**Management of acute and chronic headaches.**

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**Abstract**

**Purpose of review**

We highlight the recent clinical trials for the management of acute and chronic migraine.

**Recent findings**

In women with menstrual migraine, triptans seem well-tolerated irrespective of whether or not patients are taking oestrogen-containing contraceptives or have comorbidities that indicate increased cardiovascular risk.

The new acute drug telcagepant, a CGRP-antagonist, is safe for long-term use (up to 18 months) in migraine patients with stable coronary artery disease in whom the use of triptans is not advisable.

From the pooled analysis of the two PREEMPT studies of onabotulinumtoxinA (BOTOX®) in chronic migraineurs, it clearly emerged that efficacy increases over time (up to 56 weeks) and paralleled self-perceived improvement in quality of life. Effectiveness was also observed in patients with severely disabling headaches, who met criteria for triptan abuse and were refractory to several prophylactic treatments. Finally, combination of preventive pharmacological agents with different action mechanisms may be the next frontier in therapeutic advancements for treating migraine.

**Summary**

Although triptans are safe and well-tolerated, CGRP-antagonists may be an option for non-responsive patients or those in whom the use of triptans is not advisable. New drugs and combinations of old therapeutic options may help patients with severe forms of headache.

**Key words:** migraine, acute, preventive, treatment, review.

**Introduction**

Headaches are the most common pain syndrome in middle-aged adults. Among them, migraine headache has the highest prevalence and is the most severe and disabling. It affects as many as 15% of adults in North America and Western Europe and is probably one of the commonest reasons that patients visit their doctors, thus constituting a heavy social and individual burden. A rich and varied symptomatology characterizes migraine, especially migraine with aura. The latest clinical trial results in migraine treatment up to mid-2010 were comprehensively reviewed in a recent article [[1]](http://wizfolio.com/?citation=1&ver=3&ItemID=1360&UserID=12369&AccessCode=9A79C6D57BFE4252A3A5E489678C9D3C&CitationSuffix=), we thus chose to focus this update on the most recent advances in the acute and prophylactic therapy of the most prevalent primary headache, migraine, leaving aside other primary headaches.

**Treatment of the migraine attack**

Novel information is coming out from studies of established antimigraine drugs triptans and of new nonpeptide calcitonin gene-related peptide receptor antagonists, the so-called gepants.

*Triptans*

 During the last 2 decades the effectiveness of 5-HT1B/1D agonists, triptans, in the treatment of attacks has been proved several times. Triptans are able to act as vasoconstrictors via vascular 5-HT1B receptors and to inhibit neurotransmitter release on the peripheral as well as the central endings of trigeminal nociceptors via 5-HT1B/1D receptors. Sumatriptan, the first triptan, was followed by six commercially-available second-generation triptans (zolmi-, nara-, riza-, ele-, almo-, frovatriptan), which, despite sharing similar characteristics with sumatriptan, differ in their dose-dependent efficacy, adverse-effects profiles, onset of relieving effects, sustained pain-free duration and rates of recurrences [[2]](http://wizfolio.com/?citation=1&ver=3&ItemID=1361&UserID=12369&AccessCode=A2D664CB367A4FB3998BA87A6838DD53&CitationSuffix=).

A latest pooled analysis [[3]](http://wizfolio.com/?citation=1&ver=3&ItemID=1362&UserID=12369&AccessCode=24820637FD5944CCB61F415A7F5828FF&CitationSuffix=) systematically reviewed three recent individually-published, double-blind, randomized, cross-over trials, which compared the efficacy and safety of frovatriptan with that of zolmitriptan [[4]](http://wizfolio.com/?citation=1&ver=3&ItemID=1364&UserID=12369&AccessCode=57AFD1FA65FF4C0B9567CFF8BDAE8211&CitationSuffix=), rizatriptan [[5]](http://wizfolio.com/?citation=1&ver=3&ItemID=1366&UserID=12369&AccessCode=A6407F2E6BDD45D5B1DC1CCE4FD5C5C6&CitationSuffix=) and almotriptan [[6]](http://wizfolio.com/?citation=1&ver=3&ItemID=1352&UserID=12369&AccessCode=B4290A301FEA4D809B784E28F4E1522A&CitationSuffix=). Despite the fact that the rates of pain free, of pain relief episodes at 2h, and of pain-free episodes at 48h were not significantly different between frovatriptan (30%, 55% and 22% respectively) and the compared triptans (34%, 59%, and 21% respectively), frovatriptan showed a significantly lower rate of recurrent episodes at 48h (27% versus 40%), and this was also the case when recurrence was expressed as a cumulative hazard ratio over the observation period. Moreover, adverse events occurred significantly less often with frovatriptan (55 events, 5% of the attacks) than with the compared triptans (78 events, 8% of the attacks), with only three cardiovascular symptoms reported with frovatriptan compared to a total of 25 with the compared triptans [[3]](http://wizfolio.com/?citation=1&ver=3&ItemID=1362&UserID=12369&AccessCode=24820637FD5944CCB61F415A7F5828FF&CitationSuffix=). Taken together, the Authors suggest that these triptans have a similar immediate pain-relieving effect; frovatriptan seems to have the advantage in the long term, since it showed a lower risk of recurrence as well as more sustained efficacy.

Many prospective, randomized, controlled trials have proved that triptans are effective and preferable for menstrual migraine (MM) treatment [[7]](http://wizfolio.com/?citation=1&ver=3&ItemID=1367&UserID=12369&AccessCode=6FC53B89517A4698A856045AF6ECD15E&CitationSuffix=). Allais et al. (2011) first compared head-to-head efficacy of frovatriptan with that of zolmitriptan. Results showed similar proportions of pain relief episodes at 2h (52% and 53% respectively for frova and zolmi-triptan) and 24h (83% and 82%) and of pain-free episodes at 2h (22% and 26%) and 24h (74% and 69%), indicating that frova- and zolmitriptan have equal efficacy in the treatment of MM. However, frovatriptan showed a lower risk of headache recurrence over 24h in comparison to zolmitriptan (15 vs. 22% respectively) [[8]](http://wizfolio.com/?citation=1&ver=3&ItemID=1363&UserID=12369&AccessCode=3EEC551212BD48B5B8CCBE44CF4BA696&CitationSuffix=). The efficacy of frovatriptan in the treatment of MM was confirmed in a new analysis of data from five previously published studies [[9]](http://wizfolio.com/?citation=1&ver=3&ItemID=1368&UserID=12369&AccessCode=09A5AEC6D54447A0BDA2B82455B1D13E&CitationSuffix=). Using data from 2 phase III acute treatment trials (N= 496 women)[[10]](http://wizfolio.com/?citation=1&ver=3&ItemID=1370&UserID=12369&AccessCode=C1150AE38AE848AC906E8ADED4697564&CitationSuffix=) and from 3 phase IIIb short-term preventive trials (N= 1487 women)[[11](http://wizfolio.com/?citation=1&ver=3&ItemID=1372&UserID=12369&AccessCode=5AE43D867A864F268C99885BD326EA51&CitationSuffix=)[-13]](http://wizfolio.com/?citation=1&ver=3&ItemID=1371&UserID=12369&AccessCode=4ADCF41848DE4057828E01320DE88AEF&CitationSuffix=) in MM, MacGregor and colleagues (2010) evaluated the safety and tolerability of frovatriptan compared with sumatriptan or placebo. The authors showed that 27.3% of frovatriptan-, 33.4% of sumatriptan- and 14.8% of placebo- treated patients in the acute treatment trials experienced generally mild to moderate adverse events (AEs). No significant differences were observed between groups with sustained pain-free status with no AEs at 4 and 24h or with a sustained pain response with no AEs at 2 to 24h or at 4 to 24h. In the short-term preventive trials 57.8% (bis in die) and 63.4% (once daily) of frovatriptan-treated patients reported AEs versus 62.8% of placebo-treated patients. There were similar proportions of AEs reported by patients with potential cardiovascular risks (around 17% of women in each treatment group) or AEs related to the use of oestrogen-containing contraceptives (32.0% of women in the pooled analysis) [[9]](http://wizfolio.com/?citation=1&ver=3&ItemID=1368&UserID=12369&AccessCode=09A5AEC6D54447A0BDA2B82455B1D13E&CitationSuffix=). However, patients in the short-term preventive analysis were women and because patients with known cardiovascular disease were excluded, more trials are needed to adequately investigate the safety of frovatriptan in the high-risk population.

Interestingly, when another triptan, sumatriptan, was used in combination with naproxen sodium to treat MM, patients were significantly more satisfied than those randomized to placebo at 24 hours post dose, although they had minimal AEs [[14]](http://wizfolio.com/?citation=1&ver=3&ItemID=1382&UserID=12369&AccessCode=FBE9CDC6F06646418930EE2A22297AE5&CitationSuffix=).

To verify whether the presence of cutaneous allodynia, i.e. the perception of discomfort resulting from an ordinarily painless stimulus involving the skin, can influence antimigraine treatment outcome, researchers treated a population of the “Act when Mild” (AwM) study with almotriptan 12.5mg within 1h from the onset of an attack, when the pain intensity is still mild [[15]](http://wizfolio.com/?citation=1&ver=3&ItemID=1359&UserID=12369&AccessCode=C889CCFAD03749018850252BD8929C66&CitationSuffix=). Allodynia was assessed by a specific questionnaire and the clinical outcome was investigated in the presence or absence of allodynia. 39% of the study’s population experienced allodynia, which impaired the efficacy of almotriptan only in patients experiencing moderate to severe pain, causing longer migraine attack duration, less patients achieving pain-free status, and more requiring rescue medication. This was not the case when the migraine pain was early to mild, which helps to explain the improvement achieved with the early-treatment strategy in AwM study [[16]](http://wizfolio.com/?citation=1&ver=3&ItemID=1369&UserID=12369&AccessCode=0BBBD958E9884BC2B66996F7F11B6087&CitationSuffix=). Interestingly, in a sub-analysis of a randomized, double-blind, placebo-controlled parallel group phase III study that assessed the efficacy of a novel, orally-inhaled formulation of dihydroergotamine (MAP0004, LEVADEXTM; MAP Pharmaceuticals) for the acute treatment of migraine, the verum was superior to placebo for pain relief and pain freedom at 2h, and for 2- to 24h sustained pain relief and pain freedom similarly in patients with and without allodynia [[17]](http://wizfolio.com/?citation=1&ver=3&ItemID=1376&UserID=12369&AccessCode=35041476022245D682C6AC8A62B97BB5&CitationSuffix=).

In the TEMPO study [[18]](http://wizfolio.com/?citation=1&ver=3&ItemID=1355&UserID=12369&AccessCode=9618727D4E564E8B8B289247DAAD98C1&CitationSuffix=), 79 patients treated at least two migraine attacks within 1h (early intervention) and were advised to continue to treat early, whereas 42 patients who had treated at least two attacks 1h after headache onset (late intervention) were advised to switch from late to early dosing. Spontaneous early intake achieved better control of migraine attacks than late intake; the switch from late to early intake following advice from the physician improved treatment efficacy. Overall analysis confirmed that early intervention is associated with significantly greater rates of pain-free state at 2h (from 38.1% with late to 53.7% with early intervention), headache relief at 2h (from 66.7% to 80.5%) and sustained pain-free state [[18]](http://wizfolio.com/?citation=1&ver=3&ItemID=1355&UserID=12369&AccessCode=9618727D4E564E8B8B289247DAAD98C1&CitationSuffix=).

These studies once again underline the need to educate migraine patients so that they give up inadequate practices or unjustified prejudices about triptan use.

*CGRP-antagonists*

Because triptans have major shortcomings such as specific adverse events (the so-called “triptan symptoms”, i.e. burning, heat sensations, numbness, tightness, tingling, etc) and there is doubt about their cardiovascular safety, new better-tolerated and efficacious drugs are needed. Since calcitonin gene-related peptide (CGRP) may play a role in the pathophysiology of migraine, possible use of selective CGRP receptor antagonists as a novel treatment mechanism was tested. Olcegepant and, in particular, telcagepant, oral CGRP receptor antagonists, are novel acute antimigraine drugs with efficacy that appears comparable to that of triptans but with fewer overall adverse side effects [[19](http://wizfolio.com/?citation=1&ver=3&ItemID=1375&UserID=12369&AccessCode=7C24922CD2144683AC6780251A5D9FFB&CitationSuffix=)[,20]](http://wizfolio.com/?citation=1&ver=3&ItemID=1374&UserID=12369&AccessCode=A5BB2726001943F1B0939C0767A947AE&CitationSuffix=).

CGRP-antagonists, which do not appear to cause vasoconstriction, may allow treatment of migraine in patients with coronary disease. In a randomized, double-blind, placebo-controlled, cross-over study, it was proved that telcagepant (two 300mg doses administered 2h apart) was generally safe and well tolerated in a small cohort of migraine patients with stable coronary artery disease, since there were no consistent treatment-related changes in cardiovascular parameters [[21]](http://wizfolio.com/?citation=1&ver=3&ItemID=1383&UserID=12369&AccessCode=01A9E644480E42B2B162377A02A7B108&CitationSuffix=).

Following a previous work which assessed the therapeutic efficacy of telcagepant over four consecutive treated attacks [[22]](http://wizfolio.com/?citation=1&ver=3&ItemID=1345&UserID=12369&AccessCode=0653E5F7EF944647BC89A064C33FC3A5&CitationSuffix=), Connor et al. [[23]](http://wizfolio.com/?citation=1&ver=3&ItemID=1343&UserID=12369&AccessCode=E700AD4526674950B0F5526FDDD30FD0&CitationSuffix=) confirmed this result in a large trial of 1068 patients in which patients could treat up to 8 attacks per month for up to 18 months either with 280/300mg of telcagepant or 10mg of rizatriptan. Both telcagepant and rizatriptan were generally well tolerated. Treatment groups showed similar overall incidence of AEs but fewer triptan-related AEs (5% for telcagepant and 11.2% for rizatriptan) and drug-related AEs (30.7% for telcagepant and 46.3% for rizatriptan) were reported for telcagepant vs. rizatriptan. The most common AEs with telcagepant were dry mouth, nausea, dizziness, and somnolence, and each occurred in less than 10% of patients. Only 3 AEs (confusion, dissociation, euphoria), which all occurred in the telcagepant group but did not recur during subsequent attacks, were identified as having potentially greater clinical significance for abuse liability. Overall, these findings suggest that CGRP receptor antagonists do not have potential for abuse liability. There were no serious cardiovascular events during the trial but having cardiovascular disease was in the exclusion criteria [[23]](http://wizfolio.com/?citation=1&ver=3&ItemID=1343&UserID=12369&AccessCode=E700AD4526674950B0F5526FDDD30FD0&CitationSuffix=).

With the scope of verifying whether the same or different patients respond to triptans and telcagepant, Ho and colleagues [[24]](http://wizfolio.com/?citation=1&ver=3&ItemID=1344&UserID=12369&AccessCode=830F76336B3643E0992B867CF3FB0B2B&CitationSuffix=) performed a post-hoc analysis of the data from a large previously published study which evaluated the efficacy and tolerability of telcagepant 150/300mg, zolmitriptan 5mg, and placebo [[25]](http://wizfolio.com/?citation=1&ver=3&ItemID=1384&UserID=12369&AccessCode=B5747020E6564461B6F6D45B9AD210D4&CitationSuffix=). They found that patients with a poor historical response to triptans or who never take triptans had a substantially better response to telcagepant 300mg than to zolmitriptan. Conversely, patients who indicated a good historical response to triptans responded better to zolmitriptan than to telcagepant 150/300mg [[24]](http://wizfolio.com/?citation=1&ver=3&ItemID=1344&UserID=12369&AccessCode=830F76336B3643E0992B867CF3FB0B2B&CitationSuffix=). This would suggest that patients who respond poorly to/did not take triptans might benefit from telcagepant, but these results should be validated in a placebo-controlled trial.

The therapeutic efficacy and tolerability of telcagepant (280mg) when co-administered with ibuprofen (400mg) or acetaminophen (1000mg) was evaluated in a randomized, double-blind, placebo-controlled trial [[26]](http://wizfolio.com/?citation=1&ver=3&ItemID=1342&UserID=12369&AccessCode=87ABAFF12EF24B35B1323BB83A0FC6C4&CitationSuffix=). Both in co-administration with ibuprofen and acetaminophen, telcagepant resulted more effective than placebo (percentages of patients with 2-hour pain freedom 35.2%, 38.3%, and 10.9% respectively), but was associated with a higher percentage of AEs. Combination therapy did not provide superior efficacy compared with telcagepant monotherapy (31.2%) with regards to primary (pain freedom at 2h), secondary (pain relief at 2h), tertiary (presence of accompanying symptoms) and exploratory (2-48 hour sustained pain freedom) endpoints [[26]](http://wizfolio.com/?citation=1&ver=3&ItemID=1342&UserID=12369&AccessCode=87ABAFF12EF24B35B1323BB83A0FC6C4&CitationSuffix=).

**Advances in preventive migraine management**

The criteria for chronic migraine (CM) have been revised in the new appendix of the second edition of the International Classification of Headache Disorders (ICHD-II) [[27]](http://wizfolio.com/?citation=1&ver=3&ItemID=592&UserID=12369&AccessCode=4E2D70792B074C7EB5930AAE04554FF5&CitationSuffix=). A vast proportion of chronic migraine disorder (headache present on ≥15 days/month) may develop or markedly worsen during >3 months of medication overuse (analgesics or triptans or both). Chronic headache is a disabling health problem that affects 2–5% of the general population and causes considerable long-term morbidity and disability [[28]](http://wizfolio.com/?citation=1&ver=3&ItemID=476&UserID=12369&AccessCode=0&CitationSuffix=). Any progress in chronic migraine management is thus very welcome.

The two Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies demonstrated the efficacy, safety and tolerability of onabotulinumtoxinA (BOTOX®) as headache prophylaxis in adults suffering from CM [[29](http://wizfolio.com/?citation=1&ver=3&ItemID=1387&UserID=12369&AccessCode=17F1E07695F24BDF835552564E6756A9&CitationSuffix=)[,30]](http://wizfolio.com/?citation=1&ver=3&ItemID=1386&UserID=12369&AccessCode=91CB362F1EB046559AB1D582C8FDA095&CitationSuffix=), although the real clinical benefit may not be consistently relevant [[1]](http://wizfolio.com/?citation=1&ver=3&ItemID=1360&UserID=12369&AccessCode=9A79C6D57BFE4252A3A5E489678C9D3C&CitationSuffix=). The data of the entire 56-week PREEMPT clinical program were pooled to evaluate the integrated summary of efficacy, safety, and tolerability of onabotulinumtoxinA as headache prophylaxis in adults suffering from CM [[31]](http://wizfolio.com/?citation=1&ver=3&ItemID=1388&UserID=12369&AccessCode=F30BB73685A74C1AA74F2ED0AED0D01C&CitationSuffix=) and its impact on patients’ quality of life [[32]](http://wizfolio.com/?citation=1&ver=3&ItemID=1389&UserID=12369&AccessCode=2C4425B0E2C6458BA8D54A9490EF5F94&CitationSuffix=). The PREEMPT trials included 687 and 692 patients randomized to onabotulinumtoxinA or placebo (injection every 12 weeks) with a blinded follow-up period of 24 weeks and a subsequent open-label phase of 32 weeks in which both groups received onabotulinumtoxinA.

Statistically significant reductions favouring onabotulinumtoxinA over placebo in the double-blind phase were observed at week 24 for the primary outcome variable of headache-day frequency and for the secondary outcome change from baseline in mean migraine days, moderate/severe headache days, and total cumulative hours of headache on headache days, with differences observed throughout the open-label phase. However, almost 70% of patients treated with onabotulinumtoxinA throughout the entire study exhibited a ≥50% decrease from baseline in migraine and headache days at the week 56 visit, suggesting that the efficacy of onabotulinumtoxinA increases over time [[31]](http://wizfolio.com/?citation=1&ver=3&ItemID=1388&UserID=12369&AccessCode=F30BB73685A74C1AA74F2ED0AED0D01C&CitationSuffix=). The proportion of patients who experienced a serious AE during the double-blind phase (onabotulinumtoxinA 4.8%, placebo 2.3%) or open-label phase (3.8%) was low. The proportion of patients with a severe Headache Impact Test (HIT-6) score and higher values at the Migraine-Specific Quality of Life Questionnaire (MSQ) notably decreased from baseline in both the placebo and verum groups. However, significantly fewer patients with severe HIT-6 scores and with less improvements on the MSQ questionnaire were observed in the onabotulinumtoxinA-treated group at all weeks during the double-blind phase, including week 24 [[32]](http://wizfolio.com/?citation=1&ver=3&ItemID=1389&UserID=12369&AccessCode=2C4425B0E2C6458BA8D54A9490EF5F94&CitationSuffix=). This study suggests that prophylactic therapy with onabotulinumtoxinA is an option for this highly-disabled patient population.

OnabotulinumtoxinA also proved effective in chronic refractory headache patients. Oterino et al [[33]](http://wizfolio.com/?citation=1&ver=3&ItemID=1351&UserID=12369&AccessCode=FB65271317A941AD9F2F61888FA71F96&CitationSuffix=) treated 35 patients suffering from chronic severely disabling headaches, who met criteria for triptan abuse. Patients were enrolled who had failed in at least one withdrawal attempt and had resulted irresponsive to several prophylactic treatments. After a number of onabotulinumtoxinA infiltrations (ranging between 2 and 16), 32% of patients experienced at least a 50% reduction of headache days per month, and halved their monthly triptan consumption (from 22 to 11 oral triptans/month on average) [[33]](http://wizfolio.com/?citation=1&ver=3&ItemID=1351&UserID=12369&AccessCode=FB65271317A941AD9F2F61888FA71F96&CitationSuffix=). Moreover, effective onabotulinumtoxinA treatment substantially reduced the cost of acute migraine medications taken by patients with chronic migraine and triptan overuse [[34]](http://wizfolio.com/?citation=1&ver=3&ItemID=1349&UserID=12369&AccessCode=DA61CFD8C6594D9FB59D202FD611422F&CitationSuffix=).

With the scope of verifying whether prophylactic polytherapy is associated with improved outcomes as compared to maintaining monotherapy, researchers compared in a randomized pilot study the effectiveness of long-term use of flunarizine and topiramate alone and in combination for migraine prophylaxis in a Chinese population [[35]](http://wizfolio.com/?citation=1&ver=3&ItemID=1385&UserID=12369&AccessCode=8E2AE9A6A18248509678731A5D59FFF3&CitationSuffix=). In this study, 126 patients were randomized and 39 were treated with flunarizine alone (5 mg/day), 44 with topiramate alone (100 mg/day), and 43 with both drugs in combination. There was no significant difference among the three groups in regards of primary endpoint change of mean monthly migraine frequency. Among the three groups, the combination therapy group decreased more significantly in secondary endpoint mean monthly migraine days and subjective perceived pain (measured on the visual analogue scale) than the flunarizine and topiramate group; no significant difference was found between the topiramate group and the flunarizine group. The combination of topiramate with flunarizine reduced the impact on body weight (flunarizine increases and topiramate decreases) of either drug taken alone [[35]](http://wizfolio.com/?citation=1&ver=3&ItemID=1385&UserID=12369&AccessCode=8E2AE9A6A18248509678731A5D59FFF3&CitationSuffix=). However, the major limitation of this study is the lack of a placebo group, which may have an impact on treatment effectiveness. With the same scope of testing the efficacy of combination of preventive drugs, Krymchantowski and co-workers tested, in a randomized controlled trial, the effectiveness of 6 weeks’ combination therapy of topiramate (TPM, 100mg/day) and nortriptyline (30mg/day) in a group of 44 episodic migraineurs versus placebo. Patients were selected from those who had less than 50% reduction in headache frequency after a previous 8-week open-label trial with TPM or nortriptyline alone. At the 6th week, differences between switching to combination therapy and continuing monotherapy were significant. In fact, overall, almost 80% of patients randomized to receive both medications combined achieved the primary endpoint (reduction of headache frequency by at least 50%), while less than 50% of patients randomized to receive placebo in addition to nortriptyline or TPM achieved this endpoint [[36]](http://wizfolio.com/?citation=1&ver=3&ItemID=1377&UserID=12369&AccessCode=871A8AF000AC4BD78CA405BC50C2A3F4&CitationSuffix=). In another small study, the same group of researchers published an open-label study where they tested combined lower-than-reported therapeutic doses of topiramate (75 mg/day) and sodium divalproate (DVS, 500 mg/day) in a group of patients previously treated with a full dosage of one of the two drugs alone (topiramate 100mg or sodium valproate 1000mg) and, despite a therapeutic gain, had reported intolerable side effects 6 weeks after starting the drug. Of the 38 patients (22 from the TPM group and 16 from the DVS group) who completed the study after the initiation of combination therapy, 17 from the original TPM monotherapy group (77.3% of those who could not tolerate TPM 100 mg/day) and 10 from the original DVS monotherapy group (62.5% of those who could not tolerate DVS 1000 mg/day) reported a decrease in side effects and persistence of the improvement in headache initially exhibited [[37]](http://wizfolio.com/?citation=1&ver=3&ItemID=1378&UserID=12369&AccessCode=774CDE1F9B954B29B246B4F8AA27EC02&CitationSuffix=). Small sample size and lack of placebo are the major study biases.

**Conclusion**

In the past 2 decades triptans, 5HT1B/1D agonists, have proven efficacious in the treatment of acute migraine attack. New studies have once again underlined the small, but sometimes useful, differences between various triptans which, despite sharing almost the same immediate efficacy in aborting the attacks (including those related to the menses), include some that showed a significantly lower rate of recurrent episodes and drug-related adverse events. In women with menstrual migraine, triptans seem to be well tolerated irrespective of whether or not patients are taking oestrogen-containing contraceptives. Furthermore, in women, triptans’ efficacy seems not to be influenced by the presence of comorbidities that may indicate increased cardiovascular risk. Further studies should address the cardiovascular safety issue of triptans in men, who are known to have less favourable cardiovascular risk factors. Data suggest that pain intensity is the main driver of the response to triptans, and not the presence or absence of cutaneous allodynia, an indirect marker of central sensitization.

The new acute drug telcagepant, a CGRP-antagonist, may be the best hope for treating migraine patients who are nonresponders to triptans. It was proved to be safe in the long-term (up to 18 months), and was generally well tolerated in a small cohort of migraine patients with stable coronary artery disease, in whom the use of triptans is not advisable.

Some progress was made with regard to the pharmacological preventive treatment of episodic and chronic migraine.

When the data from the two PREEMPT studies of onabotulinumtoxinA (BOTOX®) as headache prophylaxis in adults suffering from CM were pooled, the stable safety and tolerability of the injections clearly emerged. Moreover, the efficacy increases over time (up to 56 weeks) and in parallel with self-perceived improvement in quality of life. Efficacy of onabotulinumtoxinA was also observed in patients with severely disabling headaches, who met criteria for triptan abuse and resulted irresponsive to several prophylactic treatments (called “refractory”). Future trials may help to identify subgroups of patients that will better respond to botulinum toxin and to clarify the role of analgesic-overuse withdrawal in improving response to preventive treatment with botulinum.

Finally, since multiple pathogenic mechanisms are likely to be involved in perpetuating the recurrence of the migraine attacks, the combination of pharmacological agents with different mechanisms of action may be the next frontier in therapeutic advancements for treating migraine.

**Key points** - 8-10 bullet points summarising the review

* The new antimigraine drugs, the CGRP-antagonists, will be available in the near future. They will be the best hope for treating migraine patients who are nonresponders to triptans.
* Available data in chronic headache patients suggest that botulinum toxin effectiveness might increase when injections were repeated over time, particularly in patients irresponsive to several prophylactic treatments and who met criteria for drug abuse.
* The combination of two preventive pharmacological agents with different mechanisms of action may help to reduce the impact of adverse effects, improving patients’ compliance.

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**References and recommended reading**

Papers of particular interest, published within the annual period of review, have

been highlighted as:

● of special interest

●● of outstanding interest

[**References**](https://wizfolio.com/?style=1&ver=3&UserID=12369&StyleName=Current%20Opin%20Palliative%20Care)

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