

Journal Watch

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Poulain P, Denier W, Douma J, Hoertauf K, Šamija M, Sopata M, Wolfram G. Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. *J Pain Symptom Manage* 2008; 36:117-125

Abstract: Strong opioids are recommended for treating severe cancer pain in the advanced stages of the disease. Few data are available concerning the efficacy of buprenorphine in cancer pain. We compared transdermal buprenorphine 70 µg/h (BUP TDS) to placebo in an enriched design study. Opioid-tolerant patients with cancer pain requiring strong opioids in the dose range of 90–150 mg/d oral morphine equivalents entered a two-week run-in phase, during which they were converted to BUP TDS. Patients who could be stabilized on BUP TDS were randomized to BUP TDS or placebo patch for a two-week maintenance phase. Rescue medication (buprenorphine sublingual tablets 0.2 mg) was allowed as required. Response was defined as a mean pain intensity of <5 (0–10 scale) and a mean daily buprenorphine sublingual tablet intake of ≤2 tablets during the maintenance phase. Of 289 patients who entered the run-in phase, 100 discontinued treatment due to lack of efficacy or adverse events; 189 patients continued treatment in the maintenance phase (94 BUP TDS, 95 placebo), of whom 31 discontinued treatment (7 BUP TDS, 24 placebo). A significant difference in the number of treatment responders was observed: 70 BUP TDS (74.5%, 65.7–83.3) vs. 47 placebo (50%, 39.9–60.1) ($P = 0.0003$). This result was supported by a lower daily pain intensity, lower intake of buprenorphine sublingual tablets and fewer dropouts in the BUP TDS group. The incidence of adverse events was slightly higher for BUP TDS. In conclusion, BUP TDS 70 µg/h is an efficacious and safe treatment for patients with severe cancer pain.

Strengths/uniqueness: This study appeared to be appropriately executed in terms of concealment of allocation, randomization, double-blinding, accounting for withdrawals/dropouts, and analysis on an intent-to-treat basis. Apparently, it is the largest placebo-controlled trial for treatment of cancer pain.

Weaknesses: The inclusion of a placebo arm for patients requiring strong opioids is questionable, although the risk of inadequately controlled pain and opioid withdrawal is partly mitigated by the provision of buprenorphine tablets for breakthrough pain. The use of an enriched design, i.e. only randomizing patients who already demonstrate response to the drug, limits generalizability of the findings. The rationale for treating all patients with the same dose of buprenorphine, regardless of the dose of previous opioid, requires justification. The study population is poorly described in terms of types of cancer and pain syndromes.

Implications for Palliative Care: Buprenorphine is a partial agonist at the mu opioid receptor. The transdermal formulation has been used in Europe since 2001, and will

become available in Canada in the near future. Patch strengths will be 5, 10 and 20 mcg/h (lower than in this study), with a duration of effect of 7 days. Accordingly, this analgesic will only be suitable for very stable pain of moderate intensity. As the drug and its active metabolite are not excreted renally, it may be advantageous in patients with renal insufficiency. Also, the partial agonist activity appears to confer a lower addictive potential, and possibly a lower frequency of constipation.