Opinion

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Do the Endpoints Used in Most Migraine Clinical Trials Adequately Reflect Patients' Desire for Rapid, Complete, and Sustained Relief of Their Attacks?

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For more than 20 years, migraine patients have rated rapid onset of action, freedom from headache pain, and no attack recurrence among the most important outcomes of acute treatment [1-5]. In line with these insights, as well as the consensus among migraine specialists that freedom from pain before use of rescue medication is clinically relevant and reflects patients' expectations [3,5,6], pain-free at 2 hours post-dose has replaced headache response as the primary measure of efficacy in acute migraine treatment studies [4]. Although this has taken the migraine bench a sensible step closer to the bedside, do the migraine endpoints currently used in most clinical trials adequately reflect patients' expectations of acute therapy?

Two-hour pain freedom remains an important clinical and research outcome [6]. However, an analysis of the relationship between migraine endpoints and satisfaction found that while more than 90% of patients who were pain-free at 2 hours were at least somewhat satisfied with treatment, their satisfaction was dependent on relatively rapid relief [3]. Given the chance to define their own outcome measures, migraineurs report that they want their medication to treat their pain within 30 min [4]. Guidelines for controlled trials nod to this clinical reality by recommending that investigators consider pain freedom at time points earlier than 2 hours post-dose for parenteral drugs [6]. With the development of novel methods of administration, new formulations, and triptan combination therapies that are designed to hasten migraine drug absorption [7,8] perhaps the advice to emphasize earlier pain-free assessments should also apply to "fast-acting" reformulations of established drugs.

Medications with shorter times to maximum plasma concentration (t_{max}) provide faster pain relief. For example, in showing that a 3 mg SC dose of sumatriptan delivered via auto injector (Zembrace™ SymTouch™, Promius Pharma, LLC, Princeton, NJ, USA) provides relief of migraine pain and associated symptoms comparable to a 6 mg SC dose of sumatriptan, Cady et al. also noted that half of the study's subjects experienced headache response within 30 min and complete pain relief by 60 min [9]. Munjal and colleagues, comparing a novel intranasal spray containing sumatriptan 10 mg and a permeation enhancer with 4 mg and 6 mg SC sumatriptan, reported a median t_{max} for the intranasal spray (10 min) that was significantly earlier than the 4 mg and 6 mg SC injection (15 min; $P<0.0001$) [10]. If triptans, nonsteroidal anti-inflammatory drugs, and other reformulations that can shorten the t_{max} to 30-45 min can be designated as "fast-acting", it seems reasonable to propose that clinical trials involving them should use pain-free at 1 hour post-dose as a primary endpoint. The more exacting endpoint will provide a more nuanced appreciation of efficacy that better aligns with patient expectations of acute migraine treatment.

In addition to a rapid onset of action, for most migraine patients, avoiding recurrence of symptoms for at least 24 hours is clearly important and may be an even higher priority to improve current treatments [4,11]. Unfortunately, sustained pain freedom—the percentage of study participants who are pain-free at 2 hours with no use of rescue medication or recurrence within the subsequent 22 hours—is not often used as a key secondary efficacy endpoint. Yet sustained pain freedom is a guidelines-recommended secondary efficacy measure that has been described as the ideal migraine treatment response and the ultimate goal in drug development [6]. Held in high regard by policymakers and patients alike, its wider use in clinical trials should be encouraged.

Despite major improvements in acute treatment since migraine patients started telling researchers what they want out of therapy, unmet needs remain. Among the most important is that currently available treatments still tend to work too slowly and do not last long enough. Changing the way acute medications are evaluated may be the best way to accommodate patient expectations and meet the twin goals of rapid pain relief and sustained therapeutic effect.

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