Review Article
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Prophylactic Treatment of Migraine

Migrende Profilaktik Tedavi

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ABSTRACT

Migraine is a common chronic neurological disease characterized by episodic attacks of headache and associated symptoms. The pharmacological treatment of migraine may be acute or prophylactic, and patients with frequent, severe headaches often require both approaches. Prophylactic treatment is used to reduce the frequency, duration, or severity of attacks, to enhance the benefits of acute treatments, and to improve patient's ability to function normally. Prophylactic treatment may also prevent progression from episodic migraine to chronic migraine and may result in reductions in health-care cost. The currently available pharmacological options for migraine prophylaxis include a wide array of medications. The major medication groups for prophylactic treatment include ß-blockers, anticonvulsant, drugs such as topiramate and valproate, antidepressant drugs, such as amitriptyline and selective serotonin and selective serotonin-norepinephrine reuptake inhibitors (SNRIs), calcium channel antagonists and neurotoxins. The agent for prophylactic treatment should be chosen based on the efficacy and side-effect profile of the drug, and the patient's coexistent and comorbid conditions. *(Archives of Neuropsychiatry 2013; 50 Supplement 1: S30-S35)*

Key words: Migraine, prophylactic treatment

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ÖZET

Migren epizodik başağrısı atakları ve eşlik eden semptomlarla karakterize sık rastlanılan kronik nörolojik bir hastalıktır. Migrenin farmakolojik tedavisi akut veya profilaktik tedavileri içerir, sık ve şiddetli başağrısı atakları olan hastalar her iki tedaviye de gereksinim duyarlar. Profilaktik tedavi başlıca atak sıklığı, süresi ve şiddetini azaltmak, akut tedavi yararlanımını artırmak ve hastanın fonksiyonel durumunu iyileştirmek amacıyla kullanılır. Profilaktik tedavi ayrıca epizodik migrenin kronik migrene dönüşümünü önleyebilir ve sağlık harcamalarında azalma sağlayabilir. Migren profilaksisinde kullanımda olan farmakolojik ilaç seçenekleri oldukça geniştir. Profilaktik tedavide kullanılan başlıca gruplar ß-blokerler, topiramat ve valproat gibi antikonvülzan ilaçlar, amitriptilin ve selektif serotonin ve selektif serotonin-norepinefrin gerialım inhibitorleri (SNRI'lar) gibi antidepresanlar, kalsiyum kanal antagonistleri ve nörotoksinlerdir. Profilaktik tedavide kullanılacak ilaç, etkinlik ve yan etki profiline göre seçilmeli, hastanın eşlik eden ve komorbid hastalıkları da göz önünde bulundurulmalıdır. *(Nöropsikiyatri Arşivi 2013; 50 Özel Sayı 1: S30-S35)*

Anahtar kelimeler: Migren, profilaktik tedavi

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Migraine is a chronic neurologic disease characterized with episodic headache attacks and accompanying symptoms (1). In our country, the predicted definite and potential prevelance of migraine in one year was found to be 28.8 % and it was reported that only 4.9% of the patients received prophylactic treatment, although the monthly number of attacks was four and above in more than half of the patients with migraine (the mean monthly frequency of attacks 5.9±6.0) (2). In the American Migraine Prevalence and Prevention Study, it was found that only 13% of the patients were receiving prophylactic treatment, although prophylactic treatment was required in approximately 38% of the patients with migraine (3). The primary aim in prophylactic treatment of migraine is to decrease the frequency, severity and time of attacks. In addition, it is also aimed to increase the benefit of acute attack treatment, improve the functional status and decrease the disability caused by headache with prophylactic treatment (4). It was found that a reduction in presentation of the patients to outpatient clinics and emergency departments and in the number of CT and MR imaging tests occured with addition of prophylactic treatment to acute treatment (5). Although there is no clear consensus on the indications for starting prophylactic treatment, treatment guidelines have established some general rules (6, 7, 8, 9).

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Decision for prophylactic treatment ;

· In presence of recurrent attacks which affect the quality of life and daily life despite acute attack treatment,

· Inefficient acute attack treatment, presence of contraindications of acute atttack treatment or intolerable side effects,

· Overuse of the drugs used in acute treatment,

· Because of the risk of development of chronic migraine or drug overuse headache in patients with attacks more frequent than once a week and

· In presence of special conditions including hemiplegic migraine, frequent, long or incomfortable auras, attacks with a risk of leading to permanent neurologic demage

· Should be given considering the patient's preferance

The drugs which are frequently used in prophylactic treatment include beta-adrenergic blockers, antidepressants, calcium channel antagonists, serotonin antagonists and anticonvulsant drugs (Table 1). In the migraine prophylaxis guideline of the American Headache Association and American Academy of Neurology (AHS, AAN), prophylactic drugs were evaluated according to their evidence-based efficiencies (Table 1). The drug to be used in prophylaxis should be selected considering the efficiency of the drug, the side effects which may develop and the comorbid diseases accompanying migraine (Table 2, Table 3). Some general principles should be taken into consideration in prophylactic treatment .

These principles include:

· Starting treatment with the drug with the highest evidence-based efficiency;

· Starting treatment with the lowest efficient dose, increasing the dose until clinical benefit occurs or treatment limiting side effects occur;

· Waiting for a sufficient period for clinical benefit to appear (2-3 months);

· Avoiding overuse of acute attack treatment;

· Preferring extended release formulations to increase treatment compliance;

· Making the patients to keep a headache diary to monitor headache attacks;

· Reviewing treatment with 3-month intervals at the longest and evaluating in terms of decreasing or discontinuing treatment;

· Selection of the drug which will treat both migraine and the accompanying condition considering comorbid diseases or conditions which are observed in association accidentally including epilepsy, depression, anxiety disorder and hypertension; ensuring that migraine treatment will not lead to exacerbation of the accompanying diseases;

· Interrogating pregnancy and ensuring that treatment of pregant patients do not carry a risk of fetal anomaly (4, 10).

Giving sufficient information about the disease to the patient, explaining treatment objectives clearly, giving information about potential side effects, learning the expectation of the patients in relation with treatment and determining realistic objectives when giving a decision of prophylactic treatment increase treatment compliance and the chance of success.

Mechanisms of Action of Prophylactic Treatment

The potential mechanisms of action of migraine prophylaxis include increasing the migraine activation treshold by stabilization of activated nervous system, increasing antinociception, decreasing peripheral ans central sensitization, bloking of neurogenic inflammation and modulation of symphathetic, parasympathetic and serotonergic tonus (4). In the study performed by Ayata et al., it was shown that topiramate, valproate, amiltriptyhline propranolol and methisergid used in migrain prophylaxis decreased the frequency of cortical spreading depression (CSD) by 40-80% when used chronically depending on the dose and treatment period and increased the electrical stimulus treshold required for experimental CSD. The authors proposed that the common efficiency of these drugs might be related with inhibition of CSD (11). Elucidating the mechanisms of action of the drugs used in migraine prophylaxis will contribute to development of efficient drugs for this objective.

Drugs Used in Migraine Prophylaxis:

β-adrenergic Blockers:

β-adrenergic blockers constitute a drug group which is widely used in migraine prophylaxis. The efficiency of propranolol which is a nonselective β blocker and metoprolol which is a selective β-blocker in migraine prophylaxis has been shown in many controlled studies (12, 13, 14, 15). While atenolol, nebivolol, bisoprolol, nadolol and timolol were also found to be efficient, asebutolol, alprenolol, oxprenolol and pindolol which show intrinsic sympathomimetic activity do not have efficiency in prophylactic treatment of migraine (16, 17, 18, 19). Propranolol is efficient in migraine prophylaxis in the dose range of 120-240 mg/day. The potential central action of β-adrenergic blockers occurs by way of inhibiton of central β –receptors which interact with adrenergic pathways increasing vigilance, interaction with 5-HT receptors and cross-modulation of serotonergic system (20, 21). Propranolol also inhibits production of nitric oxide (NO) by blocking inducable nitric oxide synthase (iNOS) (20, 21). In addition, propranolol decreases neuronal activity and acts as a membrane stabilizator by way of inhibition of cellular flows induced by kainate and synergistic effect with N-metyl-D-aspartate blockers (20, 21). Bronchial asthma, chronic obstructive lung disease, congestive heart failure, atrioventricular conduction disorders, Raynaud phenomenon, peripheral vascular diseases and uncontrolled diabetes are contraindications for β-adrenergic blockers. The side effects of β-adrenergic blockers include fatigue, decreased exercise tolerance, coldness in the peripery of the extremitis, gastrointestinal symptoms including diarrhea, constipation and floating, orthostatic hypotension, bradicardia and impotence. Side effects originating from the central nervous system include dizziness, sleep disorders and nightmares, depressison, memory disorders and hallucinations (4, 20, 22). In patients with depressive symptoms, β-adrenergic blockers should be given in combination with antidepressant treatment or another prophylactic drug should be selected.

Antidepressants

Tricyclic Antidepressants

Amitriptyline which is a tricyclic antidepressant has a proven efficiency in migraine prophylaxis (23, 24). It is known that its efficiency in migraine prophylaxis is independent from its antidepressant action and antimigraine effect occurs earlier compared to the expected efficiency time in depression treatment. the efficient dose range of tricyclic antidepressants is wide and therefore, the appropriatre dose should be determined individually. Lower doses (frequently 25 mg/day) compared to antidepressant doses may be efficient in migraine prophylaxis. When sufficient response is not obtained, the dose should be increased up to 100 mg/day. In elderly patients, lower doses (10 mg/day) are recommended to be used initially (25). The side effects of tricyclic antidepressants are common. Dry mouth, metallic taste, epigastric tenderness, constipation, dizziness, confusion, tachycardia,

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palpitation, blurred vision and urinary retentions are antimuscarinic side effects. Orthostatic hypotension and weight gain are also among the frequently observed side effects. Care should be taken especially in elderly patients because of the risk of cardiac conduction disorder, confusion and delirium.

Selective Serotonin and Serotonin-Noradrenaline Reuptake Inhibitors

Although the efficiency of this group of drugs in migraine prophylaxis is weaker compared to tricyclic antidepressants, they are an alternative treatment option, because their side effects are more tolerable (26). The efficiency of fluoxetine at doses of 10-40 mg /day in migraine prophylaxis has been demonstrated (27, 28). Similarly, venlafaxine has also been found to be effective in migraine prophylaxis (29, 30). The recommended daily dose of venlafaxine is 150 mg/day. the treatment is recommended to be initiated at a dose of 37,5 mg/day and the dose is recommended to be increased to 150 mg/day with weekly increments.

Calcium Channel Antagonists

The mechanisms of action of calcium channel antagonists in migraine prophylaxis are not clear. Potential mechanisms include 5-HT release and inhibitor effects on neurovascular inflammation and initiation and extension of CSD (31). The efficiency of flunarisine which is a nonselective calcium channel antagonist with antidopaminergic properties has been demonstrated in migraine prophylaxis (32, 33, 34). The recommended dose is 5-10 mg/day. side effects include wieght gain, somnolance, dry mouth, hypotension, exacerbation of depression and rare extrapyramidal reactions. Although verapamil has been found to be efficient in treatment of migraine in some studies with a limited number of patients, evidence is not sufficient and it is not a good option. Calcium channel antagonists are a good option in hypertensive patients or in patients who can not use β-blockers because of side effects.

Anticonvulsants

Assuming that hyperexitability in migraine can be inhibited with antiepileptic drugs anticonvulsant drugs have been started to be used in migraine prophylaxis. In this group, the anti-migraine efficiency of valproate and topiramate has been found to be high. In patients who can not tolerate high dose of monotherapy, combination of topiramate and sodium valproate at lower doses has been proposed to be an efficient treatment option (35).

Valproate

Valproic acid or sodium valproate is a very efficient prophylactic drug used in migraine prophylaxis at doses of 500-2000 mg/day (singel dose of divided doses) as a long-acting preperation (36, 37). Valproate shows its action by increasing GABA-mediated transmission, inhibiting low treshold T-type Ca++ channels, blocking voltage-dependent Na+ channels and decreasing plasma protein extravasation (38,39). The most common side effects include nausea and vomiting. In the late period, tremor in the hand and hair loss may occur. It rarely leads to sedation and disruption in cognitive functions. Severe side effects which are observed rarely include hepatitis and pancreatitis. In young female patients, hyperandrogenism, over cysts and weight gain may be observed. Definite contraindications include pregnancy, previous history of pancreatitis and liver diseases. Other contraindications include thrombocytopenia, pancytopenia and bleeding disorders.

Topiramate

Topiramate shows its action by way of Ca++ and Na+ channel blockage, glutamate blockage, inhibition of carbonic anhydrase and stimulation of GABA production (38, 39). It shows its antimigraine efficiency at doses of 50-200 mg/day (40, 41, 42). Paresthesias are among the commonly observed side effects and informing the patients about this side effect will increase patient compliance to treatment. Other side effects include fatigue, loss of appetite, nausea, diarrhea, abdominal pain and weight loss (42). In migraine studies, baseline body weight was reported to be reduced by 2.3% in the 50 mg/day group, by 3.2% in the 100 mg/day group and by 3.8% in the 200 mg/day group. Topiramate is a good option in overweight patients, since most drugs used in migraine prophylaxis lead to weight gain as a side effect. Central side effects include paresthesias, somnolance, insomnia, affection of mood, anxiety, memory, speech and concentratiın disorders (42). Formation of renal stones is found 2-4 times more frequently compared to the normal population.

Antiserotonergics

Methisergide (3–6 mg/day) and pizotifen (1.5–3 mg/day) act by by blocking 5-HT1and 5-HT2 recors and inhibiting histamin release from mast cells (43, 44). The fact that the antimigraine efficiencies of Methisergide and pizotifen are not correlated with affinity to 5-HT-2A, 5-HT-2B and 5-HT-2C receptors and mianserine and ketanserin which have similar mechanisms of action are not efficient in prophylactic treatment or have a very low efficiency

Table 1. Drus used in migraine prophylaxis according to their evidence-based efficiencies in the 2012 American Neurology Academy and American Headache Society (AAN/AHS) Migraine Prophylaxis guideline.

Drug	Doses
Proven efficiency(A level evidence)	
Valproate	400-1000 mg/day
Topiramate	25-200 mg/day
Metoprolol	47.5-200 mg/day
Propranolol	120-240 mg/day
Timolol	10-15 mg/day
Probable efficiency (B level evidence)	
Amitriptyline	25-150 mg/day
Venlafaxine	150 mg/day
Atenolol	(uzun salınımlı)
Nadolol	100 mg/day
Possible efficiency(C level evidence)	
Lisinopril	10-20 mg/day
Candesartan	16 mg/day
Clonidine	0.75-0.15 mg/day
Guanfacin	0.5-1 mg/day
Carbamazepine	600 mg/day
Nebivolol	5 mg/day
Pindolol	10 mg/day
Cyproheptadine	4 mg/day

Source of the table: Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78:1337-1345.

Table 2. Comorbid diseases observed with migraine.

Cardiovascular	Psychiatric	Neurologic	Gastrointestinal	Others
Hyper/hypotension	Depression	Epilepsy		
Raynaud phenomenon	Mania	Essential tremor		Asthma
Mitral valve prolapsus	Panic disorder	Positional vertigo	Irritable bowel syndrome	Allergies
Myocardial infaction/ angina pectoris	Anxiety disorder	Restless leg syndrome		
Stroke				
Patent foramen ovale				

Source of the table: Silberstein SD. Preventive migraine treatment. Neurol Clin 2009;27: 429-443.

Table 3. Evaluation of the drugs used in migraine prophylaxis according to efficiency and side effects

High efficiency Side effects mild/moderate	Low efficiency Side effects mild/morderate	KUnproven efficiency Side effects mild/moderate	Low efficiency or inefficient
Beta-blockers :	NSAI drugs:	Antidepressants:	Acebutolol,
Propranolol	Aspirin	Doxepine	Carbamazepine
Timolol	Flurbiprophen	Nortriptyline	Clomipramine
Antidepressants:	Ketoprophen	Imipramine	Clonazepam
Amitriptyline	Naproxen sodium	Protriptyline	Endomethazine
Anticonvulsants:	Beta-blockers:	Venlafaxine	Lamotrigine
Valproate	Atenolol	Fluvoxamine	Nabumeton
Topiramate	Metoprolol	Mirtazapine	Nicardipine
Calcium channel blocker:	Nadolol	Paroxetine	Nifedipine
Flunarizine	Calcium channel blocker:	Protriptyline	Pindolol
	Verapamil	Certraline	
	Anticonvulsants:	Trazadon	
	Gabapentine		
	Others:		
	Fenoprofen		
	Tanacetum parthenium ekstract		
	Vitamine B12		
	Pizotiphen		

Source of the table: Silberstein SD. Preventive migraine treatment. Neurol Clin 2009; 27:429-443.

supports the view that anti-migraine efficiency is independent from antiserotonergic action. Methisergide is a very old molecule which is not available in our country. It is no longer used worldwide in current treatment because of its side effects. Pizotifen has side effects including weight gain and sedation. It is accepted to have a weak efficiency in migraine prophylaxis.

A Type Botulinum Toxin

The efficiency of A type botulinum toxin (BTA) has not been found in treatment of episodic migraine and tension type headache, but it has been shown to be superior to placebo in terms of the number of days with headache and the number of headache episodes in chronic migraine considering the total data of the PREEMPT1 and PREEMPT2 studies (45, 46, 47). BTA acts on peripheral sensitization by inhibiting release of substance P, calcitonin gene related peptide (CGRP) and glutamate from the primary trigeminal and cervical peripheral endings. It is a well tolerated treatment option (47).

Antihypertensive Drugs

Angiotensin converting enzyme (ACE) inhibitors (lisinopril) and angiotensin II type 1 receptor blockers (telmisartan, candesartan) have been found to be efficient in migraine prophylaxis (48, 49, 50). They do not have a strong prophylactic efficiecny. It has been proposed that their efficiencies occur by way of vasoreactivity, change in sympathetic tonus, inhibition of oxidative stres, destruction of proinflammatory factors including substance P, enkephalin, bradykinin and modulation of the endogeneous opiate system.

Nonsteroid Anti-Inflammatory Drugs

Naproxen sodium, flurbiprophen, ketoprophen and mephenamic acid which are nonsteroid anti-inflammatory drugs (NSAID) have been shown to be moderately effective in migraine prophylaxis. Naproxen has an efficiency similar to beta adrenergic blockers.

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Their long-term use is limited because of increased risk in terms of gastrointestinal side effects, renal toxicitiy and cardiovascular diseases (51, 52). NSAİDs are not included in migraine prophylaxis in the AHS/AAN 2012 treatment guideline (8, 53). It is known that their daily and regular us emay lead to drug overuse headache (53).

Vitamins and Herbal Substances

Riboflavine (400 mg/day), coenzyme Q10 (300 mg/day) and magnesium (600 mg/day) have been found to be superior to placebo in decreasing the frequency of migraine attacks. Magnesium may be a treatment option especially in pregnancy (54, 55, 56). Petasites hybridus root extract (Petadolex) was used in a placebo controlled study in migraine prophylaxis at a dose of 25 mg two times a day and a significant decrease was found in the frequecny of migrain attacks (57). In another study, Petadolex was used at higher doses (150 mg/day) and the decrease in the frequency of attacks was found to be greater compared to the dose of 100 mg/day and placebo (58). In a randomized, placebo-controlled, double-blind study, the herbal extract obtained from Tanacetum partheniumdan (Feverfew) was shown to significantly reduce the number of migraine attacks compared to placebo. In another study, the efficieny was found in patients who had at least 4 attacks in a month (59, 60).

New Treatment Strategies

CGRP is a vasoactive neuropeptide which is one of the key mediators in migraine headache. CGRP which is released from the terminals by stimulation of perivascular trigeminal afferents leads to neurogenic inflammation and nosiceptive transmission by vasodilatation and mast cell degranulation (61, 62). With injection of CGRP migraine-like headache occured in 57-75% of migraine patients with and without aura. Since this effect of CGRP did not occur in healthy controls, it was proposed that the trigeminovascular systems of patients with migraine were more sensitive to exogenous CGRP (63, 64). Blocking release of CGRP and receptor activation is one of the treatment strategies in migraine. In treatment of acute migraine attack, the efficiencies of olcegepant and telcagepant has been demonstrated (65, 66, 67). A study in which telcagepant was used as 2 doses a day for prophylaxis was discontinued, since a great elevation in liver enzymes was found in 2 patients (68). Monoclonal antibodies against human CGRP receptors are being developed for long-term treatment (9, 69). In the study of Zeller et al., it was shown that anti-CGRP antibodies inhibited dermal vasodilatation and the increase in the middle meningeal artery diameter similar to CGRP receptor antagonists, this inhibitor effect was observed even 1 week after the administration of the dose and chronic treatment with anti-CGRP antagonists did not change the heart rate and blood pressure. This long-term inhibitor effects of anti-CGRP antibodies in neurogenic vasodilatation render them a candidate for prophylactic treatment of migraine (70). It was found that LY2951742 which is another monoclonal antibody prevented the increase in dermal blood flow induced by capsaicin in rats, primates and healthy humans and a Phase II, randomized, placebo-controlled, double-blind study is being conducted. In this study, LY2951742 will be administered subcutaneously at a dose of 150 mg every 2 weeks. The primary endpoint has been defined as change in the number of days with headache in 28 days compared to baseline (9, 71). Development of mehanism-based specific treatment options in migraine prophylaxis will increase the chance of success in treatment.

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