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COMMENTARY

Interpreting Effect Sizes and Clinical Relevance of Pharmacological Interventions for Fibromyalgia

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ABSTRACT

Duloxetine, milnacipran, and pregabalin are approved by the United States Food and Drug Administration for the management of fibromyalgia. A number of meta-analyses, pooled analyses, and systematic reviews have been published in recent years involving the efficacy of these three medications for pain in fibromyalgia. Despite being based on the same clinical data, some analyses found these treatments to have a clinically relevant effect on pain, while others concluded that the advantages were small or of questionable clinical relevance. This commentary discussed possible reasons behind these differing conclusions and explored ways of evaluating the clinical relevance of pharmacological treatments for fibromyalgia. In particular, we considered: (1) the importance of judicious and careful interpretation of average treatment effect size and the recognition that average treatment effect sizes do not always tell the whole story; (2) the utility of individual patient response data to assess clinical relevance; and (3) the importance of considering pain reduction within the context of other benefits due to the presence of associated symptoms in patients with fibromyalgia.

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INTRODUCTION

Fibromyalgia (FM) is a common chronic pain condition with multiple associated symptom

domains. While FM is diagnosed based on the presence of chronic pain and tenderness [1], patients also frequently experience other symptoms, including fatigue, poor sleep, anxiety, and depression [2]. Three medications (duloxetine [3], milnacipran [4], and pregabalin [5]) have been approved by the United States Food and Drug Administration (FDA) for the management of FM. Several well-controlled, high-quality clinical trials have demonstrated the efficacy of these treatments for the management of FM [6–18]. A number of meta-analyses, pooled analyses, and systematic reviews of pharmacological interventions for FM have been published in recent years [19–35]. However, these analyses have not always reached the same conclusions regarding the clinical meaningfulness of trial results, despite often involving data from the same studies. This is likely due, in part, to differences in how a clinically meaningful result was defined, as there is no definitive definition of what constitutes a clinically relevant or meaningful improvement in symptoms in FM.

In this commentary, we highlight some key points we believe should be considered when determining the clinical relevance of pharmacological treatments for FM: (1) the importance of judicious and careful interpretation of average treatment effect size and the recognition that average treatment effect sizes do not always tell the whole story; (2) the utility of individual patient response data to assess clinical relevance; and (3) the importance of considering pain reduction within the context of other benefits due to the presence of associated symptoms in patients with FM.

USE OF AVERAGE TREATMENT EFFECT SIZE TO DETERMINE CLINICAL RELEVANCE

Average treatment effect sizes have been used by several meta-analyses and systematic reviews [19, 23, 27, 32, 34] to evaluate the efficacy of interventions for FM based on thresholds defined by Cohen, which categorize effect sizes as small [standardized mean difference (SMD) of 0.2], medium (SMD of 0.5), and large (SMD of 0.8) [36] (SMD is the difference in means between active and control groups divided by their pooled standard deviation). Among these is a recent analysis by Nuesch et al. [19], the most comprehensive meta-analysis of pharmacological and non-pharmacological interventions for FM published to date. Nuesch et al. concluded that current evidence best supports the use of serotonin-norepinephrine reuptake inhibitors (SNRIs; specifically, duloxetine or milnacipran) or pregabalin in combination with non-pharmacological therapies as treatment for FM, an approach supported by recent guidelines and recommendations for FM management [37–39]. However, regarding the efficacy of individual interventions for FM, Nuesch et al. [19] remarked that the "benefits for SNRIs and pregabalin compared with placebo were statistically significant but small and not clinically relevant".

While the observed effect sizes of FM medications were not large according to Cohen's classification [36], we question whether use of these categories as a stand-alone gauge of clinical meaningfulness is appropriate, since they are based solely on statistical distributions and not on clinical

criteria per se. Categorization of effect sizes can help to summarize the signal-to-noise magnitude of therapeutic effects; however, we believe more can be done to assess fully the therapeutic benefit to patients. Many approved treatments are expected to have average effect sizes in the small-to-moderate range, which explains why larger sample sizes are needed in clinical trials, but that is not to say that treatment effects are not clinically significant. It is important to consider, for example, that average treatment effect sizes do not fully characterize the spectrum of treatment responses observed in chronic pain patients. It is also worthwhile to distinguish between responders and non-responders by evaluating individual patient data, based on predefined thresholds that are relevant to the condition [20, 29, 40, 41].

IMMPACT RECOMMENDATIONS AND USE OF PATIENT RESPONSE THRESHOLDS TO DETERMINE CLINICAL RELEVANCE

The initiative on methods, measurement, and pain assessment in clinical trials (IMMPACT) has recommended classifying pain responses in chronic pain patients as minimally important (10–20% pain reduction from baseline), moderately important (≥30%), and substantial (≥50%), based on three chronic pain studies that assessed changes in pain scores (on a numerical rating scale from 0 to 10) along with patient impressions of overall improvement [42]. A threshold of 30% change from baseline in the Brief Pain Inventory average pain and severity scores has been confirmed in a recent study as a minimally clinically relevant response in an FM population [43]. Responder analysis is a useful way to complement and supplement an analysis based on means, and has been recommended by regulatory bodies as a way to establish clinically relevant benefits [44, 45]. Responder analysis can also be extended to show the cumulative proportion of responders and of all patients over a range of possible cutoff points [44, 46, 47], further enhancing the interpretation of patient responses.

Several meta-analyses and pooled analyses of clinical trials of the FDA-approved FM medications have used the IMMPACT ≥30% threshold to define a clinically relevant response [20, 24–26, 29, 30, 33–35]. These analyses have estimated response rates (≥30% improvement in pain score) of up to 49% for 60–120 mg/day duloxetine (compared with up to 32% for placebo) [26, 33, 35], up to 61% for 100–200 mg/day milnacipran (compared with up to 36% for placebo) [20, 24], and up to 43% for 150–450 mg/day pregabalin (compared with up to 29% for placebo) [25, 29, 30, 34]. These data indicate that a substantial proportion of patients experience a clinically meaningful response to active treatment of pain associated with FM. Even after accounting for a placebo effect, differences in responder rates between active and placebo treatments are noteworthy.

ADDITIONAL BENEFITS

Patients with FM identify several symptoms in addition to chronic pain that have a negative impact on their quality of life, including sleep disturbance, fatigue, depression, anxiety, and cognitive impairment [48]. A recent analysis of FM responder definitions suggested that inclusion of assessments of symptom and functional domains in addition to pain could significantly improve the ability of clinical trials to identify clinically meaningful improvements [49]. In addition, improvements in fatigue,

physical function, and sleep, as well as pain, have individually been shown to correlate well with improvements on the patient global impression of change scale [24, 49–51], which provides an indication of overall patient improvement.

Duloxetine, milnacipran, and pregabalin have been shown to have positive effects not only on pain but also on secondary symptom domains of FM [27]. Specifically, duloxetine was shown to be effective for sleep disturbance, depressed mood, and health-related quality of life (HR-QoL); milnacipran for fatigue, depressed mood, and HR-QoL; and pregabalin for fatigue, sleep disturbance, and HR-QoL. Pregabalin-mediated pain relief has also been shown to reduce the number of work days lost by FM patients by more than 1 day per week [52]. We suggest that all potential effects of an intervention, benefits, and harms, should be considered when evaluating the net clinical benefit, particularly for a condition such as FM. This assessment should also take into account the potential for adverse events, contraindications, and patient comorbid conditions. The most common adverse reactions to these medications (occurring in at least 5% of treated patients and at least twice the incidence of placebo patients) are nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis for duloxetine [3]; nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, increased heart rate, dry mouth, and hypertension for milnacipran [4]; and dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and abnormal thinking (primarily difficulty with concentration or attention) for pregabalin [5]. All three medications were generally well tolerated in clinical trials of patients with FM, with the majority of patients successfully completing the trials [3–5].

CONCLUSIONS AND FUTURE PERSPECTIVES

It is important for clinicians and patients with FM to have a realistic idea of the potential net clinical benefit of pharmacological FM treatments. Clinical trials and meta-analyses of FM treatments should evaluate not only the statistical significance of a study outcome, but also its clinical significance. Studies should attempt to clearly define, when possible, a clinically important change for key measures at their outset, and examine patient-level responses in addition to average treatment effects in order to enhance the clinical interpretation of treatment benefit. The fact that standards and practices in evidence-based health care depend on conversion from the research to clinical setting should not be underestimated. Finally, it is important to consider the benefits of treatments for FM beyond their effect on pain, taking into account their effects on other related comorbidities and symptoms, and overall patient function and quality of life.

This commentary has focused on pharmacological interventions for FM; however, several studies have showed the positive effects of non-pharmacological interventions, including exercise [53], hydrotherapy [54], and cognitive-behavioral therapy [55]. Multi-modal treatment, including at least one educational treatment and one exercise therapy, has also been shown to have short-term benefits [56]. While it may not be feasible for trials of non-pharmacological therapies to achieve the same high methodological and regulatory standards as trials of pharmacological therapies (for instance, in exercise trials it is not possible to blind participants to their treatment), we believe that the points raised in this commentary could be

also worthy of consideration for trials of non-pharmacological interventions.

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