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Views and Perspectives

Clinical Implications for Breath-Powered Powder Sumatriptan Intranasal Treatment

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The acute treatment of migraine requires matching patient need to drug and formulation. In particular, nausea and vomiting, quick time to peak intensity, and the common gastroparesis of migraineurs, all call for a variety of non-oral formulations for treatment of attacks. A novel breath-powered powder sumatriptan intranasal treatment offers an improvement, at least in pharmacokinetics, over conventional liquid nasal sumatriptan spray.

The device for delivery in this breath-powered nasal sumatriptan uses natural nose anatomy to close the soft palate and propel the sumatriptan high up in the nasal cavity on one side with bidirectional airflow coming out the other side. This approach has the potential to reduce adverse events and improve efficacy. Phase 3 data on this system are in press at the time of this writing and results appear promising.

The clinical role for a fast acting non-oral nasal formulation will be in those for whom tablets are bound to fail, that is, in the setting of nausea and vomiting or when the time to central sensitization, allodynia, and disabling migraine is too short for the patient to respond to a tablet. This review provides a clinical perspective on the breath-powered powder sumatriptan intranasal treatment.

Key words: sumatriptan, breath-powered powder sumatriptan intranasal treatment, OPTINOSE, migraine, acute migraine treatment, nasal spray

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Because migraine attacks frequently involve nausea and vomiting and often are fast in time to peak intensity and associated symptoms, and because those with migraine often manifest gastroparesis, non-oral formulations are an important option for optimal acute migraine management.

Each of these migraine features can be best treated with non-oral options. The presence of nausea can be worsened by tablets, while vomiting leads to loss of the medication, preventing absorption.

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In the last 12 months, he has served as a consultant for Allergan, ATI, MAP, Nautilus, NuPathe, Pfizer, and Zogenix.

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Dr. Tepper holds stock options in ATI.

Reduced gastric motility is common both during and in between migraine attacks, which can delay the absorption of medication. Conventional tablets rely on surface erosion within the stomach (shearing), assisted by peristalsis and gastric motility. In a study by Aurora and colleagues, "the time to half emptying in ten migraine subjects was delayed in migraine ictally (78%) and in the interictal period (80%). There was a significant delay compared to non-migrainous controls (migraine 188.8 minutes vs normal controls 111.8 minutes; $P < .05$)."[1]

Another study in 2012 found that migraine gastrointestinal (GI) emptying was worse ictally and different from nonmigraineurs for liquid phase gastric emptying. "Seven women with migraine and age, sex matched controls . . . were compared [in a] gastric emptying study . . . Non-migraineur controls and migraineurs were compared. The mean phamarcokinetic half life ($T_{1/2}$) was longer in the ictal period in migraineurs. The $T_{1/2}$ of migraineurs interictally and the control groups were similar . . . When patients were imaged in spontaneous attacks, the emptying half time was meaningfully increased, contrary to the studies done for solid phase gastric emptying."[2] These studies suggest that acute migraine treatment that bypasses the gut may offer clinically meaningful benefit over tablets or liquids.

In the American Migraine Prevalence and Prevention Study, among 6488 respondents with episodic migraine, approximately half (49.5%) reported high-frequency nausea (>half the time) with their attacks.[3] Further, annual health care costs for those with migraine nausea more than half the time were more than 3 times that for those without nausea.[4] Addressing acute migraine treatment with non-oral medications should reduce any worsening of nausea from oral drug presentation and may reduce overall cost.

In any migraineur, a quick time to peak intensity often precludes successful use of oral medication, with its relatively slower onset of action, in acute treatment of migraine. A particularly dramatic example of this is in pediatric and adolescent migraine, in which very fast onset of headache, nausea, and vomiting have bedeviled studies for acute migraine medications, and where non-oral formulations are often the first-line treatment. In the European Union, sumatriptan and zolmitriptan nasal sprays have regulatory approval for adolescent migraine.

These common clinical situations, that is migraine nausea and vomiting, migraine gastroparesis and related GI autonomic dysfunction, and quick time to peak intensity, force headache medicine clinicians to always be on the lookout for non-oral alternatives. There is a manifest need for increasing both the efficacy and variety of non-oral acute migraine treatments. This brief summary reviews some of the aspects of breath-powered powder sumatriptan intranasal treatment (BPPSIT) that suggest it may offer additional benefit to patients requiring an alternative to oral tablets. This device is also referred to as the OPTINOSE delivery system (OPTINOSE US Inc, Yardley, PA, USA), for the company which developed and tested it. The BPPSIT device has completed its Phase 3 regulatory study and will be submitted to the US Food and Drug Administration for approval during 2013.

DELIVERY SYSTEM

Understanding normal breathing is necessary for comparing the BPPSIT system to conventional triptan nasal devices. During exhalation through the mouth against a sufficient resistance, the soft palate closes because of positive pressure in the mouth, and this separates nasal from oral cavities. Spraying a conventional liquid nasal spray occurs with the soft palate open, leading to partial lung or GI delivery of a drug that is supposed to go only into the nose.

Drug distribution within the nasal cavity from conventional nasal sprays can be inconsistent, with liquid medication dripping out the front of the nose, down the back of the palate, or swallowed.[5] This reduces nasal absorption, can result in a very bitter taste, and may lead to irregular and unpredictable clinical outcome. That certainly has been the case with some of the conventional liquid migraine nasal sprays, and resulted in a variety of unusual recommended work-arounds to try to improve clinical acceptance and consistency,[6] often without great success.

The BPPSIT device makes it becomes possible to propel medication, in this case a dry sumatriptan powder, intranasally with the soft palate closed. This should alleviate or ameliorate inconsistent benefits, bad taste, swallowing, and nasal drip.

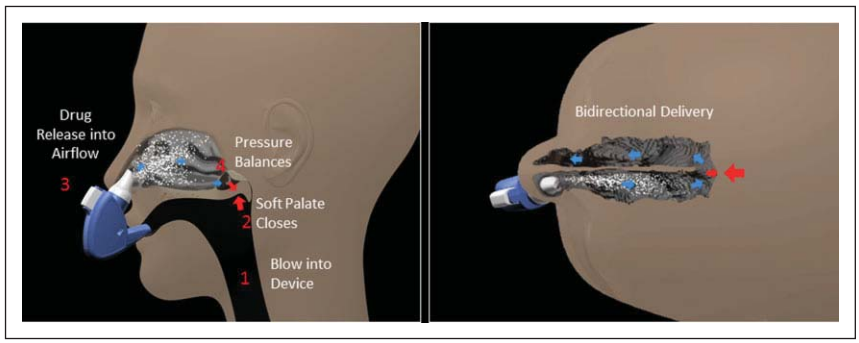

Fig 1.—Breath-powered powder intranasal delivery system.

A patient uses this device by exhaling into it. Exhalation against the device's resistance creates a positive pressure in the pharynx, elevating and sealing closed the soft palate. The sealing nosepiece of the BPPSIT device takes the positive exhalation pressure into the nose, and this pressure expands the nasal valve and puts a "balancing" pressure on the soft palate, preventing it from elevating too far. The balanced pressure across the soft palate assures that the nasal passages on the 2 sides are open with respect to each other posterior to the septum. The patent communication deep in the nasal cavity allows airflow to enter into 1 nostril, flow across to the other side, and exit from there. This is referred to as bidirectional airflow. Theoretically, with a device that works in this fashion, drug introduction into 1 side of the nose would result in deposition of the medication in the nasal cavity ipsilateral to the flow, with air exiting out the other side after this deposition.

This novel system involves having the patient place a mouthpiece in the mouth, a specially shaped nosepiece, and, leaving the other nostril open, blow a dry sumatriptan powder up the ipsilateral nasal cavity for drug delivery. The air then exits by the contralateral nostril (see Fig. 1).

Nasal sprays in general have been administered in the hopes of limiting GI delivery with all of its attendant problems, but have in fact been shown to produce mostly GI drug absorption. The BPPSIT device, by closing the soft palate and improving nasal deposition, should greatly increase nasal absorption while eliminating and reducing lung and GI tract deposition.

PHARMACOKINETICS OF THE BREATH-POWERED POWDER SUMATRIPTAN INTRANASAL DEVICE

The 20-mg nominal dose of sumatriptan dry powder with BPPSIT delivers 16 mg in the nose. This means that the total exposure to sumatriptan with the device is a lower total milligram dose than tablet, nasal spray, or injection.

However, directly comparative pharmacokinetic studies show that the 16-mg BPPSIT powder treatment produces higher peak concentration (Cmax ng/mL) than the 20-mg conventional liquid sumatriptan nasal spray (20.8 mg vs 16.4 mg, unadjusted for dose). Both intranasal formulations produce a substantially lower peak concentration (Cmax ng/mL) than either the sumatriptan tablet (100 mg tablet = 70.2, 6 mg) or the subcutaneous injection (6 mg = 111.6 mg). Similarly, total drug exposure as measured by area under the curve ($AUC_{0-\infty}$ ng*hr/mL) is much lower with the intranasal formulations (BPPSIT = 64.9 mg, conventional sumatriptan liquid nasal spray = 61.1 mg, unadjusted for dose) than with the 100 mg tablet (308.8 mg) or injection (128.2 mg).[7]

The sumatriptan powder delivered with the BPPSIT is not bioequivalent to any tested sumatriptan product. Of particular note, the pharmacokinetics of the BPPSIT show a pattern of faster and more efficient absorption than the conventional liquid nasal spray, yielding >60% higher early plasma exposure with an AUC_{0-15} minutes of 2.1 for BPPSIT vs 1.2 for liquid sumatriptan nasal spray and an AUC_{0-30} minutes of 5.8 for BPPSIT vs 3.6 for the conventional spray despite the delivery of 20% less drug.[8]

EFFICACY DATA

The Phase 2 randomized controlled trial on BPPSIT published in 2010 included 117 adult subjects with episodic migraine. There were 3 arms, a sumatriptan powder 10 mg arm, a sumatriptan powder 20 mg arm, and placebo. All treatment groups, including placebo, used breath-powered bidirectional devices. As in the Phase 3 trial discussed later, subjects were instructed to treat when migraine was moderate or severe. The Phase 3 trial used only the 20-mg nominal dose, which as noted delivers 16 mg in the nose, so only those data are reviewed.

In the Phase 2 trial, 2-hour pain freedom occurred in 57% of the 20 mg subjects and 25% of the placebo subjects ($P < .05$). Two-hour headache relief, defined as headache moving from moderate to severe down to zero or mild, was quite high and statistically significant at 80% for 20 mg, and 44% for placebo. Both doses statistically separated from placebo for headache relief by 60 minutes. The most frequent treatment-related adverse event was a metallic taste, occurring in 13% of the 20 mg subjects.[9]

The Phase 3 regulatory pivotal study on the BPPSIT 20 mg, the TARGET study, is in press for 2013 in *Headache*.[10] There were 223 subjects randomized who received treatment (112 BPPSIT and 111 device loaded with placebo). The primary outcome measure was 2-hour headache relief, which occurred in 67.6% of subjects in the BPPSIT group vs 45.2% in the placebo group ($P < .01$). For headache relief, BPPSIT reached statistically significant separation from placebo earlier than in the Phase 2 trial, this time at 30 minutes (41.7% vs 26.9%; $P < .05$). Pain freedom at 2 hours occurred with 34% of BPPSIT subjects compared with 17% for placebo ($P < .01$).

Adverse events occurring >5% included abnormal taste (22%), nasal discomfort (13%), and rhinitis (6%). No serious adverse events occurred in the pivotal trial.

DISCUSSION

There are a number of issues worth exploring with the BPPSIT data. These include the difference in efficacy between the Phase 2 and Phase 3 studies, overall efficacy, early response, and the placebo response and therapeutic gain (TG).

The data from Phase 2 were dramatic with about an 80% headache relief mark at 2 hours, but in Phase 3, the 2 hour number was not as high, coming in closer to the high end of the conventional triptan range at around 67%, with the 30 minute number at 42%, notably higher than has been reported with oral treatment and in the range of injectable triptans. This can probably be accounted for simply by the number of subjects, with more than double the number in Phase 3 than Phase 2. There are numerous instances of clinicians revising their evaluation of a medication from Phase 2 to 3 because of differences in outcomes becoming apparent with a greater number of subjects (N). With smaller numbers of subjects, results are more at the mercy of random variation.

However, it is possible that the response rate is indeed higher with BPPSIT, and one possibility is that the device is the reason. That is, perhaps a higher response accrues when sumatriptan is delivered high up in the nose, close to the lateral margins which abut the pterygopalatine canal containing the sphenopalatine ganglion and the maxillary division of the trigeminal nerve. The possibility of a direct triptan effect on these pivotal structures for migraine and cluster might merit further exploration.

Although headache relief at 2 hours has been the standard primary outcome variable for most Phase 3 migraine trials, because it is a single time point it does not provide information on the early effects that are considered by patients to be clinically important. For BPPSIT, the response at 30 minutes ranged between 42% and 49%. This is a high rate of response for this early time point. Data from randomized controlled regulatory trials included in the Food and Drug Administration-approved prescribing information for nearly all approved triptans provide graphics of pooled efficacy data describing headache response. Review of these graphics reveals that for sumatriptan injection the headache response at 30 minutes is in the range of 50%, while 30 minutes pain relief is 10-20% for oral formulations, and between 20 and 30% for conventional nasal spray formulations. These data suggest that BPPSIT early response rates may be closer to those observed with injection than has been reported with other non-parenteral delivery forms.

It is interesting that such a low actual dose of 16 mg could have efficacy approaching injection early on, and comparable efficacy at 2 hours to tablets of 6 times the dose. As a clinician, exposure to lower doses with comparable efficacy is always attractive when contemplating the potential for adverse events.

Further inspecting the BPPSIT Phase 3 trial, the placebo rate seems quite high, at 45.2% for 2-hour headache relief; it was also high at 44% in the Phase 2 trial. In contrast, in Ryan and colleagues' paper summarizing the 2 Phase 3 trials for the conventional sumatriptan liquid nasal spray, the placebo rates for 2-hours headache relief were 29 and 35%.[11] There has been a trend for placebo rates to creep up over time in triptan randomized controlled trials. For example, in the trial used to approve sumatriptan oral tablets, the placebo response rate was 17%.[12] There have been numerous hypotheses to explain the rising placebo response rate, including the absence of triptan naïve patients with accompanying rising patient expectations for triptans, and changing study populations as the background pool of patients is influenced by wide availability of triptans.

In the case of BPPSIT, the device itself may be a cause for the high placebo response rate. Many investigators have noted higher placebo rates in the setting of device trials. As 1 set of investigators noted, "The placebo/nocebo response to sham therapy with a device is similar to that previously reported for prolonged drug treatment."[13] One possibility for the high placebo response rate in the Phase 3 trial was the novelty and use of the device itself.

A technical reason for the high placebo response may be that this Phase 3 trial had a notably low proportion of severe headaches at baseline at 17%, where previous triptan studies typically have shown a higher proportion of severe headaches. Fewer severe relative to moderate baseline scores would be expected to result in higher placebo response given standard scoring scale and analysis methods.

Is it possible that the placebo arm was providing active treatment? The placebo for the BPPSIT trials was treatment with the OPTINOSE device (pressure with carbon dioxide [CO_2] and lactose powder). While one would think that this was a clear sham treatment, in fact there is a literature on the beneficial effects of CO_2 on migraine. Spierings and colleagues found in a preliminary trial available only in abstract form that continuous CO_2 infusion for acute treatment of episodic migraine resulted in 2-hour pain free responses that were highly statistically significant compared with placebo (25.0% vs 4.8%) ($P = .006$).[14]

It turns out that CO_2 is probably part of the pain regulatory system. Vause and colleagues wrote about their findings in cultured rat trigeminal ganglion cells in 2007, "Incubation of primary trigeminal ganglia cultures at pH 6.0 or 5.5 was shown to significantly stimulate calcitonin gene-related peptide (CGRP) release . . . CO_2 treatment of cultures under isohydric conditions . . . significantly repressed the stimulatory effects of KCl, capsaicin, and nitric oxide on CGRP secretion. CO_2 treatment under isohydric conditions resulted in a decrease in . . . capsaicin-mediated increases in intracellular calcium [providing] the first evidence of a unique regulatory mechanism by which CO_2 inhibits sensory nerve activation, and subsequent neuropeptide release. Furthermore, the observed inhibitory effect of CO_2 on CGRP secretion likely involves modulation of calcium channel activity and changes in intracellular pH."[15]

Thus, it is possible the CO_2 "sham" of the BPPSIT may have been delivering partial treatment and is thus not a real placebo response. The fact that both Phase 2 and Phase 3 studies showed high placebo response rates of 44-45% suggests this possibility. However, there is precedent for high placebo rates in novel triptan delivery trials. In the first rizatriptan orally dissolvable tablet trial, the placebo rate was 47%.[16] We do not know the concentrations of CO_2 in the Spierings device to compare with the BPPSIT, and this further limits our opportunity currently to explore this possibility.

Another issue to consider with the BPPSIT Phase 3 data is that of TG, defined as the difference obtained when placebo response is subtracted from active response. The TG in Phase 2 for 2-hour headache relief for 20 mg was 36; in Phase 3, it was 22. This second TG at first seems to be on the low end for a triptan. If one were to choose to use TG across studies (and more on that later), in fact, the 2 BPPSIT TGs would appear comparable to those for sumatriptan liquid nasal spray. The TGs in the 5 trials of conventional sumatriptan liquid nasal spray were 25, 25, 29, 35, and 36.[1,11]

Sheftell and colleagues, including this author, evaluated whether transformation of triptan efficacy data into TG is useful.[17] The intent of TG is to tease out the true drug effect in the face of placebo variation. To our surprise, it turned out that TG correlated more strongly with placebo response than active response. We stated that TG should not be used to compare triptans, and cautioned that migraine therapies can only be compared using well-designed head-to-head studies and not by meta-analysis.

For the purposes of this review, I revisited this issue and compared 2-hour headache relief reported in package inserts by study for active and placebo responses (see the Table and Fig. 2). The theory of TG

Table.—Two-Hour Pain Relief as Reported in Package Inserts

Drug (active dose)/study # in package insert	% Active	% Placebo	Therapeutic gain
Sumatripan (IMITREX, IMIGRAN Tabs) 100 mg Study 1[18]	62	27	35
Sumatriptan (Suma) Tabs (100 mg) Study 2[18]	56	26	30
Suma Tabs (100 mg) Study 3[18]	57	17	40
Suma Injection (6 mg) Study 1[19]	70	21	49
Suma Injection (6 mg) Study 2[19]	81	31	50
Suma Injection (6 mg) Study 3[19]	82	39	43
Suma Nasal Spray (20 mg) Study 1[20]	64	25	19
Suma Nasal Spray (20 mg) Study 2[20]	55	25	30
Suma Nasal Spray (20 mg) Study 3[20]	63	35	28
Suma Nasal Spray (20 mg) Study 4[20]	62	29	33
Suma Nasal Spray (20 mg) Study 5[20]	60	36	24
Eletriptan (RELPAX) (40 mg) Study 1[21]	65	24	41
Eletriptan (Ele) (40 mg) Study 2[21]	62	19	43
Ele (40 mg) Study 3[21]	62	22	40
Ele (40 mg) Study 4[21]	62	40	22
Ele (40 mg) Study 5[21]	54	21	34
Ele (40 mg) Study 6[21]	64	31	33
Ele (40 mg) Study 7[21]	58	30	28
Rizatriptan (MAXALT) (10 mg) Study 1[16]	71	35	36
Rizatriptan (Riza) (10 mg) Study 2[16]	77	37	40
Riza (10 mg) Study 4[16]	67	40	27
Riza orally dissolvable tablet (MLT) [ODT] (10 mg) Study 5[16]	66	47	19
Riza tab ODT 10 mg Study 6[16]	74	28	46
Frovatriptan (FROVA) (2.5 mg) Study 1[22]	42	22	20
Frovatriptan (FRV) (2.5 mg) Study 2[22]	38	25	13
FRV (2.5 mg) Study 3[22]	39	21	18
FRV (2.5 mg) Study 4[22]	46	27	19
FRV (2.5 mg) Study 5[22]	37	23	14
Sumatriptan Naproxen (TREXIMET) Study 1[23]	65	28	37
Sumatriptan Naproxen (TRX) Study 2[23]	57	29	28
Almotriptan (AXERT) (12.5 mg) Study 1[24]	58.5	33.8	24.7
Almotriptan (Almo) (12.5 mg) Study 2[24]	57.1	40.0	17.1
Almo 12.5 mg Study 3[24]	64.9	33.0	31.9
Naratriptan (AMERGE, NARAMIG) 2.5 Study 1[25]	60	34	26
Naratriptan (Nara) (2.5 mg) Study 2[25]	66	27	39
Nara (2.5 mg) Study 3[25]	65	32	33
Zolmitriptan (ZOMIG) Nasal Spray (5 mg)[26]	69	31	38
Zolmitriptan (Zolmi) Tabs (5 mg) Study 1[27]	60	16	44
Zolmi Tabs (5 mg) Study 2[27]	66	19	47
Zolmi Tabs (5 mg) Study 3[27]	67	34	28
Zolmi Tabs (5 mg) Study 4[27]	59	44	15
Zolmi ODT (ZMT) (2.5 mg) Study 6[27]	63	22	41
Sumatriptan (OPTINOSE) Study 1[9]	80	44	36
Breath-powered powder sumatriptan intranasal treatment (BPPSIT) Study 2[10]	68	45	23

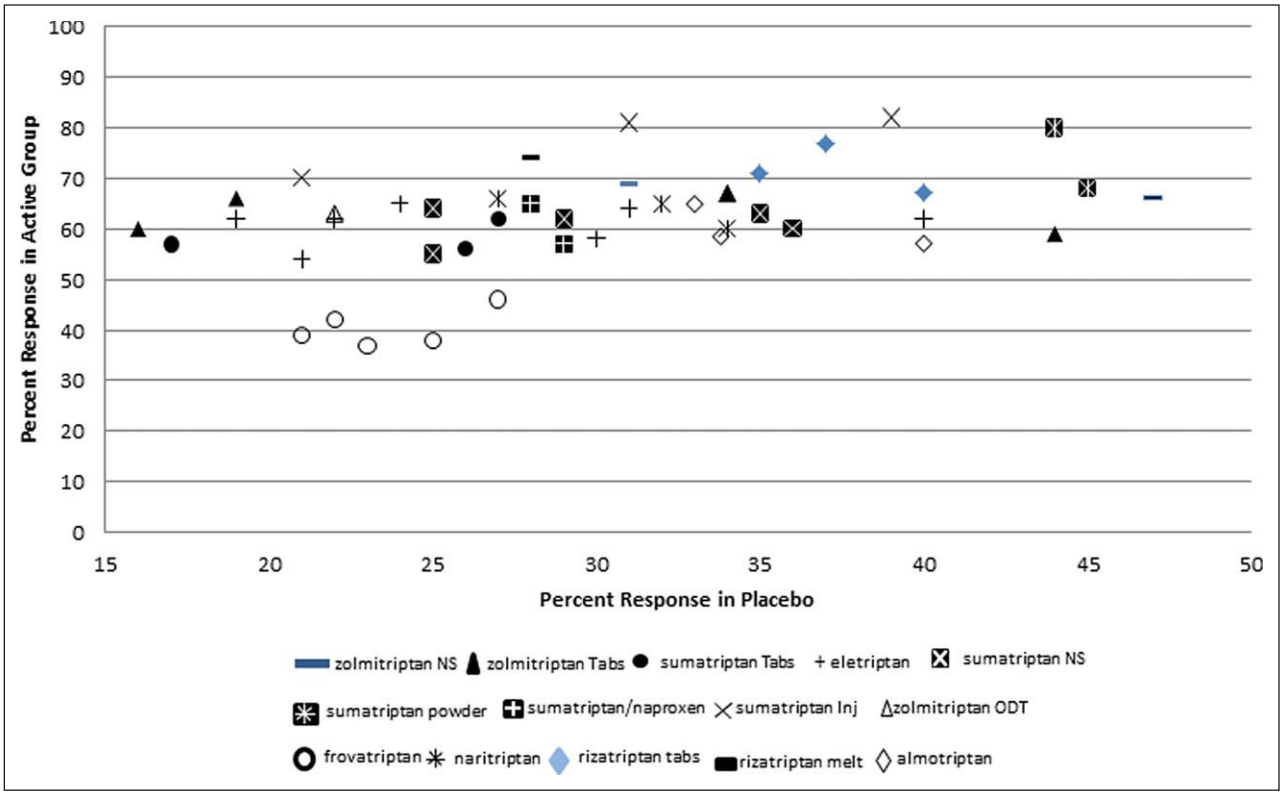

Fig 2.—Two-hour pain response rates reported in package inserts by study for active and placebo. References for Figure 2 can be found in Figure 1.

is that the active to placebo response rates should be positively correlated, better than an active-to-active correlation. The response observed with active treatment must rise and fall commensurately with the observed placebo response rate in order for TG to be a useful concept in interpretation of migraine trials.

However, perhaps unlike other applications of the TG concept, it is clear that placebo response rate is widely variable but has little or no impact on the active response rate. Data across the class of triptans show that there is large variability in placebo response between studies of a given drug, seen in Figure 2 on the *X* axis. There is much less variability in the active response rate for a given active treatment between studies, seen as a relatively flat line on the *Y* axis in Figure 2 across the placebo rates. There is no observable correlation between the response observed in placebo and active groups. For the studies pulled, the active : placebo $R^2 = 0.02$.

Active response rates are a superior reflection of true treatment effect than TG, which appears to not be a useful concept in migraine, but as stated in 2001, well-designed head-to-head studies remain the standard for comparison. As noted earlier, it may be fair to say that the headache relief rates for the BPPSIT appear in line with other triptan therapy historically at 2 hours, and possibly approaching historically reported response rates with injectable sumatriptan at 30 minutes. This fast onset may be important to patients, particularly those with a need for rapid onset as discussed earlier. And to repeat, it is notable that this response is achieved with such a low delivered dose at 16 mg. Again, this suggests the potential for desirable safety or tolerability compared with higher dose treatment, but also underscores interesting questions about the possible contributions to efficacy of a unique activity of the device or drug in the nasal cavity.

CONCLUSIONS

The acute treatment of migraine requires matching individual patient need to drug and formulation.

In particular, nausea and vomiting, quick time to peak intensity, and indeed the common gastroparesis of migraineurs, all call for a variety of non-oral formulations for treatment of attacks. As triptans go generic, attempts to use them in new formulations progress; this is old wine in new bottles. A novel BPPSIT offers an improvement, at the very least in pharmacokinetics, over conventional liquid nasal sumatriptan spray.

The device used for drug delivery in this breath-powered nasal sumatriptan uses natural nose anatomy to close the soft palate and propel the low-dose powder sumatriptan high up in the nasal cavity on one side. This approach may reduce adverse events and improve efficacy. A study is underway at the time of this writing to compare the novel system to conventional sumatriptan tablets head-to-head.

It is certainly a worthwhile endeavor to create new delivery systems for known effective migraine medications. The clinical role for a fast acting non-oral nasal formulation will be, as noted, in those for whom tablets are bound to fail, that is, in the setting of nausea and vomiting or when the time to central sensitization, allodynia, and disabling migraine is too short for the patient to respond to a tablet, given the unpredictable and slower absorption profile of oral medications. Further studies should elucidate whether this novel system affords the predicted benefits clinically in speed of onset and effectiveness, with reduced adverse events compared with earlier non-oral formulations.

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