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Marta Meana
University of Nevada, Las Vegas, marta.meana@unlv.edu

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IN REVIEW

The Meeting of Pain and Depression: Comorbidity in Women

Marta Meana, PhD

The higher prevalence of depression in women is coupled with a higher prevalence of pain complaints. Growing evidence suggests that the comorbidity of these conditions is also proportionately higher in women than men. This paper critically reviews the empirical findings relating to gender differences in comorbid pain and depression as well as findings in support of hypothesized etiologic factors that could explain why women may be more susceptible than men to comorbidity. The empirical evidence for biogenic, psychogenic, and sociogenic explanatory models is presented, and an integration of these models is proposed as a guideline to both research and clinical practice. In conclusion, it is argued that gender-differentiated treatment strategies are not clinically indicated at this time.

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Key Words: pain, depression, comorbidity, women

Women in North America have higher rates of illness and health care utilization (1–4) and a higher incidence of both temporary and chronic pain (5,6), and they report pain in multiple sites more than do men (7). The most recent review of gender differences in clinical pain focuses on 1) gender-specific pain that is limited to anatomical differences between men and women and 2) pain conditions that are more prevalent in one gender versus the other (8). First, women are much more likely than men to experience pain that has no obvious or hypothesized pathologic basis. Normal menstruation, ovulation, pregnancy, and childbirth are sources of recurrent pain for many women (9,10). Second, pathologic processes associated with reproductive cycles and function, such as ovarian cysts, uterine fibroids, and endometriosis, represent another set of potential pain sources that do not affect men (11–14). Third, a significant number of chronic pain syndromes show a marked preponderance of female patients over male patients. Among these often idiopathic syndromes are migraines, temporomandibular joint disorder, fibromyalgia, rheumatoid arthritis, osteoarthritis, interstitial cystitis, burning mouth syndrome, and vulvodynia (15).

Women also suffer from depression at twice the rate of men. The comparatively elevated prevalence figures for both clinical pain and depression thus beg the research question: Is there a relationship between the higher prevalence of depression and of pain reports in women? At the moment, the answer is equivocal. In itself, the higher prevalence of depression and of pain in women does not confirm that there is a meaningful relationship between them. To complicate matters, our current understanding of the relationship between pain and depression in women is limited both by a lack of attention to gender in pain research and the methodological problems common to pain research in
general. Often, gender is unexamined and is considered a sociodemographic variable that is not expected to moderate results. Further, most studies on the comorbidity of pain and depression have been conducted on clinical samples, making cross-study comparisons difficult because of the wide range of study conditions. And then, how are we to distinguish between sensory differences and response-style differences? Pain studies rely heavily on self-report, and this type of methodology cannot reliably distinguish a sensory difference from a cognitive or emotional response difference.

Despite limitations in the existing literature and methodological complications endemic to the study of differences in pain experience, the gender factor is becoming an important focus of investigation. Gender differences have the potential 1) to uncover basic mechanisms of disease in both men and women and 2) to inform clinical management efforts about the relative risks and benefits of differentiated treatment strategies. Considering this important potential, this paper reviews the literature on gender differences in the comorbidity of pain and depression and discusses the clinical implications of current findings.

**Comorbidity**

*Prevalence of Comorbid Pain and Depression*

A strong relationship between chronic pain and depression has been reported consistently, gender differences aside. However, estimates of the prevalence of depression in chronic pain patients have varied greatly, from 31% to 100% (16). In patients with depression, the estimated prevalence of pain complaints ranges from 34% to 66% (17). But what specific aspects of the pain experience correlate with depressive symptomatology? Attempts to answer this question have been inconclusive. Several studies have reported strong associations between pain intensity and depressive symptomatology, whereas other studies have found no association between these measures (18). Others have found duration, rather than intensity, of pain to be related to depressive symptomatology (19).

The inconsistencies in the prevalence rates reported may be partly due to some complex methodological issues. Among these is the cross-study variability in diagnosing depression and chronic pain and distinguishing between these major clinical disorders and their milder variants. The somatic content of depression measures constitutes another measurement problem in all studies of depression and pain. Physical symptoms associated with depression, such as fatigue, sleep disturbance, and decreased energy and libido, may be secondary to the pain and unrelated to depression. This symptomatologic overlap raises the possibility that the prevalence of depression in chronic pain patients is generally overestimated (20).

*Is Comorbid Pain and Depression More Prevalent in Women?*

In contrast to the voluminous literature on the association between pain and depression, only a few studies have focused specifically on gender differences in comorbidity.

Both men and women were equally likely to meet criteria for major depression in 3 different studies consisting of chronic pain samples with heterogeneous pain sites (21–23). Buckelew and others actually found higher rates of somatization, depression, anxiety, and psychoticism in men (24). However, the more frequent finding has been that higher prevalence rates for depression occur in women (25–28). In 1 of the rare prospective studies of pain and depression, Magni and others found a strong association between female gender and depression in the development of chronic musculoskeletal pain (26). In their analyses of pain predictors in a sample of 2324 chronic pain patients, male gender was a more powerful predictor of pain than female gender, which was a stronger predictor of depression. Another study found an age–gender interaction in a sample of 254 chronic pain patients, with younger women and older men reporting more depression (19).

Depression may also be differentially related, in men and women, to specific pain characteristics. In a prospective study, Haley and others found that, although depression occurred equally for women and men with chronic pain, the reported severity of the pain was related to depression in women, whereas functional impairment was related to depression in men (21). The presence of multiple symptoms may also be more strongly related to depression than regional pain (29), and women consistently report more multiple pain localizations than do men (7). Finally, with
female-specific pains and with pain syndromes that disproportionately affect women, there are higher rates of depression than in the general female population. One study reported that current and past diagnoses of depression were found in 71% of fibromyalgia patients (30). Women with temporomandibular disorder have higher rates of depression than similarly afflicted men (31). Patients with rheumatoid arthritis, burning mouth syndrome, interstitial cystitis, chronic pelvic pain, and vulvodynia also have significantly elevated rates of depression (32–36).

Much of the existing literature suggests that pain and depression cooccur more often in women than in men, although more research is needed to determine this conclusively.

Explanatory Models

The nature of the relationship between pain and depression has eluded researchers for over 3 decades of investigation. There are at least 3 possible versions of the relationship: 1) pain leads to depression; 2) depression leads to pain; and 3) they are both products of a common underlying phenomenon and thus develop in tandem as a function of this other variable. It is also possible that the relationship between pain and depression is different for women than it is for men and that the relationship varies depending on the pain syndrome being investigated. Additionally, there are the possible confounders of cases in which the depression and pain are completely unrelated and of cases in which pain medications cause symptoms generally associated with depression. Designing studies to distinguish between these alternate possibilities and control for confounders is challenging. Prospective studies are best suited to discover the nature of the pain–depression relationship, yet most of the available research is cross-sectional and cannot claim to uncover cause and effect relationships.

The handful of prospective and causal modeling studies that have addressed the cause and effect issue find support for causality in both directions. Brown found that pain episodes preceded the increases in depressive symptomatology in rheumatoid arthritis patients, most of which were women (18). Conversely, Leino and Magni’s longitudinal study of metal industry workers found that depressive symptoms predicted the development of musculoskeletal pain in both men and women (37). In another longitudinal study of a large sample from the National Health and Nutrition Examination Surveys, Magni and others found support for a bidirectional relationship between pain and depression in chronic musculoskeletal pain (26).

Since strong empirical support for any 1 causal direction is lacking, much of the discussion has centred on the explanatory potential of different theoretical models. Akin to the literature that seeks to explain the preponderance of depression in women, the literature on pain–depression comorbidity evokes explanatory models that fall under the general categories of biogenic, psychogenic, and sociogenic. Each of these models has been invoked, singly and in combination, to support differing views about the nature of the relationship.

Biogenic Models

The possibility that depression and pain share a common pathophysiology is a commonly held view. Pain pathways are known to involve the reticulolimbic structures of the brain, which also regulate emotion (38). Serotonin and norepinephrine have been implicated in both the perception of pain and the pathogenesis of depression. Pain has also been observed to be neurotransmitted partly through serotonergic mechanisms (39). In addition, both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been shown to relieve pain in some groups of chronic pain patients (40).

If pain and depression share common neuroanatomic pathways, could gender differences in brain chemistry, metabolism, physical structures and hormonal influences affect depression, pain transmission or perception, and their relationship? Not enough research has been conducted in this area to answer that question, but there is solid theoretical reasoning and some data in the pain literature to suggest that the answer may be affirmative.

Reviewing the available literature (including animal studies), pain and gender researcher Karen Berkley deduces that there are important factors that could operate differently to affect pain in men and women. First, she considers the vaginal canal a gateway for pathological agents that, through neural mechanisms of sensitization, can give rise to referred hyperalgesia in regions removed from the initial source of the trauma. Second, she posits that both the
composition and temporal patterns of sex hormones may explain gender differences in how pain is learned and interpreted and in responses to both opioid and nonopioid mechanisms of analgesia (41). Gear and others' recent finding that kappa-opiate analgesics produced significantly greater analgesia in women than in men lends support to Berkley’s hypotheses (42).

There are biological differences that could reasonably be theorized to predispose women to more pain in general and to more pain without evidence of peripheral pathology. Together with the evidence of gender-specific biological mechanisms of depression, there is reason to hypothesize that biology (cross-gender and female-specific) can account for some of the suspected higher prevalence of pain–depression comorbidity in women.

**Psychogenic Model**

Prior to the introduction of Melzack and Wall’s gate-control theory of pain, psychological factors involved in pain were invoked, more often than not, to imply hysteria, malingering, or variations on the concept of secondary gain (43). However, the gate-control theory was instrumental in discrediting the traditional mind–body dualism and in destigmatizing the role of psychological factors in the experience of pain. There is currently little doubt that psychological factors play a major role in the perception and expression of pain, regardless of the direction of cause and effect in the pain–depression relationship.

The most intuitive model of the pain–depression relationship posits that depression develops as a consequence of pain. Chronic pain disturbs psychologically reinforcing activities, such as work, play, and social interactions, and results in the development and persistence of depression (44). Research that demonstrates a correlation between depression and functional impairment, rather than pain intensity, provides support for this model (45). But, in what ways might this process differentially affect men and women? Is functional impairment equally linked to depression in both sexes? The research has not yet answered these questions.

Cognitive appraisal of the pain (what does this pain mean? should I worry? should I seek help?) is another psychological mechanism central to the pain–depression relationship. One study found that depressed chronic pain patients had a high level of cognitive distortion for pain-related situations in contrast to depressed patients without pain who had equal levels of cognitive distortion for both pain-related and non–pain-related situations (46). There is also evidence that women may engage in different cognitive distortions than men. Novy and others found that female depressed chronic pain patients more often endorsed body image distortion items on depression questionnaires (47). Jensen and others found that women catastrophized more than men in response to pain (48), and catastrophizing has been linked to depression and chronic pain (49). This finding is interesting, considering the popular belief by both men and women that women cope better with pain than do men (50). Perhaps men’s reports of pain to doctors and in clinical studies differ significantly from their expression of pain to spouses and family members.

A related theory posits that depressed patients have an increased somatic focus, which, coupled with negative interpretations, activates pain receptors (51). In general, women pay more attention to illness and worry more about pain (7,52). Perhaps because of women’s roles as caregivers, a somatic focus may have been sociobiologically adaptive for women, but it may also have placed them at a higher risk for depression and pain. Perhaps women attend to pain sooner in an effort to minimize its disruption of their multiple primary role responsibilities. In any case, because of the differences in pain experiences that men and women undergo over a lifespan, it is certainly probable that they have constructed different meanings around the experience of pain. One example of this is women’s perception that emotion has a great impact on pain, a view not shared by men (50).

The abundant research in the area of psychological factors that affect pain is beginning to clarify the influence of several important psychological processes on pain, if not indicate a direct cause and effect relationship. Gender differences in role expectations, cognitive appraisals, and general pain beliefs are certainly theoretically credible as mediating factors in the relationship between pain and depression.

**Sociogenic Model**
The influence of societal norms, stereotypes, and institutional biases in the diagnosis and the experience of both pain and depression, singly or in tandem, are requisite to any discussion of gender differences.

The most glaring example of this type of societal influence is a recognized propensity on the part of health care practitioners to attribute both idiopathic pain and women’s pain to psychological causes in the kind of direct cause and effect relationship that has no support in the empirical literature (53–55). Physicians may be more likely to diagnose psychiatric illness in pain patients when there is no obvious organicity. Bilkey presented 4 psychiatrists with a sample of chronic pain patients and asked that they separately determine what percentage of the patients had an identifiable personality disorder. Each psychiatrist indicated that 90% of the sample had a personality disorder. Bilkey reminds us that, incidentally, personality disordered patients are generally considered difficult to manage clinically (55). It is possible that this bias toward psychogenic causation may result in the overdiagnosis of depression in all chronic pain patients. It is even more probable that the overdiagnosis affects women even more, since they have the higher prevalence of idiopathic pain syndromes and thus constitute a larger proportion of “difficult patients.” Weir and others speculate that women may delay seeking medical help because they feel, more than men do, that they need to prove the existence of their painful condition (56). This may result in women presenting with more severe pain and more depression.

Most patients suffering from chronic pain perceive the pain as their primary problem, even if they are also suffering from depression. Psychiatric diagnoses and the psychological attributions made by health care professionals are often perceived by these patients as denials of their pain, as attempts to avoid dealing with the difficult treatment issue—the pain. Even a well-intentioned focus on the psychological aspects of their pain condition can be interpreted as a lack of validation of their pain and worsen the feelings of hopelessness and depression, which in turn can worsen the experience of pain. It is suspected that this dynamic is particularly strong in women, since traditionally they have had a more difficult time having their complaints taken seriously by physicians (56).

Depression may also be a more socially acceptable reaction to pain for women than for men. The reasoning behind this theory emanates from the depression literature and claims that women learn to turn their distress inward because this is more socially reinforced than externalization, which is the more acceptable option for men (57,58). The result of this internalization may be an increase in learned helplessness, a decrease in self-esteem, and negative cognitions that centre on personal undesirability, such as in the case of female chronic pain patients who disproportionately endorse body distortion items compared with men (47).

The relative economic impoverishment of women also places them at risk for a variety of health problems, including depression and pain. Poverty is among the life circumstances that have been consistently associated with depression and health problems (59). Although it is often treated as a sociodemographic variable, socioeconomic status continues to be the most powerful predictor of health status, and women continue to be much poorer than men.

Victimization in interpersonal relationships is also a significant risk factor for both depression and chronic pain. Survey research in nonclinical populations has found rates of childhood sexual assault to range from 21% to 37% among women and chronic pelvic pain to be associated with sexual abuse (59). Domestic violence can also result in chronic pain and depression. Women in these situations fail to seek medical care after beatings that often involve head and other injuries that result in both acute and chronic pain. Prolonged victimization is also commonly characterized by helplessness and depression (59).

**Integrative Model**

Despite the explanatory strength of any 1 of the models reviewed, it is unlikely that a single causal pathway would be sufficient to explain the probable complexity of the relationship between pain and depression, in either men or women. The pain literature and the depression literature, separately and without consideration of comorbidity, increasingly recognize that very many factors seem to contribute to the multidimensional experience of either phenomenon. Adding the issue of comorbidity to the etiologic discussion can only complicate the equation.

An integrative biopsychosocial model is the most likely candidate for understanding the nature of the relationship. Biological, psychological, and social factors interact in different ways in every individual. Rather than 1 causal
pathway being accurate, each is likely accurate, at times, for different patients in different combinations. This is a complicated proposition for research, which attempts to profile large groups of patients. However, the task is more feasible for clinicians, since they treat 1 patient at a time. This allows them the opportunity to consider carefully the unique configuration of factors contributing to their patient’s comorbid pain and depression.

**Managing Comorbid Pain and Depression**

There are important treatment implications to the cooccurrence of pain and depression. Nondepressed pain patients seem to benefit more from pain treatment than do depressed pain patients (60). This is not surprising, since pain treatment typically involves physical therapy and exercise, and depressed patients typically avoid activity. Conversely, pain patients have reported improvements with antidepressant medications. However, in the absence of clinical trials for the treatment of comorbid pain and depression, recommendations are patched together from the available evidence and some sound theoretical reasoning.

Essentially, there is little evidence of the relationship between pain and depression being unidirectional, in either direction. Even if the origins were identifiable, factors that initiated the pain and/or depression may not be the same ones maintaining the pain and/or depression. In these cases, targeting hypothesized originating factors may yield poor results. The recommended strategy is thus to assess and treat the pain and depression simultaneously.

This 2-pronged approach avoids conferring more importance on one disorder over another. The diagnosis of depression should not lead to inadequate evaluation and treatment of the pain, as has often been the case in the past. Explaining the rationale behind this bifurcated approach to patients is crucial so that they do not assume that the clinician’s assessment of their depression implies that the pain “is all in their head.” They have probably already had several such experiences to sensitize them to the suggestion of psychogenicity. It is important that both the somatic and psychological aspects of their experience be validated so as not to engage in any further iatrogenic harm.

Once a comprehensive medical and psychological assessment has been completed, both clinician and patient should engage in the process of treatment planning. Primarily, this involves setting realistic treatment goals. Crucial to this process is the distinction between acute and chronic pain. A failure to make this distinction is likely to lead to frustration for both patient and clinician when the pain is not fully resolved as expected. Minimally, appropriate goals include improving adjustment to the pain condition, increasing function in activities of daily living, improving mood, and reducing dependence on the health care system for pain control. Once these goals have been achieved, objectives can be reevaluated as needed.

Unlike the treatment of many comorbid conditions, in which the treatment for one, sometimes, is contraindicated for the other, the treatment of pain and depression significantly overlap. Both TCAs and SSRIs have shown impressive results in the treatment of depression and moderate results in the treatment of certain types of pain. In addition, cognitive-behavioural therapy consistently performs as well as antidepressants in the treatment of mild to moderate depression and is a key component of multidisciplinary pain treatment programs.

Pain treatment programs have several goals, which are attained with most pain patients. Some of these are 1) to reduce pain; 2) to reduce medication intake; 3) to reduce psychological impairment; 4) to correct range of motion abnormalities; 5) to educate patients in the roles that emotions, behaviour, and attitudes play in the experience of pain; 6) to reinforce health behaviour; and 7) to improve function (61,62). Clearly, the overall goal of pain treatment programs is rehabilitative. Chronic pain is not treated as acute pain.

But what about gender? What are the treatment implications of some of the gender differences found in the comorbidity of pain and depression? Should we be engaging in differentiated treatment strategies for men and women? The reality is that women and men in pain have been and continue to be treated differently, although not in concert with any empirical findings to support the different approaches. There is strong evidence that they have been receiving differential pharmacological care for their pain problems. After uncomplicated appendectomies and coronary artery bypass grafts, women are given less opioid analgesics than are men (63,64). In a recent study of pain management in a multicentre study of cancer pain, women were given significantly less medication than men, and in a study of pain clinics, men were prescribed more opioids than women (65,66). The general explanation for these
differences seems to be that nurses and physicians may perceive women to express pain more freely and are thus taken less seriously than men. Nurses believe that there are significant gender differences in sensitivity to pain, pain tolerance, pain distress, willingness to report pain, exaggeration of pain, and the nonverbal expressions of pain and that, accordingly, female patients require smaller amounts of narcotic analgesics (67,68).

Beliefs in gender differences about pain or illness in general often have resulted in the undertreatment of women. Currently, there seems to be little reason to recommend gender-tailored treatment strategies for women with pain and depression. Perhaps when we have more and clearer evidence of gender differences and their implications, a customized treatment approach will be warranted. For now, it would be a great improvement if women received the same treatment as men. The only gender difference that has been repeatedly empirically supported in the context of pain and depression is that more women than men appear to suffer from both.

From a research perspective, the challenge is to continue the study of potential etiologic factors while being mindful of the complex methodology needed for results to be valid and informative. Clinically, we must take care not to allow the high prevalence of these disorders in women to lead to generally unsupported attributions (for example, psychogenic pain) that result in impoverished assessment and treatment efforts. The high number of women with depression and pain should be a call to action rather than a dismissal. Finally, assessment and treatment must also start reflecting the empirically supported etiologic and phenomenological multidimensionality of both pain and depression.

Clinical Implications

- Comorbid pain and depression may be more prevalent in women.
- Biological, psychological, and societal factors are needed to explain the pain–depression relationship.
- Biopsychosocial assessment and treatment strategies are indicated.
- Gender-differentiated treatment strategies are not indicated.

Limitations

- Studies of gender differences in pain are plagued by methodological problems.
- There is insufficient evidence to conclusively determine the nature of the gender differences in comorbid pain and depression.

References


Résumé

La prévalence supérieure de la dépression chez les femmes est liée à une prévalence supérieure de plaintes de douleur. Des preuves de plus en plus nombreuses laissent croire que la comorbidité de ces états est également proportionnellement plus élevée chez les femmes que chez les hommes. Cet article donne un compte rendu critique des résultats empiriques relatifs aux différences entre les sexes dans la douleur et la dépression comorbides, ainsi que des résultats à l’appui des facteurs étiologiques hypothétiques qui pourraient expliquer pourquoi les femmes sont plus sensibles que les hommes à la comorbidité. La preuve empirique de modèles explicatifs biogènes, psychogènes et sociogènes est présentée, et une intégration de ces modèles est proposée pour orienter la recherche comme la pratique clinique. On conclut que les stratégies de traitement différentes selon le sexe ne sont pas indiquées sur le plan clinique, pour l’instant.

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1Assistant Professor, Department of Psychology, University of Nevada, Las Vegas, Las Vegas, Nevada.

Address for correspondence: Dr M Meana, Department of Psychology, University of Nevada, Las Vegas, 4505 Maryland Parkway, Box 5030, Las Vegas, NV 89154-5030

e-mail: meana@nevada.edu