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Effectiveness of Pharmacist-led medication review management: Systematic Review and Meta-Analysis

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Objective: To evaluate the effectiveness of pharmacist-led medication review in chronic pain management.

Methods: Six electronic databases (Medline, Embase, PsycInfo, CINHAL, CENTRAL, International Pharmaceutical Abstracts) reference lists of retrieved articles and relevant websites were searched for randomised controlled trials (RCTs) published in the English language involving adults with chronic pain. Studies were included if one of the intervention arms had received pharmacist-led medication review independently or as part of a multidisciplinary intervention. Risk of bias was assessed for all the included studies.

Results: The search strategy yielded 583 unique articles with five RCTs included. Compared to control, meta-analysis showed that participants in the intervention group had: a 0.8 point reduction in pain intensity on a 0 to 10 numerical rating scale (NRS) at 3-months (95% CI, -1.28 to - 0.36) and a 0.7 point reduction (95% CI -1.19 to - 0.20) at 6-months; a 4.84 point (95% CI, -7.38 to -2.29) and -3.82 point (95% CI, -6.49 to -1.14) improvement in physical functioning on a 0 to 68 point function subscale of Western Ontario and McMaster Universities Arthritis Index (WOMAC) at 3-months and 6-months respectively; and a significant improvement in patient satisfaction equivalent to a 'small to moderate effect.'

Discussion: Pharmacist-led medication review reduces pain intensity and improves physical functioning and patient satisfaction. However, the clinical significance of these findings remain uncertain due to small effect size and nature of reported data within clinical trials which limits recommendation of wider clinical role of pharmacist in chronic pain management.

Keywords: Pharmacist; Medication review; Chronic pain; Systematic review

Introduction

High prevalence, associated long term morbidity and lack of a permanent cure make chronic pain one of the most challenging diseases to manage. In the USA, chronic pain affects more than 100 million people and the prevalence is higher than for diabetes, heart diseases and cancer combined.[1] In Europe, one in every five adults suffers from chronic pain of moderate to severe intensity.[2] Both prescription and non-prescription analgesics are extensively used in chronic pain management but inappropriate and suboptimal use of analgesics has been reported.[3] In 2007, almost 12,000 cases of unintentional drug poisoning involving prescription analgesics[4] were reported and in 2008, almost 15,000 people died due to overdoses of opioid analgesics in the USA alone.[5] Therefore, the safe and effective use of analgesics is critical to ensure optimum analgesia, to prevent adverse effects and drug related problems, and to minimise abuse of analgesics.

Over the past decade, with the increase in the number of nurse and pharmacist prescribers, researchers have become interested in evaluating the effectiveness of their extended clinical role in the management of different diseases and settings.[6-9] For chronic pain, the limited capacity of general practioners (GPs) and long waiting times for appointments in secondary care[10] present an opportunity for healthcare professionals other than GPs to take on key aspects of chronic pain management. Studies evaluating the role of the pharmacist in chronic pain have reported mixed results.[11] A meta-analysis of the effectiveness of pharmacist-led educational interventions for chronic pain management showed a statistically significant reduction in pain intensity and adverse effects, and an improvement in patient satisfaction in those receiving interventions.[11] However, no benefit was seen in interference from pain on daily life and self-efficacy. Furthermore, the reduction in pain intensity was statistically, but not clinically, significant.

Since no systematic review has yet evaluated the effectiveness of pharmacist-led medication review for chronic pain management, the aim of this systematic review was to fill this gap. The systematic review was prospectively registered with PROSPRO (Registration number: CRD42012001957) and the protocol has been previously published.[12]

MATERIALS AND METHODS

Study Selection

The following databases were searched between April-June 2012 using a pre-defined search strategy.

- MEDLINE (via Ovid) …….(1946 to June 2012),
- EMBASE (via Ovid)…….. (1947 to April 2012)
- Cochrane Central Register of Controlled Trials……. (Issue 6 of 12, June 2012)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EMBSCO)….. (1960 to June 2012),
- PsycINFO…….. (1806 to June 2012)
- International Pharmaceutical Abstracts (via Ovid)…….. (1970 to June 2012)

We searched for randomized controlled trials (RCTs) and non-randomized studies (quasi-experimental, controlled before-and-after study) having at least one control group Non-randomized studies were only to be considered for inclusion if fewer than three RCTs were eligible for inclusion on searching. Waiting list controls, usual care, attention only and any other active control were accepted as appropriate controls. Studies were considered for inclusion if one of the intervention arms received either pharmacist-led medication review delivered

independently, or as part of complex multidisciplinary interventions, where the pharmacist was part of the multidisciplinary team. Websites of American, Canadian and Royal (British) Pharmaceutical societies were also searched together with the reference lists of the retrieved articles to identify additional eligible studies. Where necessary, the corresponding authors of the included studies were contacted to obtain additional information and to identify any unpublished studies. The full search strategy is available from the corresponding author on request.

Studies involving chronic pain patients 18 years and older were included regardless of participants' gender, type and aetiology of chronic pain. We used The International Association for the Study of Pain (IASP) definition of chronic pain: *"Pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be 3 months)"*.[13] Studies involving patients with malignant or cancer pain were excluded to avoid clinical heterogeneity. Studies published in the English language (full text or abstract) were only considered. Study titles and abstracts of the studies were screened independently by two authors (MAH and DPA). Full texts of all studies considered potentially relevant were retrieved. Finally, MAH and DPA independently selected studies meeting the pre-defined inclusion criteria. Disagreements were resolved through discussion and if agreement was not reached, a third review author (MB) was consulted.

Assessment of risk of bias and data extraction

The risk of bias was assessed using the Cochrane Collaborations' tool for assessing risk of bias by one reviewer (MAH) and verified by another reviewer (SJC) using a standardized form.[14] This tool is domain-based as opposed to a checklist or scale (see Results for domains). For cluster randomized controlled trials, risk of bias was assessed across two additional domains including loss of clusters and appropriate statistical analysis. Each domain was assessed and

categorised into low risk of bias, high risk of bias or unclear risk of bias based on the recommendations of Higgins and Green.[14] Disagreements were resolved through discussion and if consensus was not reached a third reviewer (MB) was consulted.

Data were extracted by MAH and verified by MB using a standardized data collection form. The data collection form was pilot tested. Disagreements were resolved through discussion, and if no consensus was reached, opinion of a third reviewer (SJC) was requested.

Data synthesis

Review Manager (RevMan 5.1) was used for data analysis. Mean difference (MD) was calculated for all continuous variables (e.g. pain intensity) when outcomes were measured using the same scale and when different scales were used, standardized mean difference (SMD) was calculated with corresponding 95% confidence intervals. Relative risk (RR) with 95% confidence intervals was calculated for dichotomous variables. The decision to pool data using meta-analysis was based on the clinical homogeneity in terms of the population, intervention, outcome measures and timing of outcome measures of all the included studies. Clinical homogeneity was determined by discussion among the review authors and clinically heterogeneous trials were not combined statistically**.** Statistical heterogeneity was determined by using chi-square (χ^2) and I^2 statistic. Statistical heterogeneity determined the choice of using a random- or fixed-effects model for meta-analysis. A χ^2 P value of greater than 0.1 and an I^2 value of less than 50% was used to indicate statistical homogeneity.[14] A random-effects model was used to combine clinically homogeneous but statistically heterogeneous clinical trials, whereas clinical and statistical homogenous trials were combined using the fixed-effects model.

RESULTS

Characteristics of Included Study

Six hundred and sixty-four articles were retrieved through database searches (578 after de-duplication). Of these 578, 27 were considered relevant after title and abstract screening. An additional five articles were found including two each through author contact and reference list searching, and one through website searching. Of these 32 articles, nine reports of five studies met the inclusion criteria for review.[15-23] Figure 1 illustrates the search process and the reasons for exclusion. Two trials were conducted in the UK[19-21] and one each in Canada,[22] Germany,[18] and the USA.[23]

The included studies comprised three individually randomized [19,21,23] and two cluster randomized controlled studies [18,22] randomizing 1035 patients in total. All followed up the patients for at least 3 months, three for 6 months and one for 12 months. All studies had their first follow-up at 3-months except for Hoffman et al[18] where follow-up was at 4 months. In total, 131 patients (12.7%) were lost to the first follow-up. Two trials included patients with chronic pain of various aetiologies,[21,23] another two involved patients with knee pain associated with osteoarthritis [19,22] and one involved chronic headache and migraine patients.[18] In four trials where gender was reported, the majority of the participants were females (61.8%).[18,19,22,23] The mean age of participants varied between 62.7 years (S.D.±9.2) in Marra et al study,[22] 67.9 years (S.D.±8.2) in the Hay et al.[19] study and 42.70 years (S.D.±13) in the Hoffman et al. study.[18] The study by Bruhn et al.[16,21] did not report age and participants in the Gammaitoni et al.[23] study ranged from 35-64 years.

Nature and delivery of Intervention

In three trials[18,19,21] the intervention was pharmacist-led medication review alone while in the other two [22-23] the intervention involved medication review as part of a multi-component intervention (Table 1). In the Marra et al study,[22] the intervention also comprised two components. First was a face-to-face consultation with a pharmacist who educated patients on aspects of osteoarthritis (OA), conducted medication review to ensure safe use of analgesics, referred patients to a physiotherapist-guided exercise programme (second component) and requested patients' primary care physicians to approve their inclusion in the exercise programme. Over the 6 months follow-up period, 297 patient-pharmacist consultations generated 255 comments and recommendations, including 49 medication-related recommendations to patients' primary care physician. The pharmacist also followed the patients' progress monthly for six months. The physiotherapist recommended an individualized home exercise programme after a one-hour consultation with each patient. The participants attended an exercise class twice per week for six weeks. Participants in the control group received an educational leaflet on knee OA developed by the Canadian Arthritis Society.

In the Gammaitoni et al trial,[23] the intervention had two components. The first was a specialised prescription service provided by a palliative care pharmacy company (PainRxperts) which delivered patients' medication to their home or to the clinic. The aim of the service was to improve accessibility to pain medicine and reduce the burden of managing medication treatment for clinical practice. The second component was proactive monitoring of patients' medication therapy for any potential or actual drug related problem (DRP) by a palliative care trained pharmacist to ensure that the drug therapy was achieving an improvement in quality of life. In total, 81 phone calls were made by the pharmacist including 45 to patients (mean 1.2 calls per

patient) and 36 to the clinic staff. Most calls concerned patient monitoring/administration of the Brief Pain Inventory (BPI) (n=36),[24] questions about medication use (n=22) and delivery of medications (n=11). On average, each patient contact lasted 12 minutes, and 9 minutes for clinic staff. Fifteen out of 16 recommendations made to the clinic staff were accepted, including: addition of an adjuvant (n=4), drug change (n=2), dose change (n=3), frequency change (n=2), or dosing conversion (n=5). The control group received usual care as prior to study with the exception of filling in questionnaires at baseline and 3 months follow up.

Hay et al,[17,19] used two independent intervention groups: pharmacy review group and community physiotherapy group. Data for the pharmacy review group only was extracted and presented in this systematic review. Participants in the pharmacy review group received an enhanced pharmacy review plus an education leaflet from an experienced community pharmacist in general practice surgeries with access to patients' medical records. The trial protocol permitted three to six sessions of approximately 20 minutes each over 10 week period. The pharmacist used a pre-defined set of questions for initial assessment and optimized/changed drug therapy, if necessary, based on an algorithm and clinical needs. In total, 335 pharmacist-patient consultations took place (mean 3.2 per patient; range 2-5). The mean time spent per patient was around 63 minutes in 3 sessions. Participants in the control group received the same education leaflet and a telephone call from a rheumatology nurse to reinforce the leaflet advice within seven days of randomization.

In the Hoffmann et al study,[18] the intervention group received an individualized counselling session by trained community pharmacists with the aim of optimising pharmacotherapy, promoting self-management, goal setting and pacing activities. Each patient received approximately two hours of counselling and each pharmacy counselled 4.6 ± 3.06

patients on average (range 1-15). Participants in the control group continued to receive usual pharmaceutical consultations with pharmacists who were not formally trained in headache/pain management.

In the Bruhn et al study,[16,20,21] there were two independent intervention groups: pharmacist medication review either with recommendations to the GP or pharmacist prescribing. Further data on the nature and duration of the intervention were not available. Authors were contacted but unable to provide data due to funding restrictions.

Risk of bias

Three trials [19,22,23] described adequate methods for random sequence generation (Figure 2). Hay et al.[19] used a random number generator which allocated to intervention or control groups in pre-determined sequence blocks of six by general practice. The study statistician generated values from a uniform (0, 1) distribution in the Marra et al study [22] and a computer programme was used to randomly assign the names to either the intervention group or the control group in the Gammaitoni et al trial.[23] However, Gammaitoni et al did not describe how the selection of 107 patients from pain clinics was undertaken prior to this random allocation to groups.[23] Methods of random sequence generation were not adequately explained by Bruhn et al [21] and Hoffman et al.[18] Only Hay et al.[19] described an adequate method of allocation concealment (sequentially numbered opaque envelops). Allocation concealment was not possible for the cluster randomized trials [18,22] and is not considered an issue.[14]

In all the trials, it was impossible to blind pharmacists delivering the intervention and the participants receiving it due to nature of intervention. Outcome assessors were blinded in two trials only [19,22] and Hoffmann et al [18] who collected data through a computer aided, standardized

telephone interview but it was not made clear whether people who handled and analysed the data were blinded or not.

All trials [18,19,21,22] except one [23] used the intention to treat principle for analysing their data, minimizing attrition bias. There was low risk of selective reporting of an outcome across four trials [18,19,22,23] and unclear risk in one of the trials. Although the study protocol was available for only one study,[22] low risk was assigned to other trials since the authors reported outcomes with non-significant P-values as well.

There were no baseline differences between intervention and control groups in any of the trials except one. In the Marra et al trials,[22] there were significant differences at baseline in pain scores measured by the Health Utilities Index-3,[25] a generic instrument to measure quality of life, between intervention and usual care groups but there were no significant differences in pain scores when measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale.[26] Furthermore, participants in the intervention group were slightly more educated (86% reported more than high school education compared to 79%), belonged to higher socioeconomic class (71% reported an income over $50,000 compared to 59%) and were of Asian origin (21% compared to 9%) compared with the usual care group.

Only one patient was lost to follow up in each group in the Marra et al. [22] study and the authors took "clustering" into consideration in sample size calculation and data analysis. However, in the Hoffmann et al cluster randomized trial,[18] the authors did not use appropriate statistical techniques and did not allow for the clustering effect in sample size calculation and data analysis.

Outcomes assessment

Pain intensity

Pan intensity was reported in the all the trials using different scales. Gammaitoni et al.[23] measured pain intensity on a 0 to 10 numerical rating scale (NRS) where 0 = no pain and 10= pain as bad as you can imagine and the Health Background Questionnaire-Initial Patient Visit. [27] Hay et al.[19] reported pain intensity with the NRS and on a 0 to 20 subscale of WOMAC.[26] Bruhn et al.[21] assessed pain intensity using the pain intensity subscale of the chronic pain grade questionnaire (CPG), a 7-item questionnaire to measure pain intensity, severity and functional disability.[28] Marra et al. [22] measured pain intensity on a 0 to 10 pain subscale of WOMAC while Hoffman et al. [18] measured it on a 1 to 10 numerical rating scale where 1=no pain and 10=pain as bad as you can imagine. Although pain intensity was measured using different scales in Gammaitoni et al, [23] Hay et al [19] and Mara et al,[22] all the scales ranged from 0 to 10 where 0 = no pain and 10 = pain as bad as you can imagine.

Four studies showed a significant reduction in pain scores at follow-up. [18-22] Although, Hay et al.[19] reported a statistically significant reduction in pain scores at 3-month follow up ($p=0.04$), they were not significant at 6 ($p = 0.3$) and 12 months ($p=0.5$). However, Marra et al.[22] reported a statistically significant reduction at both 3 and 6 month follow ups (both $p<0.05$). In the study by Hoffmann et al,[18] there was a significant reduction in 'untreated' pain intensity in both intervention ($p<0.001$) and control group ($p<0.001$); however, reduction in 'treated' pain intensity remained non-significant in both intervention ($p=0.52$) and control groups ($p=0.92$) at 4-month follow up.

Pain scores were pooled using meta-analysis. The study by Hoffmann et al.[18] involved patients with chronic headache and migraine so was clinically heterogeneous and not combined statistically. The data reported by Bruhn et al.[21] was insufficient for meta-analysis. Since pain intensity was measured on different scales, the standardized mean difference (SMD) and corresponding standard error were calculated for each of the three studies. For the purpose of meta-analysis, change in score from baseline rather than final score was used as it is more efficient and powerful, eliminating between-person variability.[14] If the 'adjusted' change in score derived from regression model accounting for baseline measurements was reported, it was preferred over the crude change in score to calculate SMD, as statistically, adjusted scores are considered most precise and least biased.[14] Meta-analysis was undertaken for 3 and 6 month follow-ups.

Compared with the control group, there was a significant reduction in pain intensity in the intervention group with SMD of – 0.37 (95% confidence interval - 0.58, - 0.16) (Figure 3). This corresponds to a 0.83 point reduction on an 11 point NRS (95% confidence interval -1.28, - 0.36). There was no heterogeneity in the result (I^2=0%). Only two studies reported pain intensity at 6-months.[19,22] Meta-analysis showed a significant reduction in pain intensity in the intervention group compared to the control [SMD – 0.31 (95% CI -0.53, - 0.09)] corresponding to a 0.7 point reduction on a 0 to 10 numerical rating scale (95% CI -1.19, - 0.20). There was slight heterogeneity in the result (I^2=39%) [Chi^2=1.64, df=1, p=0.20] which is considered statistically non- significant.[14]

Physical functioning

Physical functioning was an outcome measure in all the studies. Marra et al.[22] and Hay et al.[19] assessed physical functioning using a 0 to 10 and 0 to 68 physical functioning subscale of WOMAC respectively.[26] Higher scores on the WOMAC subscale represented worse (limited) physical functioning. Hoffmann et al.[18] and Bruhn et al.[16] used the physical health subscale of SF-36 [29] and SF-12,[30] valid instruments to measure quality of life, respectively to assess physical functioning. Gammaitoni et al.[23] assessed pain interference with various daily activities (general activity, mood, waking, normal work, relationships, sleep and enjoyment of life) as part of PhPI, a survey instrument derived from the BPI[24] and the Health Background Questionnaire-Initial Patient Visit.[27] But instead of reporting a recommended summary score calculated from these seven interference items,[24] the authors reported each item individually.

Marra et al.[22] reported a statistically significant improvement in physical functioning at 3-months [-0.65; 95% CI (-1.20 to -0.10)] and 6-months [-0.84; 95% CI (-1.45 to -0.24)] in the intervention group compared to the control. Hay et al.[19] reported a non-significant improvement in functioning at 3 months [-2.12; 95%CI (-0.5 to 4.8)], 6 months [-0.96; 95% CI (-4.0 to 2.1)] and 12 months [-0.39; 95% CI (-3.8 to 3.0)] in the intervention group. Compared with the control group, Gammaitoni et al.[23] reported non-significant improvement in pain interference with mood (p=0.07), general activity (p=0.37), walking (p=0.92), work (p=1.00), relationships (p=0.72), sleep (p=0.62) and enjoyment of life (p=0.76) at 3-months follow up. Similarly, Hoffmann et al.[18] reported a non-significant improvement in physical health (p=0.85) at the end of the 4-month study period. Bruhn et al.[21] also reported a non-significant improvement in physical health (p=0.75) at 6-months follow-up.

Data were pooled using meta-analysis for three studies excluding Hoffman et al.[18] for clinical heterogeneity and Bruhn et al.[16] for insufficient data. Meta-analysis was undertaken at 3 and 6 months follow-up. At 3-months follow up there was a statistically significant improvement in the intervention group with SMD of -0.38 (95% CI -0.58, -0.18) compared to the control group (Figure 4). This effect is equivalent to 4.84 points (95% CI -7.38, -2.29) on a 0 to 68 point function subscale of WOMAC.[26] There was no heterogeneity in the result (I^2=0%). Two trials reported physical functioning status at 6-months.[19,22] Meta-analysis showed a significant improvement in physical functioning at 6-months follow up as well in the intervention group compared to the control group with SMD -0.30 (95% CI -0.51,- 0.09) corresponding to -3.82 points (95% CI -6.49, -1.14) on WOMAC 0 to 68 function subscale.[26] There was non-significant heterogeneity in the result (I^2=33%).

Patient satisfaction

Three studies reported patient satisfaction as an outcome.[16,19,23] Gammaitoni et al[23] assessed patient satisfaction with different components of the service using the Treatment Helpfulness Questionnaire (THQ), a validated measure to assess patient satisfaction with chronic pain management service.[31] It was modified to include measures of satisfaction with the pharmaceutical care programme, including: access to medication, pharmacy service, delivery of medication, pharmacist phone calls, time spent obtaining medications, pharmacist medication counselling and information provided by the pharmacist. Each item was ranked on a 11 point scale ranging from -5 (extremely harmful) to +5 (extremely helpful). Hay et al[19] assessed satisfaction as a dichotomous outcome (satisfied, not satisfied). For Bruhn et al,[16,21] patient satisfaction was reported in another linked abstract by Bond et al.[20] Patient satisfaction was

assessed at the end of 3-months using Likert scale ratings of statements about their pain and pharmacist consultation, and open ended questions about pharmacist consultations.[20]

In the Gammaitoni et al study,[23] patients in the intervention group were significantly more satisfied with various components of the pharmaceutical care programme including pharmacy service (p=0.001), delivery of medication (p=0.001), pharmacist phone calls (p=0.003), time spent in obtaining medications (p<0.001), pharmacist medication counselling (p=0.003), and information provided by the pharmacist (p=0.013). However, there was no significant difference in satisfaction with the whole programme domain (p=0.72) of the patient satisfaction survey. In the control group, patients were only satisfied with psychological assessment and treatment (p<0.05). It should be noted here that Gammaitoni et al[23] only compared the difference in patient satisfaction from baseline to 3-month study period in both intervention and control groups independently, but did not compare control with the intervention group. In the Hay et al study,[19] intervention group patients were significantly more satisfied with treatment at 3-months [-20%; 95% CI (-33 to -6)] and 12-months-[-19%; 95%CI (-32 to -4)] follow-up but not at 6-months [-14%; 95%CI (-28 to 1)]. Bond et al,[20] linked to Bruhn et al,[16,21] reported that 85% (38/46) of the patients in the prescribing arm were totally satisfied with the received treatment. Patient satisfaction rates were not reported for the other intervention (medication review alone) and control groups.

Data for patient satisfaction were pooled for two studies (Figure 5).[19,23] Meta-analysis showed significantly greater patient satisfaction in the intervention group with SMD -0.39 [95% CI (-0.68, -0.10)]. Using the universal rule of thumb, this effect size corresponds to 'small to moderate effect'.[14,32]

3.4.4.4. Quality of Life:

Three studies assessed quality of life (QoL).[16,18,22] Hoffmann et al[18] used the Medical Outcomes General Health Survey (SF-36), a 36-item generic tool with demonstrated validity and reliability to assess QoL.[29] Bruhn et al [21] used the SF-12,[30] a validated shorter version of SF-36.[29] Marra et al[22] assessed QoL using WOMAC (global) and Health Utilities Index-3 (HUI-3), a generic and preference-scored instrument for measuring health status and health related quality of life.[27] Higher scores on HUI-3 indicate better health.[27]

In the Hoffmann et al trial,[18] compared to the control group, there was no significant difference in the intervention group in the physical health subscale (p=0.85) of SF-36 but a statistically significant difference was found in the mental health subscale (p=0.02) of SF-36 at the end of the 4-month study period. Similarly, Bruhn et al [21] reported a significant improvement in the mental health component of SF-12 (p=0.04) but not on the physical health component (p=0.75) at 6-months follow-up. Marra et al [22] reported a significant improvement in WOMAC (Global) at 3-months [-1.99; 95% CI (-3.45, -0.54)] and 6-months [-2.40; 95% CI (-4.10,-0.71)] in the intervention group compared to the control. However, HUI-3 failed to show significant differences in QoL between the intervention and control group at 3-months [0.04; 95% CI (-0.03, 0.12)] and 6-months [0.01; 95%CI (- 0.06, 0.10)].

Meta-analysis was not undertaken as clinical heterogeneity ruled out Hoffmann et al[18] from meta-analysis and insufficient data ruled out trial by Bruhn et al. [16,21]

3.4.4.5. Adverse effects

Surprisingly, none of the studies except Phelan et al,[17] linked to the Hay et al trial,[19] reported adverse effects. Phelan et al[17] reported adverse effects in 30 patients including

constipation (10), drowsiness (8), gastro intestinal upset (8) and others (4) from prescribed analgesics at the initial consultation. During follow-up the side effects were reduced or stopped in 25 patients by amending their medication. The remaining five patients continued with their medication unchanged as the medications were effective and the side effects were tolerable.

Discussion:

Main results

The search strategy identified five studies which met the inclusion criteria. The 'grey literature' was not searched and only studies published in the English language were included in the systematic review. Pharmacists delivered interventions in different settings such as community pharmacies, [18,22] general practices [19,21] and university pain clinic[23] indicating that the intervention can be potentially delivered in multiple settings. Furthermore, the included trials involved patients with various chronic pain aetiologies, demonstrating that the pharmacist-led medication review may be effective for all different types of chronic pain conditions. Two trials originated from the UK [19,21] and one each from the USA,[23] Canada[22] and Germany [18] indicating a growing interest in evaluating the role of pharmacists in chronic pain management in the developed world. This may be due to the high disease burden of chronic pain and a growing necessity to involve other healthcare professionals such as pharmacists and nurses actively in direct patient care to reduce the workload on general practitioners (GPs)/primary care physicians (PCPs) in these countries.

The risk of bias was assessed for all of the included studies. There was low or unclear risk of bias across all the domains except for blinding of participants and personnel where there was high risk of bias across all trials. The nature of the intervention, made it impossible to blind

the pharmacists conducting medication reviews and the patients receiving it as, in most instances, the medication review was conducted face-to-face. Although the nature of intervention prevented blinding of participants and personnel, outcome assessors were blinded in two of three trials used in the meta-analysis, and in the third trial the outcome assessments were carried out using a standardized computer aided interview, minimising detection bias. The research evidence suggests that, on average, lack of blinding in RCTs is associated with a 9% increment in the intervention effect when measured as odds ratio.[33] Trials with more subjective outcomes, such as pain trials, are likely to be affected more than those which measure objective outcomes.[34] Concealment of allocation is necessary to limit selection bias but allocation concealment may not be possible for cluster-randomized controlled trials. Among the included trials, only one study [19] described an adequate method for concealment of allocation (opaque envelopes). However, treatment allocation was disclosed to study nurses by 15 of 325 participants (4.6%).[19]

Clinical homogeneity was considered before pooling data statistically. Data from a study by Hoffmann et al [18] were not considered for meta-analysis as the study involved patients with chronic headache and migraine, which is a neurological condition and has an episodic nature [35] unlike other chronic pain conditions and requires different treatment. The full report of Bruhn et al [21] study has not yet been published and the data reported in conference abstracts [16,20,21] was not enough to be pooled statistically. The corresponding author was contacted to obtain additional data but had to decline due to restrictions by the funding agency. It would be interesting to re-analyse the data once the results of Bruhn et al are available. Other trials were relatively similar in terms of nature of intervention, patient follow-up and patients' pain scores. Meta-analysis was conducted at two time points; 3-months and 6-months because the studies included in the systematic review reported follow-up results ranging from 3-months to 12-months. Combining

short with long term trials is not recommended as it produces larger treatment effect than combining longer term trials alone.[36] Furthermore, the response to placebo tends to be larger in longer trials.[37] Therefore, meta-analysis was conducted at two time points to limit any bias arising from combining short-term trials with long-term trials.

Since the trials measured the same outcomes using different scales, data were pooled using SMD for each outcome. To interpret SMD, in line with the Cochrane's guidance,[14] it was re-expressed in the units of a specific measurement scale for two of the three outcome measures that were statistically combined, pain intensity and physical functioning. This was achieved by multiplying SMDs for pain intensity and physical functioning with the standard deviation of the numerical rating scale (0 to 10) and physical functioning subscale of WOMAC (0-20) respectively. Both of the standard deviations were obtained as pooled standard deviations of baseline scores from the Hay et al study.[19] Only the summary measure of effect was back-transformed to enhance clinical interpretation. For the third outcome measure, patient satisfaction, SMD was re-expressed using rules of thumbs for effect sizes [14,31] as one of the trials[19] measuring patient satisfaction reported it as dichotomous outcome measure and the other trial [23] used a modified version of a validated questionnaire, compromising its validity and reliability .

Meta-analysis showed a statistically significant reduction in pain intensity and significant improvement in physical functioning in the intervention group compared with the control group. However, the clinical significance of these findings is arguable and needs careful consideration. The use of average results of continuous data (e.g. pain intensity) can be misleading [38] as it is argued that the population distributions of pain scores and/or pain relief are usually 'U-shaped' (rather than being normally distributed) therefore patients tend to have either very good or very

poor pain relief. Pain scores/pain relief should therefore be reported as percentage of patients responding to the treatment instead of average pain scores, to reflect the actual number improved or deteriorated. All the trials included in the systematic review reported mean pain score rather than reporting percentages of patients responding to the treatment. The meta-analysis indicates potential benefit for patients; however, there is uncertainty around the clinical significance of this benefit, limiting wider clinical implementation. Furthermore, medication review was conducted as part of multi-component interventions in three of the five studies so the "active ingredient" of the intervention is not known. However, the impact of the intervention on other drug-related outcomes such as: reduction in side effects documented by Phelan et al, [17] in a report linked to Hay et al;[19] the reduction in the use of Non Steroidal Anti Inflammatory Drugs (NSAIDS) documented in Hay et al; [19] and the high acceptance of pharmacists' recommendations suggest that pharmacist-led medication review is an important component in overall pain management and can improve patient reported outcomes.[18,22,23]

Implications for pharmacy practice and policy

With the advance of the concept of pharmaceutical care,[39] the focus of pharmacist-led services has shifted from being product-centred to patient-centred. This systematic review has identified and synthesised data which demonstrates the effectiveness of pharmacist-led medication review in chronic pain management. Findings have raised two questions which need to be considered by service commissioners and policy makers before a wider role for pharmacists in chronic pain management is put into practice. Firstly, certain issues related to delivery of the intervention such as 'how much', how often', 'how long', must be carefully considered as limited exposure to the service may not be adequate to achieve desired outcomes and prolonged

use of the service may not be cost-effective and may put an additional burden on healthcare systems. Furthermore, it is still unknown whether the pharmacist-led medication review benefits all types of chronic pain patients or only certain types of patients. However, it can be argued that medication review by an expert pharmacist may reduce drug- related problems and adverse effects in all patients irrespective of the pain aetiology. Secondly, short-courses/programs/residency-training are needed to provide specialised education and training in pain management to all the pharmacists in order to achieve maximum clinical benefit. In the past, the need for specialised training programmes has also been advocated in the literature.[40] However, to date, such training programmes are not widely available for pharmacists especially outside the USA.[41,42] Training programmes to produce skilled pharmacy human recourse in pain management is essential to ensure sustainability and clinical effectiveness of pharmacist-led pain management service.

The findings of the systematic review may not be transferable to developing countries as the pharmacy profession is in transition from 'industry-oriented' to 'patient-oriented'. Over the past decade, changes in undergraduate curriculum have been made together with the development of clinical oriented postgraduate programs [43] to equip pharmacists with necessary clinical knowledge to meet growing needs of the patients.[44,45] However, there is still a long way to go before these changes can make significant impact in transforming pharmacy practice and relevant polices in these countries.

Implications for future research:

The role of pharmacists in chronic pain management is still relatively new and requires further exploration. The current evidence suggests that pharmacist-led medication review is effective in reducing pain intensity, medication-related adverse effects and improve physical

functioning. Future research should evaluate the optimum and cost-effective mode/method and duration of delivery of the intervention to achieve maximum clinical benefit. Standardization of the intervention may not be possible due to the individualized needs of the patients especially those taking opioid analgesics may need a more frequent medication review to limit abuse and ensure safety.

Improved quality of reporting of clinical trials involving chronic pain patients is needed. In addition to CONSORT guidance on the conduct and reporting of clinical trials,[45] the researchers should also adhere to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidance in designing, conducting and reporting their findings.[36,47,48] As discussed earlier, the researchers instead of reporting average pain scores only should always report percentages of patients achieving minimally important, moderately important and substantial clinical difference.[49]

Trials involving only non-malignant pain patients were included as cancer pain would have introduced clinical heterogeneity and complicated clinical interpretation of the findings. It would be interesting to evaluate the effectiveness of pharmacist-led medication review among patients with cancer pain as effective management of cancer pain is very important in overall cancer management, especially in end of life care. Finally, the cost-effectiveness of pharmacist-led medication review in chronic pain management is yet to be evaluated and this needs addressing.

The high prevalence of chronic pain and its associated burden on healthcare systems and societies across the globe calls for high quality research to improve both diagnosis and management of chronic. Unfortunately, research into chronic pain is not well funded.[50] In 2008,

in the USA, less than one percent of National Institutes of Health (NIH) budget was given for pain research.[51] Underfunding of pain research is likely to damage initiatives to improve pain management due to a lack of research evidence.

Limitations

In terms of the design of the systematic review there were two major limitations. Firstly, only studies reported in English were included, which may have led to language bias.[52] Non-English studies were not included because the review team had no funding for professional translators. One study [53] was excluded during screening of full-texts of included studies as it was published in Spanish. However, conflicting results have been reported in the literature examining the extent of the effect of language bias on the findings of systematic reviews.[54,55] Secondly, publication bias may have been introduced as no attempt was made to locate unpublished trials (grey literature). The findings of the research evaluating the impact of inclusion or exclusion of 'grey' literature in meta-analysis of RCTs are inconsistent.[56,57] The major issue with data acquisition is that only investigators with positive results may be willing to share their results which may introduce bias in to the systematic review. Finally, the located studies may only be a small part and 'unrepresentative' of all the unpublished studies.[14] Systematic review authors in future may consider including studies not published in English as well as unpublished studies, to overcome the above mentioned limitations.

Conclusion

Pharmacists can play an important role in improving chronic pain management. They can deliver interventions independently and as part of multidisciplinary teams in both community and hospital settings. The present systematic review suggests that pharmacist-led medication review

is effective in reducing pain intensity and improving physical functioning. Furthermore, patients were generally satisfied with the service provided by the pharmacists. There is also weak evidence of preventing/stopping adverse effects associated with the use of medicines among chronic pain patients. The clinical significance of these findings remains to be established. Future clinical trials evaluating the effectiveness of pharmacist-led interventions in chronic pain must adhere to IMMPACT guidance [47,48] in designing, conducting and reporting their findings in addition to CONSORT guidance.[46] This will ensure selection of the recommended uniform outcome domains and measures, and quality reporting of the trial results facilitating not only clinical interpretation but also data synthesis in future. As the focus of care shifts from hospital to community, pharmacists especially community pharmacists have the potential to reduce the chronic pain burden on healthcare system and society by ensuring the safe and effective use of medicines.

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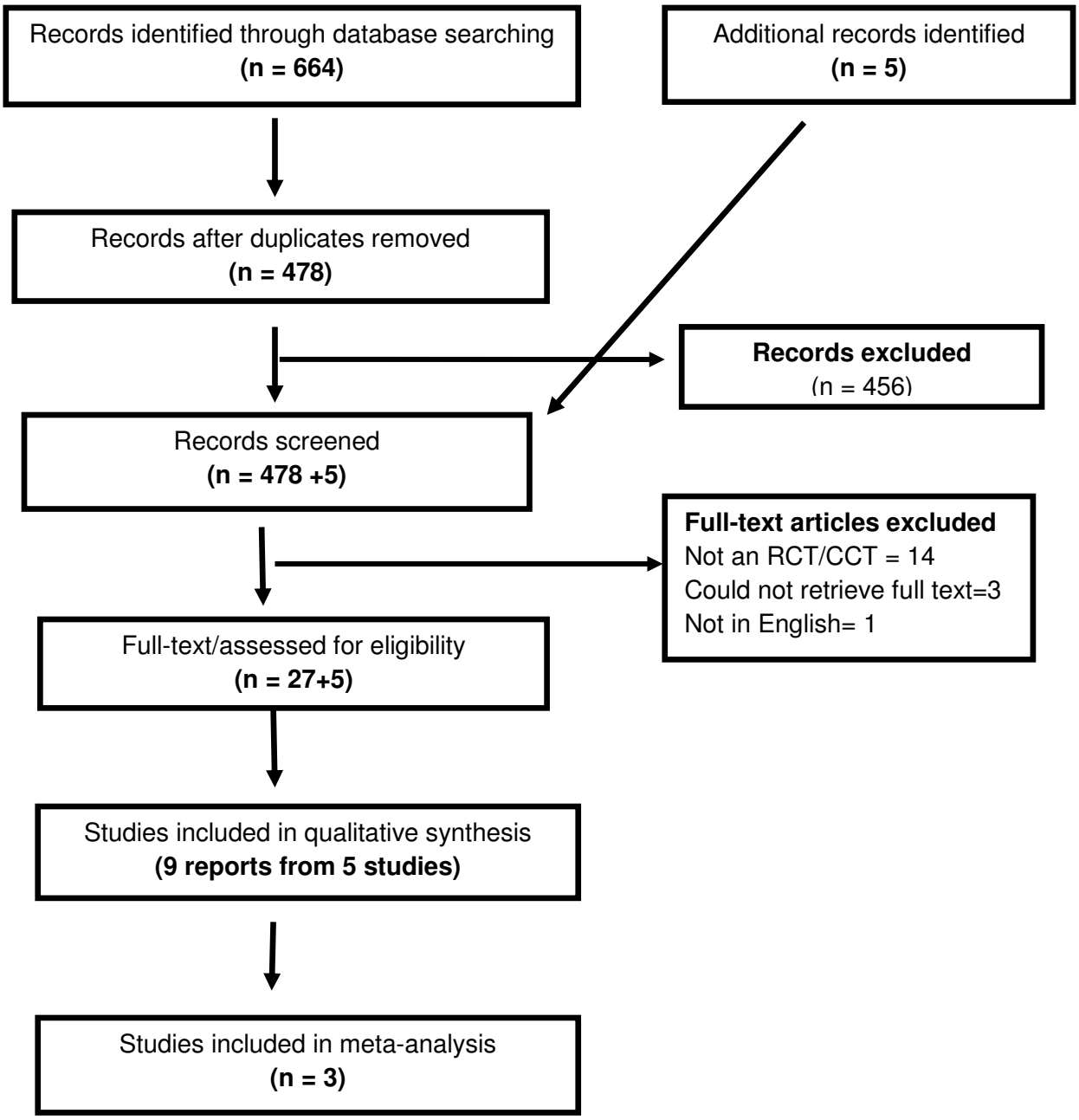

Fig 1: PRISMA flow Diagram

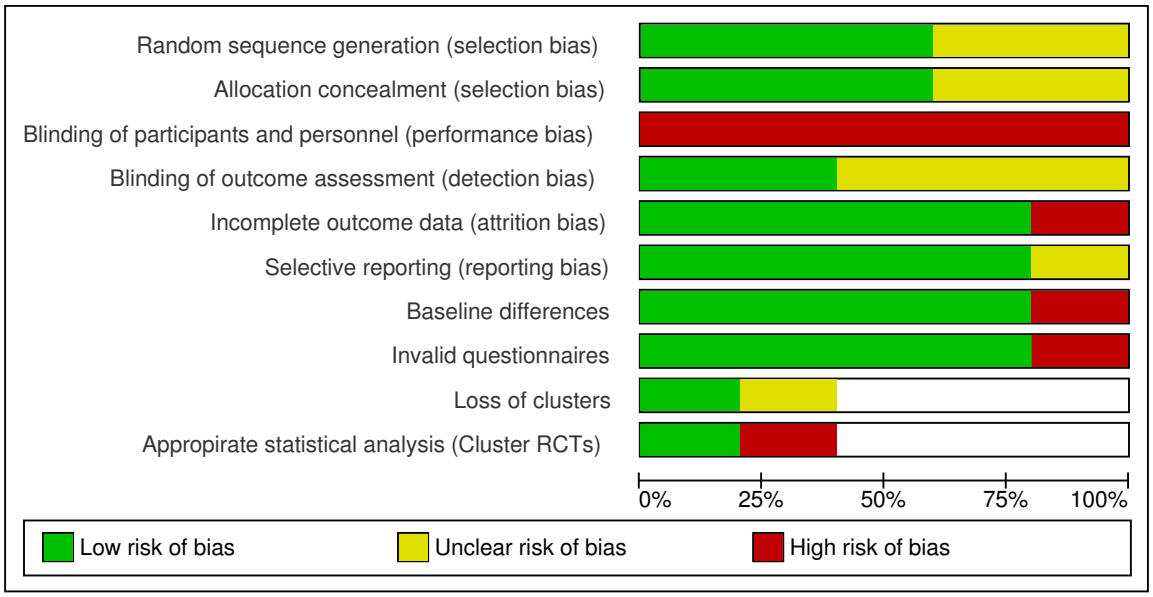

Figure 2: Risk of bias in included trials across each domain

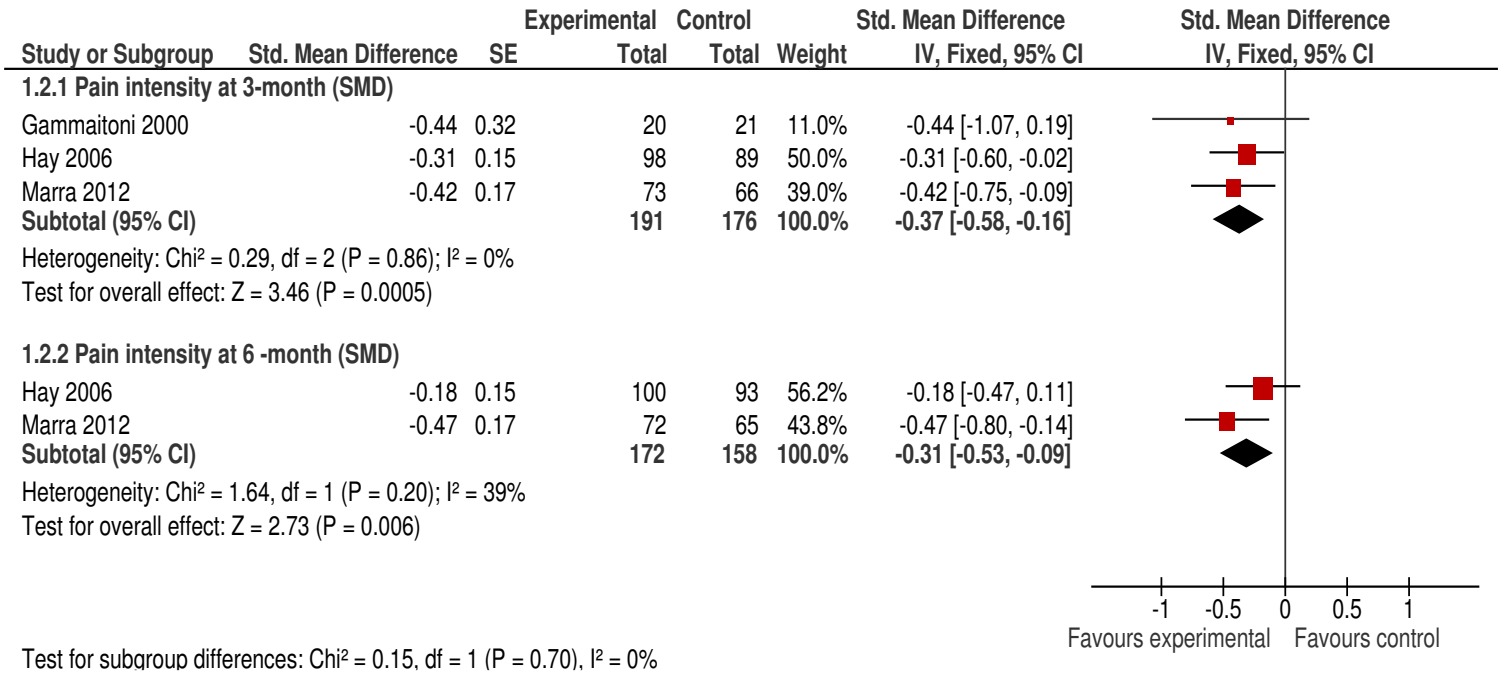

Figure 3: Meta-analysis of pain intensity at 3 and 6 month. CI= Confidence Interval, SMD = Standardized mean

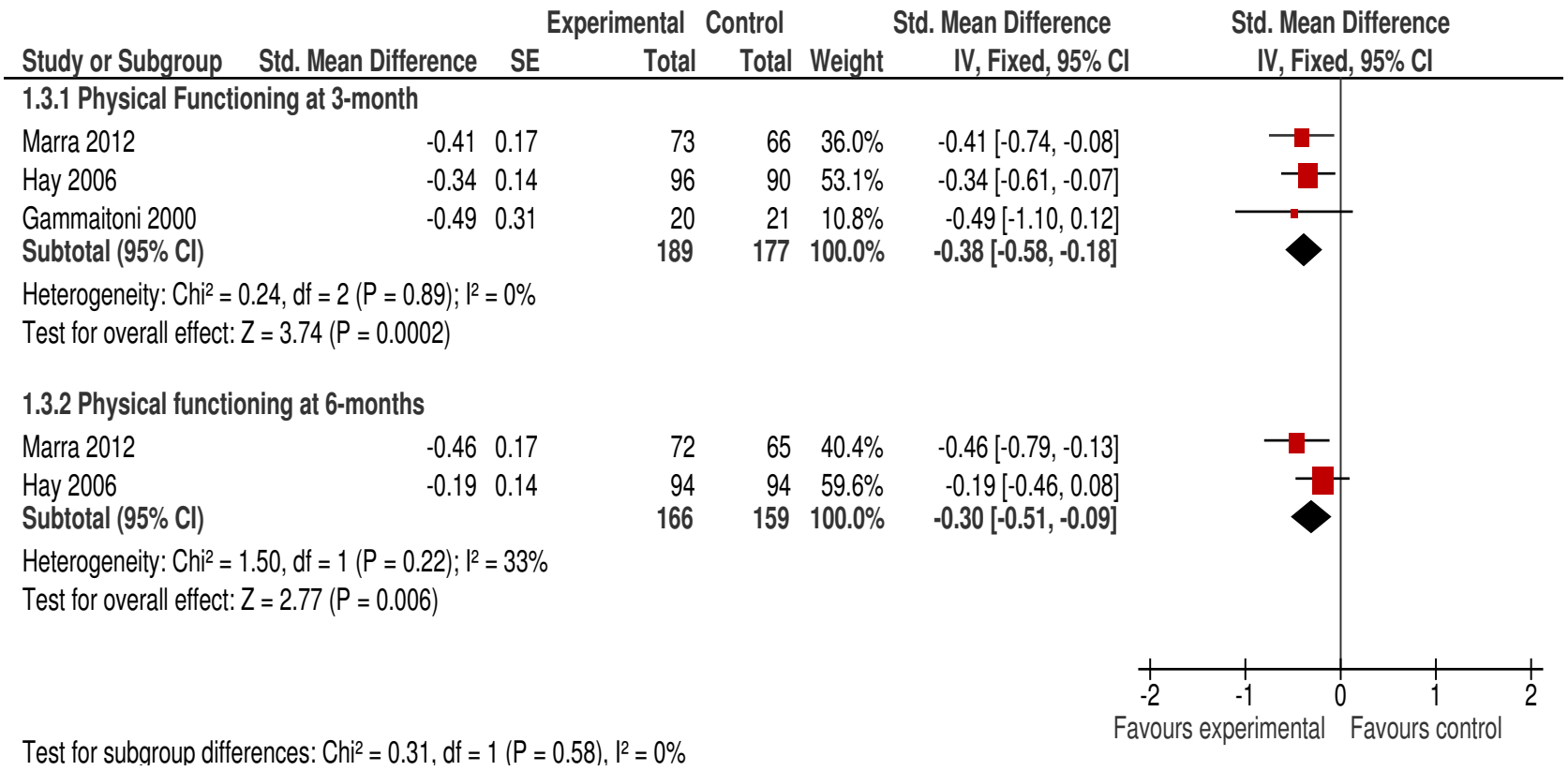

Figure 4: Meta-analysis of physical functioning at 3 and 6 month. CI= Confidence Interval, SMD = Standardized mean difference

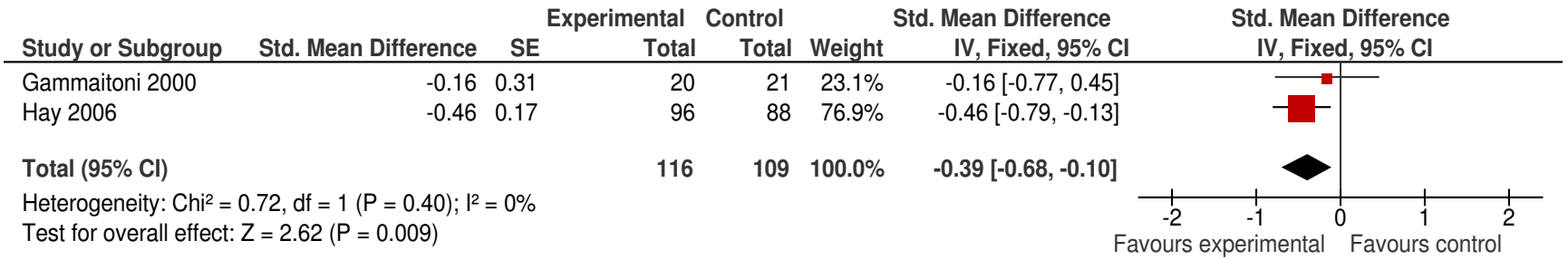

Figure 5: Meta-analysis of patient satisfaction at 3 month. CI= Confidence Interval, SMD = Standardized mean difference

Table 1: Characteristics of included studies

Study/Year country	Trial design	Setting	Chronic pain Aetiology	Sample recruited (completed)	Follow up (months)	Intervention	Dose of intervention	Pharmacist trained in pain management
Gammaitoni et al/ 2000 (USA)	I-RCT	University pain clinic	Multiple	N=74 I=38 (20) C=36(21)	3	MR through telephone interviews, and a specialized prescription delivery service	81 phone calls (45 to patients and 36 to clinic staff managing patients) were made in 12 weeks. Mean 1.2 calls per patient.	Yes
Hay et al/2006 (UK)	I-RCT	General practice	Knee pain	N=325* I=108(100,103,99) C=108(92,98,90)	3, 6 and 12	MR and advised patients face-to-face individually based on leaflet	3 to 6 sessions of 20min each over 10 weeks	Not known
Hoffmann et al/2008 (Germany)	C-RCT	Community pharmacy	Headache & migraine	N=410 I=201 (163) C=209 (194)	4	Face-to-face MR plus advice on pacing activities and goal setting.	Each pharmacy counselled on average 4.6±3.01 patients (range 1-15) corresponding to	Yes

							2hrs/per patient approximately	
Bruhn et al/2011 (UK)	I-RCT	General practice	Multiple	N=196* I=70(60,58) I**=63(50, 49) C=63(54,55)	3 and 6	MR plus recommendations to the GP	Data not available	Yes
Marra et al/2012 Canada	C-RCT	Community pharmacy	Knee pain	N=139 I=73(72) C=66(65)	3 and 6	MR + education+ Physiotherapist guided exercise	297 pharmacist-patient follow ups were performed over 6 months resulting in 355 recommendations to patients' primary care physicians (4.8 recommendations/patient)	Yes

*Two intervention groups in trial. ** The second intervention group also received medication review as part of intervention. Data for only one intervention group is presented here. I-RCT=Individual Randomized controlled trial, C-RCT= Cluster randomized controlled trial, MR= Medication review, GP=General Practitioner, I=Intervention group, C=Control group,