# UNIVERSITÀ DEGLI STUDI DI TORINO

# Efficacy of oxycodone/acetaminophen and codeine/acetaminophen vs. conventional therapy in elderly women with persistent, moderate to severe osteoarthritis-related pain

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## Abstract
We aimed to evaluate the efficacy and safety of oxycodone/acetaminophen (O/A) and codeine/acetaminophen (C/A) vs. conventional therapy (CT) without opioids in older women suffering from osteoarthritis (OA)-related pain, sub-optimally responsive to prior conventional treatments. We performed a 6 week, randomized, single blind, controlled study in three nursing homes. We enrolled 154 women with painful OA. They were assigned to treatment with O/A (n = 52) and C/A (n = 52) vs. CT (n = 50). We evaluated at baseline and at week 6: average pain in the last week (mean pain, MeP), pain at rest (RP), pain in movement (MP) (numeric rating scale, NRS); depressive symptoms (Beck Depression Inventory-II, BDI-II); functional status (activities of daily living, ADL) and cognitive status (mini mental state evaluation, MMSE). We considered the adverse events (AEs) in the study period. At week 6, MeP, RP and MP were significantly reduced in all three groups ($p < 0.001$); compared to CT, O/A and C/A were associated with greater reductions in MeP ($p < 0.001$ and $p = 0.004$, respectively), in RP ($p = 0.028$ and $p = 0.032$, respectively) in MP ($p < 0.001$ and $p = 0.002$, respectively) and with significant improvement in BDI-II score ($p = 0.05$ and $p = 0.04$, respectively) and ADL value ($p = 0.04$ and $p = 0.05$, respectively). AE rates did not differ between groups.

## 1. Introduction
Pain is a very common problem for older persons (Gibson, 2006; Pain in Europe Survey (on line), 2007): some persistent pain is reported by more than 50% of community-dwelling elderly people (Jones and Macfarlane, 2005) and by more than 80% of nursing home residents (Ferrell, 1995, Ferrell, 2004 and Bernabei et al., 1998). Among these subjects, OA is one of the most frequent causes of pain and functional impairment.

Non-steroidal anti-inflammatory drugs (NSAIDs) continue to be the most prescribed therapy for persistent non-cancer pain (PNCP), including osteoarthritic pain. However, NSAIDs are associated with high risk of AEs, which are particularly common in the elderly recipients. These drugs are therefore not recommended for long-term use in older patients. Moreover, recent concerns regarding cardiovascular AEs among patients treated with NSAIDs and COX-2 inhibitors (COX-2-IBs) have substantially reduced the conditions for which the prolonged use of NSAIDs may be considered appropriate (Schneider, 2005 and Stillman and Stillman, 2007).

The use of opioids for the treatment of PNCP is still being debated, whereas it is largely accepted for treating cancer-related pain (Von Korff and Deyo, 2004, Bloodworth, 2005, Breivik, 2005 and Trescot et al., 2006). Several recent studies have demonstrated that oxycodone and codeine are effective in reducing OA pain in adult patients (Arkinstall et al., 1995, Caldwell et al., 1999, Peloso et al., 2000, Roth et al., 2000, Markenson et al., 2005 and Hale et al., 2007). Hence, current guidelines recommend opioid use for moderate to severe PNCP if prior conventional therapies have failed or caused intolerable side-effects and there are no contraindications (AAPM and APS, 1997, AGS, 2002, Simon et al., 2002 and AUPS, 2007). Additionally, the American College of Rheumatology endorsed opioid therapy, when prior strategies provided inadequate pain relief (ACR, 2000).

However, although PNCP is an extremely common clinical problem in older patients, these subjects were largely under-represented in most studies and reviews on opioid use in PNCP (Ballantyne and Mao, 2003, Chou et al., 2003, Duhmke et al., 2004, Kalso et al., 2004, Eisenberg et al., 2005, Furlan et al., 2006 and Martell et al., 2007). Because of the limited available evidence on the efficacy and safety of these drugs in older patients, the present study aimed to investigate the efficacy and safety of two opioid combined therapies (O/A and C/A) vs. CT without opioids in elderly women suffering from moderate to severe OA pain, who have been proven sub-optimally responsive to prior treatment strategies.

## 2. Subjects and methods

The study was conducted in accordance with the Declaration of Helsinki and it was approved by the local ethical committee. All patients gave written informed consent before enrollment. We conducted this 6 week, randomized controlled clinical trial in three nursing homes in Turin, Northern Italy, in the period between January and June 2007.

Women aged 65 years and older, with OA, diagnosed according to the ACR (1996), and with persistent (more than three months) (Merskey and Bogduk, 1994) moderate to severe pain in the last week (NRS ≥4), despite conventional non-opioid drugs were eligible for the study. Exclusion criteria were known allergies to the study drugs, chronic opioid use, active neoplasm, cardio-pulmonary, liver and kidney failure (clearance of creatinine ≤30 ml/min as measured with Cockroft–Gault formula), cognitive impairment (MMSE ≤24), history of seizure, active stomach or duodenal ulceration, inflammatory bowel disease and clotting disorders.

During the screening visit, before randomization, a full clinical and pharmacological history were gathered and a thorough physical examination (including respiratory rate and oxygen saturation while breathing room air) was performed. After a 2-week wash-out period, two researchers (L.C. and E.M.) evaluated the following baseline variables: mean intensity of pain in the last seven days, MeP, PR and PM, measured with the NRS (Jensen et al., 1986 and Farrar et al., 2001). NRS is a numeric scale ranging from 0 to 10 (0 = no pain, 10 = unbearable pain), widely used in previous trials and validate for measuring PNCP in older patients (Jensen and Karoly, 2001, Allcock et al., 2002, Gilron et al., 2005, Burch et al., 2007 and Khoromi et al., 2007). The severity of depression was evaluated using the BDI-II, according to the DSM IV criteria (Beck et al., 1996). The BDI-II is a twenty-one question multiple choice self-report inventory; a value from 0 to 3 is assigned for each answer, with total score ranging from 0 to 63; higher values indicate more severe depression. BDI-II has been validated for elderly patients suffering from chronic painful diseases (Davis et al., 2000, Hassett et al., 2000 and Poole et al., 2006). The functional status has been evaluated through the ADL (Katz et al., 1963), which has been previously used to evaluate the functional implications of chronic pain in older patients (Landi et al., 2000 and Soldato et al., 2007). The cognitive status was assessed using the MMSE test: lower scores indicate higher mental impairment (Folstein et al., 1975 and Gilron et al., 2005).

Patients who were eligible for the study were randomly assigned to treatment with (a) immediate release O/A; (b) immediate release C/A; (c) CT such as acetaminophen, NSAIDs, COX-2-Inh, both alone or associated. In the O/A group the starting dose was 5 mg/325 mg every 12 h; in the C/A group 30 mg/500 mg every 8 h. Except for study medications, no other opioid analgesics were allowed. Other drugs such as antidepressants or tranquilizers, taken at a stable dose for ≥3 weeks before the study could be continued at the same as the pre-study dose.

According to defined criteria and good clinical practice principles, every week the same researchers who did the baseline clinical evaluation administered the therapy and re-evaluated the patients. During each check-up, they performed a full physical examination, including respiratory rate and

oxygen saturation and re-evaluated the severity of pain, up-titrating analgesic drugs, according to the schedule presented in Fig. 1. The same physicians performed a careful evaluation of AEs, deciding whether or not to withdraw treatments according to good clinical practice.

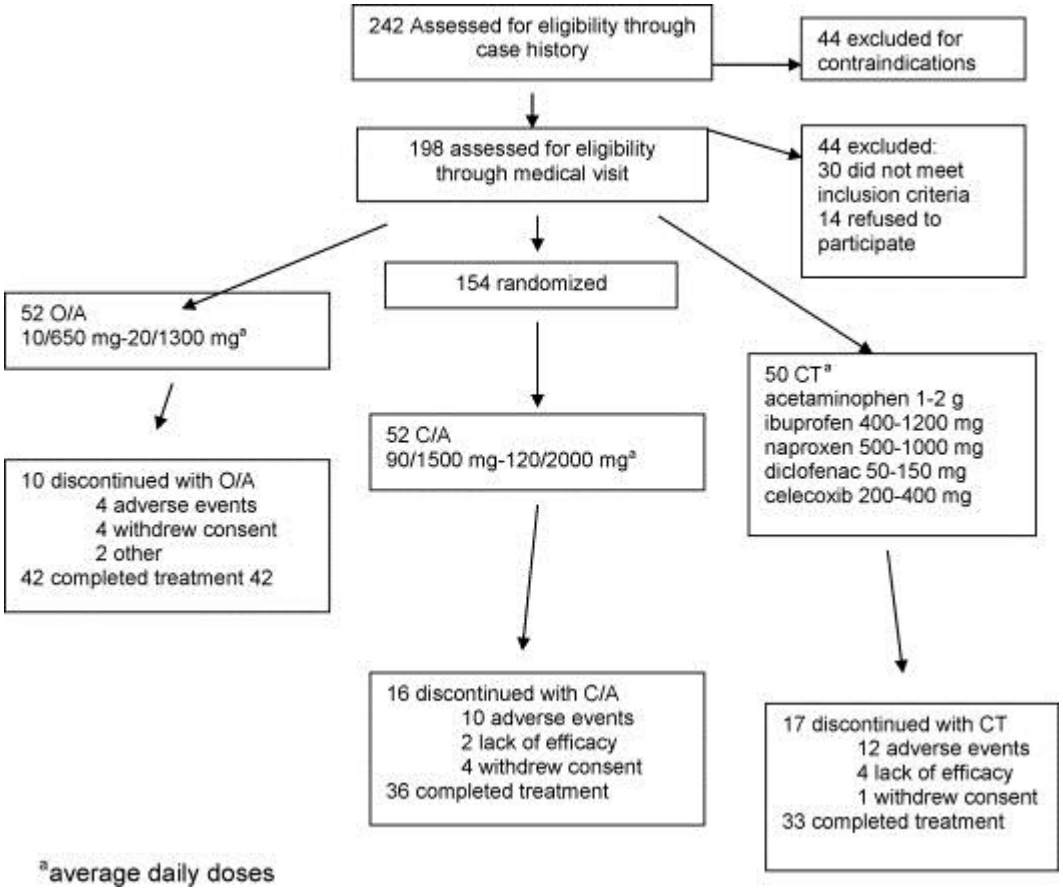


Fig. 1.
Participants flow diagram. Average daily doses.

At the end of the study period, two other researchers (M.B. and M.A.), who were blind to the patients' group assignment, re-evaluated the variables measured at baseline.

### 2.1. Statistical analysis

We used SPSS.12 package for Windows for the statistical analysis. One-way ANOVA was used to evaluate differences in demographic and clinical variables at baseline between the three groups. Differences within and between groups in treatment effects on pain intensity from baseline to the end of the study were evaluated using MANOVA for repeated measures ($\alpha = 0.05$) and post hoc pair-wise multiple comparisons (Bonferroni). Covariates included age, BDI-II, ADL and MMSE scores. We evaluated the efficacy variables using a per protocol approach.

## 3. Results

Fig. 1 shows the flow diagram of the 154 patients. Table 1 summarizes baseline characteristics of the investigated sample: there were no significant differences between groups.

Table 1.
Baseline characteristics of patients, mean ± S.D.

| Variable | O/A group | C/A group | CT group | F | p |
|---|---|---|---|---|---|
| Age (years) | 79.2 ± 8.4 | 77.8 ± 8.6 | 77.1 ± 7.9 | 0.77 | 0.465 |
| MeP | 7.7 ± 1.4 | 7.6 ± 1.4 | 7.5 ± 1.3 | 0.20 | 0.817 |

| | | | | | |
|---|---|---|---|---|---|
| PR | 4.7 ± 1.9 | 4.5 ± 1.5 | 4.5 ± 2.1 | 0.28 | 0.755 |
| PM | 7.7 ± 1.4 | 7.6 ± 1.3 | 7.8 ± 1.4 | 0.15 | 0.861 |
| BDI-II | 19.2 ± 4.2 | 19.0 ± 4.3 | 19.8 ± 5.0 | 0.42 | 0.660 |
| ADL | 2.5 ± 1.3 | 2.4 ± 1.4 | 2.6 ± 1.2 | 0.21 | 0.810 |
| MMSE | 27 ± 1.9 | 26.8 ± 2.0 | 27.5 ± 1.5 | 1.76 | 0.174 |

Table 2 shows MeP, PR and PM values at baseline and at the end of the study period in the three groups. At the end of the study, after adjustment for covariates (age, BDI-II, ADL and MMSE), pain scores were significantly lower among patients treated with combined opioid therapy than in patients assigned to CT group. At the end of the follow-up, both O/A and C/A were associated with significantly lower MeP ($p < 0.001$ and $p = 0.004$, respectively), PR ($p = 0.028$ and $p = 0.032$, respectively) and PM ($p < 0.001$ and $p = 0.002$, respectively) values, despite significant reductions in pain scores were observed in each group of treatment. The reduction in MeP score from baseline to the end of the study period was 4.3 ± 1.9 in patients treated with O/A ($p < 0.001$), 3.9 ± 2.1 in patients treated with C/A ($p < 0.001$) and 2.1 ± 1.2 in those treated with CT ($p < 0.001$). The decreases in PR score from baseline to the end of the study period in the three groups of patients were respectively 3.0 ± 2.1 ($p < 0.001$), 2.5 ± 1.3 ($p < 0.001$), and 1.2 ± 1.2 ($p < 0.001$), respectively. The reductions in PM score from baseline to the end of the study period were 4.4 ± 1.8 ($p < 0.001$), 3.8 ± 1.9 ($p < 0.001$), 2.1 ± 1.7 ($p < 0.001$), respectively.

Table 2.
The parameters MeP, PR and PM expressed as NRS score in the study groups at baseline and at the end of the study, mean ± S.D.

| MeP | | | PR | | | PM | | |
|---|---|---|---|---|---|---|---|---|
| O/A | C/A | CT | O/A | C/A | CT | O/A | C/A | CT |
| Baseline | | | | | | | | |
| 7.7 ± 1.5 | 7.6 ± 1.3 | 7.5 ± 1.3 | 4.9 ± 1.7 | 4.6 ± 1.5 | 4.9 ± 1.8 | 7.7 ± 1.4 | 7.6 ± 1.2 | 7.8 ± 1.4 |
| | | | | | | | | |
| Week 6 | | | | | | | | |
| 3.4 ± 1.1 | 3.6 ± 1.6 | 5.4 ± 1.6 | 1.9 ± 1.3 | 2.1 ± 1.5 | 3.7 ± 1.9 | 3.3 ± 1.2 | 3.8 ± 1.8 | 5.7 ± 1.9 |
| | | | | | | | | |
| Statistical comparison of the groups, Bonferroni test | | | | | | | | |
| O/A vs. C/A: $p = 1.0$ | | | $p = 1.0$ | | | $p = 0.791$ | | |
| O/A vs. CT: $p < 0.001$ | | | $p = 0.028$ | | | $p < 0.001$ | | |
| C/A vs. CT: $p = 0.004$ | | | $p = 0.032$ | | | $p = 0.002$ | | |
| | | | | | | | | |
| General linear model between groups[a] | | | | | | | | |
| $F = 8.6$, $p < 0.001$ | | | $F = 4.5$, $p = 0.014$ | | | $F = 11.5$, $p < 0.001$ | | |
| | | | | | | | | |
| General linear model within groups | | | | | | | | |
| $F = 23.2$, $p < 0.001$ | | | $F = 15.0$, $p < 0.001$ | | | $F = 22.7$, $p < 0.001$ | | |

a

Covariates used in the general linear model: age = 77.7, BDI-II = 19.0, ADL = 2.5, MMSE = 26.5.

Table 3 shows BDI-II, ADL and MMSE scores at baseline and at the end of the study: at the end of the follow-up, patients treated with O/A or C/A had significant lower BDI-II and ADL scores, than patients treated with CT.

Table 3.

BDI-II, ADL and MMSE scores in the study groups at baseline and at the end of the study, mean ± S.D.

| BDI-II | | | ADL | | | MMSE | | |
|---|---|---|---|---|---|---|---|---|
| O/A | C/A | CT | O/A | C/A | CT | O/A | C/A | CT |
| Baseline | | | | | | | | |
| 19.1 ± 4.4 | 18.6 ± 4.5 | 19.4 ± 4.9 | 2.4 ± 1.2 | 2.4 ± 1.3 | 2.7 ± 1.2 | 27.0 ± 1.9 | 26.7 ± 2.0 | 27.3 ± 1.5 |
| | | | | | | | | |
| Week 6 | | | | | | | | |
| 13.2 ± 3.1 | 13.4 ± 3.7 | 17.1 ± 4.7 | 1.3 ± 1.2 | 1.3 ± 0.9 | 2.3 ± 1.1 | 27.1 ± 2.0 | 26.9 ± 2.0 | 26.5 ± 2.7 |
| | | | | | | | | |
| Statistical comparison of the groups, Bonferroni test | | | | | | | | |
| O/A vs. C/A: $p = 1.0$ | | | $p = 1.0$ | | | $p = 1.0$ | | |
| O/A vs. CT: $p < 0.05$ | | | $p = 0.04$ | | | $p < 1.0$ | | |
| C/A vs. CT: $p = 0.04$ | | | $p = 0.05$ | | | $p = 1.0$ | | |
| | | | | | | | | |
| General linear model between groups | | | | | | | | |
| $F = 3.9$, $p < 0.023$ | | | $F = 3.9$, $p = 0.023$ | | | $F = 0.1$, $p < 0.877$ | | |
| | | | | | | | | |
| General linear model within groups | | | | | | | | |
| $F = 8.7$, $p < 0.001$ | | | $F = 6.0$, $p < 0.003$ | | | $F = 1.3$, $p < 0.28$ | | |

Overall, 43 patients (27.9% of the total sample) discontinued treatment before completing the study: 10 (19.2%), patients in the O/A group, 16 (30.8%) in the C/A group and 17 (34.0%) in the CT group (p = ns). Treatment withdrawals due to AEs occurred in 4 subjects receiving O/A (7.7%), 10 subjects treated with C/A (19.2%) and 12 patients treated with CT (24%) (p = ns). Most frequent AEs responsible for drug discontinuation were nausea, vomiting and drowsiness in patients receiving opioid combined therapy and dyspepsia and worsening of renal function in patients treated with CT.

The average drug doses at the end of the study were oxycodone 16 mg/acetaminophen 900 mg for the O/A group and codeine 115 mg/acetaminophen 1916 mg for the C/A group. In the CT group the drug most frequently used included: acetaminophen (5 patients), COX-2-Inh (20 patients), NSAIDs (20 patients) and COX-2-Inh and acetaminophen (5 patients).

## 4. Discussion

The results of this study suggest that both O/A and C/A therapies were more effective than conventional non-opioid therapy in reducing average pain in elderly women suffering from chronic moderate to severe OA pain, sub-optimally responsive to prior treatments. Despite a significant reduction of pain observed within each group at the end of the study period, the percent reduction in pain intensity scores (MeP, PR and PM) was greater for opioid treatments, than for CT: 56%, 64% and 57%, respectively, in patients receiving O/A we found reductions of 51%, 55% and 50%, respectively, and at last in patients treated with C/A reductions of 28%, 25% and 27%, respectively, were obtained, as compared to those taking CT.

Compared to subjects receiving CT, a greater proportion of patients treated with O/A and C/A reached a reduction of at least 30% in baseline pain intensity scores, conventionally considered clinically meaningful (Farrar et al., 2001). Indeed, 78% of O/A patients, 63% of C/A patients and 45% of CT patients had clinically meaningful reduction for MeP score; the corresponding numbers for PR and for PM were 76%, 75% and 42%, respectively, and 78%, 66% and 40%, respectively. In keeping with previous reports in younger populations (Ferrell and Chodosh, 2003, Furlan et al., 2006 and Trescot et al., 2006), clinical efficacy did not differ between the two opioid treatments. To our knowledge, no previous randomized studies have evaluated these therapies in elderly populations: the patients recruited in our trial are considerably older (mean age 78.1 ± 8.3 years) than those enrolled in previous similar studies (Furlan et al., 2006).

At baseline, in the overall sample mild depressive symptoms were observed, according to standardized BDI-II scores; these findings were in keeping with previous reports in patients suffering from persistent pain (Hassett et al., 2000). At the end of the study period, we observed a significant easing of depressive symptoms in patients treated with opioid therapy, but not in patients receiving CT. Similarly, we measured a greater improvement in ADL score in patients treated with opioid therapy than in patients receiving CT. Previous reports on the functional implications of different analgesic treatments are not conclusive. Although some studies reported positive functional effects from opioid therapies, other studies showed evidence of impaired function associated to these drugs (Furlan et al., 2006 and Martell et al., 2007). Present findings showing marginally significant easing of depressive symptoms and improvement in functional status appear to be reassuring for the preservation of residual functional abilities in elderly long-term resident women (Davis et al., 2000 and Soldato et al., 2007).

Furthermore, covariates adjusted analysis suggests that reduction in pain severity observed in patients treated with opioid combined therapies was independent from mood and functional status improvement. Therefore, this improvement should be considered as a consequence rather than a cause of the persistent pain relief. Furthermore, even considering the relatively short treatment period, there was no evidence of cognitive impairment among patients treated with opioid drugs.

In our study adequate pain relief was achieved with relatively low average daily doses of oxycodone and codeine if compared to those reported in a recent review on opioid therapy for PNCP (Furlan et al., 2006) and in previous trials in younger patients (Caldwell et al., 1999, Peloso et al., 2000, Roth et al., 2000 and Markenson et al., 2005). A higher sensitivity to opiod, with greater and prolonged pain relief, has been described in elderly people (Ferrell and Chodosh, 2003).

Despite this efficacy, high rates of discontinuation were observed in both opioid combined therapy (19.2% in O/A group, 30.8% in C/A group), as well as in CT group (34.0%). AEs were responsible for treatment withdrawals in 4 patients receiving O/A (40% of O/A drop out population) and in 10 patients treated with C/A (62.5% of C/A drop out population). AEs observed in both opioid treatment groups were those typical of oral opioid therapy, were of mild to moderate intensity and recovered by drug discontinuation. Drop-out rates observed in this study are in keeping with previous reports in younger patients (Ballantyne and Mao, 2003, Bloodworth, 2005, Furlan et al., 2006, Trescot et al., 2006 and McNicol, 2007), although we recorded smaller AE rate. In our view, this might well be due to lower drug doses, careful up-titration and comprehensive patient treatment. For example, the low incidence of severe constipation observed in this study might be a positive consequence of routine management with appropriate laxative therapy.

There are many investigations supporting the effectiveness of combined therapies, where two or more analgesic agents work together in relieving symptoms of diseases. This approach, by allowing a reduction of the drug doses, may translate in a reduced incidence of AEs. The oxycodone has a structure similar to codeine but is about 10-times more potent than morphine. Moreover, available formulation of this drug, with increasing doses of oxycodone and a fixed amount of acetaminophen allows easy up-titration of the opioid without increasing the acetaminophen daily dose. This is particularly favorable when treating elderly people in whom the highest recommended dose of acetaminophen is almost halved (2 g instead of 4 g) as compared with that administered in adults.

Some limitations to this study should be addressed. The specific characteristics of the sample evaluated in our study (nursing home resident elderly women with OA pain) do not permit us to extend our results to community-dwelling older people or to other sorts of PNCP. Moreover, because of the short observation period, this study does not provide strength of evidence with

regards to the effectiveness and safety of opioids on a long-term basis. As a study conceived and conducted in the real world, it was not possible to satisfy double blind criteria; however, physicians who evaluated clinical variables at the end of the study period, were blinded to the patients' group assignment. We therefore believe that this drawback does not detract from the validity of the present findings. Finally, despite the relatively small size of the sample, the comprehensive covariates adjustment should reinforce our results.

Our findings might have some important clinical implications. These results show that combined opioid–acetaminophen therapy was more effective than CT in relieving OA moderate to severe pain in elderly women, who have proved sub-optimally responsive to prior treatments. Furthermore, we observed a favorable influence on functional status and on depressive symptoms in these patients. We reported high discontinuation rates, but AE incidence and severity were not higher than in CT group.

We conclude that opioid combined therapy may represent an effective and safe option for the treatment of uncontrolled moderate to severe OA pain in older women. However, further studies with a longer period of observation, are needed to confirm these short term findings of efficacy and safety.

Conflict of interest
None.

**Acknowledgements**
Financial disclosure: No financial support for research. We would like to thank Suor Rosanna Libra and Lorenzo Gagliardi for their continuous support.

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