnic groups especially those of Chinese, Japanese and Koreans that possess the highest popularities of 97%, 95% and 97.7% for CYP2C9*1/*1, respectively. According to Table 4, the prevalence of CYP2C9*1/*1 among Iranians is similar to those of Kelara and Tamilians (two Indian tribes). While no prevalence of CYP2C9*1/*3, CYP2C9*2/*3 and CYP2C9*3/*3 is detected in Iran, their CYP2C9*2/*2 genotype frequency is significantly higher than other studied ethnic groups.

Considering CYP2C19 allele frequencies reported among Iranians (Table 5), Mazanis (Shahabi-Majd and Habashi, 2013) and Azaries (Didevar et al., 2016) own the highest prevalence of CYP2C19*1 variant. The highest prevalence of CYP2C19*2 is observed in Isfahani (Akhlaghi et al., 2011) and Turkmans (Tabari et al., 2013). A recent studies in which unrelated Iranian individuals where studied (Dehbozorgi et al., 2018), while no significant difference is observed among other origins (Azarpira et al., 2010; Ebrahimpour et al., 2017; Namazi et al., 2010; Namazi et al., 2012; Payan et al., 2014; Saber et al., 2014; Tabari et al., 2014; Zendehdel et al., 2010). Also, Turkmans possess the highest distribution of CYP2C19*3 while the prevalence is not notable in other ethnic groups of Iran. Ultimately, Turkman population own the lowest CYP2C9*1 allelic frequency across Iranian populations, while the frequencies of CYP2C9*2 and CYP2C9*3 variants are the highest in this ethnic group. As a matter of fact, it is concluded that Turkmans are the poorest PPI metabolizers among Iranians, regarding CYP2C19 allelic variants. Some recent studies has also estimated CYP2C19*17 allele with the frequency of 21.60% and 27.10% among two groups of healthy Iranian volunteers as ultra-rapid metabolizers of PPIs that further emphasize the observation that majority of Iranians are rapid metabolizers of PPIs (Ebrahimpour et al., 2017; Payan et al., 2014). Table 6 shows the distribution of CYP2C19 genotype frequency among Iranian ethnic groups. As it is already mentioned in phenotype frequency studies, Mazanis and Turkman with *1/*1 genotype frequencies of 84.0% and 37.9 % are the most and the least extensive metabolizers in Iran, respectively. On the other hand, the population of *1/*2 and *1/*3 as intermediate metabolizers and *2/*2 and *3/*3 as poor metabolizers are significantly higher in Turkmans than those of other ethnic groups in Iran. Also, two studies reveal a significant frequency of *1/*17 genotype which is considered high in compare to other genotypes. Unfortunately, the frequency of *2/*17, *3/*17 and *17/*17 have not been investigated in Iranian different ethnic groups.

According to Table 7, Iranians are among the ultra-rapid metabolizers (possessing CYP2C19*17 allele) of PPIs along with Germans (Geisler et al., 2008), Norwegians (Pedersen et al., 2010), Polish (Kurzawski et al., 2006), Saudi Arabians (Saeed and Mayet, 2013) and Turkish (Gumus et al., 2012). On the other hand, Australian aborigines (Griese et al., 2001), Chinese (Sim et al., 2006; Yamada et al., 2001), Japanese (Sugimoto et al., 2008), Koreans (Kim et al., 2010), Malaysians (Yang et al., 2004), Swedish (Ramsjö et al., 2010) and Thai (Sukasem et al., 2013) are the nations with the high population of poor metabolizers (possessing CYP2C19*2 and CYP2C19*3 alleles).

The frequency of 1*/1* genotype population between Iranians is close to those of Danish (Pedersen et al., 2010), Greek (Ragia et al., 2008), Malaysians (Yang et al., 2004), Saudi Arabians (Saeed and Mayet, 2013) and US panethnics (Strom et al., 2012), while the population with 1*/2* genotype is extremely lower than those of Japanese (Sugimoto et al., 2008), Karens (Tassaneeyakul et al., 2006), Koreans (Kim et al., 2010), Indians (Adithan et al., 2003b; Anichavezhi et al., 2012), Thai (Sukasem et al., 2013), African Americans (Strom et al., 2012; Xie et al., 1999) and Vendas (Dandara et al., 2001). Additionally, Malaysians (Yang et al., 2004) possess the highest frequency of 1*/3* genotype in their population. The frequency of 2*/2* genotype is the highest in Indians (Anichavezhi et al., 2012) and Japanese (Sugimoto et al., 2008) and Iranians are among the nations with low frequency of the genotype along with Bolivians (Bravo-Villalta et al., 2005), Danish (Pedersen et al.,

Table 5: Allele frequencies of CYP2C19 among Iranians

				CYP2C19 Alleles Frequency %					
Study groups	**Year**	**Ethnicity**	**Sample size**	***1**	***2**	***3**	***17**	**Other**	**Reference**
Healthy Volunteers	2014	Unrelated	180	65.30	13.10	0.00	21.60	-	(Payan et al., 2014)
Patients with ERE[1]	2010	Unrelated	82	84.75	13.41	1.8	-	-	(Zendehdel et al., 2010)
Healthy Volunteers	2006	Unrelated	200	86.00	14.00	0.00	-	-	(Zand et al., 2007)
Healthy Volunteers	2013	Turkman	140	56.43	23.57	20.00	-	-	(Tabari et al., 2013)
Healthy Volunteers	2013	Mazani	103	91.00	9.00	0.00	-	-	(Shahabi-Majd and Habashi, 2013)
Healthy Volunteers	2010	Fars	150	86.73	13.00	1.00	-	-	(Azarpira et al., 2010)
Patients under WT[2]	2010	Fars	99	88.00	11.00	1.00	-	-	(Namazi et al., 2010)
Patients undergoing PCI[3]	2012	Fars	112	88.99	10.09	0.91	-	-	(Namazi et al., 2012)
Healthy Volunteers	2014	Fars	140	77.80	19.20	2.80	-	-	(Tabari et al., 2014)
Patients with CAD[4]	2014	Unrelated	691	87.10	12.30	0.50	-	-	(Saber et al., 2014)
Patients with CAD	2011	Isfahani	43	72.10	27.90	-	-	-	(Akhlaghi et al., 2011)
Healthy Volunteers	2016	Azari	200	95.46	0.00	0.00	-	4.54	(Didevar et al., 2016)
Patients undergoing VRCZ[5]	2017	Unrelated	48	71.60	17.60	0.00	10.80	-	(Ebrahimpour et al., 2017)
Healthy Individuals	2018	Unrelated	1229	-	21.40	1.70	27.10	-	(Dehbozorgi et al., 2018)
Phenotype	-	-	-	**EM**	**PM**	**PM**	**URM**	-	-

[1]Erosive Reflux Esophagitis, , [2]Warfarin Therapy, [3]Percutaneouse Coronary Intervention,[4]Coronary Artery Disease , [5]Voriconazole

Table 6: Genotype frequencies of CYP2C19 among Iranians

Study groups	Year	Ethnicity	Sample size	CYP2C19 Genotype Frequency %									Reference
				*1/*1	*1/*2	*1/*3	*1/*17	*2/*2	*2/*3	2*/17	*3/*3	*17/*17	
Healthy Volunteers	2006	Unrelated	200	75.00	22.00	-	-	3.00	-	-	-	-	(Zand et al., 2007)
Patients with ERE[1]	2010	Unrelated	82	70.70	24.30	3.70	-	1.30	-	-	-	-	(Zendehdel et al., 2010)
Healthy Volunteers	2013	Mazani	103	84.00	14.00	-	-	2.00	-	-	-	-	(Shahabi-Majd and Habashi, 2013)
Healthy Volunteers	2013	Turkman	140	37.90	42.10	9.30	-	9.30	-	-	2.00	-	(Tabari et al., 2013)
Healthy Volunteers	2014	Unrelated	180	41.70	18.30	-	28.80	2.20	-	3.30	-	5.50	(Payan et al., 2014)
Healthy Volunteers	2010	Fars	150	74.14	24.49	0.68	-	ND	0.68	-	-	-	(Azarpira et al., 2010)
Healthy Volunteers	2014	Fars	140	75.00	22.10	1.40	-	1.40	-	-	-	-	(Tabari et al., 2014)
Patients with CAD[2]	2011	Isfahani	43	72.10	23.30	-	-	4.70	-	-	-	-	(Akhlaghi et al., 2011)
Patients under WT[3]	2010	Fars	99	77.00	21.00	1.00	-	0.00	1.00	-	0.00	-	(Namazi et al., 2010)
Patients with CAD[4]	2014	Unrelated	691	76.10	20.90	1.00	-	1.20	0.00	-	0.00	-	(Saber et al., 2014)
Patients undergoing VRCZ[5]	2017	Unrelated	48	48.70	24.30	-	21.60	5.40	-	-	-	-	(Ebrahimpour et al., 2017)
Phenotype	-	-	-	**EM**	**IM**	**IM**	**URM**	**PM**	**PM**		**EM**	**PM**	**URM** -

[1]Erosive Reflux Esophagitis, [2]Coronary Artery Disease, [3]Warfarin Therapy, [4]Cardiovascular Diseases, [5]Voriconazole

Table7: Genotype frequencies of CYP2C19 in different ethnic groups

			CYP2C19 Allele Frequency					CYP2C19 Genotype Frequency										
Ethnicity	**Year**	**Sample size**	***1**	***2**	***3**	***17**	**Others**	***1/*1**	***1/*2**	***1/*3**	***2/*2**	***2/*3**	***3/*3**	***1/*17**	***2/*17**	***3/*17**	**17*/17**	**Ref.**
African Americans	1999	517	81	19	0	-	-	66	30	0	3	0.1	0	-	-	-	-	(Xie et al., 1999)
African Americans	2012	149	63.0	12.0	0.0	19.0	4.6	-	-	-	-	-	-	-	-	-	-	(Strom et al., 2012)
Ashkenazi Jewish	2012	342	70	12	0	13	4.1	-	-	-	-	-	-	-	-	-	-	(Strom et al., 2012)
Australian aborigines	2001	227	50.1	35.5	14.3	-	-	-	-	-	-	-	-	-	-	-	-	(Griese et al., 2001)
Belgians	2003	121	90.0	9.1	0.0	-	-	83.5	15	0	1.6	0	0	-	-	-	-	(Allabi et al., 2003)
Bolivians	2005	778	92.1	7.8	0.1	-	-	85.3	13.5	0.1	1	0	0	-	-	-	-	(Bravo-Villalta et al., 2005)
Canadian Natives	1998	115	80.9	19.1	0	-	-	-	-	-	-	-	-	-	-	-	-	(Nowak et al., 1998)
Chinese	2001	121	50	45.5	4.5	-	-	-	-	-	-	-	-	-	-	-	-	(Yamada et al., 2001)
Chinese	2006	68	-	-	0	4	0	-	-	-	-	-	-	-	-	-	-	(Sim et al., 2006)
Colombians	2007	189	91.2	8.8	0	-	-	83.5	15.3	0	1	0	0	-	-	-	-	(Isaza et al., 2007)
Croatians	2003	200	85	15	0	-	-	73	24	0	3	0	0	-	-	-	-	(Bozina et al., 2003)
Danish	2010	276	64.9	15	0	20.1	0	44.2	18.5	0	2.2	0	0	22.8	7.3	0	5.1	(Pedersen et al., 2010)
Egyptians	2002	247	88.8	11	0.2	-	-	78.6	20.2	0.4	0.8	0	0	-	-	-	-	(Hamdy et al., 2002)
Ethiopians	1996	114	85	14	3	-	-	75	19	1	3	3	0	-	-	-	-	(Persson et al., 1996)
Ethiopians	2006	190	-	-	0	18	-	-	-	-	-	-	-	-	-	-	-	(Sim et al., 2006)
Faroese (North Germans)	2010	311	65.9	18.7	0	15.4	0	46	23.5	-	3.2	-	-	16.4	7.4	-	3.5	(Pedersen et al., 2010)
Filipinos	1997	121	54	39	8	-	-	-	-	-	-	-	-	-	-	-	-	(Goldstein et al., 1997)
Gaza Strip	2009	200	91.3	5.8	3	-	-	86.5	6.5	1.5	3	0.5	2	-	-	-	-	(Sameer et al., 2009)
Germans	2008	186	59.3	15.2	0	25.5	0	-	-	-	-	-	-	-	-	-	-	(Geisler et al., 2008)
Greek	2009	283	67.3	13.1	0	19.6	0	44.2	17.8	0	2.1	-	-	28.6	4.3	-	3.2	(Ragia et al., 2008)
Hispanics	2012	346	75	10	0	10	1.74	-	-	-	-	-	-	-	-	-	-	(Strom et al., 2012)
Indians	2012	206	42	40.2	0	17.9	0	16.1	31	0	18.4	0	0	20.7	12.6	0	1.2	(Anichavezhi et al., 2012)
Iranians	2014	180	65.3	13	0	21.7	0	41.7	18.3	-	2.2	-	-	28.9	3.3	-	5.5	(Payan et al., 2014)
Italians	2004	360	88.9	11.1	0	-	-	79.4	18.8	0	1.7	0	0	-	-	-	-	(Scordo et al., 2004)
Japanese	2008	165	57.9	27.9	12.8	1.3	0	35.5	43.8	-	18.8	-	-	1.1	1.5	-	0	(Sugimoto et al., 2008)
Karen	2006	131	71	28	1	-	-	51.1	39.7	0.8	7.6	0.8	0	-	-	-	-	(Tassaneeyakul et al., 2006)
Koreans	2010	271	60	28.4	10.1	1.5	0	35.7	36.5	10.7	5.9	7	1.1	1.1	1.4	0.3	0	(Kim et al., 2010)
Malaysians	2004	142	66	28	6	-	-	42	40	6	6	6.3	1	-	-	-	-	(Yang et al., 2004)
North Indians	2003	121	70.3	29.7	0	-	-	47.9	44.6	0	7.4	0	0	-	-	-	-	(Adithan et al., 2003b)
Norwegians	2010	309	62.8	15.2	0	22	0	39.5	20.1	-	1.3	-	-	20.5	7.8	-	4.9	(Pedersen et al., 2010)
Polish	2006	78	56.4	15.4	0	28.2	0	-	-	-	-	-	-	-	-	-	-	(Kurzawski et al., 2006)
Portuguese	1997	153	87	13	0	-	-	-	-	-	-	-	-	-	-	-	-	(Ruas and Lechner, 1997)
Russians	2003	290	88	11.4	0.3	-	-	78.7	19	0.3	1.7	0.3	0	-	-	-	-	(Gaikovitch et al., 2003)
Saudi Arabians	2013	201	62.9	11.2	0	25.7	0	40.3	14.5	-	0.4	0.4	-	30.4	7	-	7	(Saeed and Mayet, 2013)
Slovenians	2003	129	83.7	15.9	0.3	-	-	68.2	30	0.7	0.7	0	0	-	-	-	-	(Herman et al., 2003)
Swedish	2010	185	64	16	20	0	0	-	-	-	-	-	-	-	-	-	-	(Ramsjö et al., 2010)
Tamilians	2003	112	59.8	37.9	2.2	-	-	29.5	58	2.7	8	1.8	0	-	-	-	-	(Adithan et al., 2003b)
Thai	2013	1051	63	27	6	4	0	40.7	35.1	6.9	7.3	5.6	0.1	4.3	0	-	0	(Sukasem et al., 2013)
Turkish	2012	244	65.6	10	0	24.4	0	44.3	12.3	-	1.2	-	-	30.3	5.3	-	6.6	(Gumus et al., 2012)
US panethnic population	2011	1396	-	-	-	-	-	41	20	0.93	2.6	0.72	0	24	6.1	0	3.9	(Strom et al., 2012)
Venda (South Africa)	2001	76	78.3	21.7	0	-	-	61.8	32.9	0	5.3	0	0	-	-	-	-	(Dandara et al., 2001)
Genotype	-	-	**EM**	**PM**	**PM**	**URM**	-	**EM**	**IM**	**IM**	**PM**	**PM**	**PM**	**EM**	**NR**	**NR**	**URM**	-

2010), Norwegians (Pedersen et al., 2010), Saudi Arabians (Saeed and Mayet, 2013), Slovenians (Herman et al., 2003), Turkish (Gumus et al., 2012), Russians (Gaikovitch et al., 2003), Italians (Scordo et al., 2004) and Greek (Ragia et al., 2008). While the distribution of 2*/3* is not impressive worldwide, but the genotype frequency in Koreans (Kim et al., 2010), North Indians (Adithan et al., 2003b) and Thai (Sukasem et al., 2013) populations is considerable. Unfortunately, the frequency of *1/*17, *2/*17, *3/*17 and 17*/17 genotypes are only determined in few populations, but accordingly, after Saudi Arabia (30.40%) and Turkish (30.30%) ethnicities, Iranians can be marked as those with notable extensive metabolizers with *1/*17 genotype frequency of 28.90 %. Propounding *2/*17 genotypes, it is observed that Indian population possessing the genotype are substantially higher than the other studied nations. The *3/*17 genotype is quite rare, but 17*/17 genotype worth considering where American panethnics (Strom et al., 2012), Iranians (Payan et al., 2014) and Danish (Pedersen et al., 2010) populations contain notable frequencies. To sum up, Iranians can be designated as a nation with significant population of extensive and ultra-extensive metabolizers of PPIs.

PPI Pharmacokinetics

Regarding the relationship between polymorphisms and PPIs pharmacodynamics and pharmacokinetics, CYP2C19 genotype plays a main role in the outcome of therapies with lansoprazole, omeprazole, pantoprazole and according to some studies rabeprazole. For lansoprazole, CYP2C19*2/*3 polymorphisms are important determinants of its pharmacokinetics. Significant differences were found in area under concentration curve (AUC(0-T), AUC(0-∞), t(1/2)) and apparent clearance (CL/F) of lansoprazole between CYP2C19 extensive metabolizers and intermediate metabolizers (Zhang et al., 2014). In the case of omeprazole, which is the most used PPI in Iranian patients, CYP2C19*2 and CYP2C19*3 polymorphism altered the clinical response and endoscopic healing in patients with erosive reflux esophagitis. As a consequence, the rate of complete clinical response to treatment with omeprazole was 95% in the hetero-extensive metabolizers group, which was premier to the homo-extensive metabolizers group (43%) (Zendehdel et al., 2010). Another study done on a healthy Iranian population, omeprazole hydroxylation index was used as the indicator of CYP2C1 activity, considering new variant allele (CYP2C19*17). The obtained data pointed out the importance of CYP2C19*2 and CYP2C19*17 variant alleles in the metabolism of omeprazole and therefore CYP2C19 activity. Considering the high frequency of CYP2C19*17 in Iranian population, the key role of this new variant allele in metabolism of CYP2C19 substrates needs further evaluations. In addition, the result of this study shows that CYP2C19*2/*17 has an intermediate metabolic activity which may affect drug dose adjustment regimens for treatment, especially in those having narrow therapeutic indices (Payan et al., 2014). The results of Payan et al. (2014) is in agreement with the one performed by Yamada et al. (2013) on a group of Japanese healthy volunteers where they correlated omeprazole hydroxylation index to CYP2C19 genotype in studied groups. Interestingly, studies show no considerable outcome regarding the effect of CYP2C19 polymorphism on the rabeprazole-based triple therapies due to its non-enzymatic metabolic pathway (Kuo et al., 2010). However, according to a recent study by Roman et al. (2014) CYP2C19*2 carriers (except *2/*17) result in poor metabolism of rabeprozole. As a matter of fact, rabeprazole maybe a new victim of CYP polymorphism and more studies need to be done on new class of PPIs.

Up to now, five single dose trials are conducted to evaluate the pharmacokinetics of PPI, omeprazole, in Iranian population which seems to emphasis the above results. Among the first studies is a study done by Motevalian et al. which significant inter-subject variability was observed within pharmacokinetic parameters of omeprazole and its metabolites in volunteers. From nine subjects, four exhibited much higher plasma levels of omeprazole compared to the others. Analysis of serum showed the existence of another metabolite of omeprazole which has not been previously reported (Motevalian et al., 1999a; Motevalian et al., 1999b). Also in a study by Mostafavi and Tavakoli (2004) two out of twelve subjects demonstrated increase in AUCs and Cmax after administration of two different brands of omeprazole product. Furthermore, in a study, which was conducted on 30 healthy volunteers, one subject showed a high AUC, half-life and lowest elimination

rate compared with mean AUC level. The omeprazole metabolic ratio for this subject was 2.9, while for those of others, it was in the range 0.12–0.56 (Table 8) (Noubarani et al., 2012). In another study by Ala et al. no significant difference were observed in pharmacokinetic parameters between males and females except apparent clearance (CL/F) and apparent volume of distribution (V/F) which were significantly higher in females than males (Ala et al., 2013). According to the authors, the difference in clearance and volume of distribution might be due to the differences in body fat, plasma protein binding and CYP3A4 expression between the two sexes (Ala et al., 2013; Denisenko et al., 2018). As a result, in order to reduce the variability in PPI response and find the right molecule for the right patient, genotyping and phenotyping is necessary.

Conclusion

As reviewed in this article, patient variability has been observed in many fields of drug administration from drug regimens, therapeutic response, adverse effects, pharmacokinetics and pharmacogenomics in Iranian and other populations/ethnical groups. Literature survey shows that Iranians are among nations with significant population of extensive and ultra-extensive metabolizers of PPIs. It is obvious that clinical outcomes of PPI-based therapy are affected by CYP2C9 and CYP2C19 genotype or/and pharmacogenomics. Frequencies of CYP2C9*2/*3 as well as CYP2C19*2/*3 variants are the highest in Iranian ethnic groups, except Turkmans. While some studies reveal the key role of CYP2C19*2/*3 variants in rabeprazole, lansoprazole and omeprazole metabolism, no studies have been conducted to monitor pantaprazole metabolism among Iranian population. Besides, CYP2C19*17 variant and CYP3A4 (Denisenko et al., 2018), as a secondary enzyme for PPI biotransformation and its higher in CYP2C19 extensive metabolizers and ultra-rapid metabolizers, are in need of more accurate, comprehensive and multi-dimension studies reschedule PPI dosage among Iranians. Other factors such as non-genetic factors, physiologic conditions, combination therapy, alcohol, smoking, sex, age, disease state, diet have not been well studied. Also, pharmaceutical factors like different racemic forms of PPIs and formulations, different PPIs and/or increasing doses of PPIs, other polymorphisms' effects (e.g., IL-1β-511 polymorphism), new PPIs metabolites and their relation to genetic polymorphism and pediatric population pharmacogenomics should be carefully considered in order to have the best drug dosage regimen in Iranian population to avoid probable side effects and lower the risks of PPIs high dose and long term prescriptions.

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Conflict of interest

The authors declare that they have no conflict of interests.

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