Psycho-Oncology
Psycho-Oncology **24:** 1686–1693 (2015)
Published online 5 March 2015 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3781

Interventions that may reduce depressive symptoms among prostate cancer patients: a systematic review and meta-analysis

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Received: 31 July 2014
Revised: 1 January 2015
Accepted: 29 January 2015

Abstract

***Objective*: Prostate cancer patients are at increased risk of depression yet there is no standard intervention to address this. The purpose of this meta-analysis is to examine the efficacy of interventions in reducing depressive symptoms in men with prostate cancer.**

***Methods*: Searches for studies were conducted in four databases and by hand. Randomized controlled trials of any intervention relative to control for depression in prostate cancer patients at any stage of their cancer treatment were included.**

***Results*: We identified 11 studies that randomized men with prostate cancer to either an intervention meant to improve some aspect of quality of life or control and reported depressive symptoms scores before and after the intervention or control condition. Two of these were not used in our meta-analysis either for concerns about quality or for lack of depression scores. The interventions identified in the remaining nine articles were exercise (four), information (three), psychotherapy or peer support (three), massage therapy (one), and medication (one). Several publications included more than one type of intervention. A meta-analysis of all studies showed that an intervention of some types significantly improved depressive symptom scores relative to the control condition (improvement in depression score by −0.86 unit (95% CI: −1.42, −0.31)). Isolating the peer support/psychotherapy studies also showed significant improvement (improvement in depression score by −1.09 unit (95% CI: −2.05, −0.13)).**

***Conclusion*: Treatments to improve depressive symptoms in men with prostate cancer may be effective, with the best evidence supporting the use of peer support/psychotherapy.**

Background

Prostate cancer is the most common non-cutaneous cancer among men in the United States with an estimated 233,000 men expected to be diagnosed in 2014 [1]. Most of these men will not die of their disease, because they are either cured or die of a competing illness, and even those with incurable disease at diagnosis can expect a long survival [2]. Thus, the prevalence of prostate cancer is expanding. The National Cancer Institute's Surveillance, Epidemiology, and End Results database estimated that there were more than 2.5 million men in the United States living with prostate cancer in 2010 [3].

Estimated rates of depression in patients with cancer vary widely, but a reasonable estimate for major depressive disorder is around 12–18%, with 30–40% of patients having some combination of mood disorder including minor depression, and adjustment disorder, and no difference in prevalence between palliative and non-palliative care settings [4]. A recent systematic review used publications of prostate cancer patients that reported depression scores to estimate prevalence rates. The analysis estimated depression rates among those prior to prostate cancer treatment, during treatment, and after treatment: 17.27%, 14.7%, and 18.44%, respectively [5]. A prospective study of men on androgen suppression therapy found a 12.8% prevalence, which was eight times the expected rate [6]. Prostate cancer patients may be particularly prone to depression because the primary treatments (androgen suppression therapy, radiation therapy, and radical prostatectomy) cause side effects that interfere with quality of life, such as hot flashes, erectile dysfunction, weight gain, and urinary incontinence [7]. Depression is likely under-diagnosed in the cancer population for various reasons [8], so the true prevalence is difficult to determine.

Not only does depression in prostate cancer patients negatively affect quality of life, it also associated with an increased risk of death [9]. Among cancer patients who

suicide, major depressive disorder is the most common mental disorder [10]. The risk of suicide after a diagnosis of prostate cancer has been well-documented, both in the United States and in Sweden. In the United States, using data from the Surveillance, Epidemiology, and End Results Program, investigators showed that compared with the general US male population, men with prostate cancer were at an increased risk of suicide in the first 3 months after their diagnosis and that the risk remained increased throughout the first year. After adjusting for age, calendar period, and state of residence, the standardized mortality ratio was 1.4 (95% CI 1.2–1.6) in the first year and 1.9 (95% CI 1.4–2.6) in the first 3 months [11]. The risk was increased with metastatic tumors compared with local tumors, standardized mortality ratio 3.22 (95% CI 2.68–3.84). Similar numbers were seen in Sweden with a relative risk for suicide of 2.6 (95% CI 2.1–3.0) in men diagnosed with prostate cancer compared with men without cancer, with adjustment for age, calendar year of follow-up, and time since diagnosis [12].

Interventions to prevent or treat depression in prostate cancer are essential to improve quality of life and prevent suicide. Commonly used treatments for depression include pharmaceutical, physical, psychological, and informational interventions. Our analysis sought to answer the following question: In men with prostate cancer, what is the effect of the aforementioned interventions on depressive scores compared with men who did not receive one of the interventions, where depressive scores are measured at baseline and after the completion of the intervention? This analysis is the first to include pharmacological, psychosocial, and exercise interventions to determine if they influence depression scores in men with prostate cancer.

Methods

Protocol and registration

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009581

Inclusion criteria

We included randomized controlled trials that compared any intervention to treat depression with no treatment or placebo in patients with prostate cancer. Eligible studies had to report statistical measures on the depression outcomes (e.g. mean change from baseline and measures of variance). Studies that enrolled patients with other types of cancers were eligible if they stratified results for prostate cancer patients. 'Prostate cancer' is a broad category because there are prostate cancer patients who are potentially cured if treated with surgery or radiation therapy, and there are those who are incurable, that is, have metastatic disease at the time of diagnosis or a recurrence of their disease after an attempt at cure. Within the category of prostate cancer patients having incurable disease, there are those who are not currently being treated and those who are being treated, usually with androgen suppression therapy, immunotherapy, or chemotherapy. Patients with any category of prostate cancer status or current treatment were included. The term 'intervention' is also quite broad as it can include any non-pharmacological (e.g. exercise, information, social support, and psychological) or pharmacological intervention. We included studies even if entry criteria for depressive scores were not severe enough to be considered a case of Diagnostic and Statistical Manual major depressive disorder (clinical depression). We did not discriminate based on duration of treatment or time points of depression score measurement. We also did not discriminate based on depression score used (e.g. Center for Epidemiological Studies—Depression (CES-D) or Hospital Anxiety Depression Scale (HADS)). We did not exclude studies based on language or publication status. Harms assessed included overall reports of adverse events per group and discontinuations from study due to adverse events.

Search strategy

Searches of MEDLINE, Cochrane CENTRAL, and PsycINFO were conducted through April 2014. Search strategies unique to each database included terms for depression combined with terms for prostate cancer, including MeSH terms in Medline. For MEDLINE the search strategy used was Prostatic Neoplasms AND (depression OR depressive disorder OR anhedonia) AND (adaptation, psychological OR life change events OR emotions OR attitude OR attitude to death OR attitude to health OR catastrophization OR stress, psychological) AND (depress$ OR sad OR sadness OR melancholy$ OR anhedon$ OR (feel$ adj3down) .mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]) AND Self-Injurious Behavior AND ((suicid$ NOT suicide gene$) OR (hurt$ OR harm$ or injur$) adj5 (self OR themsel$ OR himsel$) .mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]). A hand search of each included study's relevant references was conducted, and searches of dissertations by WorldCat were used to help identify unpublished studies. For those studies that measured depression but did not provide raw scores for the prostate cancer patients, the authors were contacted on two separate occasions.

Study selection

Two investigators (T.A. Newby and J.N. Graff) independently reviewed citations of studies to identify potentially relevant studies and then the full text of potentially relevant

DOI: 10.1002/pon

studies to identify studies meeting inclusion criteria. Disagreements on inclusion were resolved through consensus of all authors.

Assessment of study quality

The quality of individual studies was assessed using the methods of the Drug Effectiveness Review Project [13]. We modified this tool in the several ways. (a) The Drug Effectiveness Review Project criteria require assessing blinding of outcome assessors, care providers, and patients. Because many interventions being studied here would be difficult to blind (with the exception of medications), we collapsed this to 'fully blinded'. (b) We made a category 'deviations' to include crossovers, adherence, contamination, and maintenance of comparable groups as well as any report of deviations within the publication. (c) Because our inclusion criteria required that the trial be described as randomized, we did not include this as a quality criterion. (d) Likewise, we did not include 'eligibility criteria specified' because that was a requirement for inclusion. Assessments were made independently by two investigators (T.A. Newby and J.N. Graff), with disagreements resolved through consensus. Studies were rated as good if they met all criteria, fair if they met most criteria, and poor if they had serious flaws. One article was excluded for concerns about quality. Specifically, there was no way to determine contamination (Loiselle *et al.*) [14]. In that study, the interventional arm focused on patient education, but they could not report how many patients studied their condition apart from the study.

Data analysis

Meta-analysis of standardized effect sizes (and 95% confidence intervals) for change in mean depression scale scores was undertaken using a random effects model, STATA 12.0 (StataCorp, College Station, TX, USA). Studies that did not report variance data were not included in the meta-analyses. For studies with multiple dosing levels of an intervention, we used the data set that represented the greatest exposure of subjects to the specified intervention. For studies with multiple interventional arms, we used the arm with the maximum amount of exposure to a subject. For example, in a three-armed study (i.e. exercise vs. education vs. exercise + education), we used the combination arm. For studies looking at control versus two separate interventions, we ran separate analyses for each intervention. For studies that reported outcomes at more than one time point, we focused on the pre-intervention and post-intervention scores.

Tests of homogeneity were undertaken using the I^2 statistic; greater than 50% was indicative of heterogeneity. Publication bias was assessed using Egger's test for small-study effects, STATA 12.0 (StataCorp), specifically looking at the regress standard normal deviate of the intervention effect estimate against its standard error.

Results

The combined searches identified 471 unique citations. After applying the eligibility criteria, we identified 11 randomized controlled trials (RCTs) involving 1131 patients that met our inclusion criteria. See Figure 1 for details. Of the 11 studies identified, six had only one intervention arm, four had two intervention arms, and one had three intervention arms. Most of the studies included men with newly diagnosed prostate cancer, often undergoing treatment with a goal of cure. Three of the studies looked at men receiving androgen suppression therapy.

The studies ranged in size from 21 subjects to 389 subjects. The mean age was 66.5 years. For most studies, the intervention was 6–9 weeks. Within the studies reviewed, these classifications of intervention were found: exercise (5), peer support/psychotherapy (3), education (3), medication (1), and massage (1) (Table 1). The comparison group was either no intervention (e.g. standard of care) or wait-list control.

Study quality assessment revealed that one was good, six were fair, and two were poor quality (Table 2). Three of nine studies explicitly excluded patients with a diagnosis of major depressive disorder, actively taking antidepressants, or participating in psychotherapy [15–17]. Because of lack of description in the publications, it was assumed that no other study participants were receiving an active intervention for depression.

There were four scales for determining depression: CES-D (five), HADS (three), Geriatric Depression Scale (GDS) (one), and Beck Depression Inventory (two). Interventions lasted a median of 8 weeks. Most of the exercise, informational, and psychosocial interventions were performed in a group setting. The Weber study [15] looked at 1:1 peer support between a cancer survivor and a newly diagnosed patient. There was one pharmaceutical study by Taxel [20] examining the effect of estradiol on quality of life for patients receiving androgen suppression therapy.

For studies with multiple arms involving the same type of intervention, for example, information or exercise, we used the arm that gave subjects the most exposure. However, there was one study that did not fit into our criteria, the study of relaxation therapy versus Reiki therapy [17]. We opted to use the Reiki therapy intervention because it was performed twice as often, maximizing a subject's exposure. Another study met our quality threshold, but we could not use it because the depression scores had been statistically adjusted and could not be interpreted on their own without access to the raw data set [23].

Most studies reported multiple time points for the measurement of depression scores. Seven studies included in

DOI: 10.1002/pon

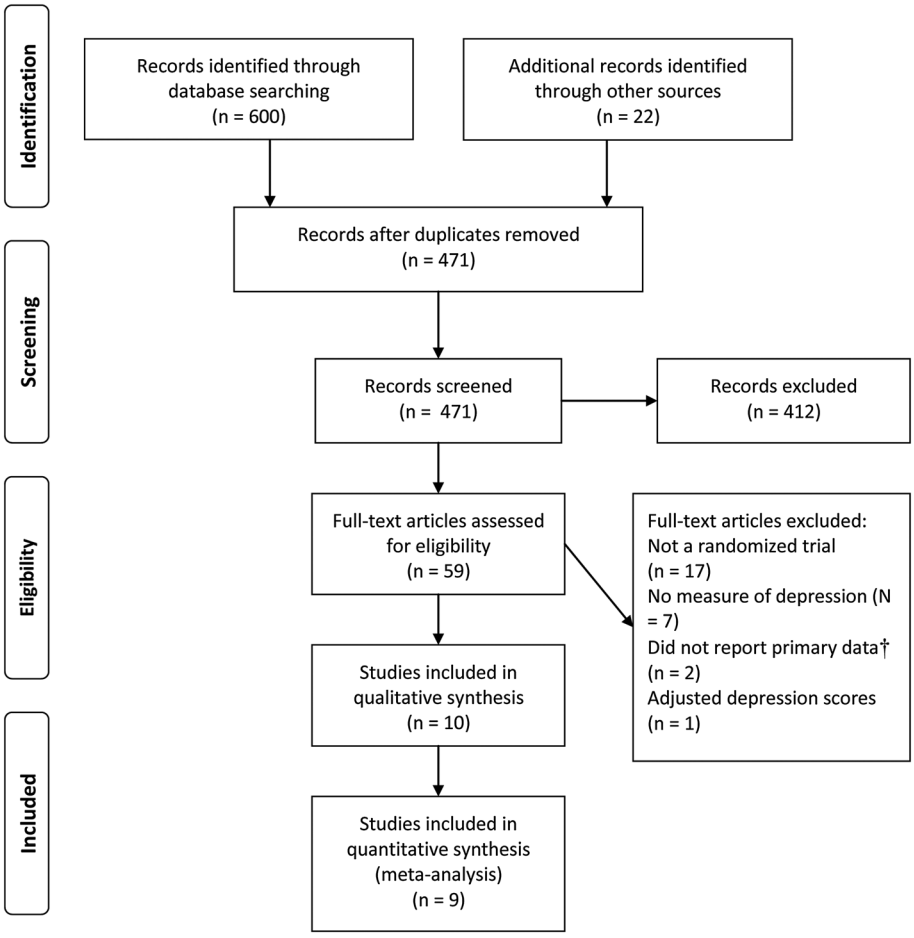

Figure 1. Flow diagram of randomized studies to decrease depression in prostate cancer patients. †Attempted to contact at least two authors on two occasions to see if we could obtain prostate cancer specific information

our meta-analysis had pre-intervention and immediately post-intervention scores. In two other studies, the post-intervention time point was 4 months after the intervention for one and 2.5 months for the other. So, we used that measurement.

The first meta-analysis looked at all 1131 prostate cancer patients and all interventions to determine if intervening in any way was better than no intervention at all (improvement in depression score by −0.86 (95% CI: −1.42, −0.31)) (Figure 2). There was a statistically significant decrease in depression scores in the intervention groups compared with the control groups. Only one study was statistically significant on its own. In the Beard study (Table 1), which looked at Reiki, relaxation therapy, or no intervention, it was found that seven (12%) subjects or 12% of the total participants had baseline CES-D scores consistent with depression, which is a score of 16 or higher. After completing 8–9 weeks of an intervention, it was found that these subjects experienced a statistically significant decrease in depression ($p = .05$), regardless of the study arm they were randomized to.

Examination of the studies that focused on an exercise intervention by meta-analysis did not show a statistically significant change in depression scores of the 125 involved, but a trend toward overall benefit −0.9 unit (95% CI: −2.04, 0.25) (Figure 2). The results were similar when looking at education/information interventions in 122 subjects −0.31 unit (95% CI: −1.42, 0.80) (Figure 2). In the studies conducted by Petersson, Weber, and Livingston (59, 37, and 16 subjects, respectively), 122 subjects were exposed to a peer support or psychotherapy intervention. A separate analysis of these three studies found that there was a statistically significant improvement in depression scores −0.96 unit (95% CI: −1.59, −0.34) (Figure 2).

Tests of homogeneity revealed that these studies were homogeneous enough to be grouped in meta-analyses, and Egger's test found no small-study effects. The I^2 values are reported in Figure 2. The Egger's tests results are as follows: for all interventions, the intercept was −0.07 ($p = 0.944$); for the exercise interventions, −0.044 ($p = 0.913$); for the information interventions, 0.518 ($p = 0.711$); and, for the psychosocial interventions, −1.69 ($p = 0.657$).

DOI: 10.1002/pon

Table I. Description of included studies

Article (country)	Population	N	Intervention	Dose	Duration	Depression scale
Berglund, 2007 (Sweden)	Recent dx	211	Physical training	60 min, weekly	7 weeks + 1 booster	HADS
			Information	60 min, weekly	7 weeks	
			Both	135 min, weekly	7 weeks	
Weber, 2007 (USA)	Recent dx, after RP	72	1:1 Peer support	Weekly	8 weeks	GDS
Livingston, 2010 (Australia)	Recent dx	389	Helpline calls – 4	Four times	Over 6 months	HADS
			Helpline calls – 1	Once	At 1 week	
Petersson, 2002 (Sweden)	Recent dx	118	Six group sessions involving CBT, plus relaxation therapy and physical therapy	Weekly	8 weeks + 1 booster at 2 months	HADS
Beard, 2011 (USA)	RT	54	RRT	60 min, weekly	8 weeks	CES-D
			Reiki therapy	50 min, 2×/week	8 weeks	
Monga, 2007 (USA)	RT	21	Exercise	50 min, 3×/week	8 weeks	BDI
Taxel, 2004 (USA)	AST	27	Micronized 17-β estradiol	1 mg/day	9 weeks	BDI
Culos-Reed, 2010 (Canada)	AST	100	Group exercise programs + home regimen	90 min, weekly	16 weeks	CES-D
Carmack Taylor, 2006 (USA)	AST	134	CBT to increase physical activity	90 min, every 1–2 weeks	6 months	CES-D
			Information	90 min, every 1–2 weeks	6 months	

N, number of prostate cancer patients; dx, diagnosis; RP, radical prostatectomy; RT, radiation therapy; RRT, relaxation response therapy; CBT, cognitive behavioral therapy; AST, androgen suppression therapy; HADS, Hospital Anxiety Depression Scale; CES-D, Center for Epidemiological Studies—Depression; GDS, Geriatric Depression Scale; BDI, Beck Depression Inventory. Each of these studies also had a 'usual care' arm, not described in the table.

Dropout rate for all interventions was low when reported, except in the case of the Culos-Reed study, where 34% dropped out, mostly from the wait-list control group. Of the 11 patients in the intervention group who dropped out, five withdrew consent for medical reasons, three voluntarily dropped out, two were lost to follow-up, and one withdrew consent for unknown reasons. Harms were not described in most of the studies, and there were no reported study-related harms that resulted in a dropout in any study.

Discussion

Several systematic reviews have been published to examine the effect of interventions to decrease depression in cancer patients. Most reviews combine cancer types. In the Cochrane Review library, there is an analysis of exercise in cancer patients actively undergoing treatment of their cancer and found a reduction in depression among those without breast cancer [24]. The other Cochrane Review analyzed studies of psychosocial interventions in recently diagnosed cancer patients and found that there were no improvements in depression [25]. An analysis of cancer survivors in exercise interventions found that exercise did result in a small reduction of depressive symptoms [26]. One analysis focused on patients who had elevated depressive symptoms prior to the intervention and found that psychosocial and pharmacologic approaches were beneficial [27]. Finally, one systematic review looks exclusively at prostate cancer patients receiving psychosocial interventions and found that, at least in the short term, the intervention was beneficial [28]. Ours is the only analysis of all interventions in prostate cancer patients.

Although there are data showing the suicide rates also increase during the period immediately following a diagnosis of cancer, none of these studies address this devastating outcome. We do not know whether an intervention can reliably decrease suicide rates in prostate cancer patients.

Our analysis has identified several studies that sought to decrease depressive symptoms in men with prostate cancer. The most common intervention was exercise, followed closely by psychotherapeutic interventions and education. Many of these studies combined modalities. Individually, only one study showed a statistically significant improvement in depression scores. However, the meta-analysis did show that some intervention was better than none and that psychosocial interventions (e.g. peer support and/or psychotherapy) help prostate cancer patients, which is consistent with the other systematic review [28].

Most studies did not elaborate on harms. It is unexpected that the study of estradiol did not report adverse events, as these would be expected at some degree by a

DOI: 10.1002/pon

Table 2. Analysis of quality using modified Drug Effectiveness Review Project score.

Article	Randomized?	Similar at baseline?	Fully blinded?	Intention to treat analysis?	Protocol deviations threaten validity?	Level of attrition threatens validity?	Quality
Berglund *et al.* [18]	Yes	Yes	No	Yes	No	No	Fair
Weber *et al.* [15]	Yes	Yes	No	Yes	No	No	Fair
Livingston *et al.* [16]	Yes	Yes	No	No	No	No	Poor
Petersson *et al.* [19]	Yes	NR	No	Yes	No	No	Fair
Beard *et al.* [17]	Yes	Yes	No	Yes	No	No	Fair
Monga *et al.* [3]	Yes	Yes	No	Yes	No	No	Fair
Taxel *et al.* [20]	Yes	Yes	Yes	Yes	No	No	Good
Culos-Reed *et al.* [21]	Yes	Yes	No	No	No	Yes	Fair
Carmack Taylor *et al.* [22]	Yes	NR	No	Yes	No	No	Poor

NR, not recorded.

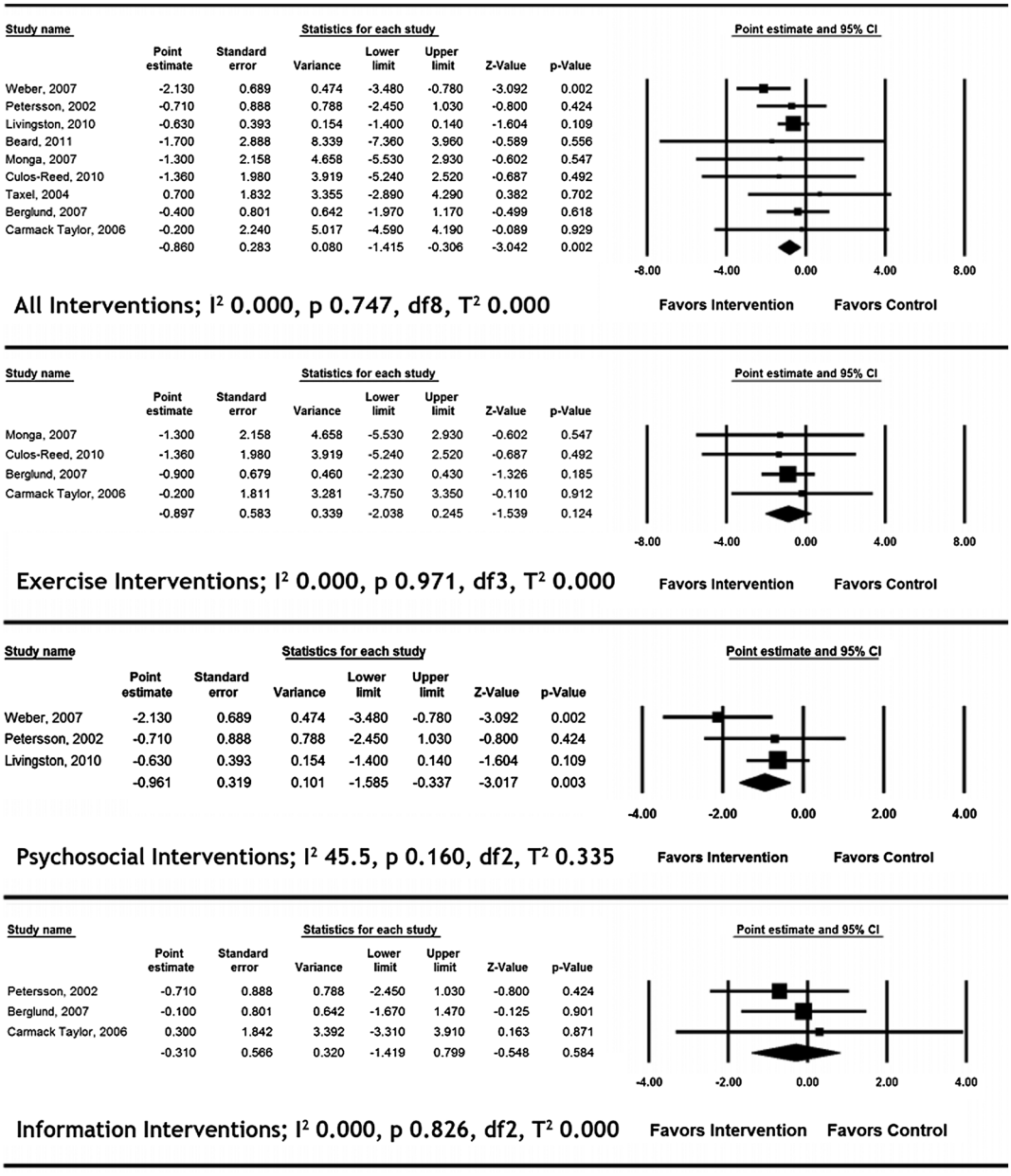

Figure 2. Forest plots of depression scale point differences for each study grouped by intervention

DOI: 10.1002/pon

pharmaceutical intervention. The Petersson study revealed therapy might uncover uncomfortable thoughts for patients as they discuss their experiences and feelings and may reveal a baseline psychological vulnerability. Specifically, during group discussions, they could be distressed by what others had to say. The Livingston study suffered from poor accrual. The group reported that some providers were too busy to counsel patients about the study and some felt that patients were overwhelmed by information regarding their disease and could not absorb the information about the study. Because it is unclear if the interventions really benefit patients, harms must be considered seriously.

The real-world application of these interventions may be difficult. The Livingston study pointed out the difficulty in expecting a provider to refer a patient to an exercise or therapy program when the provider has so much other disease-specific information to discuss with patients.

Our analysis has several strengths. We performed searches using two large databases and the Cochrane Database and had two independent reviews of the abstracts and quality of the articles selected. Two investigators offered data not included in their publications, which expanded the number of studies we were able to include in our analysis.

Our analysis also has weaknesses. None of the studies required clinically significant depression as an entry criteria for inclusion in the study, and in many of the studies, the mean depressive symptoms scores at study entry were low. This may reflect that in many of the studies, depression was not the primary endpoint of the intervention. We included all studies that had a reported measure of depression; most of these studies were not specifically designed to treat depression. These studies also include men at different stages of prostate cancer: 77% had a localized disease, which is presumably curable, and 23% were receiving androgen suppression therapy, which may have been given in conjunction with primary therapy for localized disease or for incurable cancer. Primary endpoints included quality of life, self-efficacy, fatigue, cognitive function, or physical activity. It would be highly unusual for a randomized controlled trial of an antidepressant, for example, to not require a minimum depressive symptom severity score that would constitute a 'case' of depression at study entry. As such, the clinical importance of meta-analysis is qualified in that is the severity of depressive symptoms was often in the normal range. Another over-arching issue with all of these studies is the inability to truly blind subjects so there is no way to account for a subject's bias toward one intervention over another. The closest thing to blinding is wait-list controls, and this was only utilized in one study.

The depression scales differed between studies. A five-point change on a scale with a range from 1 to 60 will make less difference than on a scale from 1 to 15 [29]. Ways to get around this issue include adjusting the scores to account for the difference in 'value' for a point on a given scale, for example, dividing the CES-D score by 4 in order to compare the value to the GDS scale. Another way to deal with these differences is to convert all scales to a new scale. Interestingly, nearly all of the published systematic reviews combine studies with different depression scales without adjustment or conversion, and we too have not adjusted. It is not clear whether the differences in these scales are significant either clinically or statistically.

Furthermore, controversy exists about which depression scales are appropriate for cancer patients [30]. Most contain questions about physical symptoms. In otherwise healthy patients, these physical symptoms may relate to depression. In cancer patients, these symptoms may relate directly to the cancer and not reflect a depressed state. Among depression researchers who study patients with cancer, the HADS is preferred for this reason [31]. In addition, the GDS, which was developed for elderly patients, minimizes questions regarding somatic symptoms of depression.

Finally, there were multiple interventions used in the studies we identified, adding to heterogeneity of the studies.

Available data seem to indicate that prostate cancer patients have an increased rate of depression, particularly in the first year after diagnosis [11]. We believe that clinicians should discuss the risk of depression with their patients and try to ascertain each patient's degree of depression. However, there is insufficient information to recommend specific interventions to decrease the risk of depression.

Conclusions

Among men with prostate cancer, interventions do improve depression scores, particularly psychosocial interventions. This analysis supports the development of programs for prostate cancer patients that include these interventions and a closer look at how they affect the suicide rate. Further studies are needed to examine the effectiveness of depression interventions for men with prostate cancer and clinical significant depression.

Acknowledgements

We would like to thank Shelley Selph, MD, for her statistical assistance; Clair Beard, MD, for providing data not included in her publication; and Patricia Livingston, PhD, BA, for providing data not included in her publication. This is an unfunded study.

Conflict of interest

The authors have no competing interests.

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