Chapter 5

A 13-Year Prospective Cohort Study on the Effects of Aging and Frailty on the Depression-Pain Relationship in Older Adults.


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ABSTRACT

Objectives
The primary aim of the study is to investigate the effect of age and aging on the association between pain and depression over 13 years. We hypothesized that (1) this association would become stronger with age and frailty, and that (2) this association is mainly driven by somatic and psychological factors.

Methods
Data were derived from the Longitudinal Aging Study Amsterdam, a prospective population-based cohort study with 4 follow-up measurements over 13 years, consisting of 1528 respondents (mean age 67.9 ± 8.1). Depressive symptoms were measured using the CES-D (Center for Epidemiologic Studies Depression Scale); pain was measured with an adapted version of the Nottingham Health Profile. Follow-up time and age were used as proxy variables for aging and gait speed as frailty marker. Cognition, mastery and neuroticism were measured using the Mini Mental State Examination, the Pearlin Mastery Scale and the Dutch Personality Questionnaire respectively.

Results
Linear Mixed Models showed that pain and depressive symptoms were associated over the 13-year follow-up: b=0.095, p<0.001. Neither aging nor frailty changed this association. Measured somatic and psychological characteristics explained 40% of the covariance between pain and depressive symptoms over time.

Discussion
When dealing with people suffering from pain and depression, interventions should be similar for all aged people, encompassing both somatic and psychological factors, irrespective of age or frailty status.
INTRODUCTION

Population-based studies among older people consistently demonstrate that both pain and depression are highly prevalent in late life. Between 29% and 86% of older adults report having painful symptoms and about 14% of older adults experience depressive symptoms that require medical attention.\(^1\)\(^2\) Cross sectional studies have shown that these two phenomena frequently co-occur, that patients with pain and comorbid depression experience more intense pain and that they are more likely to have persistent pain.\(^3\)\(^4\) Longitudinal data suggest a bidirectional association between depression and pain, in which pain predicts depression and vice versa.\(^5\)\(^-\)\(^9\) The co-occurrence of pain and depression is associated with worse clinical outcomes than either condition alone.\(^3\) This interaction between pain and depression has been labeled by some as the depression-pain dyad.\(^3\) With an increasing number of comorbidities occurring with aging, a better understanding of the reciprocal link between pain and depression may identify factors suitable for prevention or improved treatment outcomes.

It has been debated in recent years whether pain in old people has its own characteristics and clinical consequences compared to pain in younger adults, giving rise to the concept of geriatric pain.\(^10\) The existence of geriatric pain has been postulated from observations of specific pain trajectories in old people; for instance, the increased risk of post herpetic neuralgia in older people, possibly reflecting neurophysiological changes with aging.\(^10\) Late life depression also has its own specific characteristics with a particular risk profile and a more chronic course compared with depression earlier in life.\(^11\)\(^,\)\(^12\) Taking into account these specific age-related characteristics, we speculate that the strength of the association between pain and depression increases with aging. Longitudinal studies are needed to address the role of aging in the depression-pain dyad.

When studying age-related aspects, the incorporation of frailty over chronological age can yield additional information, since frailty can be regarded as a measure of biological aging.\(^13\) Frailty is conceptualized as a state of reduced reserve capacity of various physiological systems, where a small disturbance can lead to a series of complications.\(^14\)\(^,\)\(^15\) In this concept, a frail individual will be less able to respond adequately to pain or a depressed mood; consequently it can be argued that for frail and non-frail old people the association between pain and depression differs. Whether the pain-depression dyad is different in frail and non-frail old people has, to our knowledge, never previously been investigated.
In order to understand the frequent co-occurrence of pain and depression it is important to examine possible underlying mechanisms. The courses of both conditions are associated with factors from several domains of the bio-psycho-social model, such as education, chronic diseases and psychological factors such as personality and cognitive functioning. Specifically relevant for the aging population are the effects of somatic comorbidity on chronic pain in the general population. In a recent cross-sectional study independent associations with chronic pain were found for the total count of chronic conditions (the accumulated load) apart from independent effects for a range of specific physical conditions. Therefore, the association between pain and depression in older adults might be driven by both the presence and the number of somatic diseases.

Furthermore, both pain and depression are strongly associated with personality characteristics and cognitive functioning. Adaptive capabilities are viewed as essential for adequate and healthy responses to stressors. In this adaptation concept, pain can be considered a stressor and inadequate adaptation can result from inadequate coping strategies, which can, in turn, lead to depression, while the inverse association between depression and pain might result from similar inadequate coping strategies. In this regard, neuroticism, mastery and cognitive functioning are of particular interest, especially in a longitudinal perspective in aging respondents. To our knowledge no research has been conducted that takes into account the changes occurring over time in physical and cognitive functioning in older people, and how these changes affect the depression–pain dyad. Pain was chosen as independent variable since we are primarily interested in factors that influence the course of depressive symptoms in late life.

The primary aim of the study is to investigate the effect of age and aging on the association between pain and depression over 13 years. We hypothesized that: (1) this association would become stronger with age and frailty, and that (2) this association is mainly driven by somatic and psychological factors.

2 METHODS

2.1 Study sample

Data for this study were derived from the Longitudinal Aging Study Amsterdam (LASA), an ongoing cohort study of predictors and consequences of changes in physical, cognitive, emotional, and social functioning in older people in the Netherlands. The sampling, data collection procedures, and non-response have been described in detail elsewhere. In summary, a random sample, stratified according to age, gender,
degree of urbanization, and expected 5-year mortality, was drawn from the population registers of 11 municipalities in three geographical areas in the Netherlands. A total of 3107 participants were enrolled for the baseline examination in 1992–1993. Follow-up data collection cycles took place at 3 (n=2545), 6 (n=2076), 9 (n=1691) and 13 years (1257) after baseline. Depressive symptoms and pain were measured at baseline and all follow-up cycles. From baseline through the 13-year follow-up cycle, attrition was mainly due to mortality (1404/3107, 45%), and to a lesser extent to ineligibility (130/3107, 4%), refusal (268/3107, 9%) and no contact (51/3107, 2%). The study was approved by the Medical Ethics Committee of the VU University Medical Center, and informed consent was obtained from all participants.

To be able to examine the longitudinal association between pain and depression, we included persons with at least 2 measurements of pain and depressive symptoms. 1528 respondents met this criterion. Compared with the excluded cohort (N=1579), respondents in this cohort were younger (mean age at baseline 67.94 ± 8.05 versus mean age 73.50, ± 8.56, t = 18.64, df 3054, p < 0.01), more highly educated (mean years of education 9.31 ± 3.32 versus mean years of education 8.23 ± 3.23, t = -9.2, df 3097, p < 0.01), had fewer depressive symptoms (mean Center for Epidemiologic Studies Depression scale (CES-D) score 7.02 ± 7.17 versus mean CES-D 8.92 ± 8.27, t = 6.78, df 3105, p < 0.01) and fewer pain symptoms at baseline (mean score 5.64 ± 1.27 versus mean score 5.91 ± 1.48, t = 4.03, df 2040, p < 0.01).

2.2 Measurements

2.2.2 Depressive Symptoms

Depressive symptoms were measured using a self-report rating scale (CES-D) which was developed to measure depressive symptoms in the community, and consists of 20 items. The total score ranges between 0 (no symptoms) and 60. A cut-off score of 16 is usually used for clinically significant depressive symptoms resulting in good criterion validity for major depressive disorder (sensitivity 100%, specificity 88%) and high reliability (Cronbach’s α=0.87) in community-based samples of old people.

3.2.2 Pain

Pain was assessed with an adapted version of the Nottingham Health Profile, as described elsewhere. Six items were included: “I am in pain when I am standing;” “I find it painful to change position;” “I am in pain when I am sitting;” “I am in pain when I walk;” “I have unbearable pain,” and “I am in constant pain.” Response categories were “yes” and “no”, resulting in a total score range from 0 (no pain) to 6 (pain for all six items). As tested previously, the internal reliability of this score was satisfactory with a Cronbach’s α of 0.77.
2.2.3 Covariates

Baseline assessments were used for the variables age, gender, years of education, mastery and neuroticism. Baseline and follow-up assessments were used for the other covariates. Medication use was checked at the respondent’s home.

A summary measure for chronic diseases was used for somatic comorbidity. The 7 most prevalent chronic diseases were assessed by self-report, encompassing arthrosis and/or rheumatoid arthritis (osteoarthritis), peripheral arterial disease (PAD, intermittent claudication, former arterial surgery), heart disease (ischemic heart disease, arrhythmia, congestive heart failure), cancer, COPD, stroke (hemorrhagic and ischemic) and diabetes, supplemented by hypertension and other chronic diseases, refer to www.lasa-vu.nl/ for details). As a result, the somatic comorbidity variable ranges from 0-9.

Gait speed was used in the present study as a marker for frailty because of its relatedness to the frailty concept and because of its reliability and applicability in particular in the setting of community-based research of old people. Prior research demonstrated the association of gait speed with a large number of health-related outcomes, such as increased dependency in functional ADL, cognitive decline, depressive symptoms, hospitalization, institutionalization and mortality. Frailty defined in accordance with one of the standardized definitions for community dwelling older adults is associated with many of these same health-related outcomes. Gait speed (m/s) was assessed by recording the total time it took to walk 3 meters, make a 180° turn and walk the 3 meters back as quickly as possible.

Sense of mastery, which is considered a psychosocial resource when coping with stressful life events, was measured with the Pearlin Mastery Scale. Neuroticism was measured using 25 out of 36 neuroticism items from the Dutch Personality Questionnaire. Cognition was assessed using the Mini Mental State Examination.

2.3 Statistical analyses

Linear Mixed Models (LMM, unstructured correlation matrices) were used to investigate the association between pain scores and CES-D scores over a period of 13 years. LMM techniques account for the dependency of repeated observations obtained from the same individual over time. Also, subjects in LMM can be included even in the case of some missing values. The repeated measurements of the CES-D score were used as the main outcomes. Because the CES-D score was not normally distributed, the transformed score ln (1+CES-D) was used. Pain scores (per unit) at baseline and at 3, 6, 9 and 13 years follow-up were used as independent variables (main effect) for the CES-D score at these time points.
Analyses using subsequent models were performed to investigate the influence of the follow-up time (in years) and covariates on the association between pain scores and CES-D scores. In model 1 the main effect of pain and follow-up time was adjusted for potential socio-demographic confounders (age, sex, and years of education) and medication use. In model 2, the interaction term follow-up time * pain was additionally included, in order to investigate whether the strength of the association between pain and depression changes over time. It was subsequently investigated whether the association between pain and depression was the same for all age groups and in frail and non-frail persons by entering the product terms of pain*age and of pain*frailty in model 1 (models 3 and 4). In models 5, 6, 7 and 8 the possible explanatory effects of somatic comorbidity, psychological covariates (mastery, neuroticism) and global cognitive functioning (MMSE) were examined by manually adding them one by one to the adjusted model; if the coefficient of the main predictor (pain score) changed ≥ 10% a covariate was considered to be an explanatory variable. The regression coefficients (B) and their 95% confidence intervals (CIs) are presented.

For main effects, significance was evaluated at the 0.05 level. A product- or interaction-term was considered statistically significant when the p value for this term was below 0.10, because in general the power of a statistical test is lower for a higher order term than for a first-order term. \(^{38,39}\) SPSS version 20 (Chicago, IL) was used to analyze the data.

3 RESULTS

The descriptives of the sample are presented in table 1. The mean age of the respondents was 67.9 ± 8.1 years at baseline. Gender was equally distributed. At baseline, the mean CES-D score was 7.0 ± 7.2, with a CES-D ≥ 16 in 11.3% of the respondents; the mean pain score was 0.64 ± 1.27. During follow-up there was a gradual increase of depressive symptoms and of the pain score.

Pain and depressive symptoms were associated over the 13-year follow-up, independent from follow-up time, gender, age, education and medication (b=0.095, 95% C.I. 0.075-0.114, p<0.001, model 1, table 2). Since the CES-D scores were ln transformed, a b of 0.095 means that a 1 point change in the pain score at any time results in 1.10 point change on the CES-D \((e^{0.095}=1.10)\). Follow-up time did not change the strength of the association between pain and depressive symptoms, since the introduction of the pain*follow-up time interaction term in model 1 did not reach the level of significance (p>0.1, model 2, table 2). To investigate whether the association
between pain and depression is the same for all ages and for frail and non-frail persons, the product terms of pain * age and of pain * frailty were entered in model 1. Both interaction terms did not reach the level of significance (models 3 and 4).

The introduction of somatic comorbidity (model 5), mastery and neuroticism (models 6 and 7) influenced the association of pain and CES-D score by over 10%; this means that these covariates act partly as explanatory variables in the association of pain and depression over time. The MMSE (model 8) did not influence this association over time. The main effect between pain and CES-D over time remained significant after introducing all the relevant covariates in the model (model 9, full model), although the strength of the association decreased by 40% (0.095-0.057/0.095). Using a linear regression model of the full model at baseline, the effect size of the association between pain and depressive symptoms was calculated at $r = 0.54$, which is regarded as a strong effect.

Table 1. Characteristics of the sample

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<tr>
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<tbody>
<tr>
<td>Age in yrs, mean (SD)</td>
<td>67.9 (8.1)</td>
<td>67.7 (8.1)</td>
<td>67.8 (8.0)</td>
<td>67.8 (8.0)</td>
<td>68.0 (8.0)</td>
</tr>
<tr>
<td>Women, %</td>
<td>50.4</td>
<td>50.5</td>
<td>50.4</td>
<td>50.4</td>
<td>50.3</td>
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<td>Education in years, mean (SD)</td>
<td>9.3 (3.3)</td>
<td>9.2 (3.3)</td>
<td>9.2 (3.3)</td>
<td>9.2 (3.3)</td>
<td>9.3 (3.3)</td>
</tr>
<tr>
<td>Number of Chronic Diseases, mean (SD)</td>
<td>1.2 (1.1)</td>
<td>1.6 (1.3)</td>
<td>1.7 (1.3)</td>
<td>1.8 (1.3)</td>
<td>2.1 (1.4)</td>
</tr>
<tr>
<td>Gait Speed in m/s, mean (SD)</td>
<td>0.88 (0.29)</td>
<td>0.87 (0.28)</td>
<td>0.79 (0.29)</td>
<td>0.75 (0.26)</td>
<td>0.76 (0.26)</td>
</tr>
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<td>MMSE^1, mean (SD)</td>
<td>27.7 (2.0)</td>
<td>27.5 (2.1)</td>
<td>27.2 (2.8)</td>
<td>27.1 (3.1)</td>
<td>26.9 (3.2)</td>
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<tr>
<td>Use of anxiolytics, %</td>
<td>4.4</td>
<td>4.4</td>
<td>5.8</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Use of hypnotics, %</td>
<td>6.8</td>
<td>8.0</td>
<td>11.1</td>
<td>8.1</td>
<td>6.8</td>
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<tr>
<td>Use of antidepressants %</td>
<td>2.0</td>
<td>2.5</td>
<td>3.9</td>
<td>5.2</td>
<td>4.9</td>
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<td>Neuroticism, mean (SD)</td>
<td>5.8 (5.6)</td>
<td>5.8 (5.6)</td>
<td>5.8 (5.6)</td>
<td>5.8 (5.6)</td>
<td>5.8 (5.6)</td>
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<tr>
<td>Mastery, mean (SD)</td>
<td>17.7 (3.2)</td>
<td>17.7 (3.2)</td>
<td>17.7 (3.2)</td>
<td>17.7 (3.2)</td>
<td>17.7 (3.2)</td>
</tr>
<tr>
<td>Pain, mean (SD)</td>
<td>0.64 (1.27)</td>
<td>0.62 (1.25)</td>
<td>0.77 (1.37)</td>
<td>0.80 (1.37)</td>
<td>0.90 (1.45)</td>
</tr>
</tbody>
</table>

^1MMSE: Mini Mental State Examination; CES-D: Center for Epidemiologic Studies Depression; IQR: Inter Quartile Range.
Table 2. Association between pain and the ln transformed CES-D score, adjusted for confounding and explanatory variables.

<table>
<thead>
<tr>
<th>Model</th>
<th>b</th>
<th>95% C.I. Lower Bound</th>
<th>95% C.I. Upper Bound</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1:</td>
<td></td>
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<tr>
<td>Pain, adjusted for follow-up time, sex, age at baseline, education and use of medication(^1)</td>
<td>.095</td>
<td>.075</td>
<td>.114</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pain (model 1) and interaction term</td>
<td>.104</td>
<td>.074</td>
<td>.133</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pain*follow-up time</td>
<td>-.001</td>
<td>-.005</td>
<td>.002</td>
<td>.424</td>
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<tr>
<td>Model 3:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (model 1) and interaction term</td>
<td>.140</td>
<td>-.052</td>
<td>.326</td>
<td>.155</td>
</tr>
<tr>
<td>Pain*age</td>
<td>-.001</td>
<td>-.003</td>
<td>.002</td>
<td>.663</td>
</tr>
<tr>
<td>Model 4:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (model 1) and interaction term</td>
<td>.115</td>
<td>-.052</td>
<td>.162</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pain*gait speed</td>
<td>-.052</td>
<td>-.115</td>
<td>.011</td>
<td>.105</td>
</tr>
<tr>
<td>Model 5:</td>
<td></td>
<td></td>
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<tr>
<td>Pain (model 1), adjusted for number of chronic diseases</td>
<td>.076*</td>
<td>.056</td>
<td>1.236</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 6:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pain (model 1), adjusted for Neuroticism</td>
<td>.075*</td>
<td>.055</td>
<td>.095</td>
<td>&lt;.001</td>
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<tr>
<td>Model 7:</td>
<td></td>
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<tr>
<td>Pain (model 1), adjusted for Mastery</td>
<td>.085*</td>
<td>.066</td>
<td>.105</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 8:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pain (model 1), adjusted for MMSE(^2)</td>
<td>.094</td>
<td>.074</td>
<td>.114</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 9: full model</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pain adjusted for all confounders, somatic comorbidity (number of chronic diseases) and personality variables (neuroticism and mastery)</td>
<td>.057</td>
<td>.037</td>
<td>.077</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* More than 10% change of the estimate (suggesting an explanatory effect); \(^1\) Use of antidepressants, hypnotics and anxiolytics; \(^2\) MMSE: Mini Mental State Examination; \(^3\) NS: Not Significant.

**DISCUSSION**

The present study demonstrates a strong association between pain and depressive symptoms over time. Moreover, this association remained unaffected by follow-up time, by age or by frailty status. 40% of the longitudinal association is explained by measured somatic comorbidity and psychological factors. It is concluded that neither aging nor frailty influence the pain-depression dyad over time, while well-known factors partly explain their intimate association in old age. A first clinical implication of these findings is that neither age nor frailty status should affect the management strategies in old people suffering from pain and depression.
It is demonstrated that pain and depression covariate over time and this co-variance is independent of an age effect. In a cross-sectional study an inverse relation of age was found in the pain-depression association. As stated by the authors, this was only a small effect, the study had a cross-sectional design and it studied chronic back pain in particular; more importantly, the ages included in this study ranged from 12 years to 65+. We believe the longitudinal design of the present paper gives a more reliable insight into the pain-depression dyad over time in aged people.

A number of longitudinal incidence studies show that both pain and depression predict each other’s incidence. The present study shows that once pain and depression co-occur, they remain associated and covariate in time. The results are in line with a number of studies that show a simultaneous improvement of pain and depressive symptoms following antidepressant treatment.

It is additionally demonstrated that frailty does not change the strength of the longitudinal association between pain and depressive symptoms. As with aging, frailty can only serve as a marker for explanatory variables. It is therefore likely that an underlying mechanism for the tight association between pain and depression over time does not differ between frail and for non-frail old people.

After adjustment for relevant covariates, 40% of the covariance between pain and depressive symptoms over time is explained. These findings are in line with studies that demonstrate the important role of somatic comorbidity and psychological factors in the pain-depression dyad. The large percentage of explained covariance points to the lasting importance of these covariates in the management of people suffering from pain and depression, irrespective of age or frailty status.

The covariance over time remained unexplained for 60%. Non-measured covariates can explain part of the remaining covariance, for instance genetic factors or childhood adversities. Moreover, although the accuracy of the self-report data on chronic disease has been shown to be accurate, they were not measured in as much detail as would have been possible in clinical studies; this can be another reason for the unexplained co-variance.

A unique aspect of the present study is the longitudinal design with a follow-up time of 13 years; consequently, cohort effects are minimized, which is one of the caveats in cross-sectional designed studies. Aging was defined in a number of ways and by introducing frailty, the heterogeneity of aging was also accounted for. The use of LMM techniques also makes it possible to correct longitudinally for a number of relevant
covariates, resulting in a more precise estimate of the associations over time. Moreover, the present dataset included a comprehensive set of covariates, encompassing multiple health domains relevant in old age.

Besides these advantages, limitations should be mentioned. As with all longitudinal studies among older people, an important limitation is loss to follow-up, for which the most frail respondents are at risk. Selection bias is particularly worrisome in the case of the absence of an effect. Although an influence due to selective loss cannot be ruled out, it was minimized in several ways. First, in LMM techniques cases with some missing values can be included in the analyses, thereby minimizing selection bias. Second, of those respondents included, the range of all variables was wide, so not only the healthiest respondents were included in the analyses. Another limitation might be the underreporting of specific somatic conditions related to pain in old people such as polymyalgia rheumatica and Paget’s disease. Therefore, the 40% of variance explained by somatic and psychological characteristics may be an underestimate. We nevertheless think most of the relevant diseases were captured in the data-set, since the 7 most prevalent chronic diseases supplemented by any chronic disease were included in the analyses.

In old people the association between pain and depression is tight and it is not influenced by aging or frailty status. An important part of the covariance between pain and depression can be explained by somatic comorbidity and psychological characteristics. The management of co-occurring pain and depression should be similar for all aged people, encompassing both somatic and psychological factors, irrespective of age or frailty status.

A recent study showed that age is a risk factor for suboptimal pain treatment. Moreover, in adults cognitive therapies appear effective in the management of chronic pain. Our study is a strong argument not to withhold any effective somatic or psychological treatment in patients suffering from both pain and depressive symptoms, irrespective of age or frailty status.
REFERENCES


