Headache
© 2011 American Headache Society

ISSN 0017-8748
doi: 10.1111/j.1526-4610.2011.02058.x
Published by Wiley Periodicals, Inc.

Review Article

Pharmacological Synergy: The Next Frontier on Therapeutic Advancement for Migraine

Andrew Blumenfeld, MD; Chris Gennings, ••; Roger Cady, MD

The burden of migraine significantly impacts the individual sufferer, their families, the workplace, and society. The World Health Organization has identified migraine as an urgent public health priority and has initiated a global initiative to reduce the burden of migraine. Underlying the World Health Organization initiative is the need to discover means of optimizing migraine treatments and make them accessible to the broader portion of the world population.

Development of acute migraine medications over the past several decades has largely centered on engineering highly specific receptor molecules that alter migraine pathophysiological mechanisms to abort or reverse the acute attack of migraine. The first product of this line of discovery was sumatriptan and heralded as a landmark therapeutic break through. Sumatriptan is a 5-HT-1B/D receptor agonist considered to activate receptors involved in the pathophysiology specific to migraine. Large-scale regulatory/clinical studies demonstrated statistical superiority for sumatriptan over placebo in reduction or elimination of headache, nausea, photophobia, and phonophobia. Since the introduction of sumatriptan, 6 other triptan products have been released in the United States as acute treatments for migraine, all having the same mechanism of action and similar efficacy. Despite their utility as migraine abortive medications, the triptans do not successfully treat all attacks of migraine or necessarily treat all migraine associated symptoms. In fact, in less than 25% of attacks do subjects obtain and maintain a migraine-free response to treatment for at least beyond 24 hours.

A wide range of non-triptan medications also have demonstrated efficacy in acute migraine. These include non-steroidal anti-inflammatory drugs (NSAIDs), opioids, phenothiazines, and valproic acid to name a few. Given the distinctly different mechanisms of actions of these various medications, it is likely that several unique pathophysiological mechanisms are involved in terminating acute episodes of migraine. Clinicians now capitalize on this observation and use migraine medication in combination with another to improve patient outcomes, for example, using an antiemetic with an opioid or a triptan and NSAIDs.

More recently, the Food and Drug Adminstration has approved a combination product containing 85 mg of sumatriptan plus 500 mg of naproxen sodium for acute treatment of migraine. Clinical trials conducted prior to approval demonstrated that the combination of sumatriptan and naproxen was more effective as a migraine abortive than either of its components but that each component and the combination were more effective than placebo. Exactly how sumatriptan and naproxen interact to create therapeutic synergism is unknown though its mere occurrence suggests that models assisting medical understanding and prediction of pharmacological synergism may improve clinical outcome over products acting through a single receptor mechanism.

Migraine is a syndrome, meaning it is defined by observed symptoms rather than known pathophysiology. Multiple pathogenic mechanisms are likely involved in generating this diverse array of symptoms understood as the migraine symptom complex. Sumatriptan and naproxen have independent mechanisms of action and target distinct aspects of the vascular and

From The Headache Center of Southern CA—Headache Center, Encinitas, CA, USA (A. Blumenfeld); Virginia Commonwealth University—Department of Biostatistics, Richmond, VA, USA (C. Gennings); Headache Care Center—Medicine, Springfield, MO, USA (R. Cady).

Address all correspondence to A. Blumenfeld, The Headache Center of Southern CA—Headache Center, 320 Santa Fe Drive Encinitas California 92024, USA.

Accepted for publication October 9, 2011.

Conflict of Interest: The authors have acted as consultants for GSK and/or Posen in the past.

inflammatory processes hypothesized to underlie migraine. Sumatriptan acts on the 5-HT_{1B} and 5-HT_{1D} receptors, whereas naproxen inhibits the COX-1 and COX-2 enzymes. Sumatriptan has vasoconstricting effects as well as effects on neurogenic inflammation by decreasing the release of substance P and calcitonin gene-related peptide. In contrast, naproxen affects prostaglandins and other inflammatory mediators. Because sumatriptan and naproxen both relieve migraine yet interact with different cellular targets within the migraine pathway, it is reasonable to assume there is a unique synergy between these medications that improves treatment outcomes. Clinical trials supported this contention by demonstrating the combination of sumatriptan/naproxen alleviated migraine pain quickly (primarily based on the sumatriptan mechanism of action), and sustained the response longer (primarily based on the naproxen mechanism of action) than is possible when either drug is given alone. The working hypothesis is that when sumatriptan and naproxen are given at the same time, they affect different mechanisms of the migraine pathway and produce an enhanced therapeutic effect.

The purpose of this article is to apply statistical analyses to data from phase II and phase III studies of the combination of sumatriptan and naproxen to determine if this enhanced therapeutic effect is synergistic. This methodology of accessing synergy can be used in the development of future combination migraine treatments to improve treatment outcomes.

Key words: synergy, sumatriptan, naproxen sodium, migraine

(*Headache* 2011;••:••-••)

Migraine is not just a debilitating disease for the individual sufferer; it also places a significant burden on affected families, workplaces, and society as a whole. The World Health Organization considers migraine to be an urgent public health priority and has initiated a global initiative to reduce the burden of migraine. Underlying the World Health Organization initiative is the need to optimize migraine treatments and make them accessible to a broader portion of the world population.

Development of acute migraine medications over the past several decades has largely centered on engineering highly specific receptor molecules that alter migraine pathophysiological mechanisms to abort or reverse the acute attack of migraine. The first product of this line of development was sumatriptan and heralded as a landmark therapeutic breakthrough. Sumatriptan is a 5-$HT_{1B/1D}$ receptor agonist considered to activate receptors involved in the pathophysiology specific to migraine. Large-scale clinical studies demonstrated statistical superiority for sumatriptan over placebo in reduction or elimination of headache, nausea, photophobia, and phonophobia.[1,2] Since the introduction of sumatriptan, 6 other triptan products have been released in the United States as acute treatments for migraine, all having the same mechanism of action and similar efficacy.[3] Despite their utility as migraine abortive medications, the triptans do not successfully treat all attacks of migraine or necessarily treat all migraine-associated symptoms. In fact, subjects obtain and maintain a migraine-free response to treatment for at least 24 hours in less than 25% of attacks.[4,5]

A wide range of non-triptan medications also have demonstrated efficacy in acute migraine. These include non-steroidal anti-inflammatory drugs (NSAIDs),[6] opioids,[7-9] phenothiazines,[10] and valproic acid[11] to name a few. Given distinctions in the scientifically understood mechanisms of action of these various medications, it is likely that several unique pathophysiological mechanisms are involved in terminating acute episodes of migraine. Clinicians now capitalize on this observation and use migraine medication in combination with another to improve patient outcomes, for example, using an antiemetic with an opioid or a triptan and NSAIDs.[12,13]

More recently, the Food and Drug Administration (FDA) has approved a combination product containing 85 mg of sumatriptan and 500 mg of naproxen sodium for acute treatment of migraine.[14] Clinical trials demonstrated that the combination of sumatriptan and naproxen was more effective as a migraine abortive than either of its individual components. Exactly how sumatriptan and naproxen interact to create an improved therapeutic benefit is unknown though its mere occurrence suggests that models assisting medical understanding and prediction of pharmacological synergism may aid in the development of combination products that improve clinical outcome over products acting through a single receptor mechanism.

Migraine is a syndrome; thus it is defined by observed symptoms rather than known pathophysiology. Multiple pathogenic mechanisms are likely involved in generating this diverse array of symptoms understood as the migraine symptom complex.[15-17] Sumatriptan and naproxen have independent mechanisms of action and target distinct aspects of the vascular and inflammatory processes hypothesized to underlie migraine. Sumatriptan acts on the 5-HT_{1B} and 5-HT_{1D} receptors,[18] whereas naproxen inhibits the COX-1 and COX-2 enzymes.[19] Sumatriptan has vasoconstricting effects as well as effects on neurogenic inflammation by decreasing the release of substance P and calcitonin gene-related peptide.[20] In contrast, naproxen affects prostaglandins and other inflammatory mediators.[16] Because sumatriptan and naproxen both relieve migraine yet interact with different cellular targets within the migraine pathway, the 2 drugs have recently been studied in combination to determine if there is a unique synergy between these medications that improves treatment outcomes. Clinical trials of the combination support the conclusion that the combination of sumatriptan and naproxen alleviate migraine pain quickly (primarily based on the sumatriptan mechanism of action), and sustain the response longer (primarily based on the naproxen mechanism of action) than is possible when either drug is given alone. In addition, pharmacokinetic studies suggest a therapeutically advantageous pharmacokinetic profile when sumatriptan and naproxen are administered in combination.[21] The working hypothesis is that when sumatriptan and naproxen are given at the same time, they affect different mechanisms of the migraine pathway and produce an enhanced therapeutic effect.

The purpose of this article is to apply statistical analyses to data from phases II and III studies of the combination of sumatriptan and naproxen to determine if this enhanced therapeutic effect is synergistic. This methodology of accessing synergy can be used in the development of future combination migraine treatments to improve treatment outcomes.

Phase II Study Analysis.—Smith TR et al contains a detailed description of the protocol used, data collected, and analyses conducted in the phase II study of combination treatment of sumatriptan and naproxen for migraine.[13] The study was designed to determine if the sustained pain response rate in subjects treated with the combination of sumatriptan 50 mg and naproxen sodium 500 mg was superior to that of subjects treated with the individual components (sumatriptan 50 mg or naproxen sodium 500 mg) or placebo.[13] This was a phase II, randomized, double-blind, placebo-controlled, multicenter study consisting of a screening visit, at home treatment of a single migraine attack, and a follow-up visit occurring 24-72 hours after the treated migraine attack.[13]

At the time of an eligible migraine attack (pain of moderate or severe intensity), subjects recorded their pain intensity and associated migraine symptoms on a diary card prior to taking study medication and at pre-defined intervals after taking study drug.[13] Subjects recorded the pain intensity scores (none [0], mild [1], moderate [2], or [aevere (3): just prior to taking study medication, and every 15 minutes for 2 hours, every 30 minutes until 4 hours and then hourly while awake for the next 20 hours.[13]

The primary efficacy endpoint was sustained pain response, defined as a pain score of 0 (no pain) or 1 (mild pain) at 2 hours post-dose, which did not return to a pain score of 2 (moderate pain) or 3 (severe pain) for the succeeding 22 hours, and no rescue medication was taken during the 24 hours following dosing with study medication.[13] Several secondary efficacy endpoints were assessed, including sustained pain-free response, which was defined as a pain score of 0 (no pain) at 2 hours, which remained at 0 at all subsequent time points, and no rescue medication was taken during the 24 hours.[13] Smith et al concluded that the combination group produced significantly greater initial pain relief at 2 hours post-dose, sustained pain response, and sustained pain-free effects than did sumatriptan alone, naproxen alone or placebo.[13] The combination was particularly superior to its components in subjects with severe baseline migraine pain.[13] The combination was also effective for the relief of the secondary symptoms of migraine: nausea; phonophobia; and photophobia.[13] Smith et al did not, however, analyze whether the combination group showed synergistic therapeutic efficacy for any of the efficacy endpoints (because the study was prospectively designed to compare data from the combina-

tion group with the individual components [sumatriptan or naproxen] alone or placebo).[13]

Phase III Study Analysis.—Brandes et al contains a detailed description of the protocol used, data collected, and analyses performed for the phase III studies of combination treatment of sumatriptan and naproxen for migraine.[22] Brandes et al reports 2 clinical studies that were identically designed and concurrently conducted at 118 clinical study centers.[22] These studies were designed to demonstrate the superiority of the combination of sumatriptan 85 mg and naproxen 500 mg vs the individual components (sumatriptan 85 mg or naproxen 500 mg) and placebo in the acute treatment of migraine.[22]

At the time of an eligible migraine attack (pain of moderate or severe intensity), subjects recorded their pain intensity and associated migraine symptoms on a diary card prior to taking study medication and at pre-defined intervals after taking study drug.[22] Subjects recorded the pain intensity scores (none [0], mild [1], moderate [2], or severe [3]) just prior to taking study medication; 0.5, 1, and 1.5 hours after dosing; and hourly from 2 to 24 hours after dosing.[22]

Various primary and secondary efficacy endpoints were assessed in the phase III studies, including both 2- and 24-hour endpoints.[22] The most rigorous endpoint evaluated was sustained pain-free response, defined as no pain at 2 hours and no relapse of pain (to mild, moderate, or severe) and no use of rescue medication during the 24-hour period after dosing.[22]

Brandes et al concluded that the combination of sumatriptan plus naproxen for the acute treatment of migraine resulted in more favorable clinical benefits compared with either monotherapy.[22] These phase III studies did not analyze whether the combination group showed synergistic therapeutic efficacy for any of the efficacy endpoints.[22]

Testing for Synergy From Combination Treatment.—Synergy is a biological process by which 2 factors act together, or interact, to produce an enhanced effect that would not be predicted by the effects of the individual components.[23,24] While synergy is a biological effect, not a numerical value, biostatisticians use mathematical models to evidence the synergistic effect of biological interactions such as those that take place with combination drug therapies.[24] That is, statistical analyses are useful to find evidence, by analyzing the available data, that drugs are producing a synergistic effect in a biological system. To analyze synergy, statisticians use various reference models to predict the effect of the combination based on the effects of the individual components.[24] If the actual (or observed) effect of the combination is the same as the predicted effect based on the effects of the individual components, the drugs do not interact.[24]

Thus, the *reference model* for the *no interaction case* predicts the effect of the combination from the effects of the individual components.[24] Combinations that have merely an *additive effect* (meaning their effect can be predicted from the effects of the individual components) demonstrate no interaction between the individual components of the combination.[24] Alternatively, if the actual effect of the combination is different from the effect predicted by the reference model, the 2 drugs are understood to interact with one another, either synergistically or antagonistically.[24] Combinations that have a greater than additive effect demonstrate a synergistic interaction.[24] Combinations that have a less than additive effect demonstrate an antagonistic interaction.[24]

There are 2 general approaches used to assess synergy in biological systems: the independent action approach[25-27] and the dose addition approach.[28,29] Independent action assumes that the probability of an effect from one drug is independent of the probability of an effect from a second drug.[27] Dose addition assumes the dose–response relationship of one drug does not change the dose–response relationship of another drug when given in combination.[28,30] In both approaches, departure from the reference model (ie, independent action or dose addition) that enhances the effects is considered to be evidence of an underlying biological process that is synergistic.[27,28,30]

An independent action model is based on the idea of statistically independent action of each component.[26,27] The independent action model is particularly appropriate for assessing synergy in the combination of sumatriptan and naproxen because these 2 drugs act on different mechanisms within the migraine pathway.[26,27] It is commonly used to evaluate 2 or more agents that are assumed to act on different

Table 1.—Phase II Data Described in Smith et al[13]

	Combination (Sumatriptan 50 mg Plus Naproxen 500 mg)	Sumatriptan (50 mg)	Naproxen (500 mg)	Placebo
Number of subjects in each group	250	226	248	241
Number of subjects achieving sustained pain response†	115	66	61	41
Percentage of subjects achieving sustained pain response	46%	29%	25%	17%
Number of subjects achieving sustained pain-free response†	63	25	29	12
Percentage of subjects achieving sustained pain-free response	25%	11%	12%	5%

†Based on total number of subjects in each group and percentage of subjects achieving response.

sites (eg, in evaluating the effects associated with various carcinogenic compounds).[31]

Under the independent action approach, the probability of a response from a combination of drugs A and B considers the probability of response from drug A plus the probability of response from drug B minus the probability of response to both drug A and drug B (because some patients will respond to both drug A and drug B).[27]

The Reference Model for Independent Action.— When 2 drugs, say A and B, act independently (and there is no interaction) we can predict the probability (P) of therapeutic response from the combination by knowing the probability of A and the probability of B. Mathematically, independent action is calculated according to the following formula:

$$P_{(\text{A or B})} = P_{\text{A}} + P_{\text{B}} - (P_{\text{A}} \times P_{\text{B}})$$

where $P_{(\text{A or B})}$ is the probability of response to either A or B, P_{A} is the probability of response to A, and P_{B} is the probability of response to B. This model subtracts the overlap between the probability of responding to A, and the probability of responding to B (this overlap correction is analogous to correcting for overlapping Venn diagrams). This basic model can be adjusted to take into account various factors, such as the observed placebo effect.[26]

If the effect of the combination is greater than the probability of response to either drug A or B (as calculated under the independent action model), then the combination is synergistic.

METHODS

The Independent Action Model.—There are a variety of tests that can be used to assess independent action. For this article a statistical test from Piegorsch et al was used.[26] The article also derives and evaluates several statistical tests of independent action and identifies a preferred test that is rigorous, powerful, and conservative.[26] The Piegorsch et al preferred test was selected for its elegant design and because it is particularly applicable to the design of the studies reported in Brandes et al and Smith et al, which are studies of 2 treatments, with a 2×2 factorial experimental design with binary responses.[26]

Statistical Synergy Analysis of Smith et al Data.— The sustained pain response and the sustained pain-free response endpoints were analyzed to determine whether the combination treatment demonstrates statistically significant synergy. The outcome measures chosen were the sustained pain response and the sustained pain-free response endpoints because they reflect short-term relief, long-term relief, and whether rescue medication was taken and thus provided a robust assessment of the combination.[32] In addition, sustained pain response is the primary efficacy endpoint for this study.[13]

The sustained pain response and sustained pain-free response data are described in Smith et al and included in Table 1.

Statistical Synergy Analysis of Brandes et al Data.—The sustained pain-free response endpoint was analyzed to determine whether the combination

Table 2.—Phase III Data Described in Brandes et al[22]

		Combination (sumatriptan 85 mg plus naproxen 500 mg)	Sumatriptan (85 mg)	Naproxen (500 mg)	Placebo
Number of subjects in each group	Study 1	364	361	356	360
	Study 2	362	362	364	382
	Total	726	723	720	742
Number of subjects achieving sustained pain-free response	Study 1	90	59	37	30
	Study 2	83	51	37	25
	Total	173	110	74	55
Percentage of subjects achieving sustained pain-free response	Study 1	25%	16%	10%	8%
	Study 2	23	14	10	7
	Total	24	15	10	7

treatment demonstrates statistically significant synergy. This was chosen as the sustained pain-free response reflects short-term relief, long-term relief, and whether rescue medication was taken.[32] Brandes et al identifies this endpoint as the only 24-hour "primary outcome measure."[22]

The sustained pain-free response data are described in Brandes et al and included in Table 2.

RESULTS

Phase II Study (Smith et al) Results.—To assess statistical synergy, the Piegorsch et al preferred test of independent action was applied to the Smith et al study data. The Piegorsch et al preferred test culminates in calculating a statistic, referred to as the "W" statistic.[26] As explained by Piegorsch, et al, values of W that are greater than 1 indicate synergy; values of W that are less than 1 indicate antagonism.[26]

Sustained Response Data.—The analysis concludes that the combination demonstrates a statistically significant synergistic therapeutic effect in achieving a sustained pain response in migraine sufferers. For the sustained pain response data, the W statistic was 1.19. This value was statistically greater than 1 ($P = .04$), thus indicating that the combination is statistically significantly synergistic. Under the independent action model, the predicted proportion of patients who would be expected to achieve a sustained pain response using the combination treatment was 36%. In other words, if there were no synergy, 36% of patients would be predicted to observe a sustained pain response with the combination treatment. The actual observed proportion of patients who achieved sustained pain response using the combination treatment was 46%.[13] Therefore, about 10% more patients achieved a sustained pain response when taking the combination treatment than what was expected under the independent action model. Table 3 contains the observed response for the combination, predicted response for the

Table 3.—Observed and Predicted Responses for the Combination Treatment (Smith et al)[13]

Endpoint	Observed Response for the Combination Treatment (%)	Predicted† Response for the Combination Treatment (%)	*P* value
Sustained pain response	46%	36%	.04
Sustained pain-free response	25%	17%	.05

†Predicted response based on the independent action model. Since the observed response from the combination treatment was statistically significantly greater than the response predicted from the independent action model, there is evidence of statistically significant synergy.

combination, and *P* value of the independent action test statistic for the sustained pain response analysis.

Sustained Pain-Free Response Data.—The analysis concludes that the combination demonstrates a statistically significant synergistic therapeutic effect in achieving a sustained pain-free response in migraine sufferers. For the sustained pain-free response data, the W statistic was 1.10. This value was statistically greater than 1 ($P = .05$), thus indicating that the combination is synergistic. Under the independent action model, the predicted proportion of patients who would be expected to achieve a sustained pain-free response using the combination treatment was 17%. In other words, if there were no synergy, 17% of patients would be predicted to observe a sustained pain-free response with the combination treatment. The actual observed proportion of patients who achieved a sustained pain-free response using the combination treatment was 25%.[13] Therefore, about 8% more patients achieved a sustained pain-free response when taking the combination treatment than what was expected under the independent action model. Table 3 contains the observed response for the combination, predicted response for the combination, and *P* value of the independent action test statistic for the sustained pain-free response analysis.

Phase III Study (Brandes et al) Results.—The Piegorsch et al preferred test of independent action, was applied to assess statistical synergy.[26] For the sustained pain-free response data in the first study described in Brandes et al ("Study 1"), the W statistic was 1.09. This value was greater than 1, but it was not statistically greater than 1 using a 5% significance level ($P = .07$). Thus, this W statistic indicates a trend toward synergy without statistical significance. Under the independent action model, the predicted proportion of patients who would be expected to achieve a sustained pain-free response using the combination treatment was 18%. In other words, if there were no synergy, 18% of patients would be predicted to observe a sustained pain-free response with the combination treatment. The actual observed proportion of patients who achieved a sustained pain-free response using the combination treatment was 25%.[22] Table 4 contains the observed response for the combination, predicted response for the combination, and *P* value of the independent test statistic for the sustained pain-free response analysis.

For the sustained pain-free response data in the second study described in Brandes et al ("Study 2"), the W statistic was 1.07. This value was greater than 1, but it was not statistically greater than 1 using a 5% significance level ($P = .10$). Thus, this W statistic indicates a trend toward synergy without statistical significance. Under the independent action model, the predicted proportion of patients who would be expected to achieve a sustained pain-free response using the combination treatment was 17%. In other words, if there were no synergy, 17% of patients would be predicted to observe a sustained pain-free response with the combination treatment. The actual observed proportion of patients who achieved a sustained pain-free response using the combination treatment was 23%.[22] Table 4 contains the observed

Table 4.—Observed and Predicted Responses for the Combination Treatment (Brandes et al)[22]

Endpoint	Study	Total Sample Size	Observed Response for the Combination Treatment (%)	Predicted† Response for the Combination Treatment (%)	*P* value
Sustained pain-free response	Study 1	1441	25%	18%	.07
	Study 2	1470	23%	17%	.10
	Studies 1 & 2 combined	2911	24%	18%	.01‡

†Predicted response based on the independent action model.
‡By combining the 2 studies the larger sample size allowed for increased power to detect synergy in these data. Since the observed response from the combination treatment was statistically significantly greater than the response predicted from the independent action model, there is evidence of statistically significant synergy.

response for the combination, predicted response for the combination, and *P* value of the independent test statistic for the sustained pain-free response analysis.

We initially analyzed the 2 studies separately simply because they were described by the authors as 2 distinct—although identically designed and concurrently conducted using the same protocol—studies. Both analyses indicated a trend toward synergy. Thus, we combined the results of the 2 studies to investigate whether the lack of statistical significance was because of true lack of synergy or to lack of power. Power is the probability of correctly identifying the theorized result (eg, synergy) when it exists.[33] In other words, the larger the sample size, the greater the ability to distinguish between "signal" and "noise." That is, larger sample sizes increase the precision of the statistical test to distinguish between differences in the data that are caused by actual effects (ie, the true "signal") vs differences in the data that are caused by random variation (ie, "noise").[33] Therefore, by combining and analyzing the studies together, the analysis has more power.

The analysis concludes that when the results from the 2 studies are combined, the sustained pain-free response data show that the combination demonstrates a statistically significant synergistic therapeutic effect in achieving a sustained pain-free response in migraine sufferers. For the combined sustained pain-free response data, the W statistic was 1.18. This value was statistically greater than 1 ($P = .01$), thus indicating that the combination is statistically significantly synergistic. Under the independent action model, the predicted proportion of patients who would be expected to achieve a sustained pain-free response using the combination treatment was 18%. In other words, if there were no synergy, 18% of patients would be predicted to observe a sustained pain-free response with the combination treatment. The actual observed proportion of patients who achieved sustained pain-free response using the combination treatment was 24%.[22] Therefore, about 6% more patients achieved a sustained pain-free response when taking the combination product than what was expected under the independent action model. Table 4 contains the observed response for the combination, predicted response for the combination, and *P* value of the independent test statistic for the sustained pain-free response analysis.

DISCUSSION

Migraine is a complex neurobiological process capable of generating a wide array of clinical symptoms. Clinical trials have demonstrated that not all attacks or all symptoms of specific attacks are always relieved by intervention with triptans, even within the same subject. Further, certain aspects of migraine pathophysiology do not appear to be altered by triptan intervention (eg, aura[34-37]). Consequently, there is a clinical need to explore the potential synergy of different medications presumed to act on different pathways of migraine pathophysiology in successfully treating acute migraine.

Migraine is an excellent disease model for exploring synergistic mechanisms of pharmacological agents used in its treatment. Given the divergence of symptomatology frequently observed during an attack, it is reasonable to assume that no single receptor mechanism can fully explain the totality of symptom expression. The FDA has recently supported a concept of migraine specific medications for acute interventions whereby the intervention demonstrates statistical superiority over placebo in relief of headache, nausea, photophobia, and phonophobia.[38] While each endpoint is considered independent, it is important to note that only a minority of subjects treated during moderate to severe headache experience complete relief of all acute symptoms. This strongly underscores the limitations of single receptor pharmacology and the hope of finding a "magic bullet" to treat a complex disease like migraine.

It is advantageous to use multiple drugs working in synergy to relieve migraine. The complexity and diversity of migraine symptoms that are observed during episodes of migraine suggest that physiological "networks" rather than single receptors are generating these diverse symptoms. Considering the "process of migraine" as developing over time, specific drug interventions may be more or less effective depending on the pathophysiological phase of migraine when they are delivered. This has been demonstrated in part by numerous "early intervention" studies that clearly demonstrate better efficacy for

multiple migraine related symptoms when oral triptans are delivered early in the mild headache phase of migraine.[39,40] Likewise, Burstein presented data that demonstrated ketorolac was more efficacious than sumatriptan when migraine had evolved to a point where central sensitization had developed.[41] This again suggests that as migraine progresses, so too does the pathophysiology that drives the symptom expression observed clinically.

Additionally, independent mechanisms of pharmacological intervention appear to have varying effects on specific symptoms associated with migraine. For example, while triptans appear more efficacious for migraine associated nausea than placebo, there are no peer-reviewed published studies to suggest that triptans have efficacy in treating nausea unrelated to migraine. This suggests that relief of nausea by triptans during migraine is mediated through an indirect mechanism(s). Similarly, there are no peer-reviewed published studies to suggest that triptans have efficacy in other primary headache disorders such as tension-type headache.

The analysis of the studies described in this article clearly support differences in various aspects of migraine relief using a combination of sumatriptan and naproxen. As demonstrated in the analysis in this article there is a clear example of synergism among medications with different mechanisms of action that resolve migraine-associated symptoms. Designing studies that explore synergistic interaction is of paramount importance for the welfare of patients. Unfortunately, while the advent of sumatriptan was indeed a breakthrough innovation for the treatment and scientific understanding of migraine, it is not a "magic bullet" for treating migraine, and its development was followed by 2 decades of drug development that focused on improving the triptan molecule rather than advancing new therapeutic directions.

Development of pragmatic approaches that tangibly improve patient care requires an understanding that treating a complex clinical conundrum such as migraine may often require a combination of medications rather than a single drug. Standards of care for other disease states appear to have already recognized this principle. For example, treatment of hypertension is frequently accomplished with combinations of medications working through different mechanisms of action.[42]

Demonstrating strategies to evaluate the potential synergy of unique and different pharmacological interventions for migraine has value for both patient outcome and future drug development. Utilization of a predictive model such as described in this article could be a significant step forward in defining potentially synergistic migraine interventions and improving treatment outcome.

CONCLUSIONS

As more new migraine treatments are developed, the possibility of developing combination treatments increases. Currently, the combination of sumatriptan and naproxen (marketed as Treximet®) is the only FDA-approved combination treatment for migraine. Rational polytherapy addressing the multiple mechanisms of migraine, however, opens up many new possibilities for the development of both acute and preventive migraine therapies. In determining the efficacy of these potential combination treatments, synergy should be included in this assessment. Another potential benefit of combination treatments is increased patient compliance because multiple medications can be contained in one formulation.

The combination of sumatriptan and naproxen is the only migraine treatment to date for which statistically significant synergy has been demonstrated. The statistical method outlined in this article could be used to assess many other potential combination treatments. This may allow for more effective treatment development and fill the need for more migraine treatments.

APPENDIX I

Worked Example for Independent Action.—The term "independent action," as it is used in statistics, describes a model that is used to compare the effect of drugs or chemicals in the assessment of synergy in biological systems. The independent action is applicable when 2 drugs act independently when given in combination.[26,27,43,44] With this model the response from a combination treatment of 2 (or more) drugs can be predicted using definitions of probabilistic independent events. If the effect of the combination treat-

ment is greater than the predicted response (as calculated under the independent action reference model), the combination is said to be synergistic. Likewise, if the effect of the combination is less than the predicted response, the combination is said to be antagonistic.

To set notation for a 2 drug combination, define P_A as the probability of response from a patient given drug A, and P_B as the probability of response from drug B; define $Q_A = 1 - P_A$ as the probability of no response from a patient given drug A, and $Q_B = 1 - P_B$ as the probability of no response from drug B. Assuming a response from drug A is independent of a response from drug B, by definition of probabilistic independent events, a response from either drug A or drug B is given by the equation

$$P_{AB} = P_A + P_B - P_A \times P_B \qquad \text{(A1)}$$

and the probability of no response from either drug A or drug B is given by equation (Finney[42])

$$Q_{AB} = Q_A \times Q_B. \qquad \text{(A2)}$$

Thus, under independent action, the probability of response (Eqn A1), or no response (Eqn A2), for a combination treatment can be predicted from knowing the probabilities of response from either drug alone.

In the case where there is a non-zero placebo effect, a conditional model can be used. Define P_0 as the probability of response from placebo and $Q_0 = 1 - P_0$ as the probability of no response from placebo. That is, the probability of no response from treatment with the combination of drugs is the probability of no response from both drug A and drug B given no response from a placebo (3, 4):

$$Q_{AB} = \frac{Q_A \times Q_B}{Q_0} \text{ and equivalently,}$$
$$Q_{AB} \times Q_0 = Q_A - Q_B.$$

Following Piegorsch et al define W as the ratio of sample proportions for these probabilities, denoting sample proportions with $\hat{Q}$:

$$W = \frac{\hat{Q}_A \times \hat{Q}_B}{\hat{Q}_{AB} \times \hat{Q}_0}$$

Values of W significantly greater than 1 indicate synergistic departure from independent action; values of W significantly less than1 indicate antagonistic departure. Under independent action, an estimate for the proportion of subjects with no response given the combination treatment is given by the equation

$$\hat{Q}_{AB(\text{independent action})} = \frac{\hat{Q}_A \times \hat{Q}_B}{\times \hat{Q}_0}.$$

As described in Piegorsch et al the hypothesis of independent action can be tested by noting $\left(\frac{\ln(W)}{\sqrt{\text{var}_{\text{est}}(\ln(W))}}\right)$ has an asymptotic standard normal distribution, so that $\left(\frac{\ln(W)}{\sqrt{\text{var}_{\text{est}}(\ln(W))}}\right)^2$ has an asymptotic chi-square distribution with 1 degree of freedom, where $\ln(W)$ is the natural log of W with large sample variance estimated by

$$\text{var}_{\text{est}}(\ln(W)) = \frac{1-\hat{Q}_0}{N_0\hat{Q}_0} + \frac{1-\hat{Q}_A}{N_A\hat{Q}_A} + \frac{1-\hat{Q}_B}{N_B\hat{Q}_B} + \frac{1-\hat{Q}_{AB}}{N_{AB}\hat{Q}_{AB}}$$

where N_0 is the sample size in the placebo group, N_A is the sample size in the group given drug A, N_B is the sample size in the group given drug B, and N_{AB} is the sample size given the combination treatment of the doses of drugs A and B. When $\left(\frac{\ln(W)}{\sqrt{\text{var}_{\text{est}}(\ln(W))}}\right)^2$ exceeds the critical value from the chi-square distribution, there is statistically significant evidence that the hypothesis of independent action can be rejected, and when $W > 1$, synergy can be claimed. For convenience, a worked example is presented in Table A.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Andrew Blumenfeld; Chris Gennings; Roger Cady

(b) Acquisition of Data

Andrew Blumenfeld; Chris Gennings; Roger Cady

Table A.—Worked Example for Results From Analysis of Independent Action

$\hat{Q}_0$	83%
$\hat{Q}_A$	75%
$\hat{Q}_B$	71%
$\hat{Q}_{AB}$	54%
$\hat{Q}_{AB(independent\ action)}$	64%
$P_{AB} = 1 - \hat{Q}_{AB}$	46%
$P_{AB(indep\ act)} = 1 - \hat{Q}_{AB(indep\ act)}$	36%
W	1.19
$\ln(W)$	0.17
$SE_{est}(\ln(W))$	0.09
P value	.04

(c) Analysis and Interpretation of Data
Andrew Blumenfeld; Chris Gennings; Roger Cady

Category 2

(a) Drafting the Article
Andrew Blumenfeld; Chris Gennings; Roger Cady

(b) Revising It for Intellectual Content
Andrew Blumenfeld; Chris Gennings; Roger Cady

Category 3

(a) Final Approval of the Completed Article
Andrew Blumenfeld; Chris Gennings; Roger Cady

REFERENCES

1. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA*. 1991;265:2831-2835.
2. The Subcutaneous Sumatriptan International Study Group. Subcutaneous sumatriptan in the acute treatment of migraine. *N Engl J Med*. 1991;325:316-321.
3. Bigal ME, Bordini CA, Antoniazzi AL, Special JG. The triptan formulations: A critical evaluation. *Arq Neuropsiquiatr*. 2003;61:313-320.
4. Garcia-Ramos G, MacGregor EA, Hilliard B, Bordini CA, Leston J, Hettiarachchi J. Comparative efficacy of eletriptan vs naratriptan in the acute treatment of migraine. *Cephalalgia*. 2003;23:869-876.
5. Cady R, Martin V, Mauskop A, et al. Efficacy of rizatriptan 10 mg administered early in a migraine attack. *Headache*. 2006;46:914-924.
6. Tfelt-Hansen P. Triptans vs other drugs for acute migraine. Are there differences in efficacy? A comment. *Headache*. 2008;48:601-605.
7. Rothrock JF. Opiate and opioid ("narcotic") therapy for acute migraine headache. *Headache*. 2010;50:1255-1256. [11]
8. Hoffert MJ, et al. Transnasal butorphanol in the treatment of acute migraine. *Headache*. 1995;35:65-69.
9. Goldstein J, et al. Comparison of butorphanol nasal spray and fiorinal with codeine in the treatment of migraine. *Headache*. 1998;38:516-522.
10. Kelly AM, Walcynski T, Gunn B. The relative efficacy of phenothiazines for the treatment of acute migraine: A meta-analysis. *Headache*. 2009;49:1324-1332.
11. Freitag FG. Divalproex in the treatment of migraine. *Psychopharmacol Bull*. 2003;37(Suppl. 2):98-115.
12. Hurtado TR, Vinson DR, Vandenberg JT. ED treatment of migraine headache: Factors influencing pharmacotherapeutic choices. *Headache*. 2007;47:1134-1143.
13. Smith TR, Sunshine A, Stark SR, et al. Sumatriptan and naproxen sodium for the acute treatment of migraine. *Headache*. 2005;45:983-991.
14. ••. •• GlaxoSmithKline news release, April 16, 2008, Treximet (sumatriptan and naproxen sodium) tablets approved by FDA for acute treatment of migraine. http://www.gsk.com/media/pressreleases/2008/2008_us_pressrelease_10034.htm [12] [13]
15. Goadsby PJ, Ramadan NM. Potential new drugs for acute and prophylactic treatment of migraines. In: Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA, eds. *The Headaches*. 4th edn. ••: Lippincott Williams & Wilkins; 2006:569-576. [14]
16. Welch KM. Drug therapy of migraine. *N Engl J Med*. 1993;329:1476-1483.
17. Moskowitz MA. The neurobiology of vascular head pain. *Ann Neurol*. 1984;16:157-168.
18. Ahn AH, Basbaum AI. Tissue injury regulates serotonin 1D receptor expression: Implications for the control of migraine and inflammatory pain. *J Neurosci*. 2006;26:8332-8338.

19. Duggan KC, et al. Molecular basis for cyclooxygenase inhibition by the non-steroidal anti-inflammatory drug naproxen. *J Biol Chem*. 2010;285:34950-34959.
20. Welch KM. The therapeutics of migraine. *Curr Opin Neurol Neurosurg*. 1993;6:264-269.
21. Haberer LJ, et al. Distinct pharmacokinetic profile and safety of a fixed-dose tablet of sumatriptan and naproxen sodium for the acute treatment of migraine. *Headache*. 2010;50:357-373.
22. Brandes JL, et al. Sumatriptan-naproxen for acute treatment of migraine. *JAMA*. 2007;297:1443-1454.
23. Fleiss JL. *The Design and Analysis of Clinical Experiments* 97. ••: John Wiley & Sons; 1999:••-••.
24. Berenbaum MC. What is synergy? *Pharmacol Rev*. 1989;41:93-141.
25. Holt MA, Stamey JD, Seaman JW, Young DM. A note on tests for interaction in quantal response data. *J Stat Comput Simul*. 2004;74:683-690.
26. Piegorsch WW, Weinberg CR, Haseman JK. Testing for simple independent action between two factors for dichotomous response data. *Biometrics*. 1986;42:413-419.
27. Finney DJ. *Probit Analysis*. 3rd edn. ••: Cambridge University Press; 1971:136-146.
28. Carter WH, Gennings C, Staniswalis JG, et al. A statistical approach to the construction and analysis of Isobolograms. *J Am Coll Toxicol*. 1988;7:963-973.
29. Berenbaum MC. The expected effect of a combination of agents: The general solution. *J Theor Biol*. 1985;114:413-431.
30. Gennings C, Carter WH Jr, Carchman RA, Teuschler LK, Simmons JE, Carney EW. A unifying concept for assessing toxicological interactions: Changes in slope. *Toxicol Sci*. 2005;88:287-297.
31. US EPA. 2000) Supplementary guidance for conducting health risk assessment for chemical mixtures. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533
32. Vandenhende F, Lambert P, Ramadan N. Statistical models for the analysis of controlled trials on acute migraine. *Pharm Stat*. 2003;2:199-210.
33. Milton SJ. *Statistical Methods in the Biological and Health Sciences*. ••: McGraw Hill; 1998:242-245.
34. Dowson A. Can oral 311C90, a novel 5-HT1D agonist, prevent migraine headache when taken during an aura? *Eur J Neurol*. 1996;36(Suppl. 2):28-31.
35. Olesen J, Diener HC, Schoenen J, Hettiarachchi J. No effect of electriptan administration during the aura phase of migraine. *Eur J Neurol*. 2004;11:671-677.
36. Bates D, Ashford E, Dawson R, et al. Subcutaneous sumatriptan during the migraine aura (Sumatriptan Aura Study Group). *Neurology*. 1994;44:1587-1592.
37. Aurora SK, Barrodale PM, McDonald SA, Jakubowski M, Burstein R. Revisiting the efficacy of sumatriptan therapy during the aura phase of migraine. *Headache*. 2009;49:1001-1004.
38. Rodgers AJ, Hustad CM, Cady RK, et al. Total migraine freedom, a potential primary endpoint to assess acute treatment in migraine: Comparison to the current FDA requirement using the complete rizatriptan study database. *Headache*. 2011;51:356-368.
39. Cady RK, Lipton RB, Hall C, Stewart WF, O'Quinn S, Gutterman D. Treatment of mild headache in disabled migraine sufferers: Results of the Spectrum Study. *Headache*. 2000;40:792-797.
40. Goadsby PJ. The "Act when Mild" (AwM) study: A step forward in our understanding of early treatment in acute migraine. *Cephalalgia*. 2008;28(Suppl. 2):36-41.
41. Jakubowski M, Levy D, Goor-Aryeh I, Collins B, Bajwa Z, Burstein R. Terminating migraine with allodynia and ongoing central sensitization using parenteral administration of COX1/COX2 inhibitors. *Headache*. 2005;45:850-861.
42. Chobanian AV, Bakris GL, Black HR, et al., National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *JAMA*. 2003;289:2560-2572.
43. Bliss CI. The toxicity of poisons applied jointly. *Ann Appl Biol*. 1939;26:585-615.
44. Wahrendorf J, Zentgraf R, Brown CC. Optimal design for the analysis of interactive effects of two carcinogens or other toxicants. *Biometrics*. 1981;37:45-54.

Toppan Best-set Premedia Limited	
Journal Code: HEAD	Proofreader: Emily
Article No: 2058	Delivery date: 22 November 2011
Page Extent: 12	Copyeditor: Ivan

AUTHOR QUERY FORM

Dear Author,

During the preparation of your manuscript for publication, the questions listed below have arisen. Please attend to these matters and return this form with your proof.

Many thanks for your assistance.

Query References	Query	Remark
q1	AUTHOR: Please supply the academic degree for author Gennings.	
q2	WILEY-BLACKWELL: Please check and confirm if the length of the Abstract is OK.	
q3	AUTHOR: In the Abstract, the phrase “make them assessable” has been changed to “make them accessible”. Please check and confirm if this is correct.	
q4	AUTHOR: Should “5-HT-1B/D” be changed to “5-$HT_{1B/1D}$”?	
q5	AUTHOR: The number “14” at the end of the sentence “In contrast, naproxen affects prostaglandins and other inflammatory mediators.” has been deleted. Please check and confirm if this is correct.	
q6	AUTHOR: “Non-steroidal anti-inflammatories” has been changed to “non-steroidal anti-inflammatory drugs”, to refer to the abbreviation NSAIDs. Please check and confirm if this is correct.	
q7	AUTHOR: “The Piegorsch et al . . . binary responses.”: This sentence has been reworded for clarity. Please check and confirm it is correct. Also, please check and indicate if the reference citation for Smith et al. should also be inserted in the sentence.	
q8	AUTHOR: Should “Rational polytherapy addressing the multiple me**chanisms of migraine, however, opens** ..migraine therapies.” be changed to “Rational polytherapy addressing the multiple mechanisms of **migraine opens** . . . migraine therapies.”?	
q9	AUTHOR: “Finney, 1971” in the Appendix has been changed to “Finney[42]”, to follow journal style (Vancouver). Please check and confirm if this is correct.	
q10	AUTHOR: Please check and confirm what “3, 4” refers to in the phrase “given no response from a placebo (3, 4):” in the Appendix (eg, equation numbers or reference citations).	
q11	AUTHOR: For references with et al: If there are more than 6 authors, please list the first 3 plus et al, and if there are six or less number of authors, please list all their names, to follow journal style.	
q12	AUTHOR: Please supply the authorship and the year of publication for Reference 14.	
q13	AUTHOR: Please check all the website addresses and confirm that they are correct. (Please note that it is the responsibility of the author(s) to ensure that all URLs given in this article are correct and useable.)	

q14	AUTHOR: Please supply the city location of publisher for Reference 15.	
q15	AUTHOR: Please supply the city location of publisher and page range for Reference 23.	
q16	AUTHOR: Please supply the city location of publisher for Reference 27.	
q17	AUTHOR: Please supply the city location of publisher for Reference 33.	