Patients presenting with somatic complaints: epidemiology, psychiatric co-morbidity and management

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ABSTRACT Somatic symptoms are the leading cause of outpatient medical visits and also the predominant reason why patients with common mental disorders such as depression and anxiety initially present in primary care. At least 33% of somatic symptoms are medically unexplained, and these symptoms are chronic or recurrent in 20% to 25% of patients. Unexplained or multiple somatic symptoms are strongly associated with coexisting depressive and anxiety disorders. Other predictors of psychiatric co-morbidity include recent stress, lower self-rated health and higher somatic symptom severity, as well as high healthcare utilization, difficult patient encounters as perceived by the physician, and chronic medical disorders. Antidepressants and cognitive-behavioural therapy are both effective for treatment of somatic symptoms, as well as for functional somatic syndromes such as irritable bowel syndrome, fibromyalgia, pain disorders, and chronic headache. A stepped care approach is described, which consists of three phases that may be useful in the care of patients with somatic symptoms.

Key words: somatic symptoms, co-morbidity, depression, anxiety disorder

Introduction

Symptoms are conventionally classified as either psychological (for example, depressed mood, anxiety, guilt) or physical. Physical symptoms constitute bodily sensations such as pain, dizziness, palpitations, and fatigue. Such symptoms are commonly referred to as 'physical' by physicians who care predominantly for medical disorders, and 'somatic' by psychiatrists and psychologists in the context of mental disorder. Although the terms 'physical' and 'somatic' are interchangeable, it is inaccurate to equate physical symptoms with physical (medical) disorders because many patients with physical disorders (such as hypertension, well-controlled diabetes mellitus, stable coronary artery disease) are asymptomatic, and many patients with physical symptoms do not have a medical disorder that accounts for the presence and/or severity of their physical symptoms.

The co-occurrence of physical and psychiatric disorders has been a topic of increasing interest; it has been well established that there is at least a twofold greater risk of experiencing a depressive or anxiety disorder in patients with concomitant cardiovascular disease, neurological disorders, cancer, diabetes, HIV disease, and many other physical disorders. However, the topic of 'medical co-morbidity' will not be the focus of this paper. Rather, the relationship between somatic symptoms and psychiatric disorders, especially depression and anxiety, will be reviewed. In addition, the epidemiology and management of somatic symptoms will be addressed.

Prevalence and prognosis of somatic symptoms

Somatic symptoms account for over 50% of all outpatient visits, or an estimated 400 million clinic visits in the US alone each year (Schappert, 1992). This includes visits for pain, headache, fatigue and dizziness (Figure 1) as well as other physical complaints. Indeed, somatic symptoms in the general population are ubiquitous. An estimated 80% of individuals will experience one or more symptoms in any given month (Reidenberg et al., 1968; Kroenke et al., 1990; Green et al., 2001). These symptoms are often self-limited, because only about one in four patients seeks healthcare

for their symptoms (Green et al., 2001). Besides the severity or duration of a symptom (or symptoms), specific concerns and expectations as well as psychological factors are important reasons why patients seek health care for their somatic symptoms (Jackson and Kroenke, 2001; Kroenke, 2001).

The prognosis for most patients is favourable (Brody et al., 1989; ; Speckens et al., 1996; Marple et al., 1997; Kroenke and Jackson, 1998; Jackson and Passamonti, 2001). Approximately 75% of patients report resolution or improvement of their somatic symptoms within a few weeks of seeing a health care provider. Even in those patients whose symptom has been present for a year or more, 50% report improvement within two weeks of seeking care (Kroenke and Jackson, 1998).

As 75% of patients improve within several weeks, this suggests that approximately 25% of patients report persistence of their symptoms (unchanged or worse). This proportion has been consistent across multiple studies as shown in Table 1. Interestingly, it appears that the persistence rate of symptoms holds constant at 25%, with follow-up intervals as long as five years (Jackson and Passamonti, 2001). Thus, although the majority of patients with somatic symptoms improve, an important minority suffers from chronic or

recurrent symptoms. While most individual types of somatic symptoms have a persistence rate of 20% to 25%, some symptoms such as back pain, headache, and musculoskeletal complaints have an even higher one-year persistence rate of between 35% and 45% (Khan et al., 2000; Gureje and Simon, 1999).

Medically unexplained symptoms

At least 33% of somatic symptoms in primary care and population-based studies are 'medically unexplained' (Khan et al., 2000; Kroenke and Mangelsdorff, 1989; Kroenke and Price, 1993; Kroenke et al., 1994; Marple et al., 1997). As shown in Table 2, the proportion ranges from 20% to 74%, depending on the method used for classifying a symptom as medically unexplained. The classification method used in the two outlier studies makes it likely that 74% is an overestimate and 20% is an underestimate. The fact that three other studies using different samples and methods each concluded that one-third of somatic symptoms are medically unexplained makes this a reasonable estimate.

It appears that medically unexplained symptoms are also prevalent among patients referred to sub-specialty clinics. The proportion of patients with medically unexplained symptoms, attending seven different types

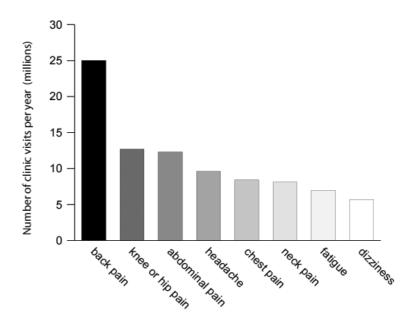


Figure 1. Estimated number of clinic visits due to somatic symptoms in the US each year (Shappert 1992).

Table 1. Persistence of somatic symptoms in primary care patients

Author	N	Study sample	Symptom persistence by follow-up inter			up interval
			1–2 weeks	3 months	1 year	5 year
Marple	328	Somatic symptom as presenting complaint in primary care	22%	-	_	_
Kroenke Jackson	500	Somatic symptom as presenting complaint in primary care	29%	21%	_	24%
Brody	117	Minor acute somatic complaint in primary care	27%	_	_	_
Speckens	100	Medically unexplained somatic symptom in primary care	_	-	24%	_

of medical and surgical sub-specialty clinics in the UK, has been evaluated (Reid et al., 2001). As the analysis was limited to 'frequent attenders', the proportions may overestimate the prevalence among all clinic attenders. Nonetheless, the proportion of frequent attenders with medically unexplained symptoms was 54% in gastroenterology clinics, 50% in neurology clinics, 34% in cardiology clinics, 33% in rheumatology clinics, 30% in orthopedics clinics, 27% in otolaryngology clinics, 17% in general surgery and gynaecology clinics, and 15% in pulmonary clinics (Reid et al., 2001).

Functional symptom syndromes

Many patients present with individual somatic symptoms, such as back pain, headache, dizziness, and dyspnea. However, others present with common functional syndromes manifested by constellations of somatic symptoms, such as irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome (CFS), temporomandibular disorder (TMD), and the highly controversial multiple chemical sensitivity (MCS). The overlap between functional syndromes in terms of symptoms, functional impairment, psychiatric co-morbidity and response to generic treatments has previously been summarized (Wessely et al., 1999; Barsky and Borus, 1999). Recently, 53 studies that examined the co-occurrence of two or more syndromes in patient groups have been reviewed (Aaron and Buchwald, 2001). The co-occurrence rate (overlap) was 35% to 70% for FM and CFS, 32% to 80% for FM and IBS, 58% to 92% for CFS and IBS, 33% to 55% for FM and MCS, and 30% to 67% for CFS and MCS.

The degree of overlap is not surprising considering how these functional syndromes are diagnosed, which is predominantly or exclusively on the basis of somatic symptoms. The prevalence of individual symptoms such as fatigue, sleep disturbance, musculoskeletal

Table 2. Proportion of somatic symptoms that are medically unexplained

Lead author	N	Study sample and design	Method for classifying as medically unexplained	Medically unexplained
Kroenke	1000	Primary care chart review study	One physician chart auditor using implicit criteria	74%
Khan	450	Primary care chart review study	Two physician chart auditors using explicit criteria;	
			interrater reliability also assessed	34%
Kroenke	13,328	Population-based survey	Structured lay interview of subjects using	
			Diagnostic Interview Schedule	35%
Marple	338	Primary care prospective cohort study	Clinical judgment of patient's primary care physician	33%
Kroenke	1000	Primary care survey	Clinical judgment of patient's primary care physician	* 20%

^{*} Certain somatic symptoms were not counted as 'medically unexplained' if they were part of diagnostic criteria for a depressive disorder (such as fatigue or insomnia) or an anxiety disorder (such as chest pain or palpitations in patient with panic disorder), and patient-met criteria for that particular depressive or anxiety disorder.

pains, headache, and gastrointestinal complaints is high across all syndromes (Gardner et al., in press).

Depression and anxiety

The majority (70–90%) of patients with depression or anxiety who present in primary care complain of somatic symptoms rather than volunteering psychological symptoms such as 'I'm depressed', or 'I've been feeling anxious' (Simon et al., 1999). On the other hand, most patients with a depressive or anxiety disorder will admit to psychological symptoms if specifically asked about them (Whooley et al., 1997; Simon et al., 1999; Williams et al., 1999). Thus, somatic symptoms present an 'opening' for the primary care clinician to inquire about co-existing psychological distress.

Several aspects related to somatic symptoms should heighten the clinician's suspicion of a depressive or anxiety disorder. First, symptoms that remain medically unexplained after initial evaluation carry a higher risk of psychiatric co-morbidity. Notably, the specific type of somatic symptom does not matter. Approximately 50% to 75% of patients with medically unexplained symptoms have a depressive disorder, and 40% to 50% have an anxiety disorder, whether the symptom is pain, fatigue, disturbed sleep, a gastrointestinal complaint, or any other unexplained somatic symptom (Kroenke et al., 1994).

The number of somatic symptoms is also a powerful marker of psychological co-morbidity. As shown in Table 3, there is a powerful relationship between the number of somatic symptoms and the likelihood of a concomitant depressive or anxiety disorder (Kroenke et al., 1994; Kroenke and Jackson, 1997). It might be useful to think of the somatic symptom count as a 'sed rate' for potential psychopathologic inflammation. Analogous to the erythrocyte sedimentation rate (ESR), which is a sign of physical inflammation, the somatic symptom count is non-specific, but the higher the latter, the greater the likelihood of a patient meeting criteria for a coexisting (and potentially treatable) depressive or anxiety disorder.

Several other predictors of depression and anxiety have been revealed in a series of studies and are captured in the 'S4' model (Kroenke et al., 1997; Jackson et al., 1998; Jackson et al., 2001). One of the predictors – a high somatic symptom count – has already been mentioned. The other three predictors are recent stress, low self-rated health, and high

severity of the patient's presenting somatic symptom. As shown in Table 4, the presence of any of these four predictors individually increases the risk of an underlying depressive or anxiety disorder, and the likelihood of these disorders increases incrementally with the number of predictors.

The clinician's perception that the patient encounter is difficult is also a surprisingly good predictor of co-morbid depression or anxiety. About one out of every six outpatient visits is considered difficult by the primary care physician, and patients whose visits are rated as difficult are two to three times more likely to have a depressive or anxiety disorder (Jackson and Kroenke, 1999; Hahn et al., 1996; Hahn 2001). Moreover, difficult encounters are strongly associated with medically unexplained symptoms as well as high somatic symptom counts. Physicians' attitudes towards caring for patients with psychosocial problems may be one potentially modifiable factor: physicians with poor attitudes find 23% of their patient visits difficult, whereas physicians who feel more positive about evaluating and managing psychosocial problems find only 8% of their patient visits difficult (Jackson and Kroenke, 1999). A high case mix of complex psychosocial problems is one factor associated with career dissatisfaction among primary care physicians (Wetterneck et al., 2002), and improving physician training in the management of depression, anxiety and other mental disorders may therefore be valuable for both improved care of patients with somatic complaints, as well as diminished physician frustration.

High utilization of health care services (for example, frequent clinic visits) is another predictor of psychological distress (Katon et al., 2001). Medical comorbidity also increases the risk of depression and anxiet; these include the 'three Cs' (cardiovascular disease, central nervous system disorders, and cancer), diabetes, HIV disease and numerous other physical conditions (Cassem, 1995). Table 5 summarizes some of the factors that should increase clinical suspicion of depression or anxiety in patients presenting with somatic symptoms.

Some argue that routine screening for depression is warranted in primary care (US Preventive Services Task Force, 2002). However, the large volume of patients seen, short appointments, and other 'competing demands' make screening of every single patient potentially burdensome (Klinkman, 1997; Williams, 1998).

To reduce the number of patients screened and to lessen the number of false positives, a case-finding approach in which patients at greater risk are selectively evaluated is an attractive option. This can still be done efficiently because it has been shown that a single question about depressed mood identifies 85% and 90% of patients with major depression, and a second question about anhedonia may increase the sensitivity to 95% (Whooley et al., 1997; Williams et al., 1999). Patients who screen positive can have the severity of their depression graded with any number of simple instruments (Mulrow et al., 1995; Williams et al., 2002).

Screening for depression is also warranted in patients with persistent or unexplained somatic symptoms who are seen in sub-specialty clinics. Studies in patients newly referred to gastroenterology, rheumatology, and neurology clinics have shown a prevalence of depression of 25–30% (O'Malley et al, 1998a,b; Ekstrand et al., 2000). In these same studies, depressed patients were only 25% as likely to have a physical disorder diagnosed by the sub-specialist. Thus, screening for depression may be more cost-effective than many of the expensive diagnostic tests and procedures often performed in patients with persistent and unexplained somatic symptoms.

Management of somatic symptoms in primary care: a stepped care approach

An algorithm that uses a stepped care approach for managing somatic symptoms in primary care is illustrated in Figure 2. It is clinically useful to think of patients initially presenting with somatic complaints as falling into one of three categories:

- acutely serious <5% of patients;
- minor and self-limited 70% to 75% of patients;
- persistent (either chronic or recurrent) 20% to 25% of patients.

As reviewed earlier in this paper, the evidence supporting the proportion of patients falling into the last two categories is fairly strong. Although the epidemiology of 'acutely serious' symptoms has been less well studied, it is probable that this category represents less than 5% of all somatic symptoms presenting in primary care – a number derived partly from clinical experience but mainly by subtracting the last two categories.

Step 1

Certain symptoms are occasionally acutely serious (chest pain, dyspnea, new abdominal pain), whereas others are seldom acutely serious (back pain, headache, fatigue, dizziness). The presence or absence of other 'red flags' on history or physical examination typically dictates whether immediate diagnostic evaluation is warranted. For the majority of primary care patients with somatic symptoms, a focused history and physical examination provides most of the diagnostic and prognostic information (Kroenke, 2001). Follow-up is preferable to an initial and expensive work-up; a 'waiting period' of two to six weeks can clarify whether the symptom will be self-limited or persistent. The fear of missing an occult but serious medical diagnosis is

Table 3. Relationship between somatic symptom count and likelihood of a depressive or anxiety disorder in primary care patients

Number of somatic symptoms*	Study A (Kroenke) (N = 1000)			Study B (Kroenke) (N = 499)		
	N	% Mood disorder	% Anxiety disorder	N	% Mood or anxiety disorder	
0–1	215	1%	2%	106	4%	
2–3	225	7%	12%	131	18%	
4–5	191	13%	23%	129	31%	
6–8	230	30%	44%	96	52%	
≥9	139	48%	60%	37	78%	

^{*} Number of symptoms that the patient reports being 'bothered a lot' by in the past month selected from the PRIME-MD checklist of 15 somatic symptoms.

Table 4. S4 Model: type and number of predictors of depressive or anxiety disorders: odds and ratio percentages

Variable	Study A [Kroenke]	Study B [Jackson]	Study C [Jackson]	
Number of subjects Study population	500 Primary care patients presenting with somatic complaints	250 Primary care patients presenting with somatic complaints	185 New patients referred to rheumatology clinic	
Individual predictor*	Odds ratio for depressive or anxiety disorder †			
Stress in past week	4.9	6.7	3.3	
Symptom count >5	3.1	4.0	4.5	
Self-rated health as low	2.7	2.2	3.4	
Severity of symptom >5	2.0	1.2	1.6	
Number of predictors	Percentag	e with depressive or anxiety disorder		
0	8	2	0	
1	16	19	16	
2	43	39	37	
3	69	72	70	
4	94	-	94	

^{*} The four S4 predictors are (1) recent stress (yes/no); (2) symptom count >5 on PRIME-MD checklist of 15 somatic symptoms; (3) self-rated overall health of poor or fair on a 5-point scale (excellent, very good, good, fair, poor); (4) self-rated severity of presenting somatic symptom of >5 on 0 (none) to 10 (unbearable) scale.

Table 5. Predictors of depression or anxiety in patients with somatic symptoms

Symptom characteristics

- Medically unexplained
- Multiple somatic symptoms
- Persistent/chronic (possibly)

S4 model predictors (the three predictors, besides multiple somatic symptoms)

- Stress current
- Self-reported health is rated low
- Severity of symptom is rated high

Difficult encounter (as rated by clinician)

High utilization of health services (e.g., frequent clinic attender)

greatly overestimated. Studies of specific physical symptoms as well as somatic symptoms in general have shown that the physician's initial judgement is quite accurate, and that serious diseases thought unlikely at the index visit rarely emerge with long-term follow up (Kroenke, 1997, 2001; Khan et al., 2000).

In lieu of costly testing or referral, there are several things the physician can do at the index visit. Reassurance itself may be therapeutic in some patients (Thomas, 1987). A more targeted type of reassurance is to identify and address the patient's symptom-specific concerns and expectations, which commonly

[†] All odds ratios are significant (ie, lower bounds of 95% confidence interval exceeds 1.0) except for severity of symptom in Study B.

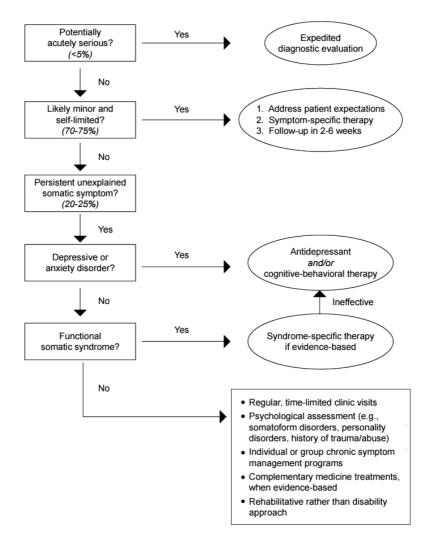


Figure 2. Stepped care approach to managing somatic symptoms in primary care.

include an explanation of the symptom's cause and prognosis, as well as a desire for specific physician actions such as medication prescribing, test ordering, sub-specialty referral, or administrative actions. Studies have shown that addressing such expectations is both efficient and effective (Jackson et al., 1999; Jackson and Kroenke, 2001; Rao et al., 2000). Two simple questions are: 'was there anything else you were worried about?' and 'was there anything else you thought might be helpful?' There are also pharmacological and non-pharmacological therapies that can be provided for certain types of somatic symptoms in patients whose symptoms have been particularly bothersome, such as simple analgesics for pain, acid suppressants for dyspepsia, gentle bowel medications for constipation, sleep hygiene for insomnia, exercise

for back pain and fatigue, and habituation exercises or meclizine for vertigo.

Step 2

Screening for depression and anxiety is certainly warranted in those patients whose somatic symptoms persist at two to six weeks' follow-up and in whom a specific, treatable medical diagnosis has not been established. In fact, psychological screening may be warranted at the index visit for those patients in whom predictors are present (Table 5) or if, for other reasons, the clinician suspects depression, anxiety or other psychological factors are causing or contributing to the patient's somatic symptoms. Ideally, one would screen for depression and possibly anxiety in all patients with somatic symptoms at the index visit, but this is often

not feasible due to the competing demands of primary care (Klinkman, 1997; Williams, 1998). The Patient Health Questionnaire (PHQ) is one brief measure that makes criteria-based diagnoses of depressive, anxiety, somatoform, alcohol and eating disorders (Spitzer et al., 1999). If evaluation of depression is the primary aim, the nine-item depression module (PHQ-9) alone can be used as a diagnostic and monitoring tool (Kroenke et al., 2001). There are numerous other instruments that have similar operating characteristics for evaluating depression (Mulrow et al., 1995; Whooley et al., 1997; Williams et al., 2002).

Should a depressive or anxiety disorder be diagnosed, antidepressants as well as psychotherapy, alone or in combination, are effective treatments. What may be less well known is the efficacy of these treatments for functional somatic syndromes. A series of meta-analyses has recently documented the efficacy of antidepressants in patients with IBS, FM, migraine and tension headache, lower back pain, and several other somatic symptoms or syndromes (O'Malley et al., 1999, 2000; Jackson et al., 2000; Tomkins et al., 2001; Salerno et al., 2002). Regardless of the type of syndrome, patients were two to three times more likely to respond to an antidepressant than a placebo. While only 25% of the trials evaluated depression, it appeared in this subset of studies that somatic symptom improvement occurred independently from an improvement in depression (O'Malley et al., 1999). The majority of trials have been conducted with tricyclic antidepressants, so the efficacy of newer antidepressants for somatic syndromes is less clear. Although not conclusive, it does appear that tricyclics may be somewhat more effective for pain syndromes than selective serotonin reuptake inhibitors. There is preliminary evidence indicating that dual reuptake antidepressants, which inhibit both norepinephrine and serotonin receptors, may be beneficial in reducing pain, although clinical trials are needed.

The use of antidepressants for treating functional somatic syndromes has limitations. Discontinuation rates may be higher because of a heightened sensitivity to somatic side effects – a 'nocebo' effect (Barsky et al., 2002) – as well a causal attribution that is somatic and rejects anything suggesting a psychological etiology ('my symptoms are physical; they are not in my head'). Also, symptom reduction rather than total remission is the most common therapeutic response. Further, most trials have been short-term, and the long-term efficacy of antidepressants for the treatment of chronic somatic

syndromes is not well established. Finally, as there are evidence-based non-psychological treatments for some functional syndromes (Leventhal, 1999; Jaiwala et al., 2000), antidepressants can often be reserved as adjunctive rather than primary treatment.

A recent review of 31 controlled trials of cognitivebehavioural therapy (CBT) for somatic symptoms and functional syndromes documents the efficacy of CBT in the treatment of back pain, chest pain, IBS, CFS, somatization, and other selected somatic symptoms (Kroenke and Swindle, 2000). As few as five sessions of group therapy and interventions proved efficacious, and in some studies, benefits were sustained for up to 12 months. As with antidepressants, the benefits of CBT did not seem to be entirely mediated through amelioration of psychological distress. Finally, a recent meta-analysis of 244 studies examining the role of psychological factors in IBS, non-ulcer dyspepsia, FM, and CFS found that depression and anxiety accounted for part but not all of the symptomatology in these functional somatic syndromes (Henningsen et al., in press).

Step 3

Individuals with persistent somatic symptoms, who are either not covered by Steps 1 and 2 or who fail to respond to the suggested treatment strategies, represent a heterogeneous group of patients. Predisposing or maintaining factors can include (but are not limited to): somatoform disorders such as somatization disorder and hypochondriasis; personality disorders; past or current history of sexual or physical abuse; psychosocial reasons such as interpersonal conflict, job dissatisfaction, and disability or compensation-seeking behaviour; and opioiddependent chronic pain. In addition to the identification of these or other contributing factors, management includes: regular time-limited visits with a primary care physician; avoidance of unnecessary testing, procedures, and referrals; individual or group programmes for self-management of, and coping with, chronic symptoms; and complementary medical therapies that are evidence based for certain somatic symptoms (for example, chiropractic and acupuncture for certain pain conditions).

Conclusion

Somatic symptoms account for over half of all outpatient medical visits. Such symptoms are medically unexplained 33% of the time, and are chronic or

recurrent in 25% of patients. Medically unexplained, persistent or multiple somatic symptoms should heighten a physician's clinical suspicion of a co-morbid and potentially treatable depressive or anxiety disorder. Other predictors of depression or anxiety include recent stress, poor self-rated health, high symptom severity, perception by the physician of a difficult patient encounter, repeated clinic visits, and other chronic medical disorders. Certain somatic symptoms and functional somatic syndromes may respond to antidepressants and CBT, even in the absence of psychiatric co-morbidity. A stepped care approach may improve the care of patients with somatic symptoms, reduce health care costs, and enhance physician satisfaction.

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References

- Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med 2001; 134: 868–81.
- Barsky AJ, Borus JF. Functional somatic syndromes. Ann Intern Med 1999; 130: 910–21.
- Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. JAMA 2002; 287: 622–7.
- Brody DS, Miller SM, Lerman CE, Smith DG, Caputo GC. Patient perception of involvement in medical care: relationship to illness attitudes and outcomes. J Gen Intern Med 1989; 4: 506–11.
- Cassem EH. Depressive disorders in the medically ill: an overview. Psychosomatics 1995; 36: S2–S10.
- Ekstrand J, O'Malley PG, Labutta R, Jackson JL. Mental disorders in a neurology clinic setting. J Gen Intern Med 2000; 15(1, suppl): 112.
- Gardner JW, Gibbons RV, Hooper TI, Cunnion SO, Kroenke K, Gackstetter GD. Identifying new diseases and their causes: the dilemma of illnesses in Gulf War veterans. Milit Med (in press).
- Green LA, Fryer GE, Yawn BP, Lanier D, Dovey SM. The ecology of medical care revisited. N Engl J Med 2001; 344: 2021–5.
- Gureje O, Simon GE. The natural history of somatization in primary care. Psychol Med 1999; 29: 669–76.
- Hahn SR. Physical symptoms and physician-experienced difficulty in the physician-patient relationship. Ann Intern Med 2001; 134: 897–904.
- Hahn SR, Kroenke K, Spitzer RL, et al. The difficult patient in primary care: prevalence, psychopathology and impairment. J Gen Intern Med 1996; 11: 1–8.

- Henningsen P, Zimmermann T, Sarrel H. Medically unexplained physical symptoms, anxiety and depression: a meta-analytic review. Psycho Med (in press).
- Jackson JL, Houston JS, Hanling SR, Terhaar KA, Yun JS. Clinical predictors of mental disorders among medical outpatients. Arch Intern Med 2001; 161: 875–9.
- Jackson JL, Kroenke K. Difficult patient encounters in the ambulatory clinic: clinical predictors and outcomes. Arch Intern Med 1999; 159: 1069–75.
- Jackson JL, Kroenke K. The effect of unmet expectations among adults presenting with physical symptoms. Ann Intern Med 2001; 134: 889–97.
- Jackson JL, Kroenke K, Chamberlin J. Effects of physician awareness of symptom-related expectations and mental disorders: a controlled trial. Arch Fam Med 1999; 8: 135–42.
- Jackson JL, O'Malley PG, Kroenke K. Clinical predictors of mental disorders among outpatients: validation of the 'S4' model. Psychosomatics 1998; 39: 431–6.
- Jackson JL, O'Malley PG, Tomkins G, Balden E, Santoro J, Kroenke K. Treatment of functional gastrointestinal disorders with antidepressant medications: a metaanalysis. Am J Med 2000; 108: 65–72.
- Jackson JL, Passamonti ML. Symptoms in primary care: outcomes at five years. J.Gen.Intern.Med 2001; 16(1, suppl): 142 (abstract).
- Jailwala J, Imperiale T, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. Ann Intern Med 2000; 133: 136–47.
- Katon W, Sullivan M, Walker E. Medical symptoms without identified pathology: relationship to psychiatric disorders, childhood and adult trauma, and personality traits. Ann Intern Med 2001; 134: 917–25.
- Khan AA, Khan A, Kroenke K. Symptoms in primary care: etiology and outcome. J Gen Intern Med 2000; 15 (1, suppl.): 76–7.
- Klinkman MS. Competing demands in psychosocial care: a model for the identification and treatment of depressive disorders in primary care. Gen Hosp Psychiatry 1997; 19: 98–111.
- Kroenke K. Symptoms and science: the frontiers of primary care research. J Gen Intern Med 1997; 12: 509–10.
- Kroenke K. Studying symptoms: sampling and measurement issues. Ann Intern Med 2001; 134: 844–55.
- Kroenke K, Arrington ME, Mangelsdorff AD. The prevalence of symptoms in medical outpatients and the adequacy of therapy. Arch Intern Med 1990; 150: 1685–9.
- Kroenke K, Jackson JL. Outcome in general medical patients presenting with common symptoms: a prospective study with a two-week and a three-month follow-up. Fam Pract 1998; 15: 398–403.
- Kroenke K, Jackson JL, Chamberlin J. Depressive and anxiety disorders in patients presenting with physical complaints: clinical predictors and outcome. Am J Med 1997; 103: 339–47.

- Kroenke K, Mangelsdorff AD. Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. Am J Med 1989; 86: 262–6.
- Kroenke K, Price RK. Symptoms in the community: prevalence, classification, and psychiatric comorbidity. Arch Intern Med 1993; 153: 2474–80.
- Kroenke K, Spitzer RL, Williams JBW, et al. Physical symptoms in primary care: predictors of psychiatric disorders and functional impairment. Arch Fam Med 1994; 3: 774–9.
- Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001; 16: 606–13.
- Kroenke K, Swindle R. Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials. Psychother Psychosom 2000; 69: 205–15.
- Leventhal LJ. Management of fibromyalgia. Ann Intern Med 1999; 131: 850–8.
- Marple RL, Kroenke K, Lucey CR, et al. Concerns and expectations in patients presenting with physical complaints: frequency, physician perceptions and actions, and two-week outcome. Arch Intern Med 1997; 157: 1482–8.
- Mulrow CD, Williams JW Jr, Gerety MB, Ramirez G, Montiel OM, Kerber C. Case-finding instruments for depression in primary care settings. Ann Intern Med 1995; 122: 913–21.
- O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants. A meta-analysis. J Gen Intern Med 2000; 15: 659–66.
- O'Malley PG, Jackson JL, Kroenke K, Yoon K, Hornstein E, Dennis GL. The value of screening for psychiatric disorders in rheumatology referrals. Arch Intern Med 1998b;158: 2357–62.
- O'Malley PG, Jackson JL, Santoro J, Tomkins G, Balden E, Kroenke K. Antidepressant therapy for unexplained symptoms and symptom syndromes. J Fam Pract 1999; 48: 980–90.
- O'Malley PG, Wong PWK, Kroenke K, Roy MJ, Wong RKH. The value of screening for psychiatric disorders prior to upper endoscopy. J Psychosom Res 1998a; 44: 279–87.
- Rao JK, Weinberger M, Kroenke K. Visit-specific expectations and patient-centered outcomes: a literature review. Arch Fam Med 2000; 9: 1148–55.
- Reid S, Wessely S, Crayford T, Hotopf M. Medically unexplained symptoms in frequent attenders of secondary health care: retrospective cohort study. BMJ 2001; 322: 767.
- Reidenberg MM, Lowenthal DT. Adverse nondrug reactions. N Engl J Med 1968; 279: 678–9.

- Salerno SM, Browning R, Jackson JL. The effect of antidepressant treatment on chronic back pain: a meta-analysis. Arch Intern Med 2002; 162: 19–24.
- Schappert SM. National Ambulatory Medical Care Survey: 1989 summary. National Center for Health Statistics. Vital Health Stat 1992; 13(110): 1–80.
- Simon GE, Von Korff M, Piccinelli M, Fullerton C, Ormel J. An international study of the relation between somatic symptoms and depression. N Engl J Med 1999; 341: 1329–35.
- Speckens AEM, Van Hemert AM, Bolk JH, Rooijmans HGM, Hengeveld MW. Unexplained physical symptoms: outcome, utilization of medical care and associated factors. Psychol Med 1996; 26: 745–52.
- Spitzer RL, Kroenke K, Williams JBW, and the Patient Health Questionnaire Study Group. Validation and utility of a self-report version of PRIME-MD: The PHQ Primary Care Study. JAMA 1999; 282: 1737–44.
- Thomas KB. General practice consultations: is there any point in being positive? Br Med J (Clin Res Ed) 1987; 294: 1200–2.
- Tomkins G, Jackson JL, O'Malley PG, Balden E, Santoro J. Treatment of chronic headache with antidepressants: a meta-analysis. Am J Med 2001; 111: 54–63.
- US Preventive Services Task Force. Screening for depression: recommendations and rationale. Ann Intern Med 2002; 136: 760–4.
- Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999; 354: 936–9.
- Wetterneck TB, Linzer M, McMurray JE, et al. Worklife and satisfaction of general internists. Arch Intern Med 2002; 162: 649–56.
- Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instruments for depression: two questions are as good as many. J Gen Intern Med 1997; 12: 439–45.
- Williams JW Jr. Competing demands: does care for depression fit in primary care? J Gen Intern Med 1998; 13: 137–9.
- Williams JW, Mulrow CD, Kroenke K, et al. Case-finding for depression improves patient outcomes: a randomized trial. Am J Med 1999; 106: 36–43.
- Williams JW Jr, Noel PH, Cordes JA, Ramirez G, Pignone M. Is this patient clinically depressed? JAMA 2002; 287: 1160–70.

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