Letter to the Editor

To the Editor:

We have read with interest the study published by Novotna et al,[1] which was an intrapatient, randomized trial that compared a new sublingual fentanyl formulation to placebo in cancer-related breakthrough pain. Initially, there was an open-label titration phase to response, followed by a randomized phase in which patients (in a blinded manner) took either fentanyl (6 tablets) or placebo (3 tablets) for moderate to severe breakthrough pain. The investigators stated that the trial was consistent with the ethical principles of the Declaration of Helsinki. The results demonstrated that fentanyl was better than placebo, and by response analysis, the number needed to treat ranged between 5 and 15, depending on the definition of *response* and on the timeframe.

We have several ethical difficulties with this trial design. In general, a comparator in a trial should be the standard of care. There are no guidelines that recommend placebo, and all guidelines recommend either immediate-release opioids or rapid-acting fentanyl. Published guidelines recommend immediate-release morphine, oxycodone, transmucosal fentanyl, or intranasal fentanyl.[2–8] The open-label titration phase of the trial is an enrichment-enrollment design that highly biases the study toward response by eliminating from the study all patients who failed to respond to the open-label titration. This method violates the principle of intent-to-treat analysis. Comparison to placebo does not have clinical utility because placebo is not the standard of practice (it is below the standard of care) and largely biases the trial to be a positive drug trial. The proper comparator should involve recommended short-acting potent opioids and best practices per guidelines. It is difficult for us to understand why investigators would knowingly provide placebo and allow patients to experience pain, particularly with the large number of randomized fentanyl trials published have demonstrated benefit.[9] This is analogous to treating Stage II breast cancer after local therapy, randomizing individuals to therapy or no therapy when present-day evidence has abundantly established therapeutic benefits for adjuvant breast cancer therapy (though placebo in breakthrough-pain trials does not have the same potential fatal outcome). It is time to change this approach to breakthrough-pain trials of analgesics. Trials of analgesics should at least be consistent with the standard of care and stay within the framework of best practices. These trials should also prospectively look at the cost efficiency and efficacy of fentanyl relative to those of immediate-release morphine and oxycodone, which have been for the most part ignored in trials of rapid-acting fentanyl.[10] Studies of these agents should require measurements of adverse events potentially resulting from the rapid delivery of lipid-soluble opioid to the brain, which include addiction, falls or other accidents, and neurocognitive changes. These evaluations are essential before claims of safety can be made with regard to these agents.

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