

Journal Watch

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Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind randomized, placebo-controlled phase 3 studies

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Abstract

Background: Opioids are critical for managing cancer pain, but may provide inadequate relief and/or unacceptable side effects in some cases.

Objective: To assess the analgesic efficacy of adjunctive Sativex (Δ^9 -tetrahydrocannabinol (27 mg/mL): cannabidiol (25 mg/mL)) in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy.

Methods: This report describes two phase 3, double-blind, randomized, placebo-controlled trials. Eligible patients had advanced cancer and average pain numerical rating scale (NRS) scores ≥ 4 and ≤ 8 at baseline, despite optimized opioid therapy. In Study-1, patients were randomized to Sativex or placebo, and then self-titrated study medications over a 2-week period per effect and tolerability, followed by a 3-week treatment period. In Study-2, all patients self-titrated Sativex over a 2-week period. Patients with a $\geq 15\%$ improvement from baseline in pain score were then randomized 1:1 to Sativex or placebo, followed by 5-week treatment period (randomized withdrawal design).

Results: The primary efficacy endpoint (percent improvement (Study-1) and mean change (Study-2) in average daily pain NRS scores) was not met in either study. Post hoc analyses of the primary endpoints identified statistically favorable treatment effect for Sativex in US patients < 65 years (median treatment difference: 8.8; 95% confidence interval (CI): 0.00–17.95; $p = 0.040$) that was not observed in patients < 65 years from the rest of the world (median treatment difference: 0.2; 95% CI: –5.00 to 7.74; $p = 0.794$). Treatment effect in favor of Sativex was observed on quality-of-life questionnaires, despite the fact that similar effects were not observed on NRS score. The safety profile of Sativex was consistent with earlier studies, and no evidence of abuse or misuse was identified.

Conclusions: Sativex did not demonstrate superiority to placebo in reducing self-reported pain NRS scores in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy, although further exploration of differences between United States and patients from the rest of the world is warranted.

Strengths of studies

Both trials are Phase III double-blind, multi-centered (international), randomized and placebo-controlled, and adequately powered, met IMMPACT II criteria and received ethics approval. Statistical analysis seems appropriate, though it is not clear if the tools used (SGIC, PGIC & PSQ) are validated.

Weaknesses of studies

The study was industry funded and 6 of the authors are employed by pharmaceutical companies. Despite this, these studies were reported as negative. Using NRS as the measure of the primary endpoint may be too insensitive. It may be argued that MEDD of 200 mg may not represent optimal analgesia and opioid use during the study was not clearly indicated.

Relevance to palliative care

The use of cannabinoids for medical use is legal in Canada (with a valid prescription), and many palliative patients use these agents as adjunct analgesics or anti-emetics. Their efficacy is not well described and the two studies represented in this paper provide no compelling evidence to suggest otherwise.

However, it could be postulated that Canadians under the age of 65 may perform well with cannabinoids as their US counterparts did, in a sub-group analysis of study 1.

Considering these agents are not without adverse effects, particularly dizziness and somnolence, we should be cautious when prescribing and vigilant in the assessment of toxicities that may be attributed to them.