Chronic Multisystem Illness Among Gulf War Veterans

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Relapse of Depressive Symptoms After Discontinuing Sertraline

To the Editor: Dr Keller and colleagues[1] report marked differences between continuing and discontinuing previously successful treatment with sertraline hydrochloride in patients with chronic depression. New episodes occurred in 10% of patients continuing sertraline (146 mg/d) for up to 18 months vs 30% after discontinuing sertraline and changing to placebo (over a period of 2.9 weeks), with new symptoms developing in 45% vs 72%, respectively. These differences (20%-27%) indicate a moderate sparing of relapse. It is remarkable that so many formerly long-term ill patients did so well after switching to placebo, but some may represent previously undertreated but reversible disorders.

The reported pattern of relapses is well-known in discontinuation trials, with a sharp, early separation of treated and discontinued patients, and little difference after the first few months.[2-4] Computed rates (95% confidence interval [CI]) of return of depressive symptoms in weeks 1 to 24 were 1.91 (95% CI, 1.58-2.24) per week after discontinuation vs 0.77 (95% CI, 0.59-0.95) with sertraline continued, a 2.5-fold difference. At weeks 25 to 80, corresponding rates were much lower and indistinguishable: 0.14 (95% CI, 0.12-0.16) vs 0.13 (95% CI, 0.11-0.15) per week. This pattern suggests a time-limited impact of drug discontinuation itself, or early culling of patients particularly vulnerable to treatment discontinuation.[2-5]

These findings indicate that (1) remarkably, many subjects meeting criteria for chronic depression did well after relatively rapid discontinuation of ongoing antidepressant treatment (45%-70%), (2) overall drug and placebo differences were modest (20%-27%), and (3) nearly all of the difference occurred within the first months after discontinuation. Benefits of treatment were thus limited in both magnitude and time.

Treatment discontinuation trials in general medicine and psychiatry probably do not represent straightforward comparisons of treated vs untreated patients, as is often assumed.[3] Rapid drug discontinuation may contribute to early relapse risk, which can be limited by a slower taper.[2-4] Cost-benefit considerations in planning long-term care of patients with recurrent depressive illness should include the adverse effect, financial burden, and risk of destabilizing persons with undiagnosed bipolar mood disorders with overuse of antidepressants, as well as early impact of rapidly discontinuing ongoing treatment, and a more critical appraisal of true-effect sizes. A final implication is that findings from antidepressant discontinuation trials do not provide compelling support for indefinitely prolonged maintenance treatment as a routine clinical policy.[5]

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In Reply: We disagree with the statement by Drs Baldessarini and Viguera that the maintenance effects of sertraline in our study represent only "moderate sparing of relapse." A 4-fold reduction in depression recurrence (23% with placebo vs 6% with sertraline) represents a substantial reduction in risk. Further, we are not as surprised as Baldessarini and Viguera at the relatively low relapse rate observed when switching to placebo in our study, which probably resulted from several factors: (1) patients randomized to sertraline or placebo were a compliant and responsive subset (38%) of the original patient sample, (2) placebo treatment was not a "no treatment" condition since study participation necessarily involved a high degree of nonspecific supportive therapy, and (3) chronicity may constitute less of an immediate relapse risk than a high number of prior episodes.

Baldessarini and Viguera further comment that the pattern of relapse "suggests a time-limited impact of drug discontinuation itself." In fact, the discontinuation of sertraline was carried out gradually, using a 50-mg/wk dosage reduction and a phased-in substitution of placebo, resulting in a 2- to 4-week taper period for most patients. Two to 4 weeks is precisely the definition of "gradual" used by Baldessarini and colleagues[1,2] in their research on this topic. Also arguing against a discontinuation-triggered "sharp, early separation of treated and discontinued patients" in terms of relapse were the similar weekly depression-symptom reemergence probabilities based on Kaplan-Meier estimates for the first 2 months of the maintenance phase compared with months 3 to 6. Specifically, the

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weekly depression symptom reemergence probabilities for maintenance phase treatment weeks 0 to 8 were 1.68% and 3.72% per week for sertraline and placebo, respectively (ie, 2.21 times higher for placebo); and the weekly depression symptom reemergence probabilities for weeks 9 to 24 were 0.46% and 1.22% per week for sertraline and placebo, respectively (ie, 2.65 times higher for placebo).

We agree that our findings do not provide compelling support for indefinitely prolonged maintenance treatment. But in light of the known high risk of recurrence[3] and associated morbidity, we think that the prophylactic benefit of sertraline treatment is substantial in the long-term. The clinician and patient, of course, must weigh the increased risk of recurrence after drug discontinuation against the financial cost and adverse effect burden associated with continuing a successful medical regimen.

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Alendronate and Fracture Prevention

To the Editor: The Editorial by Dr Heaney[1] concludes that 4 years of treatment with alendronate sodium produced disappointing results for women with low bone density. It may be too much to expect that only 4 years of modest increases in bone density with alendronate, estrogen, tamoxifen citrate, or other agents would reduce nonspine fracture risk in women with only a modest risk.[2-4] However, this should not obscure the important finding that just 3 to 4 years of alendronate substantially reduced the risk of painful fractures in women who have hip bone density at least 2.5 SDs below normal. These findings reinforce National Osteoporosis Foundation guidelines[5] that women 65 years and older who are willing to consider treatment for osteoporosis should have a measurement of bone density to determine whether they would benefit from treatment.

The implication that calcium and vitamin D are as effective as alendronate for women with osteoporosis is misleading: the 35% to 50% reductions in fracture risk in the Fracture Intervention Trial occurred in addition to calcium and vitamin D supplementation that was sufficient to raise average intake to more than 1200 mg/d and 250 IU, respectively. Randomized trials have shown that addition of alendronate or raloxifene hydrochloride to calcium and vitamin D supplementation reduces the risk of vertebral fractures and addition of alendronate to these supplements also reduces the risk of hip fractures in women with osteoporosis.[2-4,6]

Finally, the editorial refers to multiple benefits of hormone replacement therapy. We think, however, that the recent findings that estrogen and progestin increased the coronary heart disease risk during the first year of treatment of women with coronary heart disease[3] should make clinicians cautious about assuming that estrogen will have multiple benefits until this is demonstrated by randomized trials.

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In Reply: Dr Cummings and colleagues are correct in noting that those alendronate-treated patients in their trial who had the most severe bone loss did experience a significant reduction in fracture risk, a fact that I had acknowledged explicitly in my editorial. There is, thus, no disagreement there. But they are silent on my 2 main points: (1) the inadequacy of the bone mass paradigm as an explanation for osteoporotic fragility, and (2) the issue of what the physician ought to do when confronted with patients with bone mass values in the range that the World Health Organization Working Group[1] defined as osteopenia (ie, bone mineral density values between –2.5 and –1.0 SDs).

With regard to the first point, despite similar starting bone mineral density values and essentially identical bone mineral density responses to alendronate in the prevalent and nonprevalent fracture groups, the fracture reduction in the group free of fracture at baseline was much less than in the group with prevalent fractures. This finding suggests both that reduced bone mass per se was not a fully adequate explanation for the fragility manifested in the fracture group and that increasing bone mass does not guarantee a reduction in fragility. The authors themselves were among the first to note the seeming discordance between the large fracture benefit and the small bone mass changes that have been reported in many of these trials.[2,3] Thus I am grateful to the authors for giving me the opportunity to reiterate that the somewhat disappointing results of this trial represent not so much a weakness of the therapy as of the paradigm, and to stress once again the importance of exploring the nonmass mechanisms that underlie osteoporotic fractures.

With regard to my second point, the evidence presented by Cummings et al[4] in this arm of the Fracture Intervention Trial does not support the use of prophylactic bisphosphonates in individuals with bone mineral density values greater than –2 to –2.5 SDs below the young adult mean values and without prevalent fractures. For these individuals, other prophylactic modalities (or no intervention at all) have to be considered possibilities. This is not the place to explore these alternatives. Nevertheless, as the authors recognize, hormone replacement therapy has many benefits other than the possible secondary coronary heart disease prevention that recently has been called into question.[5]

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Increasing Prevalence of Antimicrobial Resistance Among Uropathogens

To the Editor: Dr Gupta and colleagues[1] identified an increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis. In the United Kingdom, one of the recommendations of the Standing Medical Advisory Committee regarding antimicrobial resistance was to limit antibiotic prescribing in uncomplicated cystitis to 3 days in otherwise fit young women with cystitis."[2]

Studies have suggested a benefit of a nonantimicrobial cranberry juice in an elderly patient population[3] and have found that components of cranberry juice inhibit the lectin-mediated adherence of *Escherichia coli* to urinary mucosal cells via the pili on the surface of the bacteria.[4] Perhaps efforts to limit overuse of antimicrobials should include the humble cranberry.

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In Reply: As pointed out by Drs Daniels and Zaman, cranberry juice contains compounds that competitively inhibit the attachment of *E coli* to uroepithelial cells.[1] In addition, the ingestion of cranberry juice decreased the incidence of asymptomatic bacteriuria and pyuria in a group of elderly institutionalized women.[2] However, the incidence of symptomatic urinary tract infections (UTIs) in this study was not significantly different in the cranberry juice vs placebo groups. In another study, Walker and colleagues[3] demonstrated a possible reduction in symptomatic UTIs in young women who ingested a solid cranberry extract product for 3 months. In both of these studies, standard antimicrobial agents were used for treatment of symptomatic UTIs occurring during the study period. To our knowledge, there have been no large controlled trials confirming the preventative effects of cranberry juice on symptomatic UTIs in women. Thus, further investigations are needed prior to endorsing cranberry juice for use in gen-

eral practice. More important, cranberry juice has not been studied as a treatment for symptomatic UTI, and we would recommend antimicrobials instead of cranberry juice for this circumstance.

We agree with Daniels and Zaman that in this era of increasing antibiotic resistance, novel approaches to prevention of UTIs other than antimicrobials are needed. Avenues being pursued include use of a lactobacillus probiotic to restore normal vaginal microbial flora, topically applied carbohydrates that inhibit bacterial attachment, and antiadhesin vaccines.[4]

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Increase in the Use of Breast-Conserving Surgery

To the Editor: Mr Riley and colleagues[1] identified a significant increase of breast-conserving surgery (BCS) as well as of radiation therapy following BCS from 1988 to 1993 in the Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare enrollment records. In our recent analyses using the SEER Public Use Data Set, we found that the use of BCS without radiation therapy has, in fact, also increased over time. We identified 35 267 women who were diagnosed as having local or regional stage breast cancer at age 65 years or older between 1988 and 1993 and had either a mastectomy or BCS (the definition of the surgery was the same as reported by Riley et al). The percentage of BCS increased from 23.1% in 1988 to 40.5% in 1993. Of 11 409 patients who received BCS, the use of radiation after BCS increased from 57.7% in 1988 to 63.9% in 1993. Ironically, among patients who received surgery (mastectomy or BCS), there was actually a net increase in the percentage of all women with breast cancer who received BCS without radiotherapy, so-called nondefinitive therapy. The odds ratios of the nondefinitive therapy were 1.16 (95% confidence interval [CI], 1.02-1.31) for 1989, 1.20 (95% CI, 1.06-1.36) for 1990, 1.31 (95% CI, 1.17-1.49) for 1991, 1.30 (95% CI, 1.15-1.47) for 1992, and 1.46 (95% CI, 1.30-1.64) for 1993, respectively, compared with data from 1988, after adjusting for age (65-74, 75-84, and ≥85 years), race (white, black, and others), marital status (married and unmarried), cancer stage (local and regional), tumor size (<0.5, 0.5 to <1, 1 to <2, 2 to <3, 3 to <4, and ≥4 cm), and 9 SEER areas. This was because the use of BCS increased more rapidly than did the use of radiation therapy after surgery. Our article using the SEER data from 1983 to 1995, which include all cancer patients with different insurance coverage, also showed a similar finding.[2] Physicians should strive to ensure that patients with early-stage breast cancer receive more definitive therapies as justified by the research evidence[3,4] and recommended by the authorities.[5]

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In Reply: Although the primary goal of our study was a comparison of diagnosis and treatment patterns between the health maintenance organization and fee-for-service sectors of Medicare, we reported that rates of BCS and adjuvant radiation therapy were substantially higher than we had found in earlier years.[1] Based on analyses of SEER data, Dr Du raises the additional point that the rapid increase in the use of BCS has been accompanied by a slower increase in the use of adjuvant radiation therapy, thereby increasing the number of women receiving nondefinitive therapy for early-stage breast cancer. It is possible, though, that the observed difference in rates of increase between BCS and radiation therapy may be partially attributable to underreporting of radiation therapy in SEER, which may be increasing over time with the proliferation of radiation facilities not affiliated with hospitals.

The increase in use of BCS without adjuvant radiation therapy is indeed of concern. Our earlier study found this therapy to be concentrated among women with lower life expectancies—the oldest old and those with significant comorbidities.[1] Although the lack of adjuvant radiation therapy may not be as great a concern for this group as for younger and healthier women, the National Institutes of Health considers BCS followed by adjuvant radiation therapy to be the standard of care for all age groups.[2] Du's findings suggest the need for further monitoring of the use of nondefinitive therapy in treatment for early-stage breast cancer.

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sociated with surgical and radiation therapy for early stage breast cancer in older women. *J Natl Cancer Inst.* 1996;88:716-726.
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Chronic Multisystem Illness Among Gulf War Veterans

To the Editor: In their exploratory and confirmatory factor analyses of symptoms of US Air Force Gulf War veterans, Dr Fukuda and colleagues[1] from the Centers for Disease Control and Prevention (CDC) replicated 2 of the 3 syndromes that we identified by factor analysis in Gulf War veterans of a US Naval reserve unit.[2] Their syndrome factors 1 and 2 are virtually identical to our factors 1 and 3 (TABLE).

However, 2 methodological problems prevented Fukuda et al from identifying our syndrome factor 2 ("confusion-ataxia"). First, the investigators did not measure the symptoms that would have identified it (Table). Second, they inadvertently excluded those with our syndrome 2 from their sample. By studying only veterans remaining in the service 4 years after the war, they excluded the 70% of original members of those units who left the service soon after the war, some of whom were probably too ill to continue serving. The naval reservists with our syndrome factor 2 had the strongest genetic predisposition to nerve gas injury and the most abnormal neurologic findings,[3] all left service soon after the war, and most were occupationally disabled.[2,3]

Table. Agreement Between Factor Analysis–Derived Case Definitions of Gulf War Syndrome*

	Factor Loadings				
	Haley et al[2] Factors			Fukuda et al[1] Factors	
Symptom	1	2	3	1	2
Memory problems	65†	15	19	59†	–5
Depression	62†	24	19	76†	–3
Fatigue (daytime sleepiness)	48†	25	5	50†	6
Speech problems	42†	11	–1	48†	–15
Insomnia	41†	18	26	45†	30
Distractibility	71†	10	15	NM	NM
Migraine headaches	40†	1	14	NM	NM
Moodiness	NM	NM	NM	71†	2
Anxiety	NM	NM	NM	73†	–5
Thought-processing problems	1	66†	20	NM	NM
Mental confusion	22	57†	31	NM	NM
Ataxia/vertigo	13	52†	27	NM	NM
Sexual impotence	18	48†	15	NM	NM
Joint pain: hips and extremities	33	21	73†	3	84†
Joint pain: neck and shoulders	38	33	64†		
Joint stiffness	NM	NM	NM	2	85†
Muscle pain: arms	5	–4	55†	0	63†
Muscle pain: lower body	22	26	55†		
Muscle pain: upper body	13	24	44†		
Tingling or numbness in extremities	22	18	41†	NM	NM

*NM indicates not measured. Case definitions were developed by Haley et al and Fukuda et al.
†Factor loadings (×100) indicating strong correlation ($r \geq 0.40$) between the symptom and the syndrome factor. Joint pain and muscle pain were measured as single factors by Fukuda et al.

Despite these methodological differences, this important replication of our findings confirms that there is a reproducible pattern to the symptoms reported by many Gulf War veterans, and contradicts the present US government position that there is no Gulf War syndrome, only nonspecific symptoms of unrelated illnesses.[4]

Fukuda et al[1] also presented, but did not discuss, a powerful refutation of the government's argument that wartime stress was a cause of veterans' current physical symptoms. In the most thorough study to date of risk factors and psychiatric outcomes designed specifically to prove the effects of stress, these CDC researchers found that veterans who experienced the highest levels of combat stress were no more likely to have chronic physical symptoms than those who experienced no combat stress.[1] These results confirm our findings[2] and those of Stretch et al[5] and are the coup de grâce for the government's stress theory.[6]

In addition, the simplified 2-symptom case definition proposed by Fukuda et al[1] is incongruous with their factor analysis and is invalid. Finding that this definition was satisfied in 15% of personnel who were not deployed to the Gulf proves merely that a loose definition will include many people with nonspecific symptoms besides the few with illness. It does not argue for a psychological etiology.

With replication of our case definitions[2] by the CDC study,[1] a definitive confirmatory test of our theory of the neurotoxic etiology of Gulf War syndrome in a national veteran sample is indicated. No studies currently under way will accomplish this.

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1. Fukuda K, Nisenbaum R, Stewart G, et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA*. 1998;280:981-988.
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To the Editor: The findings of Dr Fukuda et al[1] that certain symptom presentations that clinicians are seeing may not be unique to Gulf War veterans confirms our clinical impression. It is particularly interesting that the authors report increased prevalences of diarrhea among individuals with relatively severe cases of "multisymptom illness" (77% with diarrhea) and mild to moderate cases (26% with diarrhea) compared with a low prevalence of diarrhea in noncases (2%). They surmise that these symptoms may represent irritable bowel syndrome (IBS).

While serving in the Persian Gulf, many members of the armed forces experienced a wide variety of environmental exposures

and psychic traumas that could have led to negative health consequences. One result of psychic trauma is the development of posttraumatic stress disorder (PTSD). In recent years, a great deal has been learned about the physiology of stress responses and the potential for associated disturbances in the functioning of the hypothalamic-pituitary-adrenal axis, the limbic system, the locus ceruleus-adrenergic system, and the autonomic nervous system.[2] Some studies even suggest that morphologic changes in the limbic system occur following psychic trauma.[3] Additionally, the relationships between these neuroendocrine systems and the gastrointestinal tract have been described.[4] Moreover, it has been noted that individuals with PTSD have increased rates of IBS (35%)[5] and that individuals with IBS have relatively high rates of trauma history (44%) and PTSD (36%).[6]

These findings and our clinical observations suggest potential relationships between the core processes of PTSD and those of IBS, involving neurohumoral and neuroendocrine systems. There may be similarities between the altered reactivity to the external environment that characterizes PTSD and an altered reactivity to the internal environment in IBS. Aziz and Thompson[4] suggest that altered central nervous system processing of painful visceral stimuli in patients with IBS may be related to hypervigilance, a common feature of PTSD. In a more general way, this suggests that there may be variants of PTSD, or posttrauma syndromes, that involve primarily somatic disturbances and expressions as opposed to the classic manifestations established in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.

In addition to further research into the potential negative health impacts of the numerous exposures and experiences encountered by those who served in the Persian Gulf, addressing the health concerns of Gulf War veterans requires an integrated intervention involving both medical and mental health providers.

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To the Editor: In their careful exploratory study, Dr Fukuda and colleagues[1] conclude that the chronic multisymptom condition of deployed veterans "was not associated with specific [Gulf War] exposures and also affected nondeployed personnel." While some experts may feel that stress explains the veterans' illnesses, there is another possibility.

Investigators from more than a dozen countries have described exposure-induced loss of tolerance among numerous groups, including radiology workers exposed to x-ray developing solutions, Environmental Protection Agency employees exposed in a sick building episode, homeowners in Germany exposed to pentachlorophenol wood preservative, sheep dippers in the United Kingdom exposed to organophosphate pesticides, and Lake Tahoe casino workers exposed to solvents and pesticides.[2] A subset of those exposed subsequently have reported that common chemicals, foods, and drugs trigger multisystem symptoms.

This 2-step process, called *toxicant-induced loss of tolerance*, appears to be neither classic toxicity nor allergy but may represent a new general mechanism or theory of disease.[2] Initially, those affected often notice feeling ill only after they eat a meal or particular foods, smell certain perfumes or cleaning agents, drink a beer or a cup of coffee, smell engine exhaust, or take a decongestant. Such sensitivities are hallmarks of this loss of tolerance, much as fever is a hallmark for the diverse conditions caused by infectious agents.

In the article by Fukuda et al, Table 3 shows that 5% of their still-active duty veterans vs 2% of controls ($P<.05$) reported chemical sensitivity. At our request, the authors provided us with additional data: 60 of the Gulf War veterans reported chemical sensitivity, with 11 categorized as "severe" cases and 40 as "mild-moderate" (Rosane Nisenbaum, PhD, written communication, October 1998). One of us (C.S.M.) found that 52 (88%) of the first 59 consecutive patients seen at the Department of Veterans Affairs Houston Regional Referral Center for Gulf War veterans reported new-onset chemical, food, and drug intolerances since the war.

During the past 10 years, several federally sponsored conferences and congressional committees have called for an environmentally controlled hospital research unit for studying this problem.[2,3] Despite congressional appropriations for this purpose, no such facility has been funded or constructed.[2] Without it, patients' background chemical exposures cannot be controlled for sufficient periods of time (up to several weeks) so that the effects of low-level exposures can be tested fully and reliably. Ill veterans who wonder whether they are chemically sensitive face a catch-22 situation: experts attribute their illnesses to stress, yet a research facility that might elucidate chemical causes remains unavailable to them.

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In Reply: Dr Haley repeatedly contends that our study confirms some findings of his study[1] but also suggests that our study

was flawed where our findings or interpretations do not agree with his. We would like to clarify several points.

First, our study was never intended to replicate or confirm the findings of Haley et al.[1] We are skeptical of his study findings and conclusions because of substantial study design flaws already described by others.[2,3] Second, we used a very different approach than Haley et al for choosing symptoms to study by factor analysis. To prove a hypothesis that neurotoxic exposures were causing illness among selected Gulf War veterans, Haley et al used unstated criteria to choose symptoms from reports from various Gulf War registries. Because we had no preconceived ideas about a Gulf War syndrome, we used open-ended interviews and examinations of 59 Gulf War veterans and a survey of more than 3700 military personnel from 4 military bases to identify relevant symptoms for study. This lengthy process provided the most epidemiologically and clinically sound basis (ie, least open to bias) for identifying important symptoms among Gulf War veterans. Third, our objective as stated was to study illness in Gulf War veterans who remained in active service. Fourth, stress is a difficult factor to measure, because its manifestations and relations to other disorders are not clear. Although we found only 1 person who met formal criteria for posttraumatic stress disorder, such criteria are just 1 approach for measuring stress. A more fundamental observation is that we found multisymptom illness cases among both Gulf War veterans and, at lower levels, among their nondeployed peers. It is inescapably logical that important etiologic factors probably were common to both groups and were not unique to the Gulf War experience; such factors could include stress. Fifth, we flatly disagree with Haley that our symptom-based case definition is "incongruous" with our factor analysis results and is "invalid." The results were highly concordant, and this finding helped convince us that the factor analysis results were believable. The role of factor analysis in any study should not be overstated. The meaningfulness of symptom groupings (ie, factors) identified by factor analysis fundamentally depends on the symptoms that are selected for study. Claims that factors constitute disease syndromes should be received with skepticism unless strong supporting biological or clinical evidence is presented. Sixth, we agree with Haley that our findings do not necessarily implicate a psychological basis for symptoms reported by Gulf War veterans. However, unlike Haley, we do not have a particular etiology to champion. Given the nature of war, it remains probable that psychological factors have an important contributing role in the development of unexplained symptoms in some personnel after all wars.[4]

We agree with Drs Hunt and Richardson and Drs Miller and Ashford that much work remains to be done to understand the basis and relationships among the as-yet unexplained symptoms reported by Gulf War veterans.

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Update of Cost-effectiveness Analysis for Solvent-Detergent–Treated Plasma

To the Editor: In 1994 we reported a cost-effectiveness analysis for solvent-detergent–treated frozen plasma (SDFP),[1] in which we calculated a cost of $289 300 per quality-adjusted life year (QALY) saved. Solvent-detergent treatment involves pooling several thousand units of donated plasma, then applying a detergent to inactivate enveloped viruses such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV). This technique decreases the transmission risk for these viruses, although it theoretically can increase the transmission risk for nonenveloped viruses. Despite the poor projected cost-effectiveness of SDFP, the Food and Drug Administration has recently licensed it for use in the United States, with distribution being handled by the American Red Cross Blood Services.

Since our initial analysis was published, several of the assumptions used in the analysis have changed. Improved viral screening has led to new, lower estimates of HIV, HCV, and HBV transmission risk,[2] and the marginal cost of SDFP is approximately 5-fold higher than originally estimated. Updated models of HIV disease also have been published.[3] Using our original model with these updated figures, we now calculate a cost of $9 743 000 per QALY. All patient subgroup analyses yielded costs per QALY exceeding $2.8 million.

Poor cost-effectiveness, as well as continuing concern about the pooled nature of the component, suggests a need to consider alternative methods of improving plasma safety. These include "fresh frozen plasma donor retested" (for which units are released only after the donor is found to be negative for all tests at a time beyond the "window period" for serologic markers of infectious diseases[4]) and methylene blue treatment of plasma.

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Table. Association Between Unconventional and Conventional Visits in Subsamples Excluding Those With Physician Referrals or Insurance

	Increased Odds of a Physician Visit*			No. of Physician Visits†		
	OR (95% CI)‡	χ^2	*P* Value	Adjusted Mean (Median)	*t* Value	*P* Value
Total sample (N = 16 038)						
No unconventional visits	1.00	. . .	. . .	3.59 (3)	. . .	. . .
Any unconventional visits	2.00 (1.72-2.33)	80.0	<.001	6.02 (5)	11.2	<.001
Excluding physician referrals (n = 15 933)						
No unconventional visits	1.00	. . .	. . .	5.41 (3)	. . .	. . .
Any unconventional visits	1.89 (1.62-2.21)	65.2	<.001	7.52 (5)	8.5	<.001
Among uninsured only (n = 3080)						
No unconventional visits	1.00	. . .	. . .	3.94 (2)	. . .	. . .
Any unconventional visits	1.54 (1.14-2.09)	8.0	.005	5.71 (3)	2.9	.004

*Odds ratios (ORs) and statistical tests for the first 3 columns were calculated using logistic regression models controlling for physical health status, age, sex, race, education, and geographic region.
†The values reflect the number of physician visits among those with any such visits calculated using least squares mean estimates from general linear models adjusted for physical health status, age, sex, race, education, and geographic region.
‡CI indicates confidence interval; ellipses, reference group.

In Reply: Mr Barzilai and Dr Rimm propose 2 interesting and testable hypotheses: first, that physician referrals might be a major factor underlying the relationship between the 2 types of care, and second, that uninsured patients might use these therapies differently than those with health insurance do.

The TABLE shows the multivariate analysis modeling use and quantity of physician visits as a function of unconventional service use in 2 subgroups: patients not reporting a physician referral for unconventional treatment and patients without insurance. In each of these subsamples, having an unconventional visit is strongly associated with physician visits, although the magnitude of these associations is somewhat smaller than for the entire sample. These findings suggest that insurance status and physician referrals may partly mediate, but are not the primary factors driving, the association between the 2 systems of care.

Dr Katz addresses a potentially important avenue for additional research—evaluating systems of care that integrate conventional and unconventional treatments. As more data become available on the effectiveness of specific unconventional therapies, it will become possible to design systems incorporating the best of these treatments into mainstream medical care, and to study the impact of these integrated systems on patient satisfaction, cost and use, and health outcomes.

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CORRECTIONS

Incomplete Financial Disclosure: In the Letter entitled "Relapse of Depressive Symptoms After Discontinuing Sertraline," published in the July 28, 1999, issue of THE JOURNAL (1999;282:323-324), the financial disclosure statement for the reply letter is incomplete. The following should be added to what was published: "Drs Gelenberg, Rush, Koran, Klein, McCullough, Kocsis, Kornstein, Schatzberg, and Fawcett have served as consultants to and/or received grant support from numerous pharmaceutical companies, some of which manufacture sertraline or other selective serotonin reuptake inhibitors. In addition, Drs Gelenberg, Kocsis, and Schatzberg own stock in 1 or more companies that manufacture sertraline or other selective serotonin reuptake inhibitors, and Dr LaVange is affiliated with Quintiles Inc, a for-profit contract research organization, and in that role provides statistical consulting for many pharmaceutical companies, including Pfizer Inc."

Incorrect Wording: In the Grand Rounds entitled "Acquired Aplastic Anemia," published in the July 21 issue of THE JOURNAL (1999;282:271-278), there was incorrect wording in the table. On page 275, the words that read "Benzene hexachloride" should have read "Benzene."