NEW APPROACHES TO MEET PATIENTS' NEEDS IN CLINICAL PRACTICE

Summary of Presentations from The Menarini Group-Supported Satellite Symposium, held at the 4th EHMTIC, Copenhagen, Denmark, on 19th September 2014

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MEETING SUMMARY

Migraine is a primary headache disorder affecting up to four in ten women and up to two in ten men, mostly before the age of 35 years.[1] By the age of 30, migraine is 3-times more prevalent in women than in men.[1] The effects of migraine vary considerably, ranging from minimal disruption of daily activities to severe disability.[1] Migraine without aura (MWoA) is most common, followed by migraine with aura (MWA).[1] Attacks typically last 4-72 hours, with two or more specific features (unilateral location, pulsating, moderate-to-severe pain intensity, or aggravation by routine physical activity) during the attack. Migraine attacks are also accompanied by at least one of nausea, vomiting, and photophobia and phonophobia.[1]

It is 25 years since triptans first became available on prescription. Although their safety and efficacy is well established, there is still a great deal of ongoing research into the nuances of their use in treating patients with specific needs. Frovatriptan, in common with other triptans, is a serotonin (5-hydroxytryptamine, 5-HT) 1B/1D receptor agonist.[1] Frovatriptan also shows moderate affinity for 5-HT_7 receptors,[1] resulting in more potent contraction of cerebral arteries than coronary arteries, with the potential for good efficacy and low risk of unwanted effects.[1] Frovatriptan is distinctive from other triptans due to its half-life of 26 hours, which confers a longer duration of action.[1]

Weekend Migraine (WM): Myth or Reality?

Professor Carlo Lisotto

The term weekend headache (WH) was first used by Nattero and colleagues in 1989,[2] who observed that WH attacks proved to be similar to those of common migraine, but with a significantly higher incidence of concomitant symptoms. Another early study classified WH as either a predominant form of headache or an exacerbation of headache attacks at weekends.[3] WH cases were observed not only among MWoA sufferers, but also in patients with episodic tension-type headache.[3] WH did not appear to be a separate clinical entity that could be classified independently; the weekend seemed to be merely a trigger factor.[3] This initial study of 35 patients observed that WH affected men more than women.[3]

More recently, in a prospective study conducted in 89 female migraine patients, who were invited to keep headache diary cards over 12 consecutive months, migraine occurrence was almost equally distributed during the week.[4] There was no peak incidence at the weekend and there were fewer attacks at weekends and on days off. In a study of 4,576 migraine patients between 2006 and 2012, 3,700 patients with episodic migraine and tension-type headache were evaluated once secondary, other primary, and cluster headaches were excluded.[5] Of these, 218 patients (6.1%) experienced headache occurring almost exclusively at weekends. Cases were distributed almost equally between the sexes, with a female to male ratio of 1.07:1, compared to 3.61:1 observed in episodic migraine in general. The mean age of WM patients was lower than the overall study group, 37.0±9.5 years (range 12–70) and 40.7±12.5 years (range 8–86), respectively, and men were slightly older (37.2±9.5 years [range 12–70]) than women (36.7±9.7 years [range 20–60]). Patients with an International Classification of Headache Disorders (ICHD 3 beta[6]) diagnosis of MWoA made up the majority of cases (209, 91.7%). More than one-third (37, 35.6%) of women with WM also had menstrually-associated migraine.

Based on this survey, WM was defined in those patients with at least 75% of all attacks occurring at weekends, with frequency ranging from one attack every 2 months to four attacks per month. WM can be further subdivided into Type I: patients with ≥90% of all attacks occurring at weekends, with a frequency ranging from one attack every 2 months to four attacks per month, and Type II: patients with ≥75% of all attacks occurring at weekends, with a frequency ranging from one attack every 2 months to four attacks per month. The two subtypes were equally distributed between patients; however, 65.2% of Type I patients were male and 69.0% of Type II patients were female, confirming that men are particularly susceptible to WM. During follow-up, headache occurrence at the weekend was inconsistent, with 46 patients (20.2%) experiencing attacks unrelated to weekends. In most of these cases, attack frequency increased, and was associated with other or no clearly identifiable trigger. Therefore, WM seems to be a temporary disorder lasting on average 5 years, after which the weekend is no longer a trigger.

Behavioural treatment in the form of sleep optimisation was effective in 9.2% of patients, with the remaining 90.8% of patients responding to pharmacological treatment. In the pharmacological treatment group, WM attacks were severe and disabling; 104 patients (50.3%) responded to triptans only and 57 (27.5%) were treated with triptans during severe attacks and non-steroidal anti-inflammatory drugs (NSAIDs) during moderate attacks. 42 patients (20.3%) used NSAIDs only and four patients (1.9%) used paracetamol. As WM attacks are predictable, preliminary, open-label, short-term prophylaxis was attempted in 105 patients (54.1%). 64 patients received magnesium and 41 patients received frovatriptan, with the first dose administered at 20:00 hours on Friday, two doses on Saturday at 08:00 hours and 20:00 hours, and a final dose on Sunday at 08:00 hours. 26 frovatriptan patients (63.4%) reported a reduction in headache duration of at least 50% versus only 9 patients (14%) using magnesium.

In a retrospective study of frovatriptan versus other triptans in patients experiencing WM, 569 attacks were documented at weekends and 1,281 during workdays.[7] There was no significant difference between weekend and workday attacks in patients treated with frovatriptan (26% and 27%, respectively) and comparators (34% and 32%, respectively) in terms of pain-free rates at 2 hours.[7] In patients treated with frovatriptan, the relapse rate at 48 hours for headaches occurring at weekends was significantly lower than those occurring on weekdays (17% versus 30%, $p<0.05$).[7] However, there was no significant difference between weekend and weekday 48-hour relapse

rates in the comparator group (34% versus 40%).[7] These findings can be rationalised by the early intake of medication during the WM prodrome, due to the consistency and predictability of attacks.

In conclusion, WM is not rare and affects both sexes equally, in clear contrast with the distribution of migraine by gender in the general population. WM cannot be considered as a distinct subtype of migraine, such as menstrually-related migraine (MRM); the weekend appears to be merely a trigger factor. The weekend trigger role seems to be associated with chronobiological factors, such as too much or too little sleep, schedule change, or in wider terms, relaxation after stress. WM attacks are reported to be severe in intensity and markedly disabling, responding only to triptans in most cases. Frovatriptan represents a particularly favourable treatment option. It is effective as acute medication, with a lower risk of relapse compared to other triptans, and can also be used as a short-term preventive treatment.[7]

Menstrual Migraine (MM): Have the Guidelines got it Right?

Professor E. Anne MacGregor

MM was first included as a separate category in the ICHD-2.[8] An important distinction is made between women in whom menstruation is a specific and a reproducible trigger (pure MM) and women who have migraines during their menstrual cycle (MRM). The ICDH-3 beta, defines pure MM without aura as attacks, in a menstruating woman, fulfilling criteria for 1.1 MWoA and documented and prospectively recorded evidence, over at least three consecutive cycles, has confirmed that attacks occur exclusively on Day 1±2 of menstruation in at least two out of three menstrual cycles and at no other times of the cycle.[6] MRM without aura is defined as attacks, in a menstruating woman, fulfilling criteria for 1.1 MWoA and documented and prospectively recorded evidence, over at least three consecutive cycles, has confirmed that attacks occur on Day 1±2 of menstruation in at least two out of three menstrual cycles, and additionally at other times of the cycle.[6]

Pure MM is easy to identify as there are no other migraine attacks at any other time of the cycle; however, this is uncommon and MRM is far more prevalent. Nevertheless, there can be confusion when studies report 'menstrual attacks' as, strictly speaking, these are not the same as MM yet researchers may not be using the correct definitions. Meaningful research depends on identifying a homogenous population in whom the association between migraine and menstruation is greater than likely to occur by chance, in order to explore the underlying pathophysiology of menstrual attacks.

Table 1: Differences between menstrual and non-menstrual attacks in women with and without ICHD-2 menstrual migraine (MM) without aura.[9]

	Women with ICHD-2 MM*	Women with menstrual attacks but not ICHD-2 MM**
More severe pain	p≤0.05	non-significant
More severe nausea	p≤0.001	non-significant
Photophobia	non-significant	non-significant
Phonophobia	non-significant	non-significant
Longer duration	p≤0.001	non-significant
Higher number of doses of symptomatic treatment per attack	p≤0.001	non-significant

*Menstrual attacks in women with MM versus non-menstrual attacks in women with MM; **menstrual attacks in women without MM versus menstrual attacks in women with MM; non-menstrual attacks in women without MM versus menstrual attacks in women with MM.

ICHD: International Classification of Headache Disorders.

Accurate definitions are also crucial for patient management, since research shows that there is only a difference between menstrual and non-menstrual attacks in women who have a diagnosis of MRM. Women with MM who have a menstrual attack experience more severe pain ($p \leq 0.05$) and severe nausea ($p \leq 0.001$), and their attacks have a longer duration, requiring a higher number of doses of symptomatic treatment (both $p \leq 0.001$), than those who have a non-menstrual attack (Table 1).[9] Photophobia and phonophobia were not significantly different between groups.[9] In contrast, none of these features were significantly different in menstrual attacks in women without MM versus those with MM or non-menstrual attacks in women without MM versus those with MM (Table 1).[9]

This research clearly identifies two completely different populations prompting the following proposed changes to the MM diagnostic criteria; the first day of menstrual attack is on or between Day -2 to +3; attacks at other times of the cycle can be MWA or MWoA; attacks should occur with menstruation more than by chance, i.e. chronic and high frequency migraine should be excluded.

All guidelines for the management of MM recommend frovatriptan. The European Federation of Neurological Societies (EFNS) guidelines[10] state that triptans are equally effective for MM and non-MM attacks. The Danish Headache Society (DHS) guidelines[11] make similar recommendations but note that MM tends to be more difficult to treat than migraine not associated with menstruation. The French guidelines[12] recommend treating MM attacks the same way as migraine attacks occurring outside the menstrual period, and the Italian guidelines[13] note that triptans are also effective in MRM attacks. The Canadian Headache Society (CHS) guidelines[14] are the most comprehensive, recommending similar acute treatment for MM and those attacks occurring at other times during the menstrual cycle, and an early intake of triptans for moderate or severe migraine attacks.

A recent analysis of the efficacy of frovatriptan in the acute treatment of MM pooled results from three Italian studies.[15] With or without aura migraine patients were randomised to frovatriptan 2.5 mg or rizatriptan 10 mg (study 1), frovatriptan 2.5 mg or zolmitriptan 2.5 mg (study 2), and frovatriptan 2.5 mg or almotriptan 12.5 mg (study 3).[15] All studies had a multicentre, randomised, double-blind, crossover design. After treating 1–3 episodes of migraine in 3 months with the first treatment, patients switched to the other treatment for the next 3 months.[15] In 187 women with MM, the proportion of patients who were pain-free and have pain relief at 2 hours and 24 hours did not differ between frovatriptan and comparator, but relapse rates at 24 hours and 48 hours were significantly lower with frovatriptan.[15]

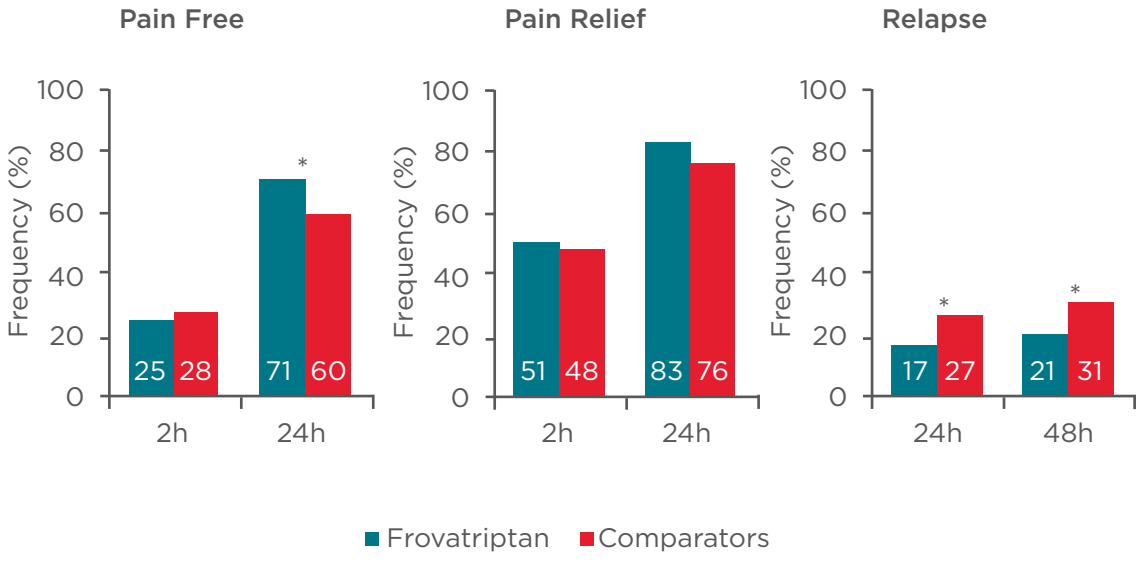


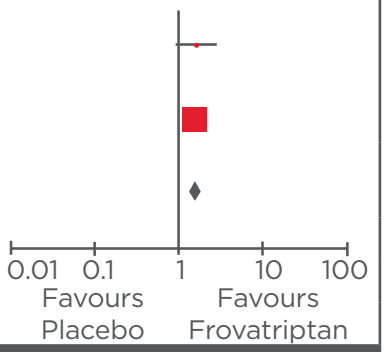
Figure 1: Efficacy of frovatriptan in acute menstrual migraine in women taking combined hormonal contraceptives.[16]

Comparators: almotriptan, rizatriptan, zolmitriptan; * p<005.

Table 2: Perimenstrual prophylaxis with frovatriptan.* Incidence of no migraine occurring during the treated perimenstrual period.[1]

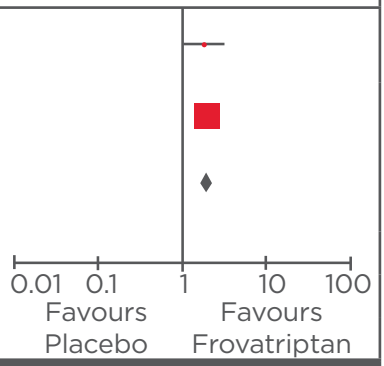
A. Frovatriptan 2.5 mg QD versus placebo

	Frovatriptan 2.5 mg QD		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, random, 95% CI
Brandes et al. 2009	28	149	19	160	10.8%	1.58 (0.92, 2.71)	
Silberstein et al. 2004	192	484	124	486	89.2%	1.55 (1.29, 1.88)	
Total (95% CI)		**633**		**646**	**100.0%**	**1.56 (1.31, 1.86)**	
Total events	220		143				
Heterogeneity: τ^2=0.00; χ^2=0.00, df=1 (p=0.95); I^2=0%							
Test for overall effect: Z=4.91 (p<0.00001)							



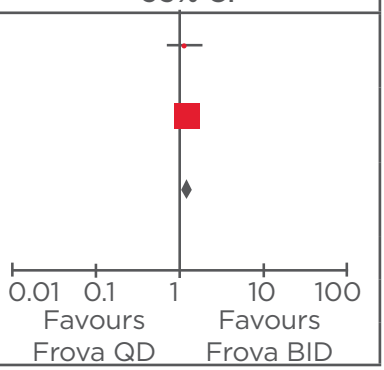
B. Frovatriptan 2.5 mg BID versus placebo

	Frovatriptan 2.5 mg BID		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, random, 95% CI
Brandes et al. 2009	22	101	19	160	8.9%	1.83 (1.05, 3.21)	
Silberstein et al. 2004	246	483	124	486	91.1%	2.00 (1.68, 2.38)	
Total (95% CI)		**584**		**646**	**100.0%**	**1.98 (1.68, 2.34)**	
Total events	268		143				
Heterogeneity: τ^2=0.00; χ^2=0.08, df=1 (p=0.78); I^2=0%							
Test for overall effect: Z=8.01 (p<0.00001)							



C. Frovatriptan 2.5 mg BID versus QD

	Frovatriptan 2.5 mg BID		Frovatriptan 2.5 QD			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, random, 95% CI
Brandes et al. 2009	22	101	28	149	7.4%	1.16 (0.70, 1.91)	
Silberstein et al. 2004	246	483	192	484	92.6%	1.28 (1.12, 1.48)	
Total (95% CI)		584		633	100.0%	1.27 (1.11, 1.46)	
Total events	268		220				
Heterogeneity: τ^2=0.00; χ^2=0.15, df=1 (p=0.70); I^2=0%							
Test for overall effect: Z=3.51 (p=0.0004)							



*Treatment started 2 days before anticipated menstrual migraine and taken for 6 days.

BID: twice daily; CI: confidence interval; df: degrees of freedom; QD: once daily; M-H: Mantel-Haenszel; Frova: frovatriptan.

Modified with permission from MacGregor.[1]

MM is not only caused by native hormonal fluctuations but can occur in women who are experiencing oestrogen withdrawal in the pill-free week of combined hormonal contraception, typically on the third day of the hormone-free interval. This provides a reliable forecast of when attacks will occur in comparison to native hormone attacks. A subset of 35 women, who were taking combined oral contraceptives and experiencing a migraine attack during the withdrawal phase, was analysed. The proportion of patients who were pain-free and had pain relief at 2 hours and pain relief at 24 hours was not significantly different between frovatriptan and comparators. However, the proportion of pain-free patients at 24 hours was significantly greater and relapse rates at 24 hours and 48 hours were significantly lower with frovatriptan than comparators (Figure 1).[16]

Thus far there are no treatments licensed for the prophylactic treatment of MM; however, guidelines do make the following recommendations: the EFNS[10] recommends perimenstrual frovatriptan, naratriptan, naproxen, and oestrogen; the DHS guidelines[11] expand on those of the EFNS by recommending perimenstrual frovatriptan and naproxen, an increase in habitual prophylactic medication, magnesium during the luteal phase and long-cycle combined oral contraceptives (LCCOCs);[11] both the French and Italian guidelines[12,13] recommend perimenstrual frovatriptan, zolmitriptan, and oestrogen. In addition, the French guidelines[12] recommend perimenstrual naratriptan and LCCOCs, and the Italian guidelines[13] recommend perimenstrual sumatriptan and naproxen. The National Institute for Health and Care Excellence,[17] the American Headache Society (AHS),[18] and the CHS[14] all recommend perimenstrual frovatriptan and zolmitriptan. The AHS[18] and CHS[14] also recommend perimenstrual naratriptan, with the CHS also recommending perimenstrual naproxen, oestrogen, and LCCOCs. Frovatriptan is the only medication with level A evidence recommended by the AHS,[18] and meta-analysis demonstrates that frovatriptan twice-daily is significantly better than when administered once daily (Table 2).[1]

In conclusion, management guidelines for acute MM require minor revisions; there is a need to recognise that menstrual attacks are more severe and have a longer duration than non menstrual attacks in women with MM. Prophylactic management guidelines are correct and the evidence supports the use of frovatriptan in both cases.

Frovatriptan plus Dexketoprofen: More than a Combination?

Professor Stefan Evers

Patients consider a rapid onset (48%) and a long-lasting effect (52%) to be the most important factors when choosing an anti-migraine therapy.[19] An ideal NSAID has a rapid onset with a decline in efficacy after about 2 hours; conversely, an ideal triptan has a slower onset of action with effects that last over 24 hours. Therefore, based on pharmacokinetic profiles, combining an NSAID with a triptan should provide an optimal treatment strategy. The first combination of this type to be investigated was rizatriptan and the selective COX-2 inhibitor rofecoxib, which proved to be superior to either drug alone;[20] however, rofecoxib has since been withdrawn due to safety concerns. A trial of rizatriptan combined with acetaminophen (paracetamol) failed to meet the primary endpoint; nevertheless, several secondary endpoints demonstrated superiority over the individual treatments alone.[21] A study of almotriptan in combination with aceclofenac showed particular efficacy in patients with allodynia versus almotriptan alone.[22] The combination of sumatriptan (85 mg) and naproxen (500 mg) (Sum-Nap) has been widely studied[23] and is approved by the FDA for the treatment of MWoA; however, the combination is not licensed in Europe. The rationale for this combination is the relatively rapid onset of sumatriptan (T_{max} 85 mg) of approximately 1 hour [range 0.3–4.0]) and the long half-life of naproxen (T_{max} 500 mg) of approximately 5 hours (range 0.3–12.0).[24] The proportion of sustained pain-free patients between 2 hours and 24 hours is significantly higher with Sum-Nap than placebo.[25]

Dexketoprofen is absorbed rapidly, has a fast onset of action (T_{max} 0.5 hours), and a short half-life (1.6 hour),[26] whereas frovatriptan has a T_{max} of 2 hours and a 26-hour half-life,[27] making them an ideal combination therapy for migraine. The efficacy of frovatriptan plus dexketoprofen (Fro-Dex) was evaluated in a multicentre, randomised, double-blind, active-controlled, three parallel-group Phase III study.[28] Over the course of the 10-month study, 106 patients received frovatriptan 2.5 mg, 105 patients received frovatriptan 2.5 mg plus dexketoprofen 25 mg, and 103 patients received frovatriptan 2.5 mg plus dexketoprofen 37.5 mg.[28] The primary endpoint, the proportion of pain-free subjects within 2 hours prior to the intake of rescue

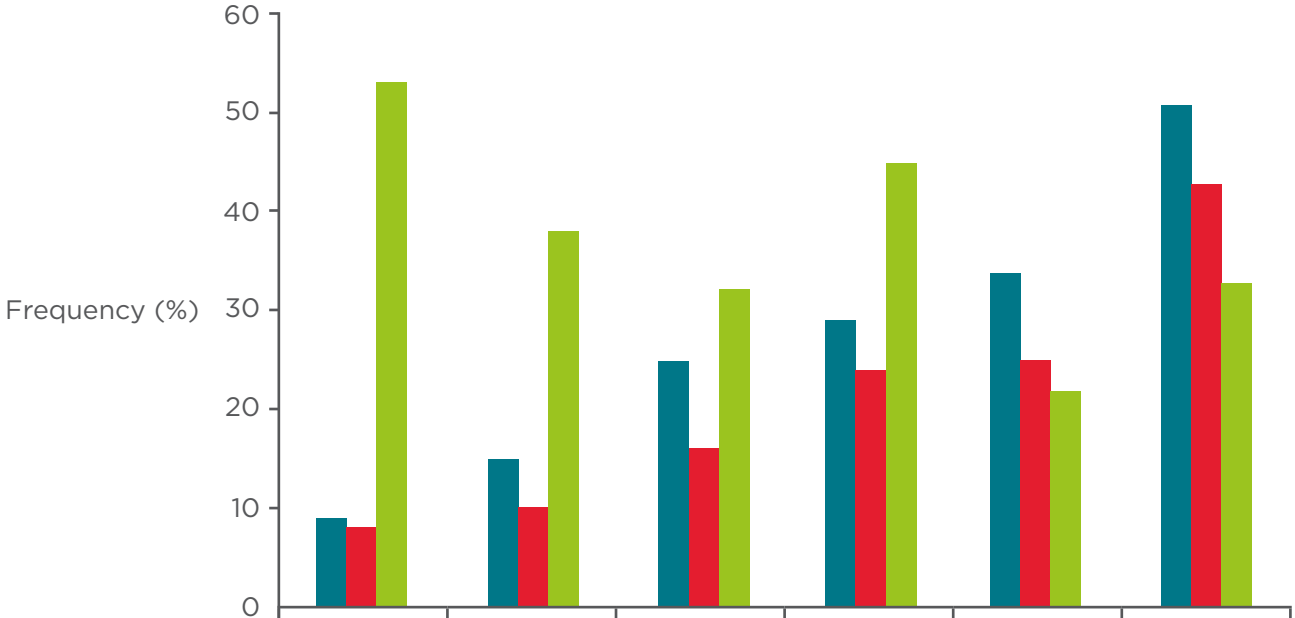
medication, was significantly higher with Fro-Dex (51%) than frovatriptan alone (29%).[28] Secondary endpoints included the proportion of sustained pain-free patients at 24 hours and those with pain relief at 2 hours, which were significantly higher with Fro-Dex. Based on patient preference scores, significantly more patients rated Fro-Dex as 'Good/Excellent'.[28] Relapse rates and the need for rescue medication were lower, though non-significant, with Fro-Dex.[28] Fro-Dex was well tolerated, with only somnolence regarded as a severe drug-related event in the Fro-Dex 25 mg group.[28] Post-hoc analysis determined that the proportion of migraine patients without aura who were pain-free at 2 hours was significantly greater with Fro-Dex, and the combination showed superior efficacy in women with MRM.[29] A comparison of the Sum-Nap[25] and Fro-Dex[28] data shows that the proportion of 2-hour pain-free and 24-hour sustained pain-free patients is highest with Fro-Dex and the proportion of patients requiring rescue medication is lowest with the combined therapies (Figure 2).

In conclusion, combining a triptan with an NSAID is a rational approach to migraine management and a number of combinations have been evaluated. These combinations capitalise on the rapid onset of the NSAID and the long-lasting effect of the triptan, to provide patients with comprehensive migraine relief. Fro-Dex is a highly effective and well tolerated combination with proven efficacy in several subgroups of patients, including those with MWoA and MRM.

Concluding remarks

Professor Stefan Evers

This symposium showed the value and importance of triptans for the treatment of migraine; no other class of drug has greater efficacy or a more favourable safety profile supported by such a wealth of data. Importantly, patients think highly of triptans, ensuring they will continue to be a mainstay of migraine treatment for years to come.



	Placebo	Nap 500 mg	Sum 85 mg	Fro 2.5 mg	Sum-Nap	Fro-Dex 25 mg
Pain-free 2 hours	9	15	25	29	34	51
Pain-free 24 hours	8	10	16	24	25	43
Rescue medication	53	38	32	45	22	33
Patients (n)	360	356	361	93	364	95

Figure 2: Comparison of sumatriptan plus naproxen versus frovatriptan plus dexketoprofen.[25,28]
Fro: frovatriptan; Fro-Dex: frovatriptan plus dexketoprofen; Nap: naproxen; Sum: sumatriptan; Sum-Nap: sumatriptan plus naproxen.

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