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Which drugs are risk factors for the development of gastroesophageal reflux disease?

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ABSTRACT

Gastroesophageal reflux disease (GERD), which is common in many communities, is associated with structural factors, eating habits, and the use of certain drugs. The use of such drugs can lead to the emergence of GERD and can also exacerbate existing reflux symptoms. These drugs can contribute to GERD by directly causing mucosal damage, by reducing lower esophageal sphincter pressure (LESP), or by affecting esophagogastric motility. In this article, we report our investigation of the relationships between GERD and medications within the scope of the "Turkish GERD Consensus Group." For the medication groups for which sufficient data were obtained (Figure 1), a systematic literature review in English was conducted using the keywords "gastroesophageal reflux" [MeSH Terms] and "anti-inflammatory agents, non-steroidal" [MeSH Terms], "gastroesophageal reflux" [MeSH Terms] and "acetylsalicylic acid" [MeSH Terms], "gastroesophageal reflux" [All Fields] and "estrogenic agents" [All Fields], "gastroesophageal reflux" [All Fields] and "progesterones" [All Fields], "gastroesophageal reflux" [All Fields] and "hormone replacement therapy" [All Fields], "gastroesophageal reflux" [MeSH Terms] and "diphosphonates" [MeSH Terms] OR "diphosphonates" [All Fields], "calcium channel blockers" [MeSH Terms] and "gastroesophageal reflux" [MeSH Terms], "gastroesophageal reflux" [MeSH Terms] and "nitrates" [MeSH Terms], "gastroesophageal reflux" [MeSH Terms] and "antidepressive agents" [MeSH Terms], "gastroesophageal reflux" [MeSH Terms] and "benzodiazepines" [MeSH Terms] and "hypnotic drugs" [MeSH Terms], "gastroesophageal reflux" [MeSH Terms] and "cholinergic antagonists" [MeSH Terms], "gastroesophageal reflux" [MeSH Terms] and "theophylline" [MeSH Terms], and "gastroesophageal reflux [MeSH Terms] AND "anti-asthmatic agents" [MeSH Terms]. The studies were analyzed and the results are presented here.

Keywords: Gastroesophageal reflux disease, non-steroidal drugs, acetylsalicylic acid, oral contraceptive drugs, hormone replacement therapy, diphosphanates, calcium chanel blockers, nitrates, antidepressive drugs, cholinergic antagonists, anti-asthmatic agents

The use of some groups of drugs may cause GERD by various mechanisms and may also lead to an increase in existing GERD symptoms and signs. The mechanisms by which drugs cause reflux include a reduction in LESP and delayed gastric emptying; drugs may also directly cause GERD by causing damage or inflammation in the esophageal mucosa (Figure 1). The drug groups that are believed to be risk factors for the development of GERD have been investigated in this study, and the results are presented as a summary in Table 1.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs directly and indirectly lead to mucosal damage in the digestive tract by inhibiting cyclooxygenase (COX) enzymes and increasing gastric acid secretion (1). They reduce LESP and delay emptying of the stomach (2). Also, these drugs exacerbate reflux symptoms; when reflux patients using NSAIDs are given proton pump inhibitors (PPIs), gastrointestinal tolerance is improved (3). The prevalence of gastroesophageal symptoms has been found to be 1.7 times greater in patients using NSAIDs and ASA on a regular basis than in patients not using these drugs (4). In two case-control studies conducted in recent years, it was reported that no change was found in the severity of symptoms of GERD patients using NSAIDs; however, the use of NSAIDs was

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Table 1. The effects of drugs on GERD

Drug	The effect on GERD	Evidence value
NSAID (+ASA)*	Increasing	2b, 3b
Estrogen	Increasing	2b
Oral contraceptives	Not increasing	2b
Bisphosphonates	No data	
Calcium channel blockers	Increasing	2b
Nitrates	Increasing	1b,3b
TCA	Increasing	3b
SSRI	Not increasing	2b
Benzodiazepines	Increasing	2b
Anti-cholinergics	Increasing	1b
Theophylline	Increasing	1b
Albuterol	increasing	1b

*Except for naproxen. GERD: gastroesophageal reflux disease; NSAID: non-steroidal anti-inflammatory; ASA: acetylsalicylic acid; TCA: tricyclic antidepressant; SSRI: Selective serotonin reuptake inhibitor

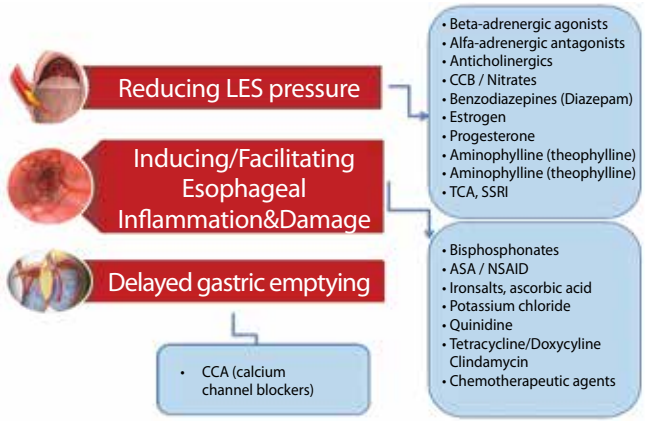

Figure 1. Drugs and GERD

demonstrated to be a risk factor for GERD (OR: 2.0, 95% CI 1.3 to 3.0) (5-7). In another study that involved a larger number of cases and included consecutive screening with upper gastrointestinal endoscopy, the development of GERD was shown to increase approximately 4 times in patients using NSAIDs (OR: 4.23, 95% CI 1.66 to 10.74) in another community-based survey study (8). In a retrospective longitudinal study that Kotzan et al. (9) conducted to investigate the prevalence of GERD in patients who were prescribed NSAIDs, 63902 patients who were prescribed NSAIDs and 99183 control patients who did not use NSAIDs were compared and it was found that the use of NSAIDs increased the incidence of GERD with age. This upward trend was evident until the age of 55, and the relative risk for absolute GERD development was 2.11. In a randomized double-blind esophageal manometry study containing a small number of healthy adults; it was found that naproxen use did not induce reflux in healthy individuals and did not lead to changes in motility parameters (10). In an observational study that was conducted in France and in which feedback was received from 6823 participants, reflux symptoms were statistically more frequent in patients using NSAIDs (27% vs. 19%, p<0.001); when the groups using NSAIDs and not using NSAIDs were compared in terms of the development of GERD symptoms, the incidence of symptoms was determined to be greater in the group using NSAIDs (OR: 1.61, 95% CI 1.42 to 1.80). It was found in the study that the use of NSAIDs in the previous 3 months increased the development risk of GERD symptoms 1.6 times (OR: 1.6, 95% CI 1.36 to 1.98) (11). In a case-control study that Ruigómez et al. (12) conducted with 7159 GERD patients and a control group of 10,000 people, it was documented that the use of NSAIDs increased the development risk of GERD by 1.5 times (OR: 1.5, 95% CI 1.3-1.7) in patients who were currently using NSAIDs and by 1.6 times (OR: 1.6, 95% CI 1.5-1.7) in patients who had used NSAIDs in the past. In another multicenter retrospective study involving 2251 GERD patients that did not involve a control group, the effects of 15-30 days of NSAID use (alone and in combination with ASA) on GERD symptoms was investigated; heartburn developed in 68% of the patients included in the study, and the use of NSAIDs was also observed to result in a statistically significant increase in acute reflux symptoms (p<0.0001) (13).

Acetylsalicylic Acid

The use of ASA may cause both systemic and topical damage in the gastroduodenal mucosa (14). No association was observed between the use of ASA and the development of reflux symptoms in two case-control studies (5,6). However, it was observed in a randomized controlled trial including patients using low doses of aspirin that development of erosive esophagitis increased in the control group after 12 weeks of ASA therapy; also, esophagitis developed less frequently in patients who were also using famotidine (4.4% vs. 19%, p<0.0001) (15). In the aforementioned case-control study by Ruigómez et al. (12), the use of ASA was determined not to increase the risk of GERD (OR: 1.1, 95% CI 0.9-1.3). Contrastingly, in the observational study by Ruszniewski et al. (11), while the prevalence of reflux symptoms was 25% in patients using ASA for 3 months, the prevalence was found to be 18% in patients not taking ASA daily (p<0.05, OR: 1.5, 95% CI 1.05-2.15). In a Spanish study in which factors were related to prevalence, the severity and progress of GERD symptoms were investigated using a reflux questionnaire which was administered to 2,500 people by telephone; it was demonstrated that the intake of 1-5 tablets of ASA per week mildly increased reflux symptoms (p<0.05) and that the severity of reflux symptoms increased with weekly intake of 6-9 tablets (16). In another retrospective multicenter study, while the development of heartburn in patients using ASA was significantly less in comparison to other NSAIDs (OR: 1.44, 95% CI 1.01-2.04), the risk was determined to increase with combined use of ASA and NSAIDs (13).

Hormone Replacement Therapy and Oral Contraceptive Drugs

Hormone replacement therapy and *oral contraceptive* (OC) drugs increase the synthesis of nitric oxide, which is a major transmitter that enables relaxation of the lower esophageal sphincter (17). In a randomized controlled study in which a to-

tal of 40 centers participated, conjugated estrogen was given to 5310 of 10739 women who underwent postmenopausal hysterectomy, and a placebo was given to the remaining 5429 women; conjugated estrogen + medroxyprogesterone was given to 8506 of 16608 women who did not undergo hysterectomy, and a placebo was given to the remaining 8102 women. One year later, the subjects were evaluated in terms of the incidence of GERD symptoms and the progression of GERD (18). The incidence of new, moderate, and severe symptomatic GERD development was found to be slightly higher in the conjugated estrogen group in comparison to the placebo group (4.2% vs. 3.1%, OR: 1.35, 95% CI 0.99-1.85). Initially, when the women with GERD symptoms who received conjugated estrogen treatment and a placebo were compared, estrogen therapy was not shown to affect the severity of existing symptoms. When the patients receiving conjugated estrogen+medroxyprogesterone and a placebo were compared, no increase was observed in the incidence of symptomatic GERD (2.4% for both) or in the severity and frequency of existing symptoms (18). In another retrospective cohort study, the relative risk was investigated for the use of PPIs or for GERD in women who used HRT (n=22101) and did not use HRT (n=29081); when multiple regression analysis was performed, a significant association was found between estrogen monotherapy and GERD risk (OR: 1.49, 95% CI 1.18-1.89, p<0.001). In contrast, no risk increase was observed with combined HRT or progesterone monotherapies. Similarly, the use of PPIs was found to be significantly higher in patients receiving estrogen monotherapy (OR: 1.46, p=0.001) (19). In a population-based, multinational case-control study conducted with female twins, a group of 4365 twin patients with reflux symptoms and a group of 17321 twin patients without reflux symptoms were compared in terms of the risk of reflux symptoms (17). The risk of reflux symptoms in women receiving postmenopausal HRT with estrogen was higher than in those not receiving this therapy (OR: 1.32, 95% CI 1.18-1.47). The risk of reflux symptoms increased at a rate of 48% in women receiving only HRT with progesterone in comparison to women who did not receive HRT (OR: 1.48, 95% CI 1.06-2.06). However, no increased risk of reflux symptoms was found in women using combined HRT compared with those not using this therapy (OR: 0.99, 95% CI 0.87-1.13). No difference was found between twins in all groups receiving HRT. No increase in the risk of reflux symptoms was observed when the groups using and not using OC drugs were compared (OR: 1.07, 95% CI 0.93-1.23). In this group, the risk of reflux symptoms was found to be slightly higher in monozygotic twins who used OCs than in those who did not (OR: 1.33, 95% CI 0.91-1.96) (17). In a prospective cohort study, 51637 postmenopausal women were evaluated, and the impact of HRT implementation on the risk of reflux symptoms and the frequency of symptoms (comparing patients receiving and not receiving HRT) were investigated (20). The odds ratios were found to be 1.66 (95% CI 1.54-1.79) in patients receiving HRT with estrogen monotherapy and 1.41 (95% CI 1.29-1.54) in those receiving combined HRT. The frequency of reflux symptoms was also observed to increase in patients who received HRT in comparison to patients who did not. In addition, it was determined that as the estrogen dose and duration increased, the risk of reflux symptoms increased; also, from the second year following the cessation of HRT with estrogen, the risk statistically significantly decreased over time (20).

Bisphosphonates

Although gastrointestinal side effects of bisphosphonates have been found to be similar to those of placebos in clinical trials, side effects occur in approximately one in three patients in real life (21). Regurgitation and heartburn develop in more than 60% of patients. The use of oral bisphosphonates is contraindicated in patients with esophageal motility disorders. Gastrointestinal side effects can regress in six months when the uses of bisphosphonates changes from weekly preparations to a form in which they are used once in a month. A retrospective database analysis was conducted involving 812 female patients using alendronate; while the detection rate of disease associated with hyperacidity was 28.5 per 100 person-years in patients who used alendronate, the rate was reported to be 17.6 in patients who did not. In other words, excluding women with a history of acid-related diseases before beginning alendronate therapy, patients taking alendronate and not taking alendronate were compared in terms of the risk of acid-related disease development; the odds ratio was found to be 1.6 (95% CI 1.2-2.7). The risk is increased in patients aged 70 years or older and in patients who use NSAIDs (21). However, this limited number of clinical observations and retrospective studies are not sufficient to conclude that the use of bisphosphonate alone may lead to GERD development or worsening of present GERD symptoms. In a study in which Perkins et al. (22) compared 15 GERD patients with 15 control patients who were compliant in terms of age and gender, it was demonstrated that film-coated risedronate did not change esophageal transit time in comparison to a placebo.

Nitrates and Calcium Channel Blockers

Nitrates and Calcium Channel Blockers (CCBs) decrease LESP dose-dependently and impair esophageal clearance. They reduce the amplitude of esophageal contractions. The use of calcium channel blockers is also a risk factor for the development of GERD; the rate of development of GERD was found to be 16.5% in non-GERD Japanese patients after 6 years of follow-up, and the use of CCBs was also determined to be a risk factor (23). In general, CCBs can cause reflux and/or exacerbate existing reflux symptoms. Felodipine, a new CCB, has been demonstrated to not increase reflux episodes in people with GERD (24). In a survey study in which the effects of cardiac drugs on GERD were investigated, 201 cardiac patients who applied consecutively were evaluated through an F-scale GERD questionnaire, and the medications that increased the score were investigated. The score was found to be high in patients taking CCBs (OR: 3.19, 95% CI 1.01-10.11, p<0.049). In addition, the F-scale score was found to be higher in patients receiving CCB treatment and using gastric acid suppressive medication

than in those who only received acid-suppressive therapy (25). In a retrospective study involving 371 patients who used CCBs because of non-cardiac chest pain, 130 of the patients had gastrointestinal symptoms (heartburn) prior to CCB treatment; symptom exacerbation was detected in 45.4% of these patients, and 241 (35.3%) of the patients developed new reflux symptoms. Symptom exacerbation occurred most commonly with the use of amlodipine and least commonly with the use of diltiazem; meanwhile, new symptom development occurred most frequently with verapamil and least frequently with diltiazem. When regression analysis was performed, the increase in reflux symptoms after CCB treatment was observed to be 2.7 times higher (OR: 2.7, 95% CI 1.24-5.73, p=0.012) in patients taking dihydropyridine CCB in comparison to the non-DHP group (26). In the case-control study by Stacher et al. (27), the use of nitrates was shown to increase the development risk of GERD (OR: 1.5, 95% CI 1.1-2.0) (12). In a double-blind placebo-controlled trial in which isosorbide dinitrate was given to 12 healthy adult males in doses of 2×20 mg/day and 2×40 mg/day, this nitrate was demonstrated to decrease LESP more than a placebo (p<0.025).

Antidepressant Drugs

The use of antidepressant drugs, particularly tricyclic antidepressants (TCAs), has been indicated to lead to the development of GERD. TCAs have anticholinergic effects, and they reduce LESP. In a case-control study conducted by Martín-Merino et al. (28), the risk of GERD in patients treated with TCAs was higher than in those not taking TCAs (statistically significantly higher even when all factors were corrected); also, it was shown that as the duration of TCA use increased, the risk of GERD also increased (while the odds ratio was 1.48 (95% CI 1.07-2.06) in patients using TCAs for 3 months or less, it was 2.06 (95% CI 1.43-2.97) in patients using TCAs for more than 3 months). Moreover, this effect is particularly evident with the use of amitriptyline, a TCA drug. When patients using and not using amitriptyline were compared, the risk of GERD in patients using this drug was greater at a rate of 71% (OR: 1.71, 95% CI 1.22-2.40); also, the increase in risk was significantly higher in patients who used amitriptyline for more than 3 months (OR: 2.19, 95% CI 1.32-3.64). In contrast, this risk is lower for patients using dothiepin (OR: 1.4) and lofepramine (OR: 1.39). In a population-based case-control study investigating the risk of reflux esophagitis with the use of tricyclic antidepressants, it was demonstrated that the use of clomipramine increased GERD risk 4.8 times (OR: 4.82, 95% CI 2.08-11.14); no risk increase occurred with the use of other TCAs (29). No risk increase for GERD was found with the use of SSRI and SNRI antidepressants (28). In a manometry study in which the use of citalopram and a placebo were compared in 10 healthy adults, citalopram was shown not to cause a change in basal esophageal parameters (30).

Benzodiazepines and Hypnotic Drugs

These drugs are believed to lead to reflux development by reducing LESP. In a 25-patient double-blind controlled study by Rushnak and Leevy (31), in which they investigated the effects of 5 and 10 mg doses of diazepam mixed with intravenous saline by monitoring LESP, it was shown that the 5 mg dose caused a dose-dependent decrease in LESP at a rate of 18.9%, and a 10-mg dose caused a decrease of 37.8%. In another randomized controlled study, alprazolam, a new generation benzodiazepine, was administered comparatively with a placebo at a dose of 3x0.25 mg/day in 10 healthy volunteers; it was found that alprazolam did not affect lower and upper esophageal sphincter pressure and motility in 24-h pH monitoring and manometry. Alprazolam led to nocturnal acid reflux in 1/3 of cases; this was attributed to the depressive effects of the drug on the central nervous system (32).

Anticholinergic Drugs

Anticholinergic drugs reduce basal LESP. Furthermore, although these drugs reduce gastric acid secretion, they extend the duration of gastric emptying. Because they reduce the production of saliva, the chemical neutralization of esophageal acid residues is delayed, and acid clearance time is prolonged. It is considered that anticholinergic drugs can lead to GERD for these reasons. In the literature, three randomized controlled studies investigating this issue have been conducted. Ciccaglione et al. (33) compared hyoscine N-butyl bromide (HNB) (3×10 mg/day orally), an anticholinergic agent, with a placebo in 10 healthy adults and in 10 GERD patients by 48-h pH monitoring analysis. It was shown that HNB increased the occurrence of acidic esophageal reflux both in healthy people and in GERD patients (increase in the number of reflux episodes and increase in the percentage of time for which pH remained <4). In a randomized, controlled, 16-h pH monitoring and manometry study which Koerselman et al. (34) conducted with 15 healthy volunteers, it was demonstrated that dicyclomine (4×20 mg/day vs. a placebo), an oral anticholinergic agent, increased pH<4 time percentage (2.6 vs. 0.5, p<0.04) in the supine position and in the first 2 h; it also prolonged clearance time (0.9 vs. 0.3, p<0.05). In another randomized controlled trial conducted using atropine, 15 GERD patients, 11 of whom had erosive esophagitis, were evaluated. After 15 ug/kg intravenous bolus and 4 ug/kg/h atropine vs. placebo infusion were applied to the patients, a 60-min esophageal manometry and pH monitoring records were taken. Atropine lowered the average basal LESP from 7.1 mm Hg to 2.9 mm Hg (p<0.01) and increased the duration of LESP of 2 mmHg and lower from 40% to 69% (p<0.05). It was demonstrated that the basic mechanism in 95% of 42 reflux episodes that occurred during atropine infusion was the absence of basal LESP; also, intravenous atropine inhibited temporary relaxation of the lower esophageal sphincter (35).

Antiasthmatic drugs, particularly methylxanthines, are known to cause the development of reflux in asthmatic patients and normal healthy volunteers (36,37). Aminophyllines increase gastric acid secretion and reduce LESP. In a randomized, double-blind, placebo-controlled study investigating the effects of theophylline on GERD in normal adults, theophylline and a pla-

cebo were compared at a single oral treatment dose (by performing manometry and measuring pH at the basal, 1.5th, 4th, and 8th h). It was shown that theophylline induced GERD by reducing LESP (100% vs. 22%) in all patients compared to the placebo, increased the frequency of reflux compared to the placebo (73% vs. 11%), and led to new reflux symptoms in 61.5% of cases (37). In a randomized, double-blind, cross-comparative study by Hubert et al. (38), 16 patients with asthma (none of whom received oral steroids or anticholinergic drugs and all of whom were stabilized with an inhaled β2 agonist) were given theophylline or a placebo in hospital at one-week intervals. In the pH monitoring analysis, while there was no difference in total reflux time or in the number of reflux episodes lasting longer than 5 min, the number of reflux episodes was shown to be greater in the theophylline group than in the placebo group (16.7±3.1 vs. 10.7±1.4, p=0.051). It is known that theophylline may exacerbate existing GERD. In a study in which groups of 25 patients with moderate-severe bronchial asthma and GERD symptoms treated with and without theophylline were compared, theophylline was indicated to increase the duration of daytime and nighttime reflux ($p<0.05$) and the total number of reflux symptoms ($p<0.01$) (39). In another study comparing inhaled β2 agonists and theophylline, 9 male patients with obstructive pulmonary disease and GERD were compared; the total reflux duration was found to be longer in the theophylline group than in the albuterol group (16.1% vs. 9.7%, $p<0.05$). Similarly, the pH<4 total time was reduced by 40% in the albuterol group compared with the theophylline group, and the number of reflux episodes lasting 5 min. was found to be greater in the theophylline group (9.6 vs. 5.1, $p<0.03$) (40). In a prospective, double-blind, placebo-controlled study in which the effect of inhaled albuterol on esophageal motility was investigated, manometry was performed on six patients with asthma who were given albuterol and a placebo at one-week intervals. Albuterol was indicated to reduce LESP in a dose-dependent manner, and it was considered that this reduction could induce reflux-related asthma attacks (41).

RECOMMENDATIONS

- The use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the development of GERD symptoms. While the use of acetylsalicylic acid (ASA) may lead to a slight increase in the development risk of GERD, the risk of GERD increases with combined use (NSAIDs + ASA) (Levels of evidence: 2b, 3b).
- The use of hormone replacement therapy (HRT) containing only estrogen increases the risk of GERD development. The use of HRT preparations with combined estrogen and progesterone and the use of oral contraceptive (OC) therapeutic agents does not lead to a significant increase in the risk of GERD development (Level of evidence: 2b).
- It can be said in light of the limited data available that the use of bisphosphonate alone does not lead to an increase in the development risk of GERD symptoms (level of evidence: 3b).
- The use of calcium channel blockers (CCBs) can lead to GERD and can exacerbate existing reflux symptoms. When considered in terms of drug subgroups, the risk of reflux development is higher with dihydropyridine CCBs than with non-dihydropyridine CCBs. Therefore, diltiazem, which has the lowest risk of reflux development, may be preferable in GERD-diagnosed patients who require CCBs (Level of evidence: 2b).
- Nitrates can increase the risk of GERD development by reducing lower esophageal sphincter pressure (LESP) (Levels of evidence: 1b, 3b).
- The use of tricyclic antidepressant medications (particularly amitriptyline and clomipramine) is a risk factor for the development of GERD. However, the use of selective serotonin re-uptake inhibitors (SSRIs) and selective serotonin and noradrenaline reuptake blockers (SSNRI) does not lead to a risk increase (Levels of evidence: 3b, 2b).
- The data indicating that hypnotics and benzodiazepine medications increase the development risk of GERD symptoms are insufficient (Level of evidence: 2b).
- The use of anticholinergic drugs can increase the number of reflux episodes in GERD (Level of evidence: 1b).
- Theophylline, an antiasthmatic drug, may induce reflux by reducing LESP; this drug increases the number of reflux episodes in patients with asthma and can exacerbate existing reflux symptoms. The use of albuterol leads to fewer reflux episodes than the use of theophylline (Level of evidence: 1b).

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