How do we understand depression in people with persistent pain?

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1

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Abstract

Depression and depressed mood are common in people with persistent (chronic) pain, exacerbating disability and worsening quality of life. Yet the relationship between persistent pain and depression remains unclear, despite its importance for designing or adapting interventions to address both pain and depression.

Meta-analysis of cognitive and behavioral interventions designed for rehabilitation of persistent pain shows small benefits for distress. However, substantial variation between studies in patients' baseline levels of depression and in quality of treatments militates against any clear conclusions. Apart from these interventions, longitudinal studies on chronic pain and depression in adults from clinical populations provide weak evidence that depression worsens pain outcomes.

We systematically searched for and reviewed 14 longitudinal studies that explored the association between persistent pain and depression, aiming to identify: (1) the effects on pain of baseline depression; (2) the effects on depression of baseline pain; and (3) possible mediating variables, with particular attention to methodology. Unfortunately, most studies used unsuitable instruments to measure depression, and we could draw only tentative conclusions about effects over time. Better models and clearer measurement strategies are required for a next generation of clinically useful treatment trials and, meanwhile, some implications for treatment are explored.

Keywords: chronic pain; systematic review; distress;

Introduction

Depression, and depressed mood, are common problems in people with persistent pain (Banks & Kerns, 1996). Several theories have attempted to explain why persistent pain and depression occur together, using psychiatric nosology and conceptualizing them as two separate conditions; other theories suggest that pain and depression are indivisible. Many of these rely on cross-sectional studies which cast little light on the nature of the postulated association. We chose to review longitudinal studies of the relationships in an attempt to avoid this problem.

Early theories that suggested conscious or unconscious transformation of distress into pain (psychosomatic) (e.g. Blumer and Heilbronn 1982) relied on perceived shortcomings in the medical evidence to assert the lack of any basis for pain. These are theoretically unsatisfactory, since persistent pain involves changes in the central nervous system, with or without overt structural evidence (Tracey and Mantyh 2007). Further, tests of the model have produced clear evidence against such an assertion (Turk and Salovey 1984; Merskey 2000; Crombez et al. 2009). Others proposed that depression caused pain or that pain caused depression (e.g. Fishbain et al. 1997), and epidemiological and cross-sectional studies were variously interpreted to support each, while the diathesis-stress model of Banks and Kerns (1996) straddled both. The diathesis-stress model suggested that individuals with increased sensitivity to particular stressors, either through genetic vulnerability or early adverse experiences, have an increased risk of developing depression, and that persistent pain is one such stressor because of its very persistence and its wide-ranging effects.

Biological models of depression in persistent pain, drawing on research with non-human animals, are largely overlooked in the human clinical literature on chronic pain treatment. One such model (Blackburn-Monro and Blackburn-Monro 2001) proposed moving away from the almost exclusive focus on neurotransmitters towards understanding persistent pain as a chronic inescapable stress, with resultant widespread effects via the hypothalamic-pituitary-adrenal (HPA) axis. Another model (Schwartz et al. 2014), in mice with chronic inflammatory or neuropathic pain, described consistent and analgesic-resistant neuroplastic changes in the nucleus accumbens, decreasing motivation to work for a reward as the ratio of reward to response became progressively less favourable. A third, using mood induction

and pain stimulus on healthy human participants during functional magnetic resonance imaging (fMRI), showed clear effects of depressed mood, involving far more emotional processing of pain, with participants experiencing the pain stimulus as much more unpleasant (Berna et al. 2010). Such models tend to conceptualize depression as affect, neglecting cognitive processes (with the exception of Berna et al. 2010), as well as behaviors and symptoms (Pincus and Williams, 1999).

More recently, Linton and Bergbom (2011) presented a model that includes a role for catastrophizing and emotion regulation in the relationship between persistent pain and depression. This model is described fully in the paper by Linton et al. (this volume). While it is a very considerable advance, using theories and evidence from both the pain field and mainstream psychology, it also risks under-recognising the extent to which persistent pain and depression are processed in common pathways and by shared neurotransmitter systems (Bair et al. 2003). In the last decade or so, evidence from neuroscience has provided a more specific basis for this emotion regulation model. The subject is too large for treatment here but studies of processing using imaging techniques (Bushnell et al. 2013; Tracey and Mantyh 2007) and using neurotransmitter balance and regulation (Bair et al. 2003) provide mechanisms whereby mood influences the facilitation or inhibition of pain information from the periphery, and provides the context in which it is processed in systems and areas where emotion is also processed.

Here we review longitudinal studies in clinical populations which examined the association between chronic pain and depression, addressing the following questions:

1. Does depression affect pain and disability outcomes in patients with chronic pain?
2. Does pain affect depression outcomes in treated or untreated depression?
3. What variables mediate depression outcomes in chronic pain and depression at follow-up?

Method

Search strategy

Given the thorough review by Bair et al. (2003), we searched from 2003 to 2013 in PsycINFO, MEDLINE, and reference lists of relevant papers, using the terms (modified as

appropriate per database): (*depress*) or (low mood)* combined with *(chronic pain) or (subacute pain) or (sub-acute pain) or (acute to chronic pain) or (enduring pain) or (continual pain) or (sustained pain) (back pain), (musculoskeletal pain), (neck pain)* and *(shoulder pain).* Studies were included in our review that: 1) were reported in a peer-reviewed journal; 2) were longitudinal; 3) tested an adult clinical population of whom at least 50% had sub-acute pain (4 weeks or longer) or chronic pain (3 months or longer) and/or depression; 5) assessed pain and depression at baseline and follow-up. We excluded studies focusing solely on treatment outcomes, or where chronic pain resulted from a specific disease process (e.g. cancer or rheumatoid arthritis).

Methodological quality assessment

The Newcastle-Ottawa Scale (NOS; Wells et al. 2000) was used to assess the quality of studies and was adapted to meet the requirements of this review. It contains items on: (1) representativeness of the sample population, for which there were four levels, from *truly representative of the average population* to *no description of the derivation of the cohort*; (2) appropriate selection of the control cohort; control for gender and age; length of time between baseline and follow-up; adequacy of follow-up; and (3) appropriate assessment of persistent pain and depression at baseline and follow-up. We detailed these (for instance, defining six months as the minimum adequate follow-up period), and we paid particular attention to the measurement of depression, since almost all severity and diagnostic scales were developed and standardized on physically healthy populations. This makes the endorsement of particular items uninterpretable, in persistent pain populations where 'vegetative' or somatic symptoms of depression are more often attributed by patients to persistent pain than to mood (Williams 1998; Morley et al. 2002; Hardt et al. 2000). The NOS awarded quality points for a sample size of more than 50 participants, time from baseline to follow-up greater than six months, fewer than 25% participants lost to follow-up and controlled for differences in participants lost to follow-up in the analyses.

Results

Overview of papers

In total, 2370 English language papers were identified after removal of duplicates. One hundred and ten from the search and one from references appeared from the abstract to be potentially eligible and were accessed as full papers. Of these, 97 were excluded for the following reasons, in descending order of frequency: not a clinical population; a treatment study; pain was related to a disease process; no pain or depression at baseline; not longitudinal; pain was acute at baseline; same data as in another eligible study (so only one was included); and duration of pain not specified.

Of the 14 studies that met our criteria, methods of data collection varied from postal questionnaires to face-to-face interviews; and time between baseline and follow-up ranged from 2 months to 5 years. Sample recruitment and data collection methods are shown in Table 1. Studies were grouped according to whether they 1) included patients with chronic pain at baseline; 2) included patients with depression at baseline; or 3) focused on identifying variables that mediated outcomes in chronic pain and depression.

1. Does depression at baseline affect pain and disability outcomes in chronic pain?

Six studies of patients with chronic pain were found and were generally of good quality, except for problems of assessment of depression and pain. All studies recruited participants representative of the chronic pain population; controlled for age and gender in their analyses; had a sample size over 50; a follow-up over six months; and analysis of attrition where this was over 25%. The two studies with adequate methodology for assessment of depression (Dunn et al. 2008; Muller et al. 2013) reported that baseline depression in patients with chronic pain led to worse outcomes of pain and disability at follow-up. This finding agrees with several reviews (Bair et al. 2003; Banks & Kerns 1996; Fishbain et al. 1997; Linton & Bergbom, 2011) that concluded with more confidence that depression at baseline leads to worse outcomes in chronic pain, though these used scales which confounded symptoms of depression and chronic pain.

2. Does chronic pain at baseline affect depression outcomes in patients with treated or untreated depression?

Three studies of moderate quality were found: their participants were representative of the chronic pain population; they controlled for gender and age in their analyses; sample size

was over 50; attrition was addressed in analyses. Two studies had follow-up periods over 6 months. However, only one (Chung et al. 2012) used the most appropriate scale for depression, the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983); this study had a small sample and pain at baseline was relatively mild. It reported that pain severity and catastrophic thinking, but not anxiety and depression, predicted quality of life three months later.

3. What variables mediate depression outcomes in chronic pain and depression at follow-up?

Six studies were found but these were of lower quality than those above. All but one recruited representative populations, but Van Liew et al. (2013) reported a large predominance of female participants. All but one (Rudich et al. 2010) had a sample size over 50, and all addressed attrition in their analyses. Follow-up periods were mostly under 6 months. The main problem was choice of scales for depression which risked inflation of scores on somatic symptomatology. The results of these studies suggested multiple possible mediators and several pathways leading to the development of depression in chronic pain but, given the likely overlap between measurement instruments, it is hard to determine whether associations were conceptually meaningful or indicated methodological shortcomings.

Discussion

Our systematic review and methodological considerations left a rather small sample of studies. Nevertheless, we have reasonable confidence in the finding that depression at baseline worsens pain and disability outcomes in people with chronic pain, when compared over six months or more. We found no clear evidence for pain at baseline worsening depression outcomes over the same time, and mediation models were too diverse to offer any distinct findings.

Exclusion on the basis of what we judged unsatisfactory choices of measurement instruments, particularly for depression, left a rather small number of studies. Our position that these measurement instruments are inadequate remains a minority one, despite more than adequate demonstrations of a different dimensional structure of responses in the

presence of persistent pain (e.g. Pincus and Williams 1999, Morley et al. 2002) and even a somewhat separate somatic symptom dimension for several common depression instruments used in non-pain populations (Shafer 2006).

Entirely different methodologies demonstrate that people with persistent pain are mainly, in their depressive thinking, preoccupied with their health (Pincus et al. 2007), and that in the focus of this preoccupation they differ from other populations with similar levels of depression (Rusu et al. 2012). The Rusu et al. study, using sentence completion (of stems such as "Next week I …" and "Things in general …") found that while participants with pain, compared to those without pain, produced more negative health statements, they were not self-denigratory as would be expected in depression (see Morley et al. 2002). Diagnosis by interview uses the same symptom lists and priorities as do these inadequate measurement instruments and so does not offer a better alternative. This issue is associated with the increasing dissatisfaction with symptom count methods of diagnosis and the resulting heterogeneity of groups which have achieved the same total score, or exceeded the same cutpoint: there are 227 different ways to achieve the DSM-5 diagnosis of major depression (Galatzer-Levy and Bryant 2013). Recognition of the natural history of specific symptoms (Costello, 1983) and their association (or lack thereof) with persistent pain would enable theorists and researchers to build more specific models to address in psychological treatment. For example, there is increasing interest in the biological interactions of disturbed sleep and persistent pain, particularly fibromyalgia (Finan et al., 2013). Motivation to act, even in rewarding pursuits, is depleted in pain, in non-human animals as well as in humans, but in humans the fear of exacerbating pain or causing injury further lowers activity levels (Vlaeyen & Linton 2000). The cost of pain associated even with activities previously highly valued, including sexual activity, renders them no longer a source of pleasure and satisfaction (Williams, 1998).

The main methodological problem with the studies included in this review was the use of measurement instruments for depression that were invalid, or whose validity was questionable, in a population with persistent pain. While the HADS remains the most suitable instrument, it is unsatisfactory because of its unstable factor structure (Coyne and van Sonderen 2012; Cosco et al. 2012). New measures will ideally arise from better models rather than from existing diagnostic taxonomies or symptom lists.

A further problem was that depression history was rarely assessed although this might help to identify the relationship between depression and persistent pain, as might a more detailed examination of cognitive bias and the content of depressive thinking. Further, depression and chronic pain can both fluctuate over time (Judd, 1997), which could be missed when assessed only at fixed time points. Gerrits et al. (2012) used a life chart assessment, which decreased the risk of missing out episodes of depression between baseline and follow-up; this or other measures that take into account such fluctuations over time could be used in future investigations. Additional methodological problems arose from: 1) a lack of preregistration of trials (Bishop 2013), giving rise to the concern that some data analyses were not related to the original hypotheses for the study; and 2) the use of cut-off points to dichotomize data, a process which was not justified by the underlying models.

Limitations of the current review

We are aware of the risk that unpublished negative findings might exist but these could only make our already tentative findings more tentative, rather than reverse them. This review used one reviewer predominantly to conduct the search and to extract data from the studies; ideally, different reviewers should perform this procedure independently and discuss their findings, to minimize error or omissions.

Further subjectivity was introduced by the content of the NOS quality scale (Stang 2010) and by its application by a single reviewer. We were aware that the quality assessment tool we used, like any such instrument, makes assumptions in its inclusions and exclusions, scoring, and weighting (Sanderson et al., 2007), and this is in part why we chose not to use the scores, except broadly, in interpreting findings. Ideally, criteria such as the minimum sample size in a study is not set by an arbitrary standard but are related to the statistical power of the study to detect the associations it investigates. Further, choice of statistical analysis was not included in the quality criteria but is an important question to ask of studies, particularly associational studies which may need to make statistical corrections for multiple comparisons.

Implications

Depression or depressed mood is likely to add to the problems of people with persistent pain. Social problems may be a particular issue, often neglected in briefer pain management programs. Nor do the problems lie only with the person with pain. Where there is no medical evidence, people affected by persistent pain are stigmatized by others' judgments of their motivation (De Ruddere et al. 2013), and their pain-related behaviors elicit adverse character judgements, although less so when observers deduce that these behaviors might be associated with pain (Ashton-James et al. 2014).

None of the studies referenced a particular theory, even the otherwise commonly invoked diathesis-stress model; none even sampled diathesis factors, such as exposure to adverse experiences in childhood, nor did any focus on possible biological mechanisms in the development or progression of persistent pain and depression. There were few longitudinal studies overall, and cultural differences were overlooked. All these gaps remain to be explored.

Psychological interventions for chronic pain, usually cognitive and behavioral therapy, vary considerably in content but often include intervention for depressed mood (more rarely for diagnosed depression). Depression or distress is commonly assessed as an outcome, with evidence that cognitive behavioral therapy (CBT) improves mood and catastrophizing outcomes (Williams et al. 2012). CBT for patients with persistent pain aims to change unhelpful patterns of thinking and behavior related to persistent pain, and includes components also used to treat depression, such as behavioral reactivation and targeting unhelpful beliefs and habits of thinking (Williams et al. 2012). Acceptance-based treatment for chronic pain may also produce improvements in depression and distress (Hunot et al. 2013; Hann & McCracken 2014), even when it is not a direct target of treatment. Reviews of antidepressant drug interventions are disappointing (Chou et al., 2007; Urquhart et al., 2008), but the combination of antidepressants with behavioral intervention is more promising (Kroenke et al., 2009).

In a summary of the situation, Morley et al. (2013) concluded that the 'signal to noise' ratio was worsening in each successive meta-analysis of CBT for persistent pain, because of the proliferation of atheoretical, single-site, and often enthusiasm-driven randomized controlled trials available for meta-analysis. They proposed that trialists and clinicians should use the current evidence as a base on which to build more theoretically coherent studies of

populations selected on clinically relevant factors (not necessarily just the site of pain). It would be valuable to see treatment of chronic pain stratified by severity of depression and designed to address pain in the context of mood problems. In depressed patients, treatment would directly address hopelessness about making treatment gains, difficulties with motivation to practice new behaviours, often impoverished relationships and social contacts, and poor sleep quality.

Many people with chronic pain, however, receive more physical or medical treatment, and a systematic review of moderators (Gurung et al. 2015) suggested that those with significant anxiety or depression at baseline made greater gains from these treatments, but that the change is in function, not depression, and furthermore it is not clear that this change is sustained beyond the end of treatment. Many trials, and physical therapy-based pain services, exclude or find it hard to retain people with psychological needs if their health care staff lack specific training (Main et al., 2012), so the prospects for depressed patients seeking chronic pain treatment outside trials is currently poor. The application of specific guidance, such as that by Dowrick (2015) for working in primary care with patients with depressive symptoms, would substantially improve the situation for patients with persistent pain and depressed mood, and enable patient and doctor to share the construction of a treatment model.

Conclusion

Overall, this review has identified a very small body of evidence that depression at baseline is associated with worse outcomes in persistent pain; we were unable to find any reliable evidence with which to provide answers to our other questions. Clearer tests of existing models, and development of models which relate more closely to patients' experiences and to social and cultural contexts, would advance the field. Arguably, social and behavioral findings from animal models are underused, but much could be gained by careful elaboration of each cognitive, emotional or behavioral problem associated with the complaint of depression (Costello 1983), and the ways in which each interacts with other health problems, such as chronic pain.

The current monolithic models of depression serve the field poorly. Depression may be far better understood as multiple disorders with some overlap of symptoms (Blackburn-Monro and Blackburn-Monro 2001) which nevertheless have their own natural histories and different responses to treatment (Costello 1983). The new DSM-5 (American Psychiatric Association 2013), while it moves away at last from the diagnosis of psychological disorder by exclusion of medical evidence characteristic of previous versions (and of other diagnostic systems), still pathologizes what many clinicians and researchers consider to be problems of adaptation to persistent medical problems with widespread adverse effects on the individual (Katz et al. 2015). It continues to rely on notions of 'excess' or 'disproportionate' responses by the individual to his or her illness, as if there is a universally agreed correct quality and quantity of response. This injudicious wording may contribute significantly to the unreliability of the DSM-5 diagnosis of somatic symptom disorder (Katz et al. 2015).

Overall, this review was able to tell us relatively little about the effect of depression on untreated chronic pain, or untreated chronic pain on depression. Future longitudinal studies of the interaction of pain and depression will ideally be pre-registered and adequately powered; will use appropriate measures (including less psychometrically standard ones, such as that in Pincus et al. (2007) and Rusu et al. (2012)); will characterize the depression history of participants at baseline; will take multiple measures over the course of the study, i.e. not only at baseline and at a single endpoint; and will include some of the important variables used in the mediation studies reviewed above (see also Ehde et al. 2014) and possibly use their more sophisticated statistical modeling. The findings of such studies should help to resolve the current inconsistent judgments across chronic pain treatment about whether people with diagnosable depression are suitable for such treatment (Morley and Williams 2006), resulting in the exclusion of many people with persistent pain and unreliably diagnosed depression who might well benefit from pain treatment.

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Table 1. Details of included studies

Author (Year) Country	Quality score /8	Recruitment method	Data collection	Population	Mean (*SD*) age in years; range	Sample size (n male)	Time from baseline to follow-up(s)
Outcome of depression in chronic pain							
Dunn et al. (2008) UK	7	Postal survey	Self report questionnaire	Patients with low back pain	47 *(8)*, 30 - 59	426 (188)	12 months
Hurwitz et al. (2003) USA	6	Postal survey	Self report questionnaire	Patients with back pain	51 *(17)*, NP	681 (327)	2 weeks, 6 weeks, 6, 12 and 18 months
Kroenke et al. (2012) USA	7	Clinic visit	Clinical interview	Patients with chronic low back, hip or knee pain – 127/250 depressed	56 *(11)*, NP	377 (187)	3 months, 6 months and 12 months
Muller et al. (2013) UK	7	Primary care consultations	Self report questionnaire	Patients with chronic pain	65 *(10)*, >50	329 (126)	12 months
Ryall et al. (2007) UK	6	Primary care consultations	Self-report questionnaire Clinical assessment Telephone interview	Patients with chronic arm pain	NP, 15 - 64	313 (127)	1 month, 3 months, 6 months and 12 months
Von Korff et al. (2005) USA	6	Primary care consultation	Telephone interview	Patients with chronic back pain	NP, 18 - 75	1213 (600)	1, 2 and 5 years
Outcome of chronic pain in depression							
Chung et al. (2012) Hong Kong	6	Clinic visit	Clinical interview	Patients diagnosed with major depressive disorder	48 *(10)* 18 – 65	82 (18)	3 months
Gerrits et al.	5	Postal	Clinical interview,	Patients with depressive	42 *(12)*,	1209 (531)	24 months

(2012) Netherlands		questionnaire	self-report questionnaire	and/or anxiety disorder	NP		
Kroenke et al. (2008) USA	5	Clinic visit	Clinical interview, telephone interview at follow-up	Patients with a diagnosis of depression	42 *(NP),* NP	405 (81)	3 months and 6 months

Studies of mediation by other variables

Lerman et al. (2012) Israel	4	Clinic visit	Self-report questionnaire Telephone interview	Patients with chronic pain Mediators: Self-criticism Sex Affective pain Sensory pain Outcome: depression	57 *(14),* 19 - 90	163 (61)	Mean 4.34 months (range 2-8 months)
McCracken and Eccleston (2005) UK	4	Clinic visit	Clinical assessment	Patients with chronic pain Mediators: Pain acceptance (activity engagement, pain willingness) Outcome variables: pain, depression	44 *(11),* NP	118 (NP)	Mean 3.9 months
McCracken et al. (2007) UK	4	Clinic visit	Clinical assessment	Patients with chronic pain Pain coping strategies: Pain management Pain control Help seeking Activity persistence Outcome variables: pain, depression	45 *(11),* NP	115 (53)	Mean 3.7 months

Rudich et al. (2010) Israel	3	Waiting for first pain specialist consultation	Questionnaire Medical assessment	Patients with chronic pain Mediators: Physician prognosis Self-criticism Sex Age Sensory Pain; Affective pain Outcome variable: depression	58 *(13)*, *24 - 81*	45 (19)	Mean 5 months (range 2-8 months)
Van Liew et al. (2013) USA	5	Advertisements in newspapers and physician offices, referrals by physicians	Questionnaire	Patients with fibromyalgia syndrome (majority female) Mediators: Physical functioning Self-efficacy Outcome variables: pain, depression	54 *(11)*, NP	462 (20)	6 months, 12 months
Velly et al. (2011) USA	6	Advertisements in dental surgeries	Clinical examination Questionnaire	Patients with chronic temporomandibular joint pain Mediators: Catastrophising Sex Age Outcome: Progression to clinically significant pain	37 *(12)*, NP	480 (276)	18 months

NP Not provided