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Relative Efficacy of Knee OA Treatments: Are All Placebos Born Equal?

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Almost 40% of the U.S. population over 45 years of age has some degree of knee osteoarthritis, and the estimated lifetime risk of developing knee OA is 14%. [1] This number is likely to rise even further.. Obesity is skyrocketing, with an estimated additional **65 million** obese U.S. adults by 2030.[2] Greater participation in sports has led to high rates of anterior cruciate ligament rupture, up to *half* of which will develop symptomatic knee OA.[3] And most significantly, the US population is aging, with at least **92 million** over 65 by 2060.

This increased prevalence of knee OA will lead to significant numbers of people living with chronic pain. To improve quality of life and minimize disability, these patients will need effective pain control. However, it is not necessarily clear which therapies work best. One reason for therapeutic uncertainly is over half of OA pain studies and >80% of those funded by industry are of less than 6 months duration [4]. OA is a chronic disease, and results from short RCTs may not necessarily reflect long-term responses. Another challenge is that most recommended treatment algorythms start with targeting elements of the peripheral nociceptive nervous system and/or decreasing inflammation. However, the peripheral nociceptive/ inflammatory model is an incomplete explanation for chronic OA pain. Central sensitization, “an amplification of the neural signaling within the CNS that elicits pain hypersensitivity” is clearly an important component of OA pain, explaining why medications such as duloxetine, which work via centrally mediated analgesic mechanisms, are effective treatments for knee OA.[5]

The complexity of chronic OA pain makes clinical research challenging, as patients with knee OA are likely extremely diverse in terms of their pain pathophysiology, despite a similar radiographic phenotype. This heterogeneity may also explain the discordance between results from well-executed randomized clinical trials, often with stringent inclusion criteria, and the choices patients make in the real world. For example, despite decades of research, the use of intra-articular hyaluronan remains extremely controversial. A recent meta-analysis and systematic review concluded that “in patients with knee osteoarthritis, viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events.” [6] There is similar disagreement about glucosamine and/or chondroitin sulphate. The American Board of Internal Medicine, along with the American Academy of Orthopedic Surgeons, state as part of their “Choose Wisely” campaign that glucosamine and chondroitin sulfate supplements do not work and are no better than placebo.[7] Regardless, patients continue to demand these therapies. The global

viscosupplementation market is estimated to be $2.5 billion by 2017, and the market for glucosamine $12 billion by 2020. [89]

Why this dichotomy? Perhaps despite our best efforts, patients with knee OA who enroll in RCT's are simply not representative of real world patients. Perhaps comparing interventions for OA pain to placebo-the gold standard for proving efficacy-fails to fully incorporate effects on centrally mediated pain, which may be similar between study arms. Or perhaps, as suggested by the study by Bannaru and colleagues in this edition of Annals, all placebos are not created equal. [10]

Bannaru and colleagues present results from a network meta-analysis that evaluates which treatments work best for knee OA. A network meta-analysis allows investigators to quantify the relative effectiveness of common treatments as compared to each other, as well as to placebo, which offers a good metric for establishing relative efficacy. This is a useful approach-particularly when it is unlikely that large trials comparing multiple interventions will ever be undertaken- as it allows the comparison of results across many different studies, increasing the variety of patients contributing data. This network meta-analysis highlights some previously seen effects and also reveals some surprising findings. Acetaminophen, often recommended as first line of treatment for knee OA, had the lowest effect size compared to oral placebo, (0.18; 95% CI 0.04- 0.33). Intra articular hyaluronan had the highest effect size, (0.63; 95% CI 0.39-0.88), almost one and a half times that of naproxen, (0.38; 95% CI 0.27- 0.49)The authors hypothesize that the strong showing for injectable therapies may reflect an integrated intra-articular placebo effect; in fact, they showed that intra-articular placebo had an effect size of 0.29; 95% CI 0.04, 0.54) compared to oral placebo. This effect of mode of placebo delivery cannot be identified in traditional meta-analyses, and may be relevant to real world clinical decision-making.

An important limitation is that these efficacy estimates are calculated over a short time period. The crucial question yet to be addressed is the durability of these treatments in individual patients. In addition, the principle of indirect comparisons is based on an assumption of consistency -which implies that all studies drew samples from the same underlying population and that samples were unbiased and representative. This is a difficult assumption to prove. A call for open access to data collected in RCTs may help the researchers conducting network meta-analyses confirm such assumptions. It is also often the case that metrics used to delineate standardized differences do not necessarily have a clear clinical interpretation. It is important that data from network meta-analyses are presented in meaningful formats that are accessible to both patients and treating physicians.

With the dramatic rise in prevalence of knee OA, it will become increasingly important to create novel, innovative research models to better understand how to optimize pain control, as well as to provide a roadmap for a rational approach to effective treatment. Research methodologies need to be designed with an understanding of the pathophysiology of OA pain, including both peripheral nociceptive/ inflammatory triggers as well as central sensitization. A clear understanding of the role of placebo, pain pathophysiology, and patient preferences should be key factors facilitating shared decision making in treating patients

with knee OA. Sophisticated analytic syntheses of existing evidence, such as presented in the paper by Bannaru et al, will help ensure patients receive the pain relief they deserve.

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