IDENTIFYING PREDICTORS OF PLACEBO RESPONSE IN OSTEOARTHRITIS CLINICAL TRIALS OF THREE AGENTS WITH DIFFERENT ROUTES OF DELIVERY: A META-ANALYSIS USING INDIVIDUAL PATIENT DATA.

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Background

Most drug treatments for osteoarthritis (OA) do not achieve a minimum clinically important difference above placebo and often associate with side-effects. On average, 75% of the analgesic effect from OA treatments in clinical trials, and potentially in clinical practice, can be attributed to placebo/contextual response, though the magnitude of this response may vary greatly between patients. We undertook this individual patient data (IPD) meta-analysis of three contrasting treatments for OA to identify placebo responders and the potential determinants of the placebo response in OA.

Methods

This study is undertaken in conjunction with the OA Trial Bank, an ongoing international consortium collecting IPD from randomised controlled trials (RCTs) for treatments of OA. Placebo-controlled RCTs for intra-articular (IA) corticosteroid injections, oral glucosamine tablets, and topical non-steroidal anti-inflammatory drugs (NSAID) have been systematically searched for and authors contacted to request the IPD.

Outcomes -The primary outcome measure for placebo response was maximum pain reduction over the duration of follow-up (1-119 weeks). Potential predictors and covariates available were intervention type, radiographic Kellgren and Lawrence (KL) score, sex, age, body mass index (BMI), duration of OA (years) and study joint.

Data Analysis – Pain was measured using different scales across trials and was normalised into a 0-100 scale for analysis. Maximum pain reduction was identified for each participant. Participants who achieved clinically important pain relief, defined as ≥20% reduction in pain score from baseline, were classified as responders.

A one-stage IPD meta-analysis was used to analyse all studies simultaneously whilst accounting for heterogeneity across studies. A multilevel mixed-effects linear regression model was fitted. Maximum change from baseline pain score was the dependent variable, whereas baseline pain, age, sex, BMI and other potential predictors were independent variables. Univariate analysis was used to select significant predictors. Significant predictors were then examined in a multivariate model to confirm the results.

Results

Characteristics of study population

Eighteen out of 19 identified trials provided IPD for this analysis. Data on 2,305 placebo participants were available for analysis. Of these studies, 4 trials (n=674 participants) used placebo tablets, 3 trials (n=78) used IA placebo injection and 11 trials (n=1,553) used topical placebo. Thirteen studies (n=1,764) included participants with knee OA, three (n=158) included participants with hip OA, and two (n=383) included participants with hand OA.

Placebo response

75% of participants reported ≥20% pain reduction from baseline. The mean age was 61.94 years (95% CI 61.45 to 62.43) for responders and 61.85 (95% CI 61.00 to 62.70) for non-responders. The response rate in females was 75% and males 75%. The mean BMI was 30.05 (95% CI 29.73 to 30.38) for responders and 29.69 (95% CI 29.18 to 30.20) for non-responders. Absolute pain reduction with placebo was significant with an overall effect size of 25.97 (95% CI 20.39 to 31.55) on the 0-100 scale.

Predictors of placebo responders

In univariate analysis there was no difference in placebo response between men and women, nor according to age, route of delivery, or severity of structural OA (KL score). However, baseline pain, duration of OA symptoms and BMI were significantly associated with the overall change in pain score. In the subsequent multivariate model, these three predictors remained significant, with the effect of BMI being reversed **(Table 1).**

Table 1. Predictors of placebo response

	Univariate				Multivariate*	
	Number of studies	**Number of patients**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
Baseline Pain (0-100)	18	2248	0.64 (0.59,0.69)	0.000	0.65 (0.58,071)	0.000
BMI (kg/m2)	16	2174	0.016 (0.01,0.31)	0.040	-0.26 (-0.47,-0.05)	0.018
Duration of OA (years)	9	772	-1.13 (-2.20,-0.06)	0.039	-0.98 (-1.88,-0.09)	0.031

*__7 studies and 703 participants involved in multivariate analysis__

Conclusion

This IPD meta-analysis demonstrates that people with higher baseline pain and shorter duration of symptoms may be more likely to respond to placebo in OA but the direct effect of BMI remains uncertain. Interestingly, the route of delivery had no effect in contrast to the conclusions of previous studies. The findings of this study can be used to stratify study participants into subgroups based on their likely response to placebo and to improve the design of RCTs in order to develop a novel treatment that is truly better than placebo.

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