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Interventions Targeting Smoking Cessation for Patients with Chronic Pain: An Evidence synthesis

Bruno T Saragiotto^{1,2,3}, Steven J Kamper^{3,4}, Rebecca Hodder^{1,3}, Priscilla V Silva^{1,3,5}, Luke Wolfenden^{1,5}, Hopin Lee^{1,3,6}, Vinicius C Oliveira⁷, Emma Robson^{1,3,5}, John Wiggers^{1,5}, Christopher M Williams^{1,3,5}

¹ School of Medicine and Public Health, Hunter Medical Research Institute, University of Newcastle, Newcastle, Australia.

² Masters and Doctoral Program in Physical Therapy, Universidade Cidade de Sao Paulo, Sao Paulo, Brazil.

³ Centre for Pain, Health and Lifestyle.

⁴ The University of Sydney, School of Public Health, Australia.

⁵ Hunter New England Population Health, Hunter New England Local Health District, Wallsend, Australia.

⁶ Centre for Statistics in Medicine, Rehabilitation Research in Oxford, Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, UK.

⁷ Postgraduate Program in Rehabilitation and Functional Performance, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Brazil.

ABSTRACT

Introduction: Smoking is a risk factor for chronic pain conditions. Epidemiological evidence suggests that smoking cessation may be an important treatment target in people with chronic pain. The aim of this study was to examine the effectiveness of smoking cessation interventions in people with chronic pain.

Methods: We systematically searched for clinical trials investigating the effectiveness of smoking cessation interventions for people with chronic pain, compared to any control comparator. Primary outcomes were pain and physical function. Secondary outcomes were smoking status, quality of life, psychological and cognitive function, and adverse events. We assessed risk of bias using the Cochrane Risk of Bias criteria, and the quality of evidence with GRADE.

Results: Searches retrieved 3,845 records and identified two trials for inclusion (total n=99 participants). There was low quality evidence of no effect of smoking cessation programs on pain and very low quality evidence of no effect on function at short term follow-up. There was conflicting evidence on the effect of smoking cessation interventions for changing the smoking status, and number of cigarettes consumed per day. There was no effect on depression and anxiety.

Conclusion: Current evidence does not indicate clinically important effects of smoking cessation interventions in people with chronic pain. There is a need for high quality trials in this area.

Implications: Our review highlights an important evidence gap. We found only two studies investigating smoking cessation programs for chronic pain conditions providing very low to low quality evidence.

INTRODUCTION

Chronic pain affects up to one third of the adult population and is responsible for an enormous societal burden.¹ The most common causes of chronic pain are musculoskeletal disorders of the back, neck and upper limbs; as well as osteoarthritis of the knee and hip.² In the recent global burden of disease study, musculoskeletal pain accounted for more than 20% of years lived with disability in the population.² Chronic pain disorders also impose enormous costs to countries due to high levels of health care use, morbidity and work absenteeism.³

Smoking is one health behaviour consistently associated with chronic pain, suggesting it is an important risk factor for many chronic pain conditions, including back pain, sciatica and rheumatoid arthritis.⁴⁻⁶ There are some possible mechanisms to explain the association between smoking and chronic pain conditions, but the most common may be related to the malnutrition of cells by carboxy-hemoglobin-induced anoxia and increased sensitivity of pain receptors in the brain.⁷⁻⁹ There is evidence that those with chronic pain who are smokers present with more severe symptoms, have poorer treatment outcomes, and more symptoms of depression compared to non-smokers.¹⁰⁻¹² As such, smoking cessation has been suggested as a potentially important treatment target in people with chronic pain.^{13, 14} Despite this potential, to our knowledge there is no systematic reviews to synthesise the state of this evidence. The aim of this systematic review is to examine the effectiveness of smoking cessation interventions compared to active or inactive controls on improving pain and function in people with chronic pain at short, intermediate, and long-term follow-up.

METHODS

This systematic review is reported according to PRISMA recommendations,¹⁵ and the protocol was prospectively registered on PROSPERO (2017: CRD42017073643).

Data Sources and Searches

We searched the following databases from inception to June 2018: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, MEDLINE in Process, EMBASE, CINAHL, AMED, and PsycINFO. The reference lists of included studies were searched. We did not place any restriction to language of publication. We used a combination of keywords to construct the search strategy (supplementary file 1). Two independent reviewers screened titles, abstracts, and full text articles for inclusion (BS, RH/PS). Disagreements were resolved by discussion and where required with input from a third reviewer (SK).

Study Selection

We considered randomised and quasi-randomised (e.g. allocation by hospital record number, birth date, or alternation) controlled trials. To be eligible, trials had to include participants, who were current smokers, with chronic pain (pain lasting ≥ 3 months) of any location verified by clinical or radiological diagnosis. There were no restrictions on participant age or care settings. We excluded trials that included participants with serious underlying causes of their pain (i.e. fracture, infectious disease, cancer).

We included trials that tested an intervention with the intent of reducing smoking behaviour (e.g. pharmacological, physical activity programs, behavioural or psychological treatments, acupuncture, or a combination of these). Interventions could be single or multicomponent. We considered all trials with a comparison group that received any active or inactive control intervention (e.g. placebo, another intervention, usual care) or no intervention (e.g. wait-list controls).

Primary outcomes were pain intensity or physical function related to chronic pain, measured using a valid instrument. The secondary outcomes were: a measure of smoking status (e.g. sustained smoking cessation, abstinence, self-reported quit data, percentage abstinent in the intervention and control group); quality of life; psychological function (e.g. depression, anxiety, fear avoidance, coping, self-efficacy); participant adherence, participant satisfaction with the treatment; and adverse events.

Data Extraction and Quality Assessment

Data extraction and quality assessment was completed independently by two reviewers (BS and PS) and any disagreements were resolved by discussion and, where required with input from a third review author (SK). We used a standardised data extraction form to extract information regarding study characteristics (design, study population, inclusion/exclusion criteria, intervention and comparison groups), and primary and secondary outcomes. We contacted the authors, and received additional data regarding the outcomes pain, depression and anxiety for one trial.¹⁵

We assessed risk of bias using the Cochrane Back and Neck Review Group 12-item criteria.¹⁶ We categorised trials as 'low risk' (at least six of the 12 criteria met) or 'high risk' (fewer than six criteria met). The quality of evidence was rated for each comparison with the GRADE system based on four domains: 1) study design and risk of bias, downgraded if $>25\%$ of the participants were from studies with a high risk of bias; 2) inconsistency of results, downgraded if significant heterogeneity was apparent on visual inspection or I^2 statistics $>50\%$; 3) indirectness (generalisability of the findings), downgraded if $>50\%$ of the participants were outside the target group); and 4) imprecision, downgraded if fewer than 400 participants were included in the comparison for continuous data and there were fewer than 300 events for dichotomous data. We did not downgrade for publication bias

due to the small number of studies included. The quality of evidence was rated as high, moderate, low or very low.

Data Synthesis and Analysis

We conducted separate random-effects meta-analyses for the following follow-up points: short (less than three months after randomisation), intermediate (at least three months but less than 12 months) and long-term (12 months or more). Heterogeneity was analysed by visual inspection of the forest plots and the I^2 test for comparisons including more than one study. We expressed pooled effects of continuous variables as mean differences (MD) and 95% confidence interval (CI) if the same outcome measure were used, and standardised mean differences (SMD) if different measures were used. For dichotomous outcomes, we calculated risk ratios (RR) with 95% CI. In the event that SMDs were statistically significant, we planned to calculate the MD in units of a common measure for that construct to interpret clinical relevance. Effect sizes were categorised in three levels: small (MD < 10% of the scale), medium (MD 10% to 20% of the scale), or large (MD > 20% of the scale).²² We deemed an effect to be clinically important when the effect size was at least medium ($\geq 10\%$ of the scale).¹⁷ We prioritised intention-to-treat analyses over per-protocol analyses if available.

We planned to perform a sensitivity analysis to explore the influence of risk of bias on pooled treatment effects of the primary outcomes, and subgroup analyses for the type of interventions. However, this was not possible due to the small number of included studies.

RESULTS

The searches retrieved 3,845 records, after screening of titles, abstracts, and full text articles, we included 2 randomised controlled trials (n=99 participants) (supplementary file 2)^{18, 19}. One trial included patients with non-cancer pain¹⁹ and the other included patients with Rheumatoid Arthritis.¹⁸ Most patients were women (69%), mean age was 49.6 years (SD 12.6). One trial included a 3-month tailored smoking cessation program, and the other trial included a 7-session (3 week), cognitive behavioural smoking abstinence program (Table 1). Control groups were; standard smoking cessation advice,¹⁸ and a 1-hour smoking abstinence intervention.¹⁹

Both trials were considered to have low risk of bias (supplementary file 3). However, allocation concealment was unclear for one trial¹⁸ and blinding of patients or care provider was not possible for both trials. Neither trial reported information on co-interventions. Registered protocols were available for both trials.

Primary outcomes

Meta-analysis of the two studies showed there was low quality evidence of no significant effect of the smoking cessation programs on pain at short term (SMD -0.33, 95% CI -0.79 to 0.12, 2 trials, $I^2=0\%$). Based on a single study, there was low quality evidence of no significant effect of the smoking cessation programs on pain at intermediate term (MD -0.27, -2.06 to 1.52) and for the outcome function at short term (MD -3.3, 95%CI -11.73 to 5.13) (Table 2).

Secondary outcomes

There was very low-quality evidence of no difference in smoking status between groups at short term (RR 0.78, 95% CI 0.60 to 1.01) based on one single study; however there was low-quality evidence from meta-analysis of a significant reduction in smoking status at intermediate term (RR 0.83, 0.70 to 0.98, $I^2=0\%$) based on two studies. The mean number of cigarettes consumed per day was significantly less in the smoking cessation group at short term (MD -6.90, -12.07 to -1.73), but there is very low-quality evidence that there was no difference at intermediate term, both based on one single study. Meta-analysis of two studies showed there was low quality evidence of no difference between groups at short term for depression (SMD 0.29, -0.16 to 0.73, $I^2=0\%$) and very low quality evidence of no difference at intermediate term based on one single study (MD 0.79, -3.25 to 4.83). For anxiety, there was no difference between groups at short term based on two studies and low quality evidence (SMD -0.02, -0.46 to 0.43, $I^2=0\%$), and intermediate term based on a single study and very low quality evidence (MD 1.89, -2.71 to 6.49).

DISCUSSION

The current evidence does not indicate clinically important effects of smoking cessation programs for improving outcomes in people with chronic pain. The evidence suggests a reduction in smoking status and for the number of cigarettes consumed per day in one study; however, the effect attenuated over time. However, this is based on two studies providing very low to low quality evidence.

Smoking cessation interventions have been successfully integrated into the management of other health conditions (e.g. posttraumatic stress disorders, cardiovascular diseases),^{20, 21} but it seems that the relationship between smoking and chronic pain may be more complex. Smoking may limit the delivery of oxygen-rich blood to bones and tissues, decreasing blood and nutrient flow, which can lead to degeneration, fatigue and slower healing, and make chronic pain conditions worse.¹⁴ However, nicotine itself has been reported as having analgesic properties.^{8, 9} There is emerging evidence on the acute analgesic effects of nicotine through the possible activation of nicotinic acetylcholine receptors distributed through the central and peripheral nervous systems.⁹ Further, previous studies showed that people with chronic pain perceive smoking as a way to cope with pain and distress, and have concerns that abstinence would result in worsening of their pain.^{13, 22} These patients also see smoking as a

distraction from their pain, which can also lead to pain reduction through neurophysiologic changes in the brain.^{13, 23} These observations make smoking cessation programs for people with chronic pain a particular clinical challenge.

This review also raises the question of whether smoking cessation programs designed for the general (smoking) public are directly transferrable to this population. It is likely that people with chronic pain face unique barriers to cessation. If so, smoking cessation interventions should be adapted to address specific barriers and meet the needs of people with chronic pain. Our review did not find any evidence for adapted cessation programs.

To our knowledge, this is the first systematic review investigating smoking cessation interventions for chronic pain. The strengths of this review include the methodological quality, due to following recommendations of the Cochrane Collaboration, and the use of the GRADE approach for assessing the quality of evidence. A limitation was that we only identified two small trials that included two diverse conditions. We considered pooling of the findings of these two trials appropriate because our study question concerned the issue of chronic pain, regardless of specific pathological cause. Readers can interpret the disaggregated results provided in Table 1.

Smoking cessation for patients with chronic pain remains an important clinical challenge. These patients are more likely to smoke, and smoking is suggested to influence pain and disability. Our review shows there is a paucity of evidence to conclude if smoking cessation can improve pain or disability in people with chronic pain. However, arguably reducing smoking in this population is equally important to reduce their overall chronic disease risk. More high-quality trials are needed in this area.

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Table 1. Characteristics of the included studies.

Author (Year)	Country	Participants	Female, n (%)	Age, mean (SD)	Symptom duration (years), mean (SD)	Outcomes	Intervention	Comparison	Main results
Aimer 2017 ¹⁸	New Zealand	39 smokers with Rheumatoid Arthritis (RA) as defined by the 2010 ACR/EULAR	21 (55%)	56.5 (11.8)	7.7 (8.4)	Pain, smoking status, cigarettes consumption, depression and anxiety at 3 and 6 months.	3-month tailored smoking cessation program (incl. barriers to smoking cessation, information on RA and smoking, pain, exercise, and coping strategies)	Standard smoking cessation advice	No significant difference in smoking cessation rates or number of cigarettes smoked daily between groups.
Hooten 2014 ¹⁹	USA	60 smokers with chronic non-cancer pain	47 (78%)	42.7 (13.5)	9.2 (7.8)	Pain (0-100 VAS), function (SF-36 physical function),	7-session cognitive behavioural smoking abstinence intervention	1-hour smoking abstinence	Statistically significant effect for

smoking status, cigarettes consumption, depression (CES- D), anxiety (PASS- 20) at 3 weeks and 6 months.	(incl. individual and group sessions based on the barriers and facilitators to smoking cessation)	intervention	pain and function for the intervention group. The number of cigarettes smoked daily decreased.
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SD: Standard deviation, **VAS:** Visual Analogue Scale, **CES-D:** Center for Epidemiologic Studies-Depression scale, **PASS-20:** Pain Anxiety Symptoms Scale short version.

Table 2. Summary of findings and quality of evidence

Outcome	Follow-up	Number of participants (Studies)	Effect Size (95% CI)	Quality of Evidence (GRADE)	Comments
Primary outcomes					
Pain	Short term	79 (2 studies)	SMD -0.33 (-0.79 to 0.12)	Low	The difference is not statistically or clinically significant
	Intermediate	15 (1 study)	MD -0.27 (-2.06 to 1.52)	Very low	The difference is not statistically or clinically significant
Function	Short term	60 (1 study)	MD -3.30 (-11.73 to 5.13)	Very low	The difference is not statistically or clinically significant
Secondary outcomes					
Smoking cessation	Short term	60 (1 study)	RR 0.78 (0.60 to 1.01)	Very low	The difference is not statistically or clinically significant
	Intermediate	98 (2 studies)	RR 0.83 (0.70 to 0.98)	Low	Statistically significant difference favouring intervention

Cigarette consumption per day	Short term	60 (1 study)	MD -6.90 (-12.07 to -1.73)	Very low	Statistically significant difference favouring intervention
	Intermediate	38 (1 study)	MD 1.40 (-4.28 to 7.08)	Very low	The difference is not statistically or clinically significant
Depression	Short term	79 (2 studies)	SMD 0.29 (-0.16 to 0.73)	Low	The difference is not statistically or clinically significant
	Intermediate	15 (1 study)	MD 0.79 (-3.25 to 4.83)	Very low	The difference is not statistically or clinically significant
Anxiety	Short term	79 (2 studies)	SMD -0.02 (-0.46 to 0.43)	Low	The difference is not statistically or clinically significant
	Intermediate	15 (1 study)	MD 1.89 (-2.71 to 6.49)	Very low	The difference is not statistically or clinically significant

SMD: Standardised Mean Difference, **MD:** Mean Difference, **RR:** Risk Ratio, **CI:** Confidence Interval. For outcomes pain, function, cigarettes consumption, depression, and anxiety, a negative effect size represents and effect in favour of the intervention group.