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Assessing Clinically Meaningful Treatment Effects in Controlled Trials: Chronic Migraine as an Example

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Abstract: In addition to headache, persons with chronic migraine (CM) experience multiple symptoms, both ictal and interictal, that may contribute to their suffering. Translating clinical trial results into practice requires assessment of the results' clinical meaningfulness. When examining treatment benefit in this disabled patient population, multiple headache-symptom measures should be considered to fully reflect clinical relevance. Currently, only onabotulinumtoxinA is approved specifically for headache prophylaxis in adults with CM. Topiramate is the only other therapeutic agent with double-blind, placebo-controlled evidence in this population. Herein we evaluate the clinical meaningfulness of onabotulinumtoxinA and topiramate as headache prophylaxis in CM by comparing primary endpoints from the placebo-controlled, double-blind phase of the Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program and the topiramate clinical trial (frequency of headache days [primary endpoint in PREEMPT; secondary in topiramate trial] and migraine/migrainous days [primary in topiramate trial, or "migraine/probable-migraine days"; secondary in

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PREEMPT]). Additionally, outcome measures such as responder rates, health-related quality of life, discontinuation rates, safety, and tolerability profiles are important clinical considerations. The clinical data indicate that statistically significant, clinically relevant treatment benefits exist for both onabotulinumtoxinA and topiramate. These data support these treatments as meaningful headache prophylaxis in adults with CM.

***Perspective:** CM is a chronic pain condition. We sought to determine the clinical relevance of recent trials in this disabled population. Clinical data indicate that statistically significant, clinically relevant treatment benefits exist for both onabotulinumtoxinA and topiramate, and support use of these treatments as meaningful headache prophylaxis in CM.*

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***Key words:** Chronic migraine, onabotulinumtoxinA, topiramate, prophylactic treatment, clinical meaningfulness.*

Chronic migraine (CM) is a severely disabling neurologic disorder with profound effects on productivity and health-related quality of life (HRQoL).[7] CM is currently defined as headache on ≥15 days per month for >3 months, of which ≥8 days have features of migraine headache.[34] Patients with CM suffer not only from the frequency, duration, and severity of headache and associated neurologic symptoms but also from multiple other dimensions that result in headache-related disability and impairment in headache-specific quality of life. Frequently, CM is associated with other pain conditions and comorbidities.[27,36,50] CM patients often seek care from pain specialists.[7] When examining treatment benefit of new agents for CM, it is valuable to examine all available scientific evidence of efficacy rather than focusing on a single efficacy dimension that may not fully reflect the clinical relevance of the outcome (ie, having a positive and meaningful impact on the patient's life).[22]

The use of all evidence to evaluate the clinical importance or meaningfulness of observed changes in outcome measures is particularly crucial in the study of chronic pain conditions, such as CM, in which 1) self-reported outcomes are inherently subjective; 2) improvements in physical and emotional functioning are often as important to patients as the actual diminution of pain; 3) results are frequently confounded by the use of rescue or concomitant pain treatments; and 4) placebo responses are often high.[19,22] Also, efficacy results usually are focused on evaluating a drug's mean benefit across a population. However, of equal or greater importance is the translation of mean changes in terms that better describe the effects for individual patients. Distribution of effects across the population is thus also very helpful to evaluate.[20]

A systematic method for interpreting the clinical importance (meaningfulness) of group differences in chronic pain studies has been recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), a consortium of participants from academia, government drug regulatory agencies, self-help groups, and the pharmaceutical industry who work to develop ways to improve the study of chronic pain conditions.[22] IMMPACT recommends that when evaluating the clinical meaningfulness of a treatment benefit, statistically significant group differences in a primary efficacy endpoint cannot be considered in isolation, as this may obscure meaningful individual patient improvements and other benefits and risks. Rather, the overall body of evidence with regard to outcomes must be considered to fully understand therapeutic benefit.[22] We have used an adaptation of the framework suggested by IMMPACT for evaluating clinical meaningfulness of treatment outcomes in chronic pain studies (Table 1).

Herein, we examine the clinical meaningfulness of both onabotulinumtoxinA and topiramate in the preventive treatment of CM in adults, focusing on the large Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program[4,19] and the phase IV topiramate CM study.[43] The totality of the evidence as well as minimally important difference (MID; ie, the difference demonstrated to be clinically meaningful to patients) for any headache-symptom measures are discussed. Although our focus is on large studies, which requires that we make indirect comparisons across studies, we also review the limited data directly comparing onabotulinumtoxinA with topiramate in the preventive treatment of CM.

Table 1. Adapted IMMPACT Framework for Evaluating Clinical Meaningfulness of Treatment Outcomes[22]

Category	Content
Efficacy	A. Headache symptom measures: statistical significance vs placebo
	B. Headache symptom measures: magnitude of improvement (individual patient benefit)
	C. Headache symptom measures: Responder analyses
	D. HRQoL measures
Safety	A. Safety and tolerability
Other	A. Treatment effect size compared to available treatments
	B. Rapidity of onset and duration of treatment benefit
	C. Convenience and patient adherence to treatment
	D. Uniqueness of mechanism of action
	E. Drug-drug interactions
	F. Limitations of oral prophylaxis treatments

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