Dr. Makris, *et al*, reply

To the Editor:

We appreciate the interest in our article[1] on the safety of topical nonsteroidal antiinflammatory drugs (NSAID) in older adults with osteoarthritis (OA). Based on our comprehensive review of the literature (from 1950 through November 2009), we concluded that topical NSAID users do report non-life-threatening gastrointestinal (GI) adverse effects, a greater number of application site reactions, and, importantly, fewer serious GI adverse effects as compared with users of oral NSAID. Altman identifies 2 randomized controlled trials[2,3] and 2 meeting abstracts[4,5] that have been published and presented since we conducted our review of the literature.

The 4 referenced studies evaluated the safety and efficacy of topical diclofenac sodium 1% gel (DSG) versus placebo vehicle for the treatment of OA. Both published reports[2,3] were 12-week randomized, double-blind, vehicle-controlled trials evaluating adults aged ≥ 35 years with symptomatic knee OA. Both studies reported that application site dermatitis was more common with DSG than with vehicle: 4.3% versus 1.7%[3] and 5.8% versus 0[2]. As indicated in Altman's letter, both RCT reported a similar range of GI adverse effects (none serious) between DSG and vehicle. Lastly, the range of participants who discontinued the medication due to adverse effects was 5.1%–6.7% in the DSG arm and 1.4%–3.8% in the vehicle arm[2,3]. These RCT provide us with additional data about the safety of DSG compared to placebo vehicle, and suggest that DSG has fewer application site reactions and a lower withdrawal rate due to adverse effects than another topical NSAID preparation, diclofenac sodium in dimethyl sulfoxide solution (D-DMSO). The RCT do not, however, provide direct evidence of efficacy or safety of topical compared with oral NSAID.

The abstract that was available for review[5] used a post-hoc analysis of pooled data from 3 similar 12-week, randomized, double-blind, parallel-group, multicenter trials to evaluate the safety of DSG versus placebo vehicle in patients (age ≥ 35 years) with symptomatic knee OA and comorbidities (hypertension, diabetes, and cardiovascular disease). This abstract would not have qualified for inclusion into our systematic review as there was no mention of age distribution (specifically, mean age ≥ 60 years). Based on pooled data, application site dermatitis was again reported more frequently in the DSG arm (5.1%) compared with the vehicle arm (0.6%). GI adverse effects were not listed in the table for "most frequent treatment emergent adverse effects (occurring in ≥ 3% of randomized patients in either group)." The higher rate of discontinuations due to adverse effects with DSG (5.4%) compared with vehicle (2.6%) was attributed to the higher rate of discontinuations due to application site reactions with DSG than with vehicle. The other referenced abstract[4] was not available for review.

Our systematic review focused on the safety of topical NSAID; however, efficacy of the medication must be weighed against potential adverse effects when making a therapeutic recommendation. Altman highlights the Osteoarthritis Research Society International guidelines[6] that list a pooled effect size for pain relief of knee and hip OA of 0.29 and 0.44 for oral and topical NSAID, respectively. Efficacy effect sizes of only the high quality trials (Jadad = 5) for oral and topical NSAID are listed as 0.39 and 0.42, respectively. Lin and colleagues[7] presented a funnel plot with significant asymmetry in the 11 RCT comparing topical NSAID to placebo; this was corroborated by Zhang and colleagues[6] using 3 additional RCT. As suggested by these authors, the superior effect size of topical NSAID is likely overestimated due to publication bias from an underreporting of negative studies[6,7]. Based on the current literature, topical NSAID are comparable to or somewhat less effective than their oral counterparts. Despite this, prior studies have shown that older adults with OA may prefer safer medications even if they are less effective[8].

It is clear that topical NSAID users report fewer serious GI adverse effects; however, they do report more application site reactions as compared with those who use oral NSAID. It is the responsibility of the healthcare provider to discuss the risks and benefits of these treatment options with older patients, since non-life-threatening systemic adverse effects and application site reactions do occur with topical NSAID, and contribute to the tolerability and compliance of this alternative treatment option.

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