



Gulf War Veterans: Treating Symptoms and Syndromes

Committee on Identifying Effective Treatments for Gulf War Veterans' Health Problems, Board on Health Promotion and Disease Prevention, Bernard M. Rosof and Lyla M. Hernandez, Editors

ISBN: 0-309-51079-1, 162 pages, 6 x 9, (2001)

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Gulf War Veterans

TREATING SYMPTOMS
AND SYNDROMES

Committee on Identifying Effective Treatments
for Gulf War Veterans' Health Problems

Board on Health Promotion and Disease Prevention

Bernard M. Rosof and Lyla M. Hernandez, *Editors*

INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C.

NATIONAL ACADEMY PRESS • 2101 Constitution Avenue, N.W. • Washington, DC 20418

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Support for this project was provided by the Department of Veterans Affairs. The views presented in this report are those of the Institute of Medicine's Committee on Identifying Effective Treatments for Gulf War Veterans' Health and are not necessarily those of the funding agencies.

International Standard Book Number 0-309-07587-4

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*“Knowing is not enough; we must apply.
Willing is not enough; we must do.”*
—Goethe



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Acknowledgments

The committee wishes to express its appreciation to the many individuals who contributed in various ways to the completion of this project. Charles C. Engel, Jr, M.D., and Wayne J. Katon, M.D., wrote a paper providing an exceptional description of current efforts to understand the clinical management of medically unexplained physical symptoms. Chapter 5 contains material abstracted from that paper. Stephen Hunt, M.D., and Ralph Richardson, Ph.D., shared with the committee their experiences in treating Gulf War veterans' health problems; Howard Spiro, M.D., provided insight into the diagnosis and treatment of irritable bowel syndrome; and many Gulf War veterans and other interested individuals addressed the committee during its August 2000 meeting. A summary of the testimony appears in the report as Appendix B.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Gerard N. Burrow, M.D., Yale University School of Medicine; Nelson Gantz, M.D., Chairman, Department of Medicine, and Chief, Division of Infectious Diseases, Pinnacle Health Hospitals; William Golden, M.D., University of Arkansas for Medical Sciences; John E. Helzer, M.D., Health Behavior

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Robert B. Wallace, M.D., University of Iowa College of Public Health, appointed by the Institute of Medicine, and Harold C. Sox, M.D., Dartmouth-Hitchcock Medical Center, appointed by the NRC's Report Review Committee, who were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Executive Summary

INTRODUCTION

Ten years after the end of the Gulf War, questions continue to be raised about the health of U.S. service personnel who fought in that war. A primary concern is whether Gulf War veterans are receiving effective treatments for their health problems. Section 105 of the Veterans Program Enhancement Act of 1998 mandates that the Department of Veterans Affairs (VA) ask the Institute of Medicine (IOM) to convene a committee that would identify a method for assessing treatment effectiveness and describe already-validated treatments for Gulf War veterans' health problems, including the problem of medically unexplained symptoms. The specific charge to the committee is to (1) identify and describe approaches for assessing treatment effectiveness; (2) identify illnesses and conditions among veterans of the Gulf War, using data obtained from the VA and the Department of Defense (DoD) Gulf War Registries, as well as information in published articles; and (3) for these identified conditions and illnesses, identify validated models of treatment (to the extent that such treatments exist), or identify new approaches, theories, or research on the management of patients with these conditions if validated treatment models are not available.

IDENTIFYING HEALTH PROBLEMS

The committee reviewed Gulf War veterans' symptoms and complaints as described in published literature, data from the VA and the

DoD, and testimony from veterans and other interested individuals. Gulf War veterans are more likely than nondeployed veterans to report symptoms, illness, and functional impairment, although no study has been able to identify a single accepted condition or group of diagnoses that explains the symptoms experienced (IOM 1999a).

Reported symptoms experienced by Gulf War veterans include fatigue, joint and muscle pain, headache, memory loss, depression, anxiety, respiratory problems, and diarrhea (Perconte et al. 1993; Southwick et al. 1993; Stretch et al. 1995; Sostek et al. 1996; Iowa Persian Gulf Study Group 1997; Pierce 1997; Fukuda et al. 1998; Proctor et al. 1998; Wolfe et al. 1998; Coker et al. 1999; Department of Veterans Affairs 1999; IOM 1999a; Kang et al. 2000). Almost 80% of Gulf War veterans examined by the VA and DoD have readily identifiable medical conditions. However, about 20% of symptomatic veterans report multiple symptoms for which no diagnosis has been identified (Department of Veterans Affairs 1999). The committee examined the most commonly reported symptoms and grouped them into (1) established and accepted symptom-based conditions experienced by people in the general population who have recognized diagnoses of unknown etiology and (2) individuals who fall into no clear diagnostic category.

In this report, conditions of unknown etiology for which treatments are examined include *chronic fatigue syndrome* (fatigue, headache, cognitive dysfunction, and other symptoms), *depression* (fatigue, loss of memory and other general symptoms, cognitive dysfunction, and sleep disturbances), *fibromyalgia* (muscle pain, sleep disturbances, fatigue), and *irritable bowel syndrome* (diarrhea, constipation, abdominal pain, nausea, vomiting, and other gastrointestinal symptoms). Other diagnoses such as headache and panic disorder are included in the report because they involve symptoms similar to those reported by Gulf War veterans. Post-traumatic stress disorder (PTSD) is included because of its increased prevalence in veteran populations.¹

The committee examined treatments for these recognized diagnoses to determine what might be learned and borrowed from the management of these conditions to apply to the treatment of Gulf War veterans. There is, however, a group of veterans with symptoms that do not fit any of the above diagnostic categories. For those veterans, the committee reviewed relevant literature and described practice approaches currently being researched. Chapter 5 provides detailed information evaluating individual treatments for each of these conditions.

¹The committee acknowledges that the VA has significant expertise in the area of PTSD. The diagnosis is included here, however, because of its prevalence in this as well as other veteran populations.

TREATMENT EFFECTIVENESS

Prior to recommending treatments, the committee reviewed and analyzed information on evaluating treatment effectiveness. Treatment *effectiveness* is defined as the benefit produced by a given treatment in day-to-day clinical practice in unselected patient populations that do not receive extra tests, education, or visits because of participation in a study. There is little formal evidence of treatment *effectiveness* for any medical treatment because relatively few true effectiveness studies have been conducted. There are, however, efficacy studies. Treatment *efficacy* is the benefit produced by a given treatment in tightly controlled, perhaps artificial, study conditions in which patients are carefully selected and may be more frequently observed, tested, and monitored than is typically the case in routine practice.

A number of study designs can provide varying levels of evidence of treatment efficacy. They include, from strongest to weakest:

- Multiple well-designed randomized controlled trials (RCTs);
- Single well-designed RCTs or multiple small RCTs;
- Cohort study, particularly one with “multiple on/off” features;
- Case-control study; and
- Series of clinical observations or anecdotes.

In addition to the above designs, there is the technique of meta-analysis. Meta-analysis was developed to fit the situation in which study results are not fully consistent or there are multiple studies of differing degrees of design rigor. In meta-analysis the results of multiple studies are combined to yield an overall cross-study estimate of effectiveness.

In its review of clinical studies, the U.S. Preventive Health Services Task Force (USPHSTF) used strict criteria for selecting admissible evidence of effectiveness in grading the *quality of evidence* (see Table ES-1). The task force gave greater weight to those study designs that, for methodological reasons, are less subject to bias and inferential error (USPHSTF 1996).

In evaluating treatments for Gulf War veterans, the committee chose to recommend as effective only those treatments with demonstrated efficacy using the highest level of evidence—the randomized controlled trial (Level I of the USPHSTF scale). However, in responding to its charge to identify and describe approaches to assessing treatment effectiveness, the committee has explored other alternatives. From the perspective of evaluating treatment effectiveness, there are two general classes of studies, each with strengths and weaknesses:

- Treatment *efficacy* studies, including prospective randomized tri-

TABLE ES-1 Quality of Evidence

Level	Evidence
I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, and case reports, or reports of expert committees.

als, emphasize internal validity at the expense of external validity. That is, the sampling, data collection, and data analysis procedures are designed to support the strongest possible inferences about associations between independent and dependent variables (i.e., cause and effect) in a tightly controlled context. The best, strongest studies in tightly controlled situations may, however, lack generalizability to routine medical practice.

- Treatment *effectiveness* studies, including the largest and most comprehensive outcomes studies, emphasize external validity often at the expense of internal validity. They may involve very large samples that are fully representative of the patients seen in routine clinical practice, but the studies may include confounding factors that weaken the inferences about cause-and-effect relationships.

The committee believes the results of a single, well-designed outcomes study (e.g., a cohort study or variation of care and outcome study) should be considered to be as compelling as the results of a single, well-controlled randomized trial in determining treatment *effectiveness*. An outcomes study will have few concerns about the generalizability of its findings to real-world settings (external validity) but perhaps some concerns about internal validity; RCTs will have the opposite pattern of strengths and weaknesses. For a detailed discussion of the various types of studies, see Chapter 3. If there were studies of both types available with similar results, the combined evidence would be quite powerful. Studies of the two types with conflicting findings would essentially cancel each other out and no conclusion could be drawn. Table ES-2 is organized to

TABLE ES-2 Hierarchy of Evidence

	Emphasis on Efficacy	Emphasis on Effectiveness
Level I	Systematic Review (e.g., meta-analysis) of Several Well-Controlled Randomized Trials—consistent results	Systematic Review (e.g., meta-analysis) of Several Well-Designed Outcome Studies or “Effectiveness RCTs”—consistent results
Level II	Single, Well-Controlled Randomized Trial	Single, Well-Designed Outcomes Study or “Effectiveness RCT”
Level III	Consistent Findings from Multiple Cohort, Case-Control, or Observational Studies*	
Level IV	Single Cohort, Case-Control, or Observational Study	
Level V	Uncontrolled Experiment, Unsystematic Observation, Expert Opinion, or Consensus Judgments	

*It is not clear in many cases whether an observational or case-control study is an efficacy study or an effectiveness study. In principle, the label or definition depends on the extent to which the study sample and study procedures reflect the complexities and realities of daily clinical practice. For any one study, though, this may not be clear; however, when it is, more credence should be given to those truly reflecting effectiveness.

suggest that types of studies at the same vertical position in the two columns should be seen as equally powerful for demonstrating treatment effectiveness.

The above hierarchy implies that when the focus of evaluation is on treatment *effectiveness*, and in the absence of RCTs specifically designed to assess effectiveness in real-world settings, evidence from well-designed outcomes studies may provide Level I or Level II evidence and serve as the basis for clinical policies and treatment guidelines. Therefore, in conducting treatment effectiveness research, **the committee recommends that the VA:**

- use a hierarchy of evidence structure that includes effectiveness studies as well as efficacy studies for any future treatment guidelines it develops for symptoms or illnesses of Gulf War veterans;
- design future studies of treatment effectiveness that include outcomes research and effectiveness randomized clinical trials; and
- develop a standard language for describing Gulf War veterans’ symptoms, including their severity and temporal patterns, and that this

standard language be used in conducting treatment effectiveness studies and developing treatment guidelines.

Further, the committee recommends that those conducting ongoing cohort studies of veterans' health (e.g., the national VA study, the Iowa follow-up study on Gulf War veterans, and the Millennium Cohort Study being implemented by DoD) include collection of data on treatments and health-related quality of life.

The committee also recommends that current VA and DoD Gulf War registries be used as one way to identify patient samples and serve as a sampling frame for future treatment effectiveness studies.

CONDITION-SPECIFIC TREATMENTS

Results of studies on conditions with unknown etiology may not generalize directly to Gulf War veterans whose similar symptoms may have a different etiology. However, given currently available diagnostic information and the lack of effectiveness studies conducted on Gulf War veterans, identification of effective treatments for such conditions as these may offer the best opportunity for alleviating the health problems of Gulf War veterans. Because there are no true effectiveness studies for the conditions chosen for study, however, the committee determined that recommended treatments would be required to demonstrate efficacy through at least one randomized controlled trial. However, there may be situations in which other approaches to treatment are taken. While the committee has chosen to recommend only those therapies with RCT-demonstrated efficacy, it is important to continue to evaluate these other therapies.

Committee members reviewed clinical practice guidelines, major literature reviews, and published studies of treatments for these conditions. Randomized controlled trials were given the greatest weight in making recommendations about specific treatments; other types of published studies were evaluated using the levels-of-evidence concepts discussed above and described in detail in Chapter 3. The approaches presented here are not clinical guidelines. Rather, this report is an effort to extrapolate from what is known about other existing diseases and apply it to the problems suffered by Gulf War veterans. Chapter 5 contains a detailed discussion of each condition, including diagnostic criteria; evaluation of therapies describing benefits, harms, and comments; practice issues; and recommendations. Table ES-3 summarizes the committee's recommendations for each identified condition.

In addition to the condition-specific treatments recommended above, the committee determined that there are general principles of a patient-centered approach to medicine that form part of the effective evaluation

and treatment of any patient. This patient-centered approach, intended to foster excellent communication between the provider and the patient, is explored in detail in Chapter 4. It involves caring, investigation of all complaints, respect for the patient's perspective, avoidance of excessive testing, and joint decision-making regarding treatment to the extent possible. Daltroy (1993) has identified three primary communication goals and nine tasks (see Table ES-4) for the health care provider that are critical components of patient-centered care. The goals are to elicit the patient's problems and history with an eye toward making a diagnosis, to negotiate a treatment regimen that the patient will accept and that is congruent with recognized medical practice, and to teach the patient about managing his/her disease and treatment regimen so that it may be effectively implemented.

Therefore, the committee recommends that the VA:

- **provide specific training to health care providers caring for Gulf War veterans to ensure that they are skilled in the principles and practice of patient-centered care and**
- **ensure that health care practitioners serving Gulf War veterans are allowed sufficient time with patients to provide patient-centered care.**

CONCLUSION

Most Gulf War veterans have not experienced the troubling and sometimes debilitating symptoms that plague some who fought in that conflict. The national survey conducted by the VA surveyed 30,000 veterans, 15,000 of whom had been deployed to the Gulf War and another 15,000 who had not. About 75% of Gulf War veterans who responded to the survey described their health as good to excellent, while the remaining 25% rated their health as fair or poor. Ninety percent of responding non-Gulf deployed veterans rated their health as good to excellent, with the remaining 10% reporting fair or poor health (Kang et al. 2000). For those Gulf War veterans who have been evaluated in the VA and DoD Gulf War registries (about 120,000 individuals), about 80% have received readily identifiable diagnoses that explain their symptoms (DVA 1999). For 20% of registry participants, however, no diagnosis has been found.

In this report the committee has attempted to extrapolate from what is known about treating patients in other circumstances who experience symptoms similar to Gulf War veterans with unexplained symptoms and to apply that knowledge to the veteran population. Many capable providers may take other valid approaches to the management of these problems based on their clinical experience or on patient preferences. In fulfilling its charge to identify already validated treatments for ill Gulf War

TABLE ES-3 Recommendations for Condition-Specific Treatments

Conditions	Recommendations
Chronic fatigue syndrome (CFS)	<p>For Gulf War veterans who meet the criteria for diagnosis of CFS, the committee recommends:</p> <ul style="list-style-type: none">• use of cognitive behavioral therapy and exercise therapies because they are likely to be beneficial;• monitoring the results of studies of the efficacy and effectiveness of NADH, dietary supplements, corticosteroids, and antidepressants other than SSRIs;• because immunotherapy and prolonged rest are unlikely to be beneficial, they should not be used as treatments;• SSRIs are unlikely to be beneficial and are not recommended unless they are used as treatment for persons with concurrent major depression; and• treatments effective for CFS should be evaluated in Gulf War veterans who meet the criteria for CFS.
Depression	<p>The committee recommends a combination of antidepressant medication and psychotherapy (either cognitive behavioral therapy or interpersonal therapy) as the core therapy for major depression.</p>
Fibromyalgia	<p>The committee recommends that:</p> <ul style="list-style-type: none">• Gulf War veterans who meet criteria for fibromyalgia not receive treatment with opioid analgesics or glucocorticoids.• In the absence of therapies of generally proven benefit, results of treatment studies of physical training, tricyclic antidepressants, and acupuncture should be further monitored in Gulf War veterans who meet the criteria for fibromyalgia
Headache	<p>For Gulf War veterans with chronic headaches, not associated with underlying pathology (e.g., tumors, vascular abnormalities), the committee recommends the following treatments:</p> <ul style="list-style-type: none">• pharmacological management of acute episodes, using agents listed in Table 5-6 , taking into consideration the clinical effectiveness and potential side effects, as listed;• prophylactic pharmacological management for headaches that occur frequently or are disruptive to the patient's functioning, as listed in Tables 5-7 and 5-8, taking into consideration the clinical effectiveness and potential side effects, as listed;• use of behavioral and physical treatments, including relaxation training, thermal biofeedback combined with relaxation training, EMG biofeedback and cognitive behavioral therapy, or behavioral therapy combined with preventive drug therapy.

TABLE ES-3 *Continued*

Conditions	Recommendations
Irritable bowel syndrome (IBS)	<p>For Gulf War veterans who meet the diagnostic criteria for IBS, the committee recommends that:</p> <ul style="list-style-type: none">• cognitive behavioral therapy, tricyclic antidepressants (TCAs), and smooth-muscle relaxants be considered in appropriate age-specific, carefully selected clinical settings and• results of treatment studies be monitored to clearly establish therapeutic effectiveness of these agents in the various subgroups of patients diagnosed with IBS.
Panic disorder	<p>For Gulf War veterans who meet criteria for panic disorder, the committee recommends treatment with antidepressant medication and cognitive behavioral therapy.</p>
Post-traumatic stress disorder (PTSD)	<p>For Gulf War veterans who meet the criteria for PTSD and with no contraindications, the committee recommends treatment with antidepressant medication and cognitive behavioral therapy.</p>
Medically unexplained symptoms	<p>For Gulf War veterans with unexplained symptoms, the committee recommends that:</p> <ul style="list-style-type: none">• for the purposes of treatment efficacy and effectiveness studies, explicit criteria for medically unexplained physical symptoms (apart from chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome) be developed and used uniformly in treatment studies and• treatment studies of antidepressant medications, cognitive behavioral therapy, and a stepped intensity-of-care program be implemented for medically unexplained symptoms.

TABLE ES-4 Nine Steps in Patient-Centered Care

- 1 The patient must express all of his or her concerns during the clinical encounter.
- 2 The physician addresses all of the patient's concerns.
- 3 The physician and the patient share models of disease and symptoms.
- 4 The physician and patient must share goals for treatment.
- 5 The physician and the patient should agree on treatment goals, state them explicitly, and set priorities.
- 6 The physician and the patient should share their respective ideas about the purpose and course of treatments.
- 7 The physician and patient should identify potential difficulties in the care plan.
- 8 The physician and the patient should plan how to overcome anticipated compliance difficulties.
- 9 The physician should provide written information on the disease and treatment regimen.

veterans, the committee developed an approach to evaluating treatments that could be consistently applied across diagnoses. Recommendations for treatment are based on efficacy as demonstrated through RCTs, the highest level of evidence available.

Much has yet to be learned about ways to prevent, or at least mitigate, health problems associated with deployment. While research into consequences of war-related illnesses and deployment-related health effects proceeds, we are faced with the task of providing effective treatments to those who are suffering from difficult-to-diagnose, ill-defined, or unexplained illnesses. It is hoped that the work of this committee will contribute to the understanding and treatment of such health problems.

1

Introduction

Potential health consequences of service in the Gulf War have been a concern since U.S. troops returned home. Research and investigations to date indicate there is no single illness or syndrome common to all ill veterans. Questions have arisen as to whether there are effective treatments for the problems ill veterans are experiencing, and whether these veterans are receiving appropriate care.

In 1998 Congress passed the Veterans Program Enhancement Act (P.L. 105-368). In response to Section 105 of this legislation, the Department of Veterans Affairs (VA) asked the Institute of Medicine (IOM) to convene a committee that would (1) identify and describe approaches for assessing treatment effectiveness; (2) identify illnesses and conditions among veterans of the Gulf War, using data obtained from the VA and the U.S. Department of Defense (DoD) Gulf War registries, as well as information in published articles; and (3) for these identified conditions and illnesses, identify validated models of treatment (to the extent that such treatments exist), or identify new approaches, theories, or research on management of patients with these conditions if validated treatment models are not available. The congressional legislation specifically requested that the IOM study address undiagnosed illnesses as well as any other chronic illness deemed to warrant review. The committee is composed of experts in internal medicine, neurology, gastroenterology, rheumatology, psychiatry, epidemiology, treatment efficacy and effectiveness research, outcomes assessment, and clinical practice guideline development.

Over the course of this study the committee has met and talked with Gulf War veterans and representatives of veterans' organizations, health

researchers, practicing physicians, and representatives of the VA and DoD. During the committee's five meetings, members reviewed and analyzed written material on symptoms, complaints, and diagnoses of Gulf War veterans; approaches to evaluating treatment efficacy, treatment effectiveness, and health outcomes; clinical practice guideline development and assessment; and completed reports of numerous investigations of illnesses of Gulf War veterans. Additionally, the committee held a public meeting and solicited testimony from Gulf War veterans about their illnesses and the treatments they have received. The remainder of this chapter provides the context within which the committee charge was carried out.

BACKGROUND

Within five days of the August 2, 1990, Iraqi invasion of Kuwait, the United States began to deploy troops to Southwest Asia. Ultimately, in response to United Nations Resolution 678, 41 nations sent nearly a million troops to the area, of which almost 700,000 were U.S. soldiers. (See Appendix A for a list of participating countries and numbers of troops.)

From August 1990 through early January 1991, troops settled into position and prepared for war (Operation Desert Shield). Air attacks against the Iraqi forces were begun on January 16, 1991 (Operation Desert Storm), and on February 24 a ground attack was launched. Within four days Iraqi resistance crumbled. Following the fighting, the number of troops in the area declined rapidly. By June 13, 1991, the last U.S. troops who participated in the ground war returned home.

U.S. casualties were low during the Gulf War. There were 148 combat deaths and another 145 deaths due to disease or injury. Despite the low number of casualties, U.S. troops were exposed to a large number of stressors. These included a wide range of biological and chemical agents, including sand, smoke from oil well fires, paints, solvents, insecticides, petroleum fuels and their combustion products, organophosphate nerve agents, pyridostigmine bromide, depleted uranium, anthrax and botulinum toxoid vaccinations, and infectious diseases.

Additional stressors were the rapid mobilization for military service, with an accompanying disruption of normal patterns; the unfamiliar character of the region; the requirement that U.S. military personnel have virtually no interaction with the indigenous populations; the primitive living conditions of U.S. troops; and the immense destruction visited on the whole nation of Iraq.

Following the war, most troops returned home and resumed their normal activities. Within a short time, however, some Gulf War veterans began to report health problems that they were concerned were connected

to their service in the Gulf. Commonly reported problems include fatigue, moodiness, memory loss, muscle and joint pain, shortness of breath, and rashes (Fukuda et al. 1998; Iowa Persian Gulf Study Group 1997).

A number of efforts have been undertaken by individual veterans, veterans' service organizations, academia, Congress, federal agencies, private-sector organizations, and others to investigate the possible causes of and treatments for the illnesses experienced by Gulf War veterans. This work includes clinical efforts aimed at understanding the nature of the illnesses and the effectiveness of potential treatments, population-based studies on the health status of Gulf War veterans, research on the potential health effects of the agents that were present in the Gulf War, advocacy efforts, and policy efforts on compensation and health care for Gulf War veterans.

CLINICAL REGISTRIES

In response to concern about possible illnesses, the VA and DoD developed special diagnostic programs. The VA program was begun in 1992 and is divided into two phases—the Persian Gulf Registry and the Uniform Case Assessment Protocol (UCAP). The Registry Exam includes basic laboratory tests and a complete medical history that records time of onset of symptoms or condition, intensity, degree of physical incapacitation, and details of any treatment received through the time of examination. The UCAP provides for additional examination and testing for those veterans who are found to have a disability but no clearly defined diagnosis that explains their health problems. Four Gulf War Referral Centers offer inpatient stays to treat serious health problems not diagnosed in the first two phases. Referral Centers provide multidisciplinary consultations, serial examinations, and treatment that is focused on individual patient needs.

The DoD clinical diagnostic program implemented in 1994 is similar to that of the VA and is called the Comprehensive Clinical Evaluation Program (CCEP). The CCEP is also a two-phase process, the first of which is conducted at the primary care level and consists of a medical history, physical examinations, and laboratory tests. Veterans may be referred to Phase II for specialty consultations if the primary care physician determines such referral is indicated. The Specialized Care Center at Walter Reed Army Medical Center provides additional evaluation, treatment, and rehabilitation for patients suffering from chronic debilitating symptoms.

As of October 2000, more than 80,000 Gulf War veterans had participated in the VA registry program, while DoD reports having completed examinations on almost 39,000 as of December that year.

SUMMARY OF GULF WAR REPORTS AND EVALUATIONS

As reports of illness continued to spread so, too, did criticism of the responsiveness of the VA and DoD, and the media began to talk about a "Gulf War Syndrome." Numerous efforts were undertaken to understand and solve the health problems of Gulf War veterans. A presidential advisory committee was established to review what was known and being done about veterans' health problems. Congress enacted legislation aimed at providing medical care to veterans experiencing problems and called for investigations into the causes. The General Accounting Office (GAO) undertook several studies. The IOM conducted scientific assessments of different aspects of the problem. The VA and DoD funded more than 120 research projects investigating the health problems of Gulf War veterans.

Presidential Advisory Committee on Gulf War Veterans' Illnesses

In May 1995, President Clinton established the Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC) to conduct an independent and comprehensive review of health concerns related to Gulf War service. The 12-member panel produced three reports. Major conclusions were (1) although the government had been somewhat slow to act at the end of the Gulf War, it was now providing appropriate medical care to Gulf War veterans; (2) the government's research portfolio was appropriately weighted toward epidemiological studies and studies on stress-related disorders; (3) DoD investigations into possible chemical and biological warfare agent exposures had produced an atmosphere of mistrust surrounding every aspect of Gulf War veterans' illnesses, and the government had lost credibility with the public; (4) many veterans have illnesses that are likely connected to their service in the Gulf; (5) there is no evidence of a causal link between reported symptoms and illnesses and specific exposures; and (6) stress is likely to be an important contributing factor in these illnesses (Presidential Advisory Committee, 1996a, b, 1997).

General Accounting Office

Several studies were conducted by the GAO. In 1993 GAO criticized the Army's preparation for and response to depleted uranium exposure during the Gulf War (GAO 1993). A report on the health concerns of Gulf War veterans from the 123rd Army Reserve Command headquartered in Indianapolis found that veterans were either dissatisfied with the medical services received from DoD and VA or were unaware such services were available (GAO 1995). Additionally, most of these veterans reported health problems they believed were caused by their service in the Gulf

and that these problems limited, to some extent, their physical and social activities.

A June 1997 GAO report was extremely critical of the DoD and VA efforts to monitor the clinical progress of Gulf War veterans. In an investigation of tumors in Gulf War veterans, GAO reported that the incidence could not be reliably determined from available data (GAO 1998a). A subsequent report observed that “[w]hile the number of Gulf War veterans who participated in the military operations known as Desert Shield and Desert Storm is well established at almost 700,000, the number who actually suffer, or believe they suffer, from illnesses related to their Gulf War service remains uncertain 7 years after the war” (GAO, 1998b:2). This report recommended that the VA provide a case management approach to the care of Gulf War veterans and that the VA work to fully and uniformly implement these systems in its facilities.

Institute of Medicine

The IOM has completed several studies that focus on the potential health implications of deployment in the Gulf War and on the responses by the DoD and the VA to address veterans’ health concerns. The IOM Medical Follow-up Agency examined the health consequences of service in the Gulf and developed recommendations for research and information systems. The first report of this group (IOM 1995:8) recommended that “the VA Persian Gulf Health Registry should be limited and specific to gathering information to determine the types of conditions reported. There should be efforts to implement quality control and standardization of data collected by the registry.” The report also recommended improved outreach to inform veterans about the availability of the registry. A second report focused on findings and recommendations concerning research and information systems needed to assess the health consequences of service during the Gulf War (IOM 1996a).

An evaluation of the adequacy of the DoD Comprehensive Clinical Evaluation Program concluded that, while the CCEP was a comprehensive effort to address the clinical needs of those who had served in the Gulf War, specific changes in the protocol would help increase its diagnostic yield (IOM 1996b). The study also concluded that the CCEP was not appropriate as a research tool but that the results could and should be used to educate Gulf War veterans and the physicians caring for them, to improve the medical protocol itself, and to evaluate patient outcomes.

IOM continued its evaluation of the CCEP, focusing attention specifically on difficult-to-diagnose problems and ill-defined conditions, the diagnosis and treatment of stress and psychiatric conditions, and the assessment of health problems of those who may have been exposed to low

levels of nerve agents. The report addressing the adequacy of the CCEP relative to nerve agents concluded that the CCEP provided an appropriate screening approach to the diagnosis of neurological diseases and conditions but recommended certain refinements to enhance the program (IOM 1997a).

In addressing the issues of medically unexplained conditions and stress and psychiatric disorders, the IOM (1997b) emphasized the need to treat veterans' symptoms whether or not a diagnosis had been determined; the need to provide increased screening for depression, traumatic exposure, and substance abuse; the importance of conducting an evaluation across facilities to determine consistency of examination procedures and patterns of referral; and the need for greater coordination between the DoD and the VA, particularly as it relates to the ongoing treatment of patients.

A separate IOM committee evaluated the adequacy of the VA medical program for Gulf War veterans (IOM 1998a). This report complimented the VA for its overall provider education and outreach efforts. Recommendations called for the development of clinical practice guidelines for the difficult-to-diagnose or unexplained symptom constellations and for the establishment of a system of feedback and continuous quality improvement to monitor the care received by Gulf War veterans.

The IOM Committee on Measuring the Health of Gulf War Veterans was charged with developing a study design and methods for measuring important aspects of the health status of Gulf War veterans. In its published report (IOM 1999a), the committee recommended a prospective cohort study designed to answer four fundamental questions: How healthy are Gulf War veterans? How does the health of Gulf War veterans change over time? How does the health of these veterans compare with others in the general population and the military? What individual and environmental characteristics are associated with observed differences in health between Gulf War veterans and comparison groups?

In September 2000 the Committee on Health Effects Associated with Exposures During the Gulf War released the first of several anticipated reports evaluating the published scientific literature regarding the adverse effects of agents to which Gulf War veterans may have been exposed. The report (IOM 2000) placed its conclusions about possible associations between health outcomes and exposures to depleted uranium, sarin, pyridostigmine bromide, and vaccines into five different categories indicating the strength of the evidence. These levels of evidence are:

- Sufficient evidence of a causal relationship
- Sufficient evidence of an association
- Limited/suggestive evidence of an association

- Inadequate/insufficient evidence to determine whether an association does or does not exist
- Limited/suggestive evidence of no association

While the committee found sufficient evidence of a causal relationship or of an association between several of the exposures and transient acute effects, there was inadequate or insufficient evidence to determine whether an association does or does not exist between most of the evaluated exposures and long-term adverse health effects. The committee found limited or suggestive evidence of an association between exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and subsequent long-term health effects. Additionally, the committee concluded that there is limited evidence of no association between exposure to uranium and kidney disease and between exposure to low levels of uranium and lung cancer. Although the committee was not charged with determining increased risk of illness to veterans due to their potential exposures, the paucity of data regarding the actual agents and doses to which individual Gulf War veterans were exposed meant that the committee could not measure the likelihood that Gulf War veterans' health problems are associated with or caused by these agents.

Two other IOM studies were to determine what lessons could be learned from the issues and problems surrounding the health of Gulf War veterans. First, the report, *Strategies to Protect the Health of Deployed U.S. Forces: Medical Surveillance, Record Keeping, and Risk Reduction* (IOM 1999b), urged that the military health system develop an improved strategy for addressing medically unexplained symptoms that includes education of care providers, detection of veterans developing such symptoms, and treatment of symptoms in the primary care setting if possible. Further, the report recommended study of predisposing, precipitating, and perpetuating factors for medically unexplained symptoms and emphasized the crucial role of risk communication for future deployments.

In response to a congressional mandate, an IOM committee was formed to assist the VA in developing a plan for establishing a national center (or centers) for the study of war-related illnesses and postdeployment health issues. The committee's report, *National Center for Military Deployment Health Research* (IOM 1999c), recommended establishing a national center that is independent of any single federal agency and guided by a board that is representative of all relevant stakeholders (veterans, federal agencies, the community at large, and independent scientists). Further, the report outlined the center's role as one of identifying research gaps and commissioning new research to fill them, fostering effective use of national data sources, and developing policy recommendations from data that emerge from the center's research.

Other Investigations

In April 1997 the U.S. Senate Committee on Veterans' Affairs created an expert bipartisan special investigation unit to undertake a comprehensive and detailed review of what may have caused the illnesses of Gulf War veterans. This unit also investigated what should be done to treat these veterans. The unit's report found that "while there does not appear to be any single 'Gulf War syndrome,' there is a constellation of symptoms and illnesses whose cause or causes eludes explanation at this time" (U.S. Senate Committee on Veterans' Affairs 1998:3). Further, the report said there is a great need to monitor Gulf War veterans to determine whether they are getting better or worse and to define the long-term health effects they may experience.

The Executive Office of the President (EOP 1998) issued a report making several recommendations aimed at ensuring that the federal government will be better able to respond promptly and effectively in the future to the health needs of its military, veterans, and their families. When health problems are identified following a military deployment, the report states, plans must be in place to improve and facilitate cooperation and coordination among DoD, VA, and the Department of Health and Human Services. The report recommended (1) creating a Military and Veterans Health Coordinating Board, (2) developing an Information Management/Information Technology Task Force, and (3) implementing strategies aimed at deployment-related health issues, record keeping, health risk communication, and research (EOP 1998).

GULF WAR VETERANS' HEALTH: RESEARCH SUMMARY

Extensive scientific research has been undertaken on the health of Gulf War veterans. Studies of mortality of Gulf War-deployed veterans compared to similar veterans not deployed to the Gulf (Kang and Bullman 1996; Writer et al. 1996; Kang et al. 2000) found no excess mortality among Gulf War veterans, with the exception of automobile accidents. Several studies have found higher prevalence of self-reported symptoms in Gulf War veterans when compared with nondeployed Gulf War-era veterans or other control groups (Perconte et al. 1993; Southwick et al. 1993; Stretch et al. 1995; Sostek et al., 1996; Stretch et al. 1996a, b; Iowa Persian Gulf Study Group 1997; Pierce 1997; Goss Gilroy 1998; Proctor et al. 1998; Wolfe et al. 1998; Unwin et al., 1999).

Some studies have sought to identify a specific illness or illnesses unique to Gulf War veterans (Haley et al. 1997a; Haley and Kurt 1997; Haley et al. 1997b; Fukuda 1998; Ismail et al. 1999). Other studies have focused on the incidence of diagnosed disease in cohorts of Gulf War veterans (Araneta et al. 1997; Cowan et al. 1997; Coker et al. 1999). In

evaluating whether Gulf War veterans were more likely to be hospitalized Gray et al. (1996) found that the risk of hospitalization for deployed veterans in the immediate postwar period was no different from that of nondeployed veterans.

According to a 1999 IOM report, *Gulf War Veterans: Measuring Health*, several conclusions can be drawn from results of recent research:

- Military personnel who served in the Gulf War have had a significantly higher risk of suffering one or more of a set of symptoms that include fatigue, memory loss, difficulty concentrating, pains in muscles and joints, and rashes. Other symptoms are noted with reduced frequency but still may be experienced more often by deployed than nondeployed veterans.

- The symptoms range in severity from barely detectable to completely debilitating.

- No single accepted diagnosis or group of diagnoses has been identified that describes and explains this cluster of symptoms.

- There is no single exposure, or set of exposures, that has been shown conclusively to cause individual symptoms or clusters of symptoms. Although some statistical associations have been seen in some studies, they have not been confirmed in other studies or through laboratory tests that would establish a cause-effect connection in individual patients.

- No diseases included in the ICD-9-CM or ICD-10 classification systems have been shown to be more frequent in deployed than nondeployed veterans, with the exception of the symptoms of posttraumatic stress disorder.

- Mortality among deployed veterans is not higher in general than among nondeployed veterans.

- Health-related quality of life, as measured through instruments such as the SF-36, is lower on average among deployed veterans than among nondeployed veterans.

- The natural course of symptom experience over time is not known, because no longitudinal studies of symptom experience have been conducted and reported in the literature (IOM 1999a).

ONGOING CLINICAL RESEARCH

Two federally funded clinical treatment trials are under way. The first is a randomized, multicenter, controlled trial of multi-modal therapy of Gulf War veterans who have unexplained chronic medical symptoms such as pain, fatigue, and/or cognitive difficulties. The treatments studied are cognitive-behavioral therapy and aerobic exercise. Both treatments have shown encouraging results in alleviating symptoms in individuals

with similar types of illnesses, such as chronic fatigue syndrome and fibromyalgia. The study is expected to be completed in November 2001.

The second federally funded clinical trial (conducted in collaboration with Pfizer Pharmaceuticals, which is donating the antibiotic and matching placebo) is designed to test the hypothesis that antibiotic treatment directed against *Mycoplasma* species will improve the functional status of patients with Gulf War veterans' illnesses who have tested mycoplasma-positive at baseline. This study is a 30-month prospective randomized double-blind clinical trial in which patients are randomized to either doxycycline (200 mg/day) or placebo treatment groups. The planned completion date is January 2002.

A jointly funded VA/DoD study of the occurrence and potential cause or causes of amyotrophic lateral sclerosis (ALS) among Gulf War veterans is also under way. The study is intended to determine if this disease is occurring more often than is reasonably expected among Gulf War veterans and will attempt to identify probable or possible causes of ALS among Gulf War veterans.

WAR-RELATED ILLNESSES AND POSTDEPLOYMENT HEALTH RESEARCH

A large body of research exists on the health effects of military conflict from the U.S. Civil War through the more recent conflicts of the 1991 Gulf War and Bosnia. Elder and colleagues (1997) conducted a longitudinal study of World War II veterans that found, after controlling for age and the effects of self-reported physical health at war's end, exposure to combat predicted that a subject would experience physical decline or death during the postwar period from 1945 to 1960. O'Toole et al. (1996) found, for Australian Vietnam veterans, that combat exposure was significantly related to reports of recent and chronic mental disorders, recent hernia and chronic ulcer, recent eczema and chronic rash, deafness, chronic infective and parasitic disease, and chronic back disorders, as well as symptoms and signs of ill-defined conditions. Hyams and colleagues (1996) summarized reports of poorly understood multisymptom clusters recorded in conflicts dating back to the Civil War and found symptoms of fatigue, shortness of breath, headache, sleep disturbance, forgetfulness, and impaired concentration. Various labels were used to describe clusters of symptoms, including shell shock, combat fatigue, irritable heart, and effort syndrome. No single etiological entity was discovered to account for these symptoms.

Thus, concerns about the health of Gulf War veterans and that of veterans of other specific conflicts have slowly broadened to include questions regarding the consequences of service in any major military engage-

ment. Further, research is beginning to focus on ways to prevent or treat deployment-related health effects.

The remainder of this report presents the committee's deliberations, findings, and recommendations. Chapter 2 summarizes symptom data and describes the process used by the committee to identify health problems on which to focus. Chapter 3 provides a discussion of the study designs that can be used to evaluate the effectiveness and efficacy of interventions in medicine and health care, while Chapter 4 explores general approaches to treating a patient, regardless of diagnosis. Chapter 5 reviews the treatments evaluated for each identified condition and provides the committee's treatment recommendations. Chapter 6 presents concluding observations.

2

Identifying Conditions for Study

As described in Chapter 1, the health of Gulf War veterans has been studied from many perspectives. Numerous organizations and individuals have sought answers to address the complex issues surrounding the Gulf War, but questions remain. Some of the questions concern how to define the kinds of health problems veterans are experiencing and to what extent already-validated treatments may exist for these problems.

Although the terms “Gulf War illness” or “Persian Gulf syndrome” have been used to describe the health problems of ill veterans returning from the Gulf War, no study has been able to identify a single accepted condition, diagnosis, group of diagnoses, or etiology that explains the symptoms experienced by these veterans (IOM 1999a). Numerous studies have examined data regarding veterans and their symptoms (Perconte et al., 1993; Southwick et al. 1993; Stretch et al. 1995; Sostek et al. 1996; Iowa Persian Gulf Study Group 1997; Pierce 1997; Fukuda et al. 1998; Goss Gilroy 1998; Wolfe et al. 1998; IOM 1999a; DVA 1999; Kang et al. 2000). While clusters of symptoms including fatigue, joint and muscle pain, headache, memory loss, depression, anxiety, respiratory problems, and diarrhea have been noted, no one group of patients has all of these symptoms nor even a majority of them. Many of the studies have shown that Gulf War veterans report a higher level of symptoms and self-reported illness, as well as functional impairment than do nondeployed veterans; however, none has been able to link these health problems to a specific condition, etiological agent, or exposure. To do so involves a long and complex process.

The process for determining whether patients have a new unique

clinical entity distinct from all other established diagnoses, while not clear-cut, does have several recognized steps. Generally, the process begins with the identification of patients who are experiencing symptoms that do not coincide with established recognizable diagnoses. An attempt is then made to determine whether there are patterns or clusters of symptoms that are common to a wide group of patients. If such patterns are detected, experts are able to develop a "case definition." A case definition strives to contain not only common symptoms but a mix of clinical, laboratory, and epidemiological criteria. This case definition is used to identify a new patient population that is distinct from other patient populations with recognized syndromes, conditions, or diagnoses (IOM 2000).

Much of the published literature on the health of Gulf War veterans has searched for an etiology or tried to prove causality in defining a specific disease or syndrome in ill Gulf War veterans. A disease can be characterized as having (1) common symptoms or signs and/or laboratory findings and (2) a defined etiology or pathophysiology with identifiable abnormalities in body structure or function. Syndromes or conditions also have common symptoms and signs, but the etiology and pathophysiology of the syndrome are often unknown. The patient's illness is defined by common symptoms or physical findings and therapy becomes symptom based. Therapy is standardized to that group of patients with common symptoms, and treatment effectiveness is often measured by improvement in quality of life indicators. For patients who have symptoms or groups of symptoms that cannot be linked to a specific syndrome or disease, and where no group of patients has the same group of symptoms (medically unexplained physical symptoms or medically unexplained illness), approaches to treatment are more difficult.

Because there has been no single identifiable disease to treat, it has not been possible to develop a uniform approach to health interventions in the Gulf War veteran population. The Department of Defense (DoD) is implementing a longitudinal study of health status that may yield useful information in planning for the future care of veterans of conflict; however, physicians treating Gulf War veterans need guidance now on treatment, and patients need to feel there is an approach to treatment that results in improved health.

The committee was asked to identify illnesses and conditions present among Gulf War veterans, to identify valid models of treatment for such illnesses to the extent they exist, and to identify new approaches, theories, or research on management of these conditions if validated treatment models are not available. To accomplish this, the committee examined the most common symptoms reported by Gulf War veterans and grouped them into established and accepted symptom-based conditions. This approach is supported by a number of well-done population studies (Iowa Persian Gulf Study Group 1997; Goss Gilroy 1998; Unwin et al. 1999).

In addition to testimony from veterans' groups, patients, and their families regarding problems they have encountered (see Appendix B for details), the committee reviewed published studies that examined symptoms and conditions reported in Gulf War veterans. Symptom reports from 10 surveys are displayed in Table 2-1. Other symptoms reported include back pain, wheezing, swelling in joints, loss of strength, blurred vision, sensitivity to chemicals, slow healing, impotence, painful intercourse, and burning semen.

Most Gulf War veterans experiencing one or more of these symptoms have readily identifiable medical conditions. However, about 20% of symptomatic veterans examined in the VA and DoD registries report multiple symptoms for which no readily identifiable diagnosis exists. Symptoms reported correspond closely to symptoms experienced by people in other than veteran populations who have recognized diagnoses of unknown etiology. Symptoms experienced by Gulf War veterans have a significant degree of overlap with symptoms of patients diagnosed with these conditions, such as fibromyalgia (joint pain, sleep disturbances, fatigue), chronic fatigue syndrome (fatigue, headache, cognitive dysfunction), depression (fatigue, loss of memory and other general symptoms, cognitive dysfunction, and sleep disturbances), and irritable bowel syndrome (diarrhea and other gastrointestinal symptoms, abdominal pain, nausea, and vomiting).

The committee decided that it would examine treatments for these recognized diagnoses of unknown etiology to determine what might be learned and borrowed from these conditions to apply to the treatment of Gulf War veterans. Headache and panic disorder were included in the report because they also involve symptoms similar to those reported by Gulf War veterans. Posttraumatic stress disorder (PTSD) was included because of its increased prevalence in this as well as other veteran populations.¹

There are also a number of patients who experience symptoms that do not fall into these defined diagnostic categories. The committee considered two alternative approaches to evaluating treatments for patients with unexplained symptoms: (1) the dimensional approach and (2) the categorical approach.

The *dimensional* approach posits that a substantial overlap exists between the individual syndromes; that is, unexplained illness occurs on a continuum of the population extending from individuals with symptoms to those without symptoms and the similarities between conditions out-

¹The committee acknowledges the VA's expertise in the treatment of PTSD but includes the diagnosis here for the sake of completeness.

TABLE 2-1 Symptoms Reported in Gulf War Veterans by Study Conducted

Symptom	Reference									
	1	2	3	4	5	6	7	8	9	10
Fatigue		+	+	+	+	+		+	+	
Skin rash/irritation	+	+	+	+	+	+	+	+	+	+
Headache	+	+	+	+	+	+	+	+		+
Muscle/joint pain	+	+	+	+	+	+	+		+	
Joint stiffness		+	+	+	+	+	+			+
Loss of memory and other general symptoms	+	+	+	+	+	+		+		
Cognitive dysfunction	+	+	+	+	+		+	+		+
Shortness of breath	+	+	+	+	+		+	+		+
Sleep disturbance	+	+	+	+	+		+	+		+
Diarrhea and other gastrointestinal symptoms	+	+	+	+	+	+	+			+
Abdominal pain	+	+	+	+	+	+		+		+
Nausea and vomiting	+	+	+	+	+	+	+			+
Chest pain/tightness	+	+	+	+	+	+				+
Choking sensation	+	+	+	+	+	+				+
Cough		+	+	+	+	+	+			+

weigh the differences (Wessely et al. 1999). Wessely and colleagues suggested that rather than approach treatment of these conditions as separate entities, a more appropriate position would be a symptom-based approach that puts “an end to the belief that each ‘different’ syndrome requires its own particular subspecialist” (p. 939). Treatments would be evaluated based on symptoms rather than diagnostic categories.

The *categorical* approach uses defined separate clinical syndromes or diagnostic entities that are based on symptoms (e.g., chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome), acknowledging they may have overlapping symptoms.

Because research on the efficacy and effectiveness of treatments has been diagnosis specific, the committee, of necessity, has followed the categorical approach in evaluating treatments and has grouped symptoms experienced by Gulf War veterans into the following diagnostic categories that have been the subject of efficacy or effectiveness research:

- Chronic fatigue syndrome
- Depression
- Fibromyalgia
- Headache
- Irritable bowel syndrome
- Panic disorder
- Posttraumatic stress disorder

As with all symptom-based conditions, however, there are veterans who have symptoms that do not fit into any of the above categories. To address these patients’ illnesses, the committee has taken a dual approach. A general approach that can be used with all patients is outlined in Chapter 4, while Chapter 5 describes a more specific approach for addressing the treatment of veterans with specific conditions.

Future efforts to determine treatment effectiveness could include outcomes research on treatment for those with symptoms but no diagnosis. Veterans with common symptoms could be evaluated using specific interventions to study response and measure outcomes in order to add to the body of therapeutics that might improve the health of ill Gulf War veterans. One could use the study approaches described in Chapter 3 to assess the effectiveness of other therapies or interventions in addressing these other symptom complexes.

It is hoped that the recommendations that follow in the chapters of this report will provide a more uniform approach to the diagnosis and treatment of difficult-to-diagnose and ill-defined conditions such as chronic fatigue syndrome and fibromyalgia. To the extent that effective treatments of specific symptom complexes and diagnoses are implemented, it is hoped that veterans will receive care that increases their

overall quality of life, regardless of where they live or at what treatment facility they receive their medical care.

Chapter 3 discusses the difference between treatment efficacy and treatment effectiveness, describes study approaches that can be used for both, and recommends an approach to use for the conduct of future studies of treatment effectiveness.

3

Determining Treatment Effectiveness

Once the committee identified the health conditions upon which to focus (see Chapter 2), it had to determine how to evaluate the effectiveness of treatments for those conditions. There are a number of ways to show that a given treatment is effective in treating a disease or clinical condition. Studies of treatments typically start either with laboratory studies establishing a possible or plausible effect of a treatment or with uncontrolled clinical observations of that effect. Small pilot studies, larger controlled trials, and, finally, studies of efficacy in large clinical populations gradually build a case for the value of a given treatment. There is no point along this sequence when a treatment is unequivocally “proven” efficacious, since no single study is totally free of all methodological flaws and even a set of studies may be flawed and produce misleading conclusions. The strength of evidence for or against a given treatment can be graded, however, and there is a point at which the medical and scientific communities can reach consensus about the efficacy (or lack thereof) of a treatment (Guyatt et al. 2000). In this chapter, we will review these “rules of evidence” and indicate how they can be applied to treatments for Gulf War veterans’ health problems.

STUDY DESIGNS AND STRENGTH OF INFERENCE

Questions of treatment effectiveness are fundamentally questions about cause-and-effect relationships. If an effective treatment is applied, some detectable improvement in a patient’s condition should occur. If the treatment is not applied, no improvement occurs or the patient gets worse.

If the treatment is applied in higher doses or more frequently (at least up to a point), the improvement should be greater or occur sooner. Because there may be other causes of improvement beside the treatment in question, the improvement must be shown in multiple patients in multiple settings and in circumstances where as many other possible causal factors can be ruled out.

Assessments of the efficacy of specific treatments typically start with some evidence of biological plausibility. Basic laboratory studies or other kinds of knowledge that do not involve direct tests of a treatment in live human patients may suggest that a treatment or class of treatments *should* work. No matter how compelling the arguments for plausibility, though, plausibility per se is not evidence for treatment efficacy.

The *randomized controlled trial* (RCT) is the most reliable methodology for assessing the efficacy of treatments in medicine. In such a trial a defined group of study patients is assigned to either receive the treatment or not, or to receive different doses of the treatment, through a formal process of randomization. A coin flip is the simplest example of a random process. In a study with two “arms” (e.g., treatment or no treatment), each eligible patient would receive whatever a coin flip indicated—heads for treatment and tails for no treatment. In a large number of patients, any clinical or demographic factors such as age, height, weight, illness history, other illnesses, or any other unknown factor that might affect the results of the treatment would be equivalent in the two groups. These will all be eliminated, then, as plausible competing explanations for any observed difference in outcome between the two groups.

Randomized trials typically include other features that increase the strength of the conclusions about cause-and-effect relationships between the treatment and the outcome of interest. Some patients may be excluded from the study because they have conditions that make it impossible to evaluate outcomes or gather data (e.g., extremely elderly patients may be excluded from a study of a cancer treatment because too many of them would die of other conditions before the end of a five-year follow-up period). The study of the efficacy of a drug may include lab tests that measure the level of the drug in the bloodstream. This is done to ensure that the patients assigned to the treatment group actually received the drug while the patients randomized to “no treatment” did not take it on their own. A study may include near-term clinical measures of benefit (e.g., reduction in blood pressure or cholesterol level) as well as long-term objective measures of benefit (e.g., remissions of tumors, mortality) or long-term subjective measures of benefit (e.g., self-reported pain or functional status levels).

Even though an RCT provides strong evidence for or against the efficacy of a given treatment being tested, no one study is ever so perfect that the results cannot be challenged. A study may show an absence of an

effect of a drug, for example, because the dose chosen for study was too low. The patients in a particular study may be unique in some way that makes them not representative of all patients to whom the treatment might be given in the future. For example, if all study subjects are middle-age white men, it is not clear whether the treatment would work in the same way for older or younger Asian women. Results that appear significant in a near-term follow-up may change with longer follow-up (e.g., a treatment shrinks tumors dramatically for two months, but the cancers recur and the patients die after 18 months). The most powerful evidence of treatment efficacy comes from the cumulative, consistent results of several RCTs, preferably in different patient populations and in different settings, and with extensive follow-up periods.

Other kinds of studies (i.e., quasi-experimental designs) can provide evidence of treatment efficacy, too. In situations where it is technically or ethically impossible to run concurrent control groups, a series of “off/on” periods of treatment in a single group of patients can be studied. In these studies treatment is administered to a single group of patients and then taken away. Evidence of efficacy is provided if the benefit is consistently seen when treatment is given and the benefit disappears when treatment is not given. This is a specific example of a *before-after* study design without controls. A single round of off/on provides very weak evidence for effectiveness unless results are unusual and dramatic, because many other things occurring at the same time as the treatment may have caused the result. Being able to repeat the effect over and over again strengthens the argument for the treatment, rather than something else, being the cause of the effect.

One could also use a *cohort study*. In this study design a large number of patients who receive a treatment are followed over time to observe a possible benefit and are compared to those who did not receive the treatment. It may offer strong evidence of treatment effectiveness if the group studied is particularly large so that other possible causes of an effect may be evaluated through statistical analysis, or if the result is unusually strong and/or consistent in the large group. For example, one might observe a lower rate of heart attacks in a large group of men taking an aspirin every day over a 10-year period compared to similar men who did not take it. One might challenge the results, though, and ask whether the men taking aspirin became more health conscious in general and also lost weight, drank less, quit smoking, or did something else that was actually the cause of the reduced rate of heart attacks. Being able to go into the database and find the effect in a subset of men who did not lose weight or quit smoking or drink less would offer an answer to the challenge.

Another possible study design is a *case-control* study. In this study design, patients are assigned to study groups based on the *results* of treatment rather than the treatment itself. One might, for example, identify

some patients who survived one year after a heart attack and other patients who died within a year. If most or all of the patients who survived received a certain kind of treatment and few or none of those who died received the treatment, the treatment might have improved the odds of survival. In this kind of study and in the cohort study, there is no direct control over who receives what treatment, so there may be competing explanations for the effect. Perhaps only healthier, stronger patients received the treatment, with the possibility that the survival benefit was related to their health and strength rather than the treatment. Because this design leaves open many competing explanations, it is less powerful than an RCT for assessing treatment effectiveness and is usually followed by an RCT to confirm findings.

Still weaker evidence for treatment effectiveness comes from *uncontrolled clinical observations* or *anecdotes*. These types of studies may involve small numbers of patients, treatments that are not well defined or that vary from patient to patient, variable periods of follow-up, unstated or varying rules for selecting patients for study, or outcome measures of unknown validity (e.g., patient says he “feels better”). They may not be studies at all in the sense that there is any organized effort to answer a scientific question about a treatment. They may simply be the collected reports of the experiences of patients who share some basic characteristics of illness and treatment. Although these kinds of studies can appear in major professional journals because they *do* provide *some* evidence of potential treatment effectiveness, they are generally not considered to provide strong evidence because of the many possible competing explanations for the observed effect that they cannot rule out.

In summary, there are a number of study designs that can provide varying levels of evidence of treatment efficacy. They include (from strongest to weakest):

- Multiple well-designed randomized controlled trials
- Single well-designed RCT or multiple small RCTs
- Cohort study, particularly one with multiple “on/off” features
- Case-control study
- Series of clinical observations or anecdotes

EFFICACY VERSUS EFFECTIVENESS

The discussion above has used the term “efficacy” to refer to the typical change in a patient’s (or group of patients’) health status brought about by a given treatment. There is an important distinction, however, between two similar-sounding terms:

- *Efficacy* is the benefit produced by a given treatment in tightly

controlled, perhaps artificial, study conditions in which patients are carefully selected and may be more frequently observed, tested, and monitored than is typically the case in routine clinical practice.

- *Effectiveness* is the benefit produced by the given treatment in day-to-day clinical practice, in unselected patient populations that do not receive extra tests, education, or visits because of participation in a study.

With this distinction in mind, most RCTs would be properly labeled efficacy studies rather than effectiveness studies. The results, then, reflect treatment *efficacy* rather than treatment *effectiveness*. Treatment effectiveness would typically be established *after* one or more RCTs, when the treatment came to be widely used in a variety of clinical settings in diverse patient populations.

It is possible to imagine an “effectiveness RCT” that would combine the design features of the RCT with a set of sampling and analytical features that would permit direct extrapolation of findings to routine clinical practice (Roper et al. 1988). An effectiveness RCT could be viewed as a hybrid that combines the real-world features of effectiveness studies with some of the study design features typically found in efficacy studies. In an effectiveness RCT, one would have relatively light (if any) patient exclusion criteria, so that the patients in the trial would be as similar as possible to those to whom the results would be generalized. The study would be run (to the extent possible) in a range of treatment settings rather than in a single academic medical center context. The treatment would be provided by the same kinds of providers (e.g., community physicians or nurses) who would provide the treatment in nonstudy settings. There would not be an elaborate data collection infrastructure (e.g., extra lab test or imaging studies) that would create a different “information environment” for treating clinicians and patients than the one that would be found in real-world treatment settings. Analysis would be done on an “intention to treat” basis. The study would have random assignment of patients to treatment arms and would have one or more control groups (e.g., placebo controls, waiting list controls, different dose or regimen controls, or other controls that would make sense for the question being asked).

If we adhere to this terminology, we will find that there is very little formal evidence of treatment effectiveness for most treatments for medical problems in Gulf War veterans because relatively few true effectiveness studies have been done on any medical condition.

OUTCOMES RESEARCH

In an influential 1988 article, Paul Ellwood coined the term “outcomes management” and challenged the medical community to formally

assess patient outcomes, not only in the context of specific research projects but also in the context of routine clinical care. His concept of outcome not only included the directly measurable outcomes of clinical trials like objective tumor shrinkage or mortality, but also a range of self-reported patient outcomes like functional health status, pain, ability to work, and overall quality of life. Part of his concept included the building of large data repositories in which clinicians would build a “collected clinical experience” of the baseline characteristics, treatments, and outcomes of thousands and thousands of patients. With this database available, he argued, future clinicians could enter the characteristics of a patient with a given problem and almost immediately obtain data on the relative effectiveness of several treatment choices in patients like the one in question.

There are a number of outcomes research projects that represent the closest approximation to a study of true treatment effectiveness (Magid et al. 2000). The National Registry of Myocardial Infarction is one example; the APACHE III and the Spine Surgery Consortium for Outcomes Research are others. The American Medical Group Association has been the sponsor of a large number of related outcomes projects that have been carried out in the past 10 years.

In the scheme of study designs described above, these studies may perhaps best be categorized as cohort studies, although the cohort is defined in terms of the clinical condition rather than by the receipt of a specific treatment. They do not typically have the tight control of patient eligibility criteria and the random assignment of treatments that are the hallmarks of the RCT. It is presumed that the effects of possible alternative causal factors can be identified and controlled through appropriate statistical techniques, and this is made possible by large sample sizes and the collection of a wide range of relevant variables.

The committee is not aware of any ongoing outcomes management or outcomes research projects involving either a specific cohort of Gulf War veterans or a specific clinical condition of particular concern to Gulf War veterans. There clearly is an opportunity, though, in both VA and DoD settings to organize such a project since some of the functions of identifying a cohort of patients and gathering baseline data have already been completed through their registry programs.

META-ANALYSIS

We have stated that the strongest form of evidence for treatment effectiveness is that of several well-designed RCTs whose results are consistent. What about the situation, though, in which study results are not fully consistent or where there are multiple studies of differing sizes and

degrees of design rigor? The technique of *meta-analysis* was developed in an attempt to fit this situation.

In a meta-analysis the results of multiple studies are combined to yield an overall cross-study estimate of treatment effectiveness (DerSimonian and Laird 1986). The key characteristics of a meta-analysis include:

- explicit criteria for deciding which studies are relevant and are to be included;
- explicit criteria for reviewing published or unpublished literature and choosing candidate studies for the analysis;
- explicit criteria for grading studies according to rigor of design and execution and resulting strength of evidence;
- explicit criteria for assigning “weights” to individual studies that reflect the strength of evidence in each one; and
- a statistical method for aggregating the results of different studies that may have widely varying sample sizes, definitions of study endpoints, follow-up intervals, and statistical tests of effect.

In principle, the results of a good meta-analysis should provide the closest possible approximation to “definitive evidence” of treatment effectiveness, since they are based on a formal, well-defined integration of the results of multiple studies conducted in different populations in different settings. Just as is the case with other study designs, however, meta-analysis does not always live up to its promise. It is necessary to carefully examine the criteria and methods used in each meta-analysis to determine the quality of evidence provided by its conclusions.

LEVELS OF EVIDENCE FOR EFFICACY AND EFFECTIVENESS RESEARCH

A recent description of levels of evidence from the Evidence-Based Medicine Working Group (Guyatt et al. 2000) repeats the well-accepted hierarchy that places multiple well-designed randomized controlled trials at the top of the hierarchy and uncontrolled clinical observations at the bottom. The article discusses “*N* of 1 randomized trials,” indicating that *for individual patients* a carefully controlled trial of potentially effective treatments (with blinding, placebo controls, etc.) provides the most compelling evidence of effectiveness *for that patient*. It is not the case, however, that a number of “*N* of 1” studies added together would be comparable to an RCT.

A revision to the generally accepted hierarchy of evidence might be indicated, however, particularly when the question of treatment *effectiveness* (rather than efficacy) is being addressed. From the perspective of the

evaluation of treatment effectiveness, there are two general classes of studies, each with a balance of strengths and weaknesses:

Treatment *efficacy* studies, including prospective randomized trials, emphasize internal validity at the expense of external validity. That is, the sampling, data collection, and data analysis procedures are designed to support the strongest possible inferences about associations between independent and dependent variables (i.e., cause and effect) in a tightly controlled context. The best, strongest studies in tightly controlled situations may still lack generalizability, and therefore applicability, to routine medical practice.

Treatment *effectiveness* studies, including the largest and most comprehensive outcomes studies, emphasize external validity at the expense of internal validity. They may involve very large samples that are fully representative of the patients seen in routine clinical practice but may include confounding factors that weaken the inferences about cause-and-effect relationships.

In determining a policy to follow in developing guidelines about effective treatments for Gulf War illnesses, we suggest that both types of studies be considered in developing a hierarchy of evidence. We suggest that this be done by considering a “parallel” hierarchy with efficacy studies on one side and effectiveness studies on the other, as illustrated in Table 3-1.

SPECIFIC LEVELS OF EVIDENCE OR WEIGHTS

Table 3-1 is organized to suggest that types of studies at the same vertical position in the two columns should be seen as equally powerful for establishing treatment effectiveness. That is, for purposes of evaluating treatment effectiveness, the results of a single well-designed outcomes study should be considered to be as compelling as the results of a single well-controlled randomized trial. The former will have few concerns about the generalizability of its findings to real-world settings (external validity) but perhaps some serious concerns about internal validity; the latter will have the opposite pattern of strengths and weaknesses. If studies of both were available with similar results, the combined evidence would be quite powerful. Studies of the two types with conflicting findings would essentially cancel each other out and no conclusion could be drawn.

In terms of the levels of evidence such as those used by the Clinical Preventive Services Task Force (CPSTF), we suggest that both effectiveness and efficacy studies at or above the split into two columns be considered “Level I or Level II evidence” in the future. The set of cohort, observational, and case-control studies would be “Level III or IV evidence”

TABLE 3-1 Hierarchy of Evidence

	Emphasis on Efficacy	Emphasis on Effectiveness
Level I	Systematic Review (e.g., meta-analysis) of Several Well-Controlled Randomized Trials—consistent results	Systematic Review (e.g., meta-analysis) of Several Well-Designed Outcome Studies or “Effectiveness RCTs”—consistent results
Level II	Single, Well-Controlled Randomized Trial	Single, Well-Designed Outcomes Study or “Effectiveness RCT”
Level III	Consistent Findings from Multiple Cohort, Case-Control, or Observational Studies*	
Level IV	Single Cohort, Case-Control, or Observational Study	
Level V	Uncontrolled Experiment, Unsystematic Observation, Expert Opinion, or Consensus Judgments	

*It is not clear in many cases whether an observational or case-control study is an efficacy study or an effectiveness study. In principle, the label or definition depends on the extent to which the study sample and study procedures reflect the complexities and realities of daily clinical practice. For any one study, though, this may not be clear; however, when it is, more credence should be given to those truly reflecting effectiveness.

NOTE: N of 1 Effectiveness Studies: This study design offers the strongest possible evidence for the effectiveness of a treatment in a given patient but does not necessarily speak to the issue of effectiveness for patients in general (Sackett et al. 1991). The VA and DOD may use this evidence to support policies on payment for treatment or for deciding on promising treatments to be investigated with more definitive designs. Evidence from a single *N* of 1 study should not be used to establish *general* treatment guidelines.

depending on whether it was based on multiple studies versus a single study, and the set of expert opinion or uncontrolled clinical observations would be “Level V evidence.” For the efficacy studies, our use is fully consistent with the CPSTF’s use of the terms. We do, however, add outcomes/effectiveness studies to those study designs capable of providing the highest levels of evidence when the major question is one of effectiveness rather than efficacy. The above hierarchy also implies that, when the focus of evaluation is on treatment effectiveness, and in the absence of RCTs specifically designed to assess effectiveness in real-world settings, evidence from well-designed outcomes studies may provide Level I or Level II evidence and serve as the basis for clinical policies and treatment guidelines. It also implies that Level I evidence of efficacy, even if based on a compelling set of RCTs, may not provide Level I evidence of treatment effectiveness.

OTHER CONSIDERATIONS

Defining an Effect

Any study of efficacy or effectiveness must have one or more defined outcomes or endpoints to assess. These can include “ultimate” endpoints like mortality rates or length of survival or can include “intermediate” endpoints like reduction in blood pressure or shrinkage of tumor size. The endpoints may also be objective (i.e., can be measured reliably by an outside observer) or subjective (i.e., only observable and reportable by the patient or based on the judgment of a clinician).

In the population of Gulf War veterans, many of the treatment outcomes will be subjective. Since the most frequently reported symptoms include dimensions of pain, fatigue, difficulty concentrating, and difficulty performing normal work and social activities, the measures of effectiveness must presumably be in these domains. There are reliable, valid, and sensitive measures in virtually all of these domains. Not all of the measures are equally reliable, valid, or sensitive in all possible study populations, however, so it is necessary to evaluate whether the measure used in any one study is an appropriate measure of treatment effectiveness. Measures designed to detect differences in large samples of relatively healthy people, for example, may not be suitable for detecting differences in individual patients who are extremely ill.

For any specific measure chosen, there is an additional question of how an effect is defined, either for an individual patient or for a group of patients. Achieving complete remission or cure, for example, is different (and presumably harder) than achieving an objectively or subjectively detectable improvement. A treatment that has a “significant effect” in a large group of patients may actually have no effect or a negative effect on some individuals in the treatment group. A group that is better off *on average* may include individuals who are not better off or who are worse off. Depending on the design of the study and the amount of statistical analysis done, it may or may not be possible to identify those who will benefit from receiving the treatment in the future and those who will not.

Defining the Study Population and Universe of Patients

Most treatment effectiveness studies are carried out on patients with well-defined diseases or other clinical conditions. There is typically a body of scientific knowledge of disease etiology, basic biological mechanisms, and the way in which treatment is expected to affect those mechanisms.

For Gulf War veterans, the situation is more complicated. Although several studies have identified specific symptoms or possibly clusters of symptoms that occur with greater frequency in Gulf War veterans, there

continues to be no single “Gulf War syndrome” or any clearly established etiology for the symptoms or symptom clusters. Veterans who are experiencing severe fatigue, for example, may or may not meet criteria for a diagnosis of chronic fatigue syndrome (CFS). Studies of CFS, then, may or may not be generalizable to the entire population of veterans experiencing fatigue even if they are deemed generalizable to veterans with CFS. Similarly, results of studies of fibromyalgia, depression, or migraine may or may not be applicable to Gulf War veterans who are experiencing symptoms of these conditions but do not have all the characteristics that would justify a formal diagnosis. One should not assume that Gulf War veterans with medically unexplained symptoms have one of the diseases of unknown etiology discussed here. Results of studies on conditions with unknown etiology may not generalize directly to Gulf War veterans whose similar symptoms may have a different etiology. However, given currently available diagnostic information and the lack of effectiveness studies conducted on Gulf War veterans, identification of effective treatments for such conditions as these may offer the best opportunity for alleviating the health problems of Gulf War veterans.

Another complication is the current absence of criteria for defining the presence, duration, progression, or severity of Gulf War veterans’ health problems that match similar criteria for diagnosable illnesses. Clinical trials may be done on conditions that are “acute” or “uncomplicated,” or “recurrent” or “severe.” The patients recruited for such trials must meet certain explicit criteria for being in that category. Although the specific symptoms experienced by veterans may be categorized in these ways, and future prospective studies may be conducted on groups defined in this way, it will be challenging in the near term (and in the context of this report) to draw conclusions from existing published literature about the possible effectiveness of treatments in Gulf War veterans. Development of a standard language for describing Gulf War veterans’ health problems (including severity and temporal characteristics) would facilitate the conduct of treatment effectiveness trials.

RECOMMENDATIONS

The preceding discussion and analysis describes approaches used for assessing treatment effectiveness. Based on this analysis, to implement well-designed and valuable treatment effectiveness studies, **the committee recommends that the VA:**

- **use a hierarchy of evidence structure that includes effectiveness studies as well as efficacy studies for any future treatment guidelines it develops for symptoms or illnesses of Gulf War veterans;**

- design future studies of treatment effectiveness that include outcomes research and effectiveness randomized clinical trials; and
- develop a standard language for describing Gulf War veterans' symptoms, including their severity and temporal patterns, and that this standard language should be used in conducting treatment effectiveness studies and developing treatment guidelines.

Further, the committee recommends that those conducting ongoing cohort studies of veterans' health (e.g., the national VA study, the Iowa follow-up study on Gulf War veterans, and the Millennium Cohort Study being implemented by DoD) include collection of data on treatments and health-related quality of life.

The committee also recommends that current VA and DoD Gulf War registries be used as one way to identify patient samples and serve as a sampling frame for future treatment effectiveness studies.

(NOTE: The current information collected and analyzed in the Gulf War registries does not include basic data on treatment approaches, health status, or outcomes. Addition of such information to the registries would greatly increase their value as a basis for identifying patient samples for more in-depth study.)

Despite the fact that treatment effectiveness studies have not been conducted for the population of Gulf War veterans, there are approaches to treatment that have been shown to be beneficial across diagnostic categories. The following chapter explores a patient-centered approach to care that can be used with all patients, regardless of diagnosis, but which may prove especially beneficial to those who are experiencing symptoms but have no identifiable diagnosis.

4

General Approach to Treating Patients

As previously stated, the committee is charged with three tasks, one of which is to identify already validated models of treatment for conditions of interest. Before reporting effective treatments for individual conditions, however, the committee determined that there are certain general principles of a patient-centered approach to medicine that form part of the effective evaluation and treatment of any patient. Even though this approach is one that will benefit any patient, it may be of particular value for patients like the Gulf War veteran who is experiencing symptoms that impact his or her daily life, who is concerned that these symptoms may signal some major health problem, and for whom no diagnosis can be made. This chapter discusses such a general approach to diagnosis and treatment.

Part of the evaluation and treatment of any patient, regardless of condition or diagnosis, is an appropriate framework or pathway for diagnosis, treatment, and, if necessary, referral for specialty care (IOM 1998a). For Gulf War veterans, the first step in evaluating persons deployed to the Gulf War is to construct an accurate history through a careful interview. The patient's history is a critical basis for assessing his or her symptoms. The history should be followed by a comprehensive physical examination.

As with any assessment, the approach taken for this interview should be patient centered. Patient-centered care has been defined as care that recognizes the patient as a person with a unique life history and needs (McWhinnney 1981). Henbest and Stewart (1990) defined patient-centered care as care in which the physician responds to the patient in such a way

as to allow him or her to express all of the patient's reasons for seeking care, including symptoms, feelings, thoughts, and expectations. Patient-centered care requires positive interaction or communication between the patient and the physician, interaction during which the physician actively seeks the patient's point of view.

Owens et al. (1995) studied the effect of physician-patient interaction on the long-term prognoses of patients with irritable bowel syndrome. They found that a positive physician-patient interaction may be related to reduced use of ambulatory health services by such patients. Daltroy (1993) studied the effect of doctor-patient communication on patients with rheumatological disorders. He found that effective communication results in increases in patient knowledge, in desirable behaviors (especially compliance with prescribed treatments), in self-confidence, and in functional status.

A review of the literature by Ong et al. (1995) reported that information giving, time spent in discussion of preventive care by the doctor, and greater interview length were positively associated with patient satisfaction while a dominant, controlling style of communication on the part of the physician produced less satisfaction. They also found that in the ideal medical interview the patient leads in areas where he or she is the expert (symptoms, preferences, concerns) and the physician leads in his or her domain of expertise (details of disease, treatment).

Stewart (1984) found that physician behavior is crucial and that a positive outcome depends on physician behavior that is facilitating rather than dominating. Kaplan et al. (1989) found that better health status was related to more patient and less physician control, more affect (i.e., expression of both positive and negative emotions) expressed by physician and patient, and more information provided by the physician in response to effective patient information seeking.

In following this patient-centered approach to care, physician questions should be asked in a manner that conveys genuine interest and does not make the patient feel that he or she is under interrogation. Once rapport is established, questions can become more detailed or specific, focusing on the patient's problems, blending open-ended questions with others that can be answered easily with a *yes* or *no*.

The goal of evaluation is to define the problem that the patient identifies with Gulf War deployment through relatively nonintrusive inquiries about the patient's problems and symptoms, only then moving on to more specific questions. Patients may need reassurance before disclosing their thoughts and behaviors; clinicians should reassure them about the confidential nature of the doctor-patient relationship. Family members and friends can be important informants, able to fill in the gaps in the patient's history or to describe behaviors they may have witnessed. Pa-

tients may not always be accurate in describing the extent of their symptoms, though relatives may be able to do so.

Comprehensive assessment of persons with symptoms attributed to Gulf War deployment would benefit from an understanding of the types of symptoms and problems that such patients experience. The evaluation begins by gathering a thorough history of signs and symptoms, which the subject attributes to Gulf War experiences, such as when the problems began in relationship to deployment, their nature and onset, and their course over time. Have the symptoms been chronic? Episodic? Has their severity fluctuated? Physicians should try to determine the onset of the symptoms and how the patient became aware of his or her symptoms, should inquire about diagnostic techniques or treatment measures used by clinicians he or she may have seen, and should document the patient's response to these interventions.

The clinician should attempt to exclude medical conditions suggested by the patient's symptom profile. This will involve recording detailed information about current and past medical illnesses, medications used, surgical procedures, typical allergies, previous diagnostic workups and treatments, and the patient's pattern of medical care utilization. Obtaining past medical records is especially helpful, particularly when the patient is a poor historian or the past history is confusing. Evaluation of a patient must also include the patient's psychiatric history since the presence of psychiatric comorbidity may suggest particular treatment strategies or approaches, as well as a possible explanation for some of the reported symptoms.

The committee recognizes that alcohol and other substances are frequently used as a self-medication strategy by patients who learn, through experience, that these drugs alleviate some of their symptoms, particularly depression, stress, and anxiety. While the committee did not choose to examine effective treatments for use and misuse of alcohol and other substances, such use, if undetected, will complicate the management of any underlying conditions. This is especially true in those situations where alcohol is in some way synergistic with the medication being prescribed.

It is very important, therefore, that health care practitioners explore these issues with all patients, including Gulf War veterans. Commonly used screening tools such as the CAGE and AUDIT interviews about alcohol use are excellent, well-validated tools for measuring the degree of alcohol use.

The patient's history should be followed by a thorough physical examination and routine laboratory testing. A physical examination and screening laboratories could help uncover a diagnosis that may explain, in part or in full, the patient's symptoms attributed to Gulf War deployment. The assessment should include routine laboratory tests such as a complete blood count, serum electrolytes, serum glucose, and urine analy-

sis. A veteran who presents with specific complaints should also receive targeted testing.

If the results of the initial examination and testing are consistent with a diagnosis that explains the complaints, that patient's diagnostic evaluation would stop and he or she would receive treatment for the diagnosed problem. If, however, the results are *not* consistent with the complaint, or if something unexplained appears as a result of the tests or the examination, the patient should continue on the diagnostic pathway for additional evaluation and testing that would be guided by the patient's signs and symptoms (IOM 1998a). Patients with prominent respiratory tract complaints, for instance, may need referral for pulmonary function tests to rule out the presence of reactive airway disease. Neuropsychological testing may be useful in some patients, particularly when the predominant complaint involves memory impairment or poor concentration.

Results of the physical examination and laboratory testing may well be within normal limits for most patients and will help to exclude the presence of well-defined illness. If a diagnosis cannot be determined, the provider must decide whether (1) the symptoms or problems are serious enough to cause disruption in the patient's life and therefore warrant continued evaluation at a special center or (2) the symptoms and complaints are not causing disruption in the patient's life and therefore the patient should receive periodic reevaluations to determine if his or her condition changes over time (IOM 1998a). Throughout the evaluation, however, positive communication is essential.

According to Ong et al. (1995), there are three purposes of physician-patient communication: creating a good interpersonal relationship, exchanging information, and making treatment-related decisions. Daltroy (1993) has identified three primary communication goals for the physician: to elicit the patient's problems and history with an eye toward making a diagnosis, to negotiate a treatment regimen that the patient will accept and that is congruent with recognized medical practice, and to teach the patient about managing his or her disease and treatment regimen so that it may be effectively implemented. The physician views empathy and building patient self-confidence as supportive rather than primary goals.

Much has been written about the effect of physician-patient communication on patient outcomes. Evidence indicates that physician-patient interactions have a substantial impact on health-related outcomes (Stewart 1984; Kaplan et al. 1989; Daltroy 1993; DiMatteo 1994; Gordon et al. 1995; Owens et al. 1995; Joos et al. 1996). Outcomes measured include patient satisfaction with care, adherence to treatment regimen, understanding of medical information, coping with disease, quality of life, and functional status. Kaplan et al. (1989) wrote that effective physician-patient communication may lead to better health outcomes for the patient because:

- Patients need information to manage their disease.
- Communication can motivate, encourage, and reassure as well as provide an opportunity for the patient and physician to change their expectations.
- Physicians may be able to change patients' perceptions about their health status as well as their beliefs about and self-confidence in their ability to influence their health status.

But what does this mean in terms of specific behaviors for the patient and the physician? Based on attribution and decision theory, Daltroy (1993) identified the following nine tasks for effective physician-patient communication:

1. *The patient must express all of his or her concerns during the clinical encounter.* To ensure that this happens the physician should ask the patient about his or her concerns and should listen and probe until he or she is confident that all concerns have been expressed. One technique is to encourage patients to bring lists of their concerns to the appointment.

2. *The physician addresses all of the patient's concerns.* While it may not be possible to immediately respond to all of the concerns, the physician should work with the patient to decide which items should be addressed immediately and which must be deferred. Even though the patient might have a diagnosed problem, it is important not to neglect unexplained symptoms. For patients with chronic symptoms it is important that the provider communicate his/her understanding of the patient's physical distress and the intent to work with the patient to maximize functioning and quality of life.

3. *The physician and the patient share models of disease and symptoms.* Patients frequently have a different understanding of the cause and course of their disease or symptoms. The physician can discover the patient's beliefs and understanding by asking the patient to explain in his or her own terms the causes of the disease and the symptoms. It is then possible to address misconceptions, reinforce accurate understanding, and provide reassurance to patients through education and advice that address the patient's beliefs.

4. *The physician and patient must share goals for treatment.* Patient's goals for treatment frequently relate to how well they function, to their loss of functioning in areas important to them. They may not always understand how the recommended treatment relates to achieving their own goals. The physician should share his or her goals for treatment, explaining what is possible. Discussion should also include the treatment's limitations.

5. *The physician and the patient should agree on treatment goals, state them explicitly, and set priorities.* Provider-patient collaboration on setting spe-

cific, incremental, realistic, and achievable goals helps the patient achieve a feeling of ownership of the treatment goals. Such goals may address occupational, household, or social tasks, as well as other areas such as physical activation, sleep hygiene, or medication adherence. Negotiation of the goals and priorities indicates respect for the patient's preferences and can increase patient commitment to a mutually agreed upon regimen.

6. *The physician and the patient should share their respective ideas about the purpose and course of treatments.* That is, specifically what is the medicine or other treatment for (e.g., pain, drowsiness, reduction of swelling) and how long might it take to work (days, weeks, months). It may be the case that the provider will have to prepare the patient for a shift in emphasis from the expectation of a full cure to one where the aim is improvement in functioning and quality of life. Such mutual understanding may affect the patient's adherence to the treatment regimen.

7. *The physician and patient should identify potential difficulties in the care plan.* It may be the case, for example, that a patient will not be able to tolerate a particular medication or will be unable to adhere completely to a rigid diet. It is important to explore the patient's home environment and social network in order to identify potential impediments or supports that could assist in maximizing the effectiveness of the care plan. Anticipating problems in order to deal with them before they interfere with the effectiveness of therapy is also very important. It may also help for patients to understand that some patients do have problems.

8. *The physician and the patient should plan how to overcome anticipated compliance difficulties.*

9. *The physician should provide written information on the disease and treatment regimen.* This information should include the diagnosis (or possibilities), each treatment with the name, purpose of treatment, instructions for use, how to evaluate its effectiveness, key drawbacks or side effects, and what to do if it fails.

No matter what the disease or condition, all evaluation and treatment of patients must involve caring, investigation of all complaints, respect for the patient's perspective, avoidance of excessive testing, and joint decision making regarding treatment, to the extent that is possible. Such an approach is important to maintain excellent communication with the patient. Patient-centered care may require more initial time spent with the patient but may, in the end, decrease the total amount of time required for effective treatment, especially for those patients with difficult-to-diagnose or unexplained conditions.

As an example, patient-centered care has been used to clinically manage patients with somatization disorder. The approach involves the scheduling of regular but brief appointments with the primary care physician; a

brief physical exam at each visit, the physician seeking signs of disease rather than taking symptoms at face value; the physician avoiding hospitalization of the patient and minimizing the use of diagnostic procedures, surgery, and laboratory evaluations; and the physician viewing the development of symptoms as an unconscious process, rather than being “all in your head.” Use of this management approach lowered annual medical care costs and improved physical functioning for the subjects (Smith et al. 1990). Following this patient-centered approach to medicine, one can then proceed to implement validated treatments for specific conditions.

RECOMMENDATION

The committee recommends that the VA provide specific training to health care providers caring for Gulf War veterans to ensure that they are skilled in the principles and practice of patient-centered care.

Further, the committee recommends that the VA ensure that health care practitioners serving Gulf War veterans are allowed sufficient time with patients to provide patient-centered care.

The preceding pages describe an approach to patient care that can be used regardless of diagnosis or condition. Chapter 5 will explore condition-specific treatments.

5

Effective Treatments

Using the levels of evidence discussed in Chapter 3 as a guide for assessing effective treatments, the committee evaluated available evidence regarding the effectiveness of treatments for chronic fatigue syndrome, depression, fibromyalgia, headache, irritable bowel syndrome, panic disorder, posttraumatic stress disorder, and medically unexplained physical symptoms. Committee members reviewed clinical practice guidelines, major literature reviews, and published studies of treatments for these conditions. Randomized controlled trials were given greatest weight in making recommendations about specific treatments; other types of published studies were evaluated using the levels-of-evidence concepts described in Chapter 3.

The following material is organized by condition studied. Each provides a definition of the condition and diagnostic criteria, describes any unique factors or difficulties related to the condition, summarizes available therapies and rates them in terms of benefit, describes practice issues and approaches that are generally recognized as acceptable by the medical community, and presents committee recommendations. In the “Harms” section of each therapy, the discussion provided is not exhaustive nor is it a substitute for reading a thorough documentation of the treatment’s nature.

The approaches presented here are *not* clinical guidelines. The Institute of Medicine (IOM) defines clinical practice guidelines as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances” (IOM 1990: 39). Rather, this chapter is an effort to extrapolate from what we

know about other existing diseases and apply it to the problems suffered by Gulf War veterans.

In extrapolating from specific clinical entities to the problems of Gulf War veterans, the committee chose to recommend only those specific therapies for which efficacy has been demonstrated through one or more randomized controlled trials. However, there may be situations where other approaches are used to manage these conditions. Some of these approaches are described in the "Practice Issue" sections included with each condition. While the committee has chosen to recommend only those therapies whose efficacy has been demonstrated through randomized controlled trials (RCTs), it is important to continue to evaluate these other therapies.

As indicated in Chapter 3, the committee believes that it is essential to demonstrate treatment *effectiveness* using other approaches to study design. The committee found, however, that there are essentially no strong effectiveness studies of treatments for the selected conditions. The best currently available evidence for potential effectiveness in a population of Gulf War veterans, therefore, is strong evidence of *efficacy* through RCTs.

CHRONIC FATIGUE SYNDROME

Introduction

Chronic fatigue syndrome (CFS) is a clinically defined condition characterized by severe, disabling fatigue that persists for at least six months and has a definite onset (Fukuda et al. 1994). Appendix C provides a discussion of unique considerations in CFS. The symptoms include self-reported problems in concentration, short-term memory, sleep, and musculoskeletal pain. A diagnosis is made only after alternative medical and psychiatric causes of fatiguing illness are excluded. There are no laboratory tests that can confirm its diagnosis, no pathognomonic physical examination findings, and no treatment that alleviates the symptoms for all patients (Buchwald and Komaroff 1991; Komaroff and Buchwald 1991, 1998). A major question regarding the diagnosis of CFS is whether it is a discrete entity as opposed to the most severe manifestation of a spectrum of fatigue, or a debilitating but nonspecific symptom complex shared by many different clinical entities.

No single cause of CFS has been identified, but many avenues of investigation have been undertaken. Since about 80% of patients diagnosed with CFS report that their condition started with a virus-like illness (Buchwald and Komaroff 1991; Komaroff and Buchwald 1991), infections were the focus of early studies. Over the last decade, many infectious agents have been suspected and investigated, including Epstein-Barr virus, but none has been found to be causative for CFS (Buchwald et al.

1996; Komaroff and Buchwald 1998). Other studies have noted that 60% to 70% of CFS patients reported allergies, compared to 20% of the general population, and CFS has been associated with heightened reactivity to allergens (Straus et al. 1988). Since allergies are immunological phenomena, scientists have examined other immunological parameters and found decreased natural killer cell number and activity, altered lymphocyte subset numbers and percentage, and increased expression of activation markers on lymphocyte subsets (Buchwald and Komaroff 1991; Straus et al. 1993; Komaroff and Buchwald 1998). Other areas have also been investigated, including neuroendocrine, especially hypothalamic-pituitary-adrenal abnormalities and psychiatric illness (Demitrack et al. 1991; Manu et al. 1988). More recently, autonomic nervous system dysfunction has been hypothesized to be associated with CFS because the symptoms of neurally mediated hypotension can overlap with those of CFS (Bou-Holaigah et al. 1995). However, no finding was ultimately found to be adequately reproducible and reliable to warrant its use as a diagnostic marker. Although many abnormalities exist in CFS, they are not observed in many patients and may not correlate with clinical status, leading to disagreement over their etiological relevance.

Diagnosis

In 1994 the Centers for Disease Control and Prevention convened the International Chronic Fatigue Syndrome Study Group to develop a conceptual framework and a set of research guidelines for use in studies of CFS (Fukuda et al. 1994). This group developed diagnostic criteria for CFS (see Table 5-1).

TABLE 5-1 Diagnostic Criteria for Chronic Fatigue Syndrome

A person must meet both of the following criteria in order to be diagnosed with CFS:

1. Clinically evaluated, unexplained, persistent, or relapsing fatigue of new or definite onset that is not due to ongoing exertion, is not substantially relieved by rest, and results in a substantial reduction in previous levels of occupational, educational, social, or personal activities; and
2. Concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred for at least six months:
 - Impaired short-term memory or concentration severe enough to cause substantial reduction in previous levels of activity;
 - Sore throat;
 - Tender cervical or axillary lymph nodes;
 - Muscle pain, multijoint pain without joint swelling or redness;
 - Headaches of a new type or severity;
 - Unrefreshing sleep;
 - Postexertional malaise lasting more than 24 hours.

There are many medical and psychiatric conditions that cause severe fatigue and, therefore, often preclude the diagnosis of CFS. These include:

1. Active medical condition that may explain the chronic fatigue, such as untreated hypothyroidism, sleep apnea, or narcolepsy;
2. Previously diagnosed medical conditions that have not fully resolved, such as previously treated malignancies or unresolved cases of hepatitis B or C virus infection;
3. Any past or current major depressive disorder with psychotic or melancholic features, including bipolar affective disorders, schizophrenia, delusional disorders, dementias, anorexia nervosa, or bulimia nervosa;
4. Alcohol or other substance abuse within two years before the onset of chronic fatigue and at any time afterward.

It is important to note that the following comorbid conditions do not exclude CFS:

1. Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests (e.g., fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or nonmelancholic depression, neurasthenia, panic disorder, and multiple chemical sensitivity disorder).
2. Any condition under specific treatment sufficient to alleviate all symptoms related to the condition for which the adequacy of treatment has been well documented (e.g., hypothyroidism in which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels and asthma in which the adequacy of treatment has been determined by pulmonary function and other testing).
3. Any condition that was previously treated with definitive therapy before the development of chronic symptomatic sequelae.
4. Any isolated and unexplained physical examination finding or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition (e.g., an elevated antinuclear antibody titer that is inadequate to strongly support the diagnosis of a discrete connective tissue disorder without other laboratory or clinical evidence).

To confirm the absence of underlying disease, the case definition requires that patients with suspected CFS have a minimum laboratory evaluation that includes a complete blood count with differential, electrolytes, blood urea nitrogen, creatinine, calcium, glucose, and thyroid function tests; erythrocyte sedimentation rate; antinuclear antibodies; and urinalysis. Although CFS patients may have abnormalities on such routine

laboratory tests, the lack of consistency precludes the use of routine laboratory tests in determining whether a patient has CFS. That is, there are no diagnostic markers available to establish a diagnosis of CFS (Bates et al. 1994).

Components of Fatigue¹

A literature on the elements or components of fatigue dates back 100 years. Please see Appendix C for a discussion of the unique considerations of fatigue. Fatigue is thought to have four components, each of which may be important in constructing outcome measures or designing tests. The first component is behavior, by which is meant the physical manifestations of fatigue, or a decline in performance, such as making more errors, or an inability to complete a race or clean the house. A second element is the sensation or perception of the fatigued state. This may occur in the absence of any actual physical or mental effort, or it may occur in, or out, of proportion to a particular task. Furthermore, the sensation of fatigue may coexist with psychological symptoms (even in the absence of a psychiatric disorder) and cognitive assessments that result in behaviors (e.g., the belief that exertion is harmful and the consequent avoidance of exercise).

The third element is the mechanisms of fatigue. Mechanisms, as examined in the literature, have tended to focus on a single explanatory model (e.g., infections, psychiatric disorders), a perspective unlikely to be useful in the vast majority of cases. Physiological mechanisms of fatigue are thought to reflect either peripheral (i.e., in the muscles or nerves) or central (i.e., in the brain) processes. In the realm of psychological mechanisms, beliefs, perceptions, expectations, and symptom amplification have all been invoked. The final component of fatigue is contextual. This includes an appraisal of the personal, social, occupational, cultural, and physical environments in which the symptom occurs. Here one may observe the influence of temperature, noise, family, and stressors on the experience of fatigue.

Measurement of Fatigue

The measurement strategy should be closely linked to one or more of the four components of fatigue described above. With few exceptions, even the basic measurement methods currently available are, at best, not

¹The sections "Components of Fatigue," "Measurement of Fatigue," and "Physical Fatigue" are from a consultant's report prepared by Dedra Buchwald for the IOM Committee on Multiple Sclerosis.

fully evaluated. Thus, this leaves open to discussion the utility of more quantitative, and typically sophisticated, tools.

The operating characteristics for many of these measures are not well established for fatigued populations. Moreover, the “gold standards,” even when they exist, are often poor. Nonetheless, if carefully selected, some currently available measures are adequate for clinical trials. These are primarily self-report measures such as the Short Form-36. For most medical conditions, a suitable biological measure or marker of fatigue has not yet been identified.

Disease-specific instruments may offer the advantage of greater sensitivity to change since they incorporate measurements of phenomena more likely to be experienced by persons with a particular condition (e.g., swollen joints in rheumatoid arthritis). On the other hand, comparability and generalizability are sacrificed. In general, standard instruments are preferable unless a floor or ceiling effect has suggested the need for alternative measures.

Physical Fatigue

Many physical health problems are associated with fatigue. For most, although several potential mechanisms may come to mind, a single unifying mechanism is often lacking. Nonetheless, given the distinction made above between “central” and “peripheral” fatigue, the problem of muscle fatigue has been placed in the central nervous system, the spinal cord, or the various components of the muscle. In other conditions a more disease-specific mechanism may be invoked. Nonetheless, one curious and disturbing finding across heterogeneous physical disorders has been that fatigue severity rarely correlates well with measures of disease activity (e.g., in rheumatoid arthritis, hepatitis C). Functioning is often more closely tied, even in physical conditions, to psychological factors and stressors. In addition, activity reduces fatigue and is well tolerated in most medical conditions, and inactivity results in fatigue. These observations suggest that fatigue, even in clear-cut medical disorders with plausible mechanisms, is likely to be multifactorial.

Evaluation of Therapies

CFS treatment trials have been limited by changing case definition criteria and lack of adjusting for psychiatric illness, as well as other factors, and have therefore yielded somewhat disparate results. In addition, many agents have only been evaluated in a single study. Reid et al. (2000) have recently summarized the majority of notable English-language randomized, controlled trials that met clinical evidence criteria. Following a brief overview, the efficacy of each therapy was rated. It is important to

TABLE 5-2 Benefit Ratings for Chronic Fatigue Syndrome Treatment Interventions

Class of Treatment	Benefit Rating
Cognitive-behavioral therapy	Likely to be beneficial
Exercise	Likely to be beneficial
Antidepressants other than SSRIs	Unknown efficacy
Oral NADH	Unknown efficacy
Dietary supplements	Unknown efficacy
Corticosteroids	Unlikely to be beneficial
SSRIs	Unlikely to be beneficial
Immunotherapy	Likely to be ineffective
Antiviral therapy	Likely to be ineffective

note that for most modalities used in treating CFS, randomized controlled trials have been performed infrequently, if at all. In Table 5-2, therapies for CFS that have been tested in a clinical trial are reviewed and rated as being beneficial, likely to be beneficial, of unknown efficacy, unlikely to be beneficial, or likely to be ineffective or harmful. The detailed discussion of each therapy is based on Reid et al. (2000).

Cognitive-Behavioral Therapy (CBT)

Benefits. Two recent controlled trials found that approximately 70% of patients receiving several months of weekly CBT versus only 20% of the placebo group (who received visits or relaxation therapy) demonstrated functional improvement. Another more complicated study design involving an immunotherapy arm, and having a high dropout rate, did not show an effect of CBT.

Harms. The committee is aware of no major adverse effects of CBT, which is generally considered safe.

Comments. The use of CBT derives from the belief that CFS may be perpetuated by ineffective coping and unhelpful health beliefs and its success in other illnesses such as depression, chronic low back pain, and atypical chest pain. The effect may be dependent, to some degree, on the therapist. Of importance, improvements are sustained and continue over 6–12 months of follow-up. Although encouraging, the exact content and duration of the CBT require careful scrutiny. All RCTs conducted on CBT did not involve the same number of sessions or duration of follow-up.

CBT was associated with little benefit in earlier studies that used shorter durations and different composition of therapy than the recent trials conducted in the United Kingdom.

Exercise

Benefits. Two randomized controlled trials have compared exercise with and without fluoxetine to appointments or flexibility training. CFS patients appear to experience short- and long-term subjective and objective functional benefits from a graded aerobic exercise program.

Harms. Exercise is generally considered safe, and most patients can perform modest exercise without negative consequences. Exercise should be undertaken at a slow and gradual pace given that most patients are considerably deconditioned and may often experience severe postexertional symptoms.

Comments. In one trial CFS patients were included only if they did not have psychiatric disease and sleep disturbances. It remains to be confirmed whether the benefits of exercise can be generalized to those with comorbid affective and sleep difficulties.

Antidepressants

Benefits. Two controlled trials have shown that selective serotonin reuptake inhibitors (SSRIs) have not shown consistent and clinically important benefits such as improvements in fatigue or mood, even in those CFS patients with concurrent depression. A small randomized controlled trial of a Monoamine Oxidase Inhibitor (MAOI) failed to show a significant effect on symptoms.

Harms. SSRIs may cause a disruption in sleep, weight loss, sexual dysfunction, and agitation. In general, however, the side effects are fewer and less severe than with the tricyclic antidepressants. Because elimination of SSRIs involves hepatic metabolism, doses need to be carefully adjusted for patients with liver disease.

Comments. No randomized controlled trials of tricyclics, bupropion, or venlafaxine have been conducted. Because of their effects on sleep, SSRIs are frequently used in conjunction with tricyclic antidepressants. When used together, SSRIs can dramatically increase the serum concentrations of tricyclics. SSRIs are unlikely to be of benefit; other antidepressants are of unknown effectiveness.

Corticosteroids

Benefits. Three randomized controlled trials, including one cross-over design, have been conducted with mixed results. One used fludro-cortisone, and two used hydrocortisone. Improvements, when noted, were modest and not consistent across measurement modalities.

Harms. There is the potential for adrenal suppression even with low doses, as well as osteoporosis, weight gain, hypertension, diabetes, and many other therapy-related complications, especially with higher doses. With higher doses, 40% of CFS patients experienced adrenal suppression; even with lower doses, 10% had minor adverse effects.

Comments. Any benefit appears to be relatively transient.

Oral Nicotinamide Adenine Dinucleotide (NADH)

Benefits. Only a single short-term, randomized, cross-over trial has been reported. About a third of treated patients improved by 10%.

Harms. Minor gastrointestinal side effects such as loss of appetite and dyspepsia were noted but did not result in cessation of treatment.

Comments. Larger trials are needed to confirm or refute these early modest findings.

Dietary Supplements

Benefits. There have been several clinical trials of dietary supplements, including magnesium (one study) and evening primrose oil (two studies). Magnesium had a significant benefit. The evening primrose oil studies yielded mixed results.

Harms. No adverse effects were reported in the trials above; however, nutraceuticals have documented side effects that clinicians and patients should be aware of.

Comments. Subsequent studies failed to reproduce the intracellular magnesium deficiency reported to be associated with CFS. One study of evening primrose oil had a poorly designed placebo.

Immunotherapy

Benefits. A modest number of trials of immunotherapy have been com-

pleted; these include four of IgG, one of alpha interferon, one of dialysable leukocyte extract, and one of terfenadine. Two trials found IgG to be of benefit; the other studies of immunotherapy did not demonstrate a positive treatment effect.

Harms. The side effects in the IgG trials were considerable and included gastrointestinal problems, headaches, arthralgias, and worsening symptoms in up to 80% of participants. Neutropenia developed in 15% of the interferon-treated patients.

Comments. Different doses and dosing schedules make comparisons of IgG trials difficult. Of importance, outcomes in at least two of the IgG trials were physician, not patient, ratings.

Antiviral Therapy

Benefits. One double-blinded placebo-controlled trial has been performed of acyclovir, and it did not demonstrate a positive treatment effect. Of the 24 patients who completed the trial, similar numbers improved with acyclovir therapy and with placebo.

Harms. Three patients had acyclovir-induced nephrotoxicity and were withdrawn from the study. Each course of treatment consisted of intravenous placebo or acyclovir administered every eight hours for seven days followed by an oral regimen.

Comments. Neither acyclovir treatment nor clinical improvement correlated with alterations in laboratory findings or levels of circulating immune complexes or of leukocyte 2',5'-oligoadenylate synthetase. Subjective improvement correlated with various measures of mood.

Practice Issues

Because the cause of CFS is still uncertain and few well-designed trials have been conducted to evaluate treatment modalities, therapy is generally directed toward relieving symptoms and improving function. Initial therapy includes education. The physician offers supportive counseling, symptom acceptance, and patient teaching about the current understanding of CFS. Specifically, the physician provides reassurance that CFS carries no excessive mortality; symptoms often improve with time, although relapse may occur; and that even though there is no specific cure, several therapeutic options can provide benefit. It is necessary for the practitioner to acknowledge that the patient's suffering is real. Patients need to establish realistic goals for managing their lives, apply stress

reduction techniques, and restructure their activities to better accommodate their needs and condition.

The basic tenets of treatment are to establish a good patient-provider relationship in which the patient's illness is validated and reassurance is provided. Additionally, as described in Chapter 4, it is important to take a global approach to care and to develop a treatment plan that is approved by both the provider and the patient. Frequent visits are important, at least initially and no more than one to two medications at low doses should be used. Physical therapy and/or an exercise program, counseling, diet modification, and acupuncture form an important part of current practice approaches. Finally, current practice calls for the treatment of comorbid psychiatric disorders.

Some investigators have found that the longer a patient has been ill with CFS, the less likely he or she is to get better. Therefore, early diagnosis and treatment are important. In summary, current practice dictates that successful therapy for CFS is built on patient-physician respect and advocacy. Specific treatment regimens are individualized, reflecting the heterogeneity of the CFS population.

Recommendations

For Gulf War veterans who meet the criteria for diagnosis of CFS, the committee recommends:

- **use of cognitive-behavioral therapy and exercise therapies because they are likely to be beneficial;**
- **monitoring the results of studies of the efficacy and effectiveness of NADH, dietary supplements, corticosteroids, and antidepressants other than SSRIs;**
- **because immunotherapy and prolonged rest are unlikely to be beneficial, they should not be used as treatments;**
- **SSRIs are unlikely to be beneficial and are not recommended unless they are used as treatment for persons with concurrent major depression; and**
- **treatments effective for CFS should be evaluated in Gulf War veterans who meet the criteria for CFS.**

DEPRESSION

Introduction

Depression is one of the most common complaints among persons with psychological distress. Cases of depression are typically categorized into one of the mood disorders according to the *Diagnostic and Statistical*

TABLE 5-3 Diagnostic Criteria for Major Depression

The patient experiences five or more of the following symptoms for at least two weeks during the same two-week period and at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood
2. Diminished interest or pleasure in all, or almost all, activities most of the day
3. Weight loss or gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive guilt
8. Diminished ability to think or concentrate
9. Recurrent thoughts of death or suicidal thoughts

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not due to the direct effect of a substance (such as alcohol) or a medical condition (such as hypothyroidism).

Manual of Mental Disorders, Fourth Edition (American Psychiatric Association 2000). These include major depression, bipolar disorder depressed type, dysthymic disorder, and minor (or subsyndromal) depression. The diagnostic criteria for major depression are listed in Table 5-3.

Major depression may manifest itself in a single episode, may be recurrent, may be interposed with periods of elated mood (mania or hypomania), may be chronic, and may occur intermittently upon a base of a less severe yet chronic variant of depression, dysthymia. Virtually all studies of treatment efficacy of depression, however, especially of efficacy using randomized clinical trials, have concentrated on major depression (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000). This review, therefore, will focus on evidence for treatment efficacy of major depression.

Evaluation of Therapies

Studies of treatment efficacy of depression in bipolar disorder, depressed type, usually explore the same therapeutic entities as used in major depression. In addition, the actual number of cases of documented bipolar disorder among Gulf War veterans is limited. Though dysthymic disorder and minor depression are more common than major depression, studies of treatment effectiveness and especially efficacy are difficult for at least two reasons. First, the lower level of symptoms responsive to treatment create a “floor effect” that renders comparison of treatment and

control groups difficult. Second, most randomized clinical trials of the treatment of depression (whether major depression or a less severe type) exhibit significant placebo effects, further limiting the comparison of treatment and control groups.

Despite the paucity of randomized clinical trials of therapies for less severe forms of depression, the same treatments typically prescribed for major depression are prescribed frequently for the less severe forms. This is especially true for the new-generation antidepressant agents such as the SSRIs which are much more frequently prescribed for less severe forms of depression than for major depression. The likelihood of a person being prescribed an antidepressant medication for major depression, however, is greater than if a person experiences a less severe form of depression.

In other words, in reality depression presents as a spectrum disorder in terms of symptoms and their severity. Psychiatrists have arbitrarily clustered depression into a series of diagnoses for purposes of more reliable diagnosis and clinical trials. Though the more severe depressions are more likely to be caused by biological factors rooted in heredity, virtually all depressions are caused by a combination of biological, psychological, and social factors and for this reason combined therapies for these disorders are intuitive. In addition, at what point along this spectrum a biological therapy is indicated is difficult to establish. It is sufficient to note that the clinical trials of therapies for major depression have not only substantiated the value of certain therapies for major depression but have also led to these therapies being used frequently for less severe forms of depression, often with anecdotal evidence that the therapies are effective.

Beneficial Therapies

- Tricyclic and heterocyclic antidepressants
- MOAIs
- SSRIs and related compounds
- Cognitive-behavioral therapy
- Interpersonal psychotherapy
- Electroconvulsive therapy (in severe/treatment-resistant depression)
- Maintenance therapy to prevent recurrences

Likely to Be Beneficial

- St. John's Wort (in mild-to-moderate depression)
- Exercise
- Group psychotherapy (especially cognitive-behavioral therapy)
- Marital and family therapy

Unknown Effectiveness

- Antianxiety agents
- Sedative hypnotic agents
- Psychoanalysis and insight-oriented therapies (in less severe forms of depression)
- Other forms of psychotherapy

Interpersonal Psychotherapy (IPT)

Benefits. There is some evidence in RCTs that IPT in controlled studies as a single agent is effective in reducing depressive symptoms in the acute phase of nonmelancholic major depressive episodes of lesser severity. It is thought to be especially valuable in reducing dysfunction in vocational and social aspects of persons experiencing depressive episodes. IPT has also been demonstrated to be effective in reducing the likelihood of relapse.

Harms. There are no known harms associated with IPT or the other psychotherapies frequently prescribed for depression. Patients are informed that the therapy is voluntary, that they may drop out at any time, and that the therapy is time-limited (usually between 12 and 20 sessions). The short duration and educational emphasis virtually eliminate the occasional problems that arise with more insight-oriented psychotherapies, such as intense and potentially pathological transference reactions (feelings for the therapist by the patient that could border on the pathological).

Comment. IPT has become the most frequent psychotherapy for depression studied in randomized clinical trials. The therapy is basically an educational/behavioral therapy with an emphasis on improving interpersonal relations rather than evaluating cognitions associated with depression (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Cognitive Therapy

Benefits. There is evidence that cognitive therapy reduces depressive symptoms during the acute phase of less severe forms of depression. The prophylactic effect of cognitive therapy to reduce the likelihood and severity of relapses of major depression (regardless of severity) has not been firmly demonstrated, as with IPT (see below).

Harms. The committee is aware of no major adverse effects of cognitive therapy, which is generally considered safe.

Comment. Cognitive therapy, as developed by Aaron Beck, has become the model for the educationally oriented, time-limited therapies that for the most part have replaced insight-oriented psychotherapy as the therapy of choice for moderately severe to severe episodes of depression (almost always in conjunction with antidepressant medication in the more severe forms (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Behavioral Therapies

Benefits. Behavioral therapy has been reported to be effective in the acute treatment of patients with mild to moderately severe depression, especially when combined with pharmacotherapy. There is little evidence that behavioral therapies reduce the likelihood or severity of relapse of major depression. The long-term benefits of behavioral therapy are not well established.

Harms. See “Harms” under “Interpersonal Psychotherapy.”

Comments. Behavioral therapy for depression is rarely used in isolation for the treatment of major depression, yet elements of behavioral therapy are frequently combined with cognitive therapy, IPT, and marital/family therapy (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Goodle 2000).

Marital/Family Therapy

Benefits. Marital/family therapy, usually directed toward changing behaviors in the marriage or family, along with psychoeducational approaches to improving the marriage/family relationship may reduce depressive symptoms and the risk of relapse of major depression in patients with marital and family problems.

Harms. See “Harms” under “Interpersonal Psychotherapy.”

Comments. Marital/family therapy for major depression is usually not prescribed unless marital/family problems are paramount in the presentation of the disorder. Issues in the marriage and family are frequently addressed during IPT and cognitive-behavioral therapy, however. Family members and spouses will occasionally be asked to participate in IPT or cognitive-behavioral therapy sessions (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Group Therapy

Benefits. Group therapy may be of benefit for major depression, especially in the context of bereavement or common stressors such as chronic illness. Medication maintenance groups have also been demonstrated to be effective for some patients who are resistant to taking medications.

Harms. See “Harms” under “IPT.” In addition, group situations may occasionally be threatening to an individual because of comments made by other members of the group, especially if the group therapist is not sensitive to these problems. Individual meetings of group members with the therapist can be useful in decreasing the likelihood of this adverse effect.

Comments. Though evidence for the effectiveness of groups is much less than for individual IPT and cognitive-behavioral therapy, the economy of group sessions coupled with the unique potential benefit of peer support and advice renders groups a potentially valuable form of therapy for major depression (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Psychoanalysis and Insight-Oriented Psychotherapies

Benefits. There is no evidence for the effectiveness of psychoanalysis or insight-oriented psychotherapies in the treatment of major depression. However, some studies that have compared the effectiveness of more educationally oriented therapies and insight-oriented psychotherapies have typically not found a difference between the two forms of therapy.

Harms. See “Harms” under “IPT.” Problems with transference and difficulty terminating therapy due to attachment of the patient to the therapist are more likely to occur in psychoanalysis and insight-oriented psychotherapies than with IPT or cognitive therapies.

Comment. Psychoanalysis and insight-oriented psychotherapy, by their very nature, are not amenable to clinical trials for efficacy. In some loosely designed comparative studies, even over a short period of time, insight-oriented psychotherapy has been as beneficial as cognitive-behavioral therapy (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Tricyclic Antidepressants (TCAs)

Benefits. TCAs have been shown to be effective therapies in many clinical trials for the treatment of major depression. Imipramine, amitriptyline,

nortriptyline, doxepin, and desipramine are tricyclic antidepressant therapies that have been demonstrated to be effective and continue to be used today. During the first three weeks, 10% to 15% of patients drop out of RCTs. For those who continue through this initial period, the rate of response is as high as 60% to 70%. These rates apply to each of the drugs listed above. Though patients may show some improvement by the end of the first week, many will not respond fully until six to eight weeks. The rate of placebo response is high in major depression, often reaching 40%.

Harms. Sedation is a common side effect but may be welcomed given the insomnia secondary to depression. Anticholinergic side effects such as dry mouth, fatigue, weight gain, and constipation may occur in up to 20% of patients. In addition, orthostatic hypotension (common) and cardiac toxicity (rare) may occur. Caution should be exercised in prescribing TCAs to patients at risk for falls due to the potential for orthostatic hypotension. Due to their potential for lethality with overdose, TCAs should be prescribed in limited quantities to patients who may pose a suicide risk.

Comment. TCAs are much less frequently prescribed for depression today than the newer SSRIs and related compounds primarily due to fewer side effects with the newer agents. For major depression, the efficacy of the TCAs is at least equivalent to these newer agents. TCAs are much less expensive (as virtually all are now manufactured as generic compounds; Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Monoamine Oxidase Inhibitors (MAOIs)

Benefits. MAOIs, including phenelzine, isocarboxazid, selegiline, and tranylcypromine, have been demonstrated to be effective in RCTs for the treatment of major depression. These drugs have been shown to perhaps be of benefit for less severe depressions in open trials. The results are similar in RCTs for TCAs.

Harms. While the MAOIs are not anticholinergic, their side effects often resemble the tricyclic medications. A major concern with MAOIs is the risk of hypertensive crisis secondary to ingestion of tyramine. Patients taking MAOIs must adhere to a low-tyramine diet. Persons unable to follow the diet should not take MAOIs. Potentially serious drug-drug interactions can occur with SSRIs, sympathomimetic amines, decongestants, dextromethorphan, and meperidine. These drugs should not be used with MAOIs. In addition, at least two weeks is recommended between discontinuation of the MAO inhibitors and use of the anesthetics for electroconvulsive therapies.

Comment. Because of the dietary restrictions, MAO inhibitors are infrequently used to treat depression today. They should be considered, however, when other agents are not of benefit to the patient (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

SSRIs and Related Compounds

Benefits. All of the currently marketed SSRIs and related compounds have been demonstrated to be effective in RCTs. These include fluoxetine, sertraline, paroxetine, nefazodone, citalopram, mirtazapine, and venlafaxine. Most have been compared to imipramine for effectiveness and have proven equivalent effectiveness. When compared with one another, trials usually show equivalent effectiveness.

Harms. SSRIs may cause a disruption of sleep, loss of weight, sexual dysfunction, and agitation. In general, however, the side effects are fewer and less severe than with the TCAs. Because elimination of SSRIs involves hepatic metabolism, doses need to be carefully adjusted for patients with liver disease.

Comment. These agents are now considered first-line therapy for major depression in the outpatient setting. They are widely used. As most of these compounds are still under patent, the cost of therapy is not insignificant (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Benzodiazepines (BZPs)

Benefits. No RCTs have demonstrated the benefit of BZPs in treating major depression. These drugs may reduce the anxiety and agitation associated with depression.

Harms. Adverse effects of BZPs include sedation, fatigue, ataxia, slurred speech, memory impairment, and weakness. BZPs have a potential to induce drug dependency and should be avoided in patients with substance abuse disorders. Discontinuation of these drugs can be difficult. Abrupt discontinuation of BZPs can lead to seizures.

Comment. BZPs should never be used as first-line therapy for major depression (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

St. John's Wort (Hypericum Perforatum)

Benefits. St. John's Wort, an herb that can be purchased over the counter, has been demonstrated to be effective in RCTs in Europe and is currently under study in the United States. The drug is considered beneficial primarily for less severe depression.

Harms. The most common adverse effects of St. John's Wort are gastrointestinal symptoms, dizziness/confusion, tiredness, and sedation. Adverse effects of St. John's Wort have been sporadically reported in the literature to date from RCTs. The drug interacts with other medications, and the full extent of these interactions in terms of harm to the patient have yet to be documented completely.

Comment. More studies of this compound are needed before definitive effectiveness is clear. One additional problem is the variation in the preparations and doses marketed to the public. In addition, the potential interactions with other medication should not be overlooked despite the fact that the drug is available over the counter (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Maintenance Therapy

Benefits. RCTs have found that continuing antidepressant drug treatment for four to six months after recovery reduces the risk of relapse. RCTs also find that augmentation of pharmacotherapy with psychotherapy (especially interpersonal therapy) is superior to the use of medications alone in preventing relapse.

Harms. Adverse effects are similar to those reported for the acute treatments listed above.

Comment. Though further large trials are needed to demonstrate the effectiveness of various medications and the combination of psychotherapy and pharmacotherapy in preventing recurrence of depressive episodes, most psychiatrists now recommend continuation of pharmacotherapy for at least six to nine months following response to the medication. A history of multiple or particularly debilitating episodes of depression suggests longer-term maintenance prophylaxis with ongoing antidepressant therapy (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Electroconvulsive Therapy (ECT)

Benefits. ECT has been proven effective in treating severe and/or psychotic depression. The rate of response is similar to antidepressant medications, even among those persons who have previously been treated without success with antidepressants.

Harms. Memory impairment is the major adverse outcome from ECT. It is usually limited to the period of treatment, except in rare cases where longer-term damage may be detected.

Comment. ECT should only be administered to persons with severe (usually psychotic) depression or to persons known to have responded to it in the past. ECT should be administered by a professional with competency in using the treatment, and proper screening for cardiovascular status and possible cerebral masses must precede administration of ECT (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Exercise

Benefits. Exercise has been demonstrated to be effective in RCTs for mild-to-moderate depression.

Harms. Exercise is generally considered safe, and most patients can perform modest exercise without negative consequences. Exercise should be undertaken at a slow and gradual pace given that most patients are considerably deconditioned and may often experience severe postexertional symptoms.

Comment. The type of exercise prescribed and the motivation of the patient to maintain an exercise regime are critical aspects of the use of exercise in the treatment of depression (Depression Guideline Panel 1993; Work Group on Major Depressive Disorder 1993; Godlee 2000).

Summary of Therapies

RCTs have found that many regimens are effective treatment for mild-to-moderate depression, including a variety of medications, psychotherapy, and exercise. There is little evidence that one drug among the prescription drugs is superior to other drugs, and the selection of a drug is usually based on its side effect profile. Maintenance therapy has been demonstrated effective once a subject has recovered from the acute episode of depression.

Practice Issues

The treatment of depression in the offices of primary care physicians and psychiatrists today is generally dominated by the use of medications, specifically the newer and safer medications available during the past 14 years (specifically the SSRIs and related compounds). Relatively few patients receive formal sessions of psychotherapy, though most will receive support and brief counseling from their physicians.

Many persons experiencing depression may seek counseling from professionals other than physicians (and may see these counselors in parallel with physicians, the physicians managing the medications). Counselors range from clinical psychologists through social workers and marriage counselors to pastoral counselors. Pharmacotherapy is usually covered by most insurance plans, but coverage for psychotherapy from physicians is limited and from other counselors even more limited. Considerable evidence has emerged over recent years that depression is a major public health problem (whether that depression is the only problem experienced by the patient or it coexists with other conditions such as a debilitating physical illness). In fact, some have suggested that it will become the most important chronic public health problem worldwide over the next generation.

We have concentrated in this report on major depression for there are very few clinical trials that focus on other depressive diagnoses. Nevertheless, many depressive symptoms of clinical significance that present to practicing physicians do not meet the criteria for major depression as noted earlier in this chapter. These depressive symptoms have been variously categorized as subsyndromal depression, minor depression, and so on. Both psychotherapy and antidepressant medications are frequently prescribed for these patients, most often by primary care physicians.

Though most physicians are more aware of depression today than they were a few years ago, the treatment of depression remains haphazard and evidence exists that depression is untreated or undertreated in most circumstances. Contributing to undertreatment are the discontinuance of medications prematurely or underdosing of medications. In addition, the emerging evidence discussed above for an added benefit from medications being combined with psychotherapy to prevent recurrences of depression has scarcely impacted the general practice of treating depression, in part due to lack of availability of CBT.

The committee recognizes that while other therapies have been demonstrated efficacious, major depression is vastly underrecognized and undertreated in medical care settings.

Recommendation

The committee recommends a combination of antidepressant medication and psychotherapy (either cognitive-behavioral therapy or interpersonal therapy) as the core therapy for major depression.

Uniform implementation of these therapies would vastly improve the treatment of Gulf War veterans diagnosed with major depression (Work Group on Major Depressive Disorder 1993). Nevertheless, Gulf War veterans who experience comorbid major depression and other conditions reviewed in this report clearly may experience improvement in depressive symptoms from therapies such as exercise. Still other Gulf War veterans who experience significant marital and family problems may benefit from marriage and family therapy.

FIBROMYALGIA

Introduction

Fibromyalgia is a disorder of widespread pain, tenderness, fatigue, sleep disturbance, and psychological distress affecting about 2% of the general population (Wolfe et al. 1995). It is up to four times more common in women than in men. Many patients with fibromyalgia have concomitant clinical features that include irritable bowel syndrome, paresthesias, chronic headaches, irritable bladder (and/or interstitial cystitis), somatization, and social dysfunction. Emphasizing a sizable overlap with other widespread pain disorders, 20 to 70% of fibromyalgia patients meet classification criteria for chronic fatigue syndrome, although myalgias are significantly more common among those with fibromyalgia (Buchwald and Garrity 1994; Aaron et al. 2000; Bradley et al. 2000).

Difficulties with the classification and diagnosis of fibromyalgia have led to development of a case definition created by a consensus panel of the American College of Rheumatology in 1990 (Wolfe et al. 1990) (see Table 5-4).

Fibromyalgia patients can sometimes be differentiated from patients with other pain disorders by allodynia, a state in which non-noxious stimuli applied to the skin cause pain (IASP 1979), and by hyperalgesia, whereby noxious stimuli result in accentuated painful responses in comparison to the general populace.

Since the major feature distinguishing fibromyalgia from other disorders is tenderness (or heightened sensitivity), this must be carefully assessed on the physical examination. Two methods for measuring tenderness are digital palpation and dolorimetry. The amount of force used in palpation is important because too large a force will elicit pain in persons without fibromyalgia, whereas too little force may lead to underdiagnosis

TABLE 5-4 Case Definition of Fibromyalgia

There must be a history of widespread pain. Pain is considered widespread when all of the following are present:

- Pain in the left side of the body,
- Pain in the right side of the body,
- Pain above the waist, and
- Pain below the waist.

In addition, axial skeleton pain (cervical spine or anterior chest or thoracic spine or low back) must be present. Shoulder and buttock pain is considered pain for each involved side. "Low back" pain is considered lower segment pain.

There is pain on digital palpation in 11 of the 18 following sites of tender points:

1. Occiput: bilateral, at the suboccipital muscle insertions.
2. Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5–C7.
3. Trapezius: bilateral, at the midpoint of the upper border.
4. Supraspinatus: bilateral, at origins above the scapular spine near the medial border.
5. Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
6. Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.
7. Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
8. Greater trochanter: bilateral, posterior to the trochanteric prominence.
9. Knee: bilateral, at the medial fat pad proximal to the joint line.

of fibromyalgia. Although the validity of palpation has been questioned, studies have shown that trained examiners can reach high levels of agreement in the identification of patients with and without fibromyalgia using tender point examination (Wolfe et al. 1992; Okifuji et al. 1997).

Dolorimetry is a more formalized technique to assess tender points utilizing a rubber endplate with a spring-loaded force gauge. Although dolorimetry may be useful in clinical trials as a method to assess exact pain threshold, digital palpation and manual palpation are sufficiently accurate diagnostic approaches for use in the routine clinical setting (Wolfe et al. 1994).

In addition to widespread pain and tender points, there are other signs and symptoms common to patients with fibromyalgia. In a 1990 ACR study of criteria for the classification of fibromyalgia, 81% of patients complained of fatigue and 74% complained of sleep disturbance. Indeed, nonrestorative sleep is traditionally considered one of the key features of fibromyalgia (Moldofsky et al. 1975). Although less than half of patients with fibromyalgia report symptoms of depression (Wolfe et al. 1994), psychological illness is an important cause of comorbidity in

fibromyalgia. Although psychological stress is an important precipitator of fibromyalgia (Dailey et al. 1997; Uveges et al. 1990), fibromyalgia is generally not considered a psychiatric illness.

Family members of fibromyalgia patients have a higher-than-expected rate of fibromyalgia. Preliminary results suggest possible genetic linkages (Offenbaecher et al. 1999; Yunus 1999). In addition, trauma, either physical or psychological, may precipitate fibromyalgia (Boisset-Piolo et al. 1994; Taylor et al. 1994).

Many investigators now agree that aberrant central nervous system pain-receptive mechanisms are likely partially involved in the pathogenesis of fibromyalgia. A central nervous system hypothesis would explain not only the high incidence of nonmusculoskeletal symptoms in a wide variety of organs and tissues, but also the affective disorders and neurological features that occur in this condition (Clauw 1995).

Evaluation of Therapies

Limited in part by variable case definition criteria, fibromyalgia treatment studies with both pharmacological and nonpharmacological agents have yielded disparate results. Leventhal (1999) recently summarized the majority of notable English-language investigations. Following an overview of the available treatment options, a compendium of fibromyalgia studies is presented, organized according to the quality of each study. The formatting and nomenclature used are from Clinical Evidence (Enkin et al. 1998). Except as otherwise noted, systematic reviews have not been performed for the vast majority of treatment approaches reviewed. In a review of these studies, the focus is on RCTs. The ability to attribute benefits to any specific treatment is attenuated by a 15 to 30% placebo response in fibromyalgia clinical trials. This finding substantially attenuates enthusiasm for studies not controlled, randomized, and double blinded. However, for therapeutic options where RCTs have been only sparingly performed or are of limited feasibility (e.g., cognitive therapies), studies of lesser methodological rigor are briefly reviewed.

Beneficial

- No therapy has been well documented to have clear benefits.

Likely to Be Beneficial

- Multidisciplinary rehabilitation combining education with physical training
 - Tricyclic antidepressants (at least in the short term)
 - Acupuncture

Unknown Efficacy

The majority of agents and approaches reviewed have been insufficiently investigated, and their true effectiveness is thus unknown. These include other antidepressants (nontricyclic antidepressants), benzodiazepines, local anesthetic injections, tramadol, malic acid/magnesium combination, growth hormone, S-adenosylmethionine, 5-hydroxytryptophan (HT), 5-HT₃ antagonists, exercise (as single therapy), hypnotherapy, and biofeedback.

While cognitive and behavioral therapies appear efficacious in chronic fatigue syndrome, the literature does not support clear efficacy in fibromyalgia.

Unlikely to Be Beneficial

- Nonsteroidal antiinflammatory agents

Likely to Be Ineffective or Harmful

- Opioid analgesics
- Glucocorticoids

TCA and Other Amine Salts

Benefits. Seven RCTs were identified that contained a placebo arm. Six examined *amitriptyline* (Carette et al. 1986; Goldenberg et al. 1986; Scudds et al. 1989; Jaescheke et al. 1991; Carette et al. 1994; Goldenberg et al. 1996) and two *cyclobenzaprine* (Bennett 1988; Carette et al. 1994). All showed short-term (4- to 12-week) improvement of outcomes such as pain scores, sleep, and tender points in 20 to 30% of subjects. However, longer-term (6-month) benefits are not as well substantiated (Carette et al. 1994). There is evidence that long-term use of tricyclic agents is associated with suppression of HPA axis function, which might explain their loss of efficacy over time (Michelson et al. 1997). No definite differences in efficacy between *amitriptyline* and *cyclobenzaprine* have been demonstrated (Carette et al. 1994).

Harms. Anticholinergic side effects such as dry mouth, fatigue, weight gain, constipation, and orthostatic hypotension may occur in up to 20% of patients (Wolfe et al. 1990). There is the potential for cardiac toxicity in older patients and those with underlying heart disease or with long-term use. Caution should be exercised in prescribing TCAs to patients at risk for falls due to the potential for orthostatic hypotension. Due to their

potential for lethality with overdose, TCAs should be prescribed in limited quantities in patients who may pose a suicide risk.

Comments. Tricyclic antidepressants are the most commonly used prescription therapy for fibromyalgia. Most patients enrolled in studies of these medications were from outpatient rheumatology clinics and may not be representative of patients with fibromyalgia in the general community. Tachyphylaxis may limit long-term use.

SSRIs and Other Nontricyclic Antidepressants

Benefits. Results of open-label and controlled clinical trials of *fluoxetine* have been equivocal at best (Geller et al. 1989; Finestone and Ober 1990; Cortet et al. 1992; Wolfe et al. 1994; Goldenberg et al. 1996). Although depression and anxiety scales improved slightly but insignificantly in one fluoxetine study, other parameters, including tender point scores, did not show a favorable response (Wolfe et al. 1994). In a placebo-controlled RCT there was no effect on the number of tender points (Cortet et al. 1992). *Venlafaxine*, a potent inhibitor of both norepinephrine and serotonin, improved symptoms in one open-label trial (Dwight et al. 1998).

Harms. SSRIs may cause a disruption in sleep, loss of weight, sexual dysfunction, and agitation. In general, however, the side effects are fewer and less severe than with the TCAs. A disruption of sleep by SSRIs has promoted their use in combination with low-dose TCAs. However, this combination must be used carefully due to heightened toxicity.

Comments. These agents seem most appropriate for the 20 to 50% of fibromyalgia patients with concomitant clinical depression (Aaron et al. 1996).

Benzodiazepines

Benefits. Only one RCT was identified of a benzodiazepine currently approved in the United States. An eight-week study demonstrated a 30% improvement in tender point index among patients randomized to *alprazolam* when given in combination with ibuprofen (Russell et al. 1991).

Harms. The adverse consequences of therapy with the benzodiazepines include dependence, withdrawal seizures, excessive daytime somnolence, and risk of falls and automobile accidents.

Steroidal and Nonsteroidal Antiinflammatory Drugs

Benefits. No significant differences were found between ibuprofen and placebo in one study (Yunus et al. 1989). A cross-over trial of 20 patients showed no improvements with *prednisone* (Clark et al. 1985). As noted above, combinations of *ibuprofen* with *alprazolam* (Russell et al. 1991) and *naproxen* in combination with *amitriptyline* (Goldenberg et al. 1986) appeared slightly superior to either drug alone.

Harms. Nonsteroidal antiinflammatory agents (NSAIDs) can cause gastrointestinal ulceration and bleeding, platelet dysfunction, hypertension, fluid retention, and, rarely, allergic reactions. Newer cyclooxygenase-2 (COX-2) selective NSAIDs have a significantly lower gastrointestinal and bleeding toxicity profile but maintain the other NSAID risks. Glucocorticoid toxicity is myriad and includes osteoporosis, weight gain, hypertension, blood sugar elevations, and eye problems.

Comments. There are no data to support a benefit of glucocorticoids in fibromyalgia.

Tramadol

Benefits. One small cross-over trial comparing intravenous *tramadol* against placebo yielded nearly identical reductions in spontaneous pain and no significant differences in tender point counts (Biasi et al. 1998). A preliminary report of a double-blind RCT showed that fewer tramadol recipients withdrew due to residual pain than placebo recipients (Russell et al. 1997). Tramadol was as effective as acetaminophen with codeine on total pain relief score among elderly patients, some of whom had fibromyalgia (Rauck et al. 1994).

Harms. Nausea and dizziness may limit even short-term use. Seizures have been reported in patients with excessive dose or altered drug elimination.

Comments. Limited numbers of patients treated with this agent, poorly generalizable study populations, and symptomatic side effects limit enthusiasm for routine use of tramadol in patients with mild-to-moderate symptoms.

Other Analgesics

Benefits. Studies have not shown a definite benefit of local injections with *lidocaine*, in contrast to its putative benefits in patients with regional

myofascial pain (Hong and Hsueh 1996). There are no RCT data on the use of opioids for fibromyalgia.

Harms. *Lidocaine* injections at standard dosage are unlikely to produce toxicity other than local injection site pain. *Opioids* have potential for dependence, tolerance, dulled sensorium, and constipation.

Comments. A placebo effect of “needling” may explain the benefits believed to occur with local anesthetics. On the other hand, needling in general may release endorphins as indicated by reversibility of beneficial effects with naloxone (Fine et al. 1988).

Novel Pharmacological Therapies

Benefits. A tablet containing *malic acid and magnesium* showed no clear treatment effect in a low-dose blinded trial (Russell et al. 1995). Reductions in severity of pain/tenderness measures were reported, however, in an open-label extension to this trial. Fifty women with fibromyalgia and low insulin-like growth factor 1 levels had significant improvements on the fibromyalgia impact questionnaire and tender point score in comparison to placebo when given *growth hormone (GH)* (Bennett et al. 1998). The dietary supplement *S-adenosylmethionine* appeared to improve symptoms and/or signs in two RCTs (Tavoni et al. 1987; Jacobsen et al. 1991) but not in a third (Volkman et al. 1997). Another dietary supplement, *5-hydroxytryptophan (HT)*, significantly improved clinical parameters in a double-blind RCT (Caruso et al. 1990). *Calcitonin* given subcutaneously in a very small double-blind RCT did not result in an appreciable benefit (Bessette et al. 1998). Blockade of the serotonin receptor, 5-HT₃, by the commonly used anti-nausea agent *ondansetron* decreased pain significantly better than paracetamol in a cross-over trial (Hrycaj et al. 1996). The related compound tropisetron also decreased tender points in an uncontrolled design (Samborski et al. 1996).

Harms. *Malic acid and magnesium* are both relatively nontoxic at the modest doses used in the study. Diarrhea and nausea can result with higher doses or more prolonged usage. Carpal tunnel syndrome may result from GH administration. The safety of growth hormone in patients without deficiency is unknown. Gastric pain and diarrhea can be caused by *5-HT*. Except for occasional rhinitis, *calcitonin* is generally well tolerated when used nasally. In contrast, the subcutaneous route may more commonly lead to flushing and diarrhea. *Ondansetron* can cause constipation.

Comments. The frequency of GH deficiency in fibromyalgia is unknown; thus the utility of GH supplementation is unknown based on the single

reported investigation. It should be noted that the high cost of GH may make its use as a therapy problematic.

Exercise

Benefits. Compared to a placebo group that continued with usual physical activity level, a 60-minute exercise program twice a week for 20 weeks did not improve pain, coping, or fatigue. However, dynamic work endurance improved significantly (Mengshoel et al. 1992). A Danish study comparing two types of exercise programs to the applications of hot packs detected no differences in pain, fatigue, or other outcomes at 12 weeks in any of the three groups (Norregaard et al. 1997). A cardiovascular exercise program did not show significant improvement in fibromyalgia symptoms or disturbed sleep compared to a flexibility program. However, patient and physician global assessments improved significantly more among those in the cardiovascular exercise group (McCain et al. 1988). Compared to sedentary controls, aerobic walking also had inconclusive effects on pain questionnaire and health-related quality-of-life instruments (Nichols and Glenn 1994).

Harms. Exercise is generally considered safe, and most patients can perform modest exercise without negative consequences. Exercise should be undertaken at a slow and gradual pace given that most patients are considerably deconditioned and may often experience severe postexertional symptoms.

Comments. Although symptoms variably improved in some studies, the results do not show consistent improvement in a particular symptom complex with exercise alone.

Biofeedback

Benefits. After a larger, partially favorable experience in an uncontrolled study, a very small RCT suggested that EMG biofeedback significantly improved most variables, compared with sham biofeedback (Ferraccioli et al. 1987). Another open-label study also reported reduction in pain with this modality (Sarnoch et al. 1997). The addition of exercise to biofeedback and relaxation training may result in longer-lasting improvements than with either alone (Buckelew et al. 1998).

Hypnotherapy

Benefits. Only one study was identified. A decrease in fatigue, improved sleep, and less pain were found in those receiving hypnotherapy com-

pared with a control group assigned to physical therapy. Tender point counts did not differ significantly, however (Haanen et al. 1991).

Acupuncture

Benefits. Compared to a sham procedure, electro-acupuncture significantly improved seven out of eight fibromyalgia outcome measures in an RCT of 70 subjects (Deluze et al. 1992). An older, open-label investigation of an average of slightly over one and a half years showed that 60% of patients had subjective improvements and nearly 70% were taking less medicine at the end of the follow-up period (Waylonis 1977).

Harms. Harms included needle insertion pain and the risk for bloodborne infections if appropriate aseptic technique is not practiced.

Comments. A National Institutes of Health consensus panel has concluded that acupuncture may have benefits in a comprehensive fibromyalgia program (Conference 1998).

CBT and Multidisciplinary Approaches

Benefits. A Cochrane review of multidisciplinary rehabilitation identified only seven studies that met inclusion criteria. Four of these RCTs, graded as low quality, suggested no quantifiable benefits. However, behavioral treatment and stress management and education combined with physical training appeared to show some positive benefits in the long term (Karjalainen et al. 2000). Although a Cochrane review examining CBT for adults with the related (and often overlapping) disorder chronic fatigue syndrome found CBT superior to other treatment approaches (Price and Couper 2000), nearly all CBT studies in fibromyalgia have been uncontrolled or quasi-experimental.

Only three CBT studies in the fibromyalgia literature have appropriate placebo controls or alternative treatments. None of these studies showed clear benefits of behavioral approaches in fibromyalgia (Nicassio et al. 1997; Vlaeyen et al. 1996; Buckelew et al. 1998). Both the Nicassio et al. and the Valeyen et al. studies found that CBT was no more effective than attention placebo. The Buckelew et al. study compared CBT to exercise alone, a combination of CBT and exercise, and to an attention placebo. It was found that all three active treatments produced lower tender point counts than did the attention placebo. However, this effect was likely artifactual since the tender point counts increased in the attention placebo group. There were no other between-group differences in reports of pain or on objective measures of pain behavior.

The follow-up analysis indicated that change in self-efficacy was significantly correlated with improvement in self-report of pain and the tender point index. No treatment was superior in increasing self-efficacy. Consistent changes were observed in the expected outcome variables in one CBT program (Nielson et al. 1992). At 30 months follow-up, 22 subjects of the original group of 25 had changes in the 10 target variables all in the direction of improvements (White and Nielson 1996). The committee is aware of no major adverse effects of CBT, which is generally considered safe.

Multimodal approaches involving education and both physical and behavioral therapy have yielded positive results in several studies. Group treatment (formal lectures, stress reduction, exercise training, and spousal support) showed considerable longitudinal improvement in tender points and on the fibromyalgia impact questionnaire (Bennett et al. 1996). A comparison of integrated group therapy and group relaxation training showed significantly more long-term benefit than a control program consisting of only autogenic training (Keel et al. 1998). In another open-label study of a multidisciplinary program involving cognitive and exercise therapy, somatic pain intensity was significantly reduced compared to baseline (Mengshoel et al. 1995). Group education plus group discussion appeared more successful than a cognitive education intervention alone in another study (Vlaeyen et al. 1996).

Practice Issues

Fibromyalgia treatment studies have been conducted mostly in women and the extrapolation of these findings to the predominantly male Gulf War veterans is unproven. The generally low costs of tricyclic antidepressants and the relatively low toxicity profile of these agents in otherwise healthy individuals have made these drugs of first choice for treating fibromyalgia in many general-practice settings. The use of non-pharmacological approaches, while meriting further study, is limited by availability and cost concerns.

Recommendation

The committee recommends that:

- **Gulf War veterans who meet criteria for fibromyalgia *not* receive treatment with opioid analgesics or glucocorticoids and**
- **In the absence of therapies of generally proven benefit, results of treatment studies of physical training, tricyclic antidepressants, and acupuncture should be further monitored in Gulf War veterans who meet the criteria for fibromyalgia.**

HEADACHE

Introduction

Migraine headache is conservatively estimated to affect about 10% of the population. Other headache types are more prevalent. However, only a small subset of affected individuals seek medical attention for evaluation and treatment. Among these, the majority have primary headaches, with only a few having headaches secondary to structural, inflammatory, or other pathological intracranial processes. Primary headaches can, in turn, be divided into migraine and nonmigraine headaches. Consensus criteria for the diagnosis of migraine are listed below. Headaches that are not of acute onset, that meet criteria 1.1.E and 1.2.C below (i.e., are not suggestive of intracranial disease) but do not meet the other criteria, can be considered primary nonmigrainous headaches, and the same therapeutic and diagnostic approach is applicable. Table 5-5 presents the International Headache Society's diagnostic criteria for migraine headache without and with aura.

Evaluation and treatment of patients with primary headache were recently addressed by the U.S. Headache Consortium, at the request of the American Academy of Neurology. Material in the following sections related to headache is based on the work of the consortium, a complete copy of which can be found online at <http://www.aan.com>.^{*} The consortium developed practice guidelines for use in the primary practice setting for the management of primary headaches, particularly migraine. Explicitly excluded were new-onset headaches or headaches secondary to identifiable pathology (mass lesions, infections, intracerebral bleeds, etc). No other guidelines are available specifically addressing nonmigrainous primary headaches (e.g., tension headaches), but there is sufficient overlap both in syndromes and in management that these guidelines provide an excellent approach for both types of primary headaches.

All available studies were reviewed by the U.S. Headache Consortium, which graded the aggregated evidence, including the number of studies and the consistency of their findings, thereby implicitly acknowledging that trials of the same treatment sometimes yield conflicting results. Consortium recommendations were graded according to the following scale, adapted from an Agency for Healthcare Research and Quality Research Guideline:

^{*}Neither the U.S. Headache Consortium nor the American Academy of Neurology is responsible for the text abstraction nor were they requested to verify the text.

TABLE 5-5 Diagnostic Criteria for Migraine Headache Without and With Aura

1.1 Migraine without aura:

- A. At least five attacks fulfilling B–D
- B. Headache attacks lasting 4–72 hours^a (untreated or unsuccessfully treated).
- C. Headache has at least two of the following characteristics:
 - 1. Unilateral location
 - 2. Pulsating quality
 - 3. Moderate or severe intensity (inhibits or prohibits daily activities)
 - 4. Aggravation by walking, stairs, or similar routine physical activity
- D. During headache at least one of the following:
 - 1. Nausea and/or vomiting
 - 2. Photophobia and phonophobia
- E. At least one of the following:
 - 1. History, physical, and neurological examinations do not suggest headaches secondary to identifiable pathology (e.g., mass lesions, infections, intracerebral bleeds, etc.)
 - 2. History, physical, and/or neurological examinations do suggest such a disorder, but it is ruled out by appropriate investigations
 - 3. Such a disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

1.2 Migraine with aura:

- A. At least two attacks fulfilling B
 - B. At least three of the following four characteristics:
 - 1. One or more fully reversible aura symptoms^b indicating focal cerebral cortical and/or brain stem dysfunction
 - 2. At least one aura symptom develops gradually over more than four minutes or two or more symptoms occur in succession
 - 3. No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased
 - 4. Headache follows aura with a free interval of less than 60 minutes (it may also begin before or simultaneously with the aura)
 - C. At least one of the following:
 - 1. History, physical, and/or neurological examination do not suggest headaches secondary to identifiable pathology (see 1.1.E.1)
 - 2. History, physical, and/or neurological examination do suggest such a disorder, but it is ruled out by appropriate investigations
 - 3. Such a disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder
-

^aIn children under age 15, attacks may last 2–48 hours. If the patient falls asleep and wakes up without migraine, duration of attack is until time of awakening.

^bAura symptoms: A preheadache prodrome, most commonly consisting of perceived flashing lights or other evolving neurological symptoms.

SOURCE: *IHS Members Handbook 1997/1998*, pp. 54–56. Reprinted with permission of the International Headache Society.

A. Multiple well-designed randomized clinical trials, directly relevant to the treatment under consideration yielded a consistent pattern of findings.

B. Some evidence from randomized clinical trials supported use of the treatment, but the scientific support was not optimal. For instance, few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant. An example of the last point would be the case where trials were conducted using a study group that differed from the target group.

C. The U.S. Headache Consortium achieved consensus on the therapy in the absence of relevant randomized controlled trials.

A key factor in determining appropriate treatment is to identify whether a patient's headaches are primary or secondary, a decision that may require neuroimaging or other evaluation. An abnormal neurological examination increases the likelihood of finding significant intracranial pathology (e.g., brain tumor, arteriovenous malformation, hydrocephalus) on neuroimaging. The absence of any abnormalities on neurological examination reduces the odds of finding a significant abnormality on imaging. Therefore, neuroimaging should be considered in patients with nonacute headache and an unexplained abnormal finding on the neurological examination (Grade B).

Headache worsened by Valsalva maneuver, headache causing awakening from sleep, new headache in the older population, or progressively worsening headache may indicate a higher likelihood of significant intracranial pathology, as reported in several small studies. One study reported that a history of headache worsening with Valsalva maneuver significantly increased the odds of finding a significant intracranial abnormality on neuroimaging. In general, however, the absence of signs and symptoms is less reliable and informative than their presence. The consortium concluded that evidence is insufficient to make specific recommendations regarding neuroimaging in the presence or absence of neurological symptoms (Grade C).

The U.S. Headache Consortium did identify three consensus-based (not evidence-based) general principles of when to perform additional testing:

1. Testing should be avoided if it will not lead to a change in management.
2. Testing is not necessary if the individual is not significantly more likely than anyone else in the general population to have a significant abnormality.
3. Testing that normally may not be necessary as a population policy may make sense at an individual level, resources notwithstanding. For

example, exceptions can be considered for patients who are disabled by their fear of serious pathology or for whom the provider is suspicious even in the absence of known predictors of abnormalities on neuroimaging studies (red flags).

Migraine and Normal Neurological Examination

Meta-analysis of studies of patients with migraine and a normal neurological examination found a rate of significant intracranial lesions of 0.18% (2/1000; previously reported rates of finding intracranial lesions with CT and MRI ranged from 0.3 to 0.4%). Neuroimaging is thus unlikely to reveal an abnormality on MRI or CT scanning in patients with migraine and a normal neurological examination.

Therefore, neuroimaging is not usually warranted for patients with migraine and normal neurological examination (Grade B). For patients with atypical headache features or patients who do not fulfill the strict definition of migraine (or have some additional risk factor), a lower threshold for neuroimaging may be applied (Grade C).

Tension-Type Headache and Normal Neurological Examination

In two studies of imaging in patients with tension-type headache (one study specified chronic tension-type headache and normal neurological examinations), no significant lesions were demonstrated. Therefore, data were deemed insufficient to make an evidence-based recommendation regarding the use of neuroimaging for tension-type headache (Grade C).

Based on the limited data in the studies reviewed, MRI appears to be more sensitive in finding white matter lesions and developmental venous anomalies than CT, a result that could be expected based upon the characteristics of the two technologies. The greater resolution and discrimination of MRI, however, appear to be of little clinical importance in the evaluation of patients with nonacute headache. Data were lacking comparing enhanced with unenhanced CT scans. Therefore, data were deemed insufficient to make any evidence-based recommendations regarding the relative sensitivity of MRI compared with CT in the evaluation of migraine or other nonacute headache (Grade C).

Evaluation of Therapies

Consortium evaluations of treatments are presented in Tables 5-6, 5-7, and 5-8. These evaluations are based primarily on findings in patients referred to headache programs. In practice, many patients will respond to simple analgesics such as acetaminophen or non-steroidal anti-inflammatories, which should generally be tried first. Patients who fail to

TABLE 5-6 Acute Pharmacological Management

Drug Class	Quality of Evidence (A, B, C)	Benefit/Clinical Effect	Harms
<i>Anti-emetics</i>			
(e.g., prochlorperazine)	C	+	Occasional to frequent
IM (e.g., chlorpromazine)	C	++	Infrequent to occasional
IV (e.g., metoclopramide)	B	++	Infrequent to occasional
IV, IM, PR. Prochlorperazine	B	++	Occasional to frequent
Serotonin receptor (5-HT ₃) antagonists	B	0	Occasional
(as adjunct for nausea)	C	+	Occasional
Butalbital-containing agents	B	+++	Occasional
<i>Ergot alkaloids</i>			
Ergotamine PO, PR	B	+	Frequent
DHE IV	B	+++	Frequent
DHE IM, SQ	B	+++	Occasional
DHE IV+antiemetics IV	B	+++	Frequent
DHE nasal spray	A	+++	Occasional
Acetaminophen	B	+/-	Infrequent
NSAIDS PO	A	++	Occasional
Ketorolac IM	B	++	Infrequent
<i>Opiates</i>			
Butorphanol nasal spray	A	+++	Frequent
Oral (e.g., acetaminophen and codeine)	A	++	Occasional
IM/IV	B	++	Frequent
<i>Triptans (serotonin 1B/1D receptor agonists) PO</i>			
Nasal, SQ	A	+++	Occasional
Isometheptene	B	+	Occasional
Corticosteroids	C	++	Infrequent

The clinical effect of each drug is indicated on a five-point scale: 0, no evidence of benefit, +/-, equivocal evidence; +, somewhat beneficial; ++, beneficial; +++, highly beneficial.

SOURCE: McCrory et al. 2000.

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TABLE 5-7 Prophylactic Pharmacologic Management I

Drug Class	Quality of Evidence (A, B, C)	Benefit/Clinical Effect	Harms
Alpha 2 agonists	B	+/-	Frequent
Anticonvulsants			
Carbamazepine	B	0	Occasional to frequent
Valproate	A	+++	Occasional to frequent
Gabapentin	B	++	Occasional to frequent
Antidepressants			
Amitriptyline	A	+++	Frequent
Nortriptyline	C	+++	Frequent
Doxepin, imipramine	C	+	Frequent
SSRIs	B, C (agent specific)	+	Occasional
Beta blockers			
Propranolol	A	+++	Infrequent
Atenolol, metoprolol, nadolol, timolol	B	+++	Infrequent
Calcium channel blockers	B, C (agent specific)	+/-	Occasional
NSAIDs			
Naproxen	B	++	Infrequent
Others	B	+	Infrequent

The clinical effect of each drug is indicated on a five-point scale: 0, no evidence of benefit; +/-, equivocal evidence; +, somewhat beneficial; ++, beneficial; +++, highly beneficial.

SOURCE: Ramadan et al. 2000.

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respond to these or simple dietary or environmental changes can be treated as indicated. In general, primary headaches can be expected to affect individuals for many years, and this must be taken into consideration in recommending treatment modalities that have potential side effects. Side effects that may be tolerable for a few days or weeks may become far less so if they will be present for years, during pregnancy, or during times when no cognitive compromise is tolerable. It is incumbent on the physician to explore these issues with the patient and decide jointly on the best long-term approach.

TABLE 5-8 Prophylactic Pharmacological Management II

Group 1	Group 2	Group 3	Group 4	Group 5
Medium-to-high efficacy, good strength of evidence, and a range of severity (mild to moderate) and frequency (infrequent to frequent) of side effects	Lower efficacy than those listed in first column, or limited strength of evidence, and mild-to-moderate side effects	Clinically efficacious based on consensus and clinical experience, but no scientific evidence of efficacy	Medium-to-high efficacy, good strength of evidence, but with side effect concerns	Evidence indicating no efficacy over placebo
Amitriptyline Divalproex sodium Lisuride* Propranolol Timolol	Aspirin Atenolol Cyclandelate* Fenoprofen Feverfew Flurbiprofen Fluoxetine(race Mic)	A. Mild-to-moderate side effects Cyproheptadine Bupropion Diltiazem Doxepin Fluvoxamine Ibuprofen	Methysergide Flunarizine* Pizotifen* TR-DHE*	Acetutolol Alprenolol* Carbamazepine Clomipramine Clonazepam Clonidine DEK* Femoxetine*

Gabapentin	Imipramine	Flumetone*
Guanfacine	Mirtazepine	Indomethacin
Indobufen*	Nortriptyline	Ipiazochrome*
Ketoprofen	Paroxetine	Lamotrigine
Lornoxicam*	Protriptyline	Miaserin*
Magnesium	Sertraline	Nabumetone
Mefenamic acid	Tiagabine	Nicardipine
Metoprolol	Topiramate	Nifedipine
Nadolol	Trazodone	Oxprenolol*
Naproxen	Venlafaxine	Oxitriptan*
Naproxen sodium	B. (Side effect concerns)	Pindolol
Nimodipine	Methylergonovine (methylethergometrine)	Tropisetron*
Tolfenamic acid*	Phenelzine	Vigabatrin*
Verapamil		
Vitamin B-2		

*Not available in United States.
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Acute Pharmacotherapy

Benefits. As summarized in Table 5-6, many classes of agents have been shown to be effective in the acute management of headaches. Selection of specific agents requires a careful consideration of demonstrated efficacy, strength of the data on which this conclusion is based (Classes A and B), and potential side effects.

Harms. Medication side effects vary widely, including cardiovascular and gastrointestinal symptoms with ergots and triptans, sedation with butalbital and opiates, and gastric irritation with NSAIDs.

Prophylactic Pharmacotherapy

Benefits. As summarized in Tables 5-7 and 5-8, many classes of agents have been shown to be effective in the prophylactic management of headaches. Selection of specific agents requires a careful consideration of demonstrated efficacy, strength of the data on which this conclusion is based (Classes A and B), and potential side effects.

Harms. Medication side effects vary widely, including cardiovascular and gastrointestinal symptoms with antidepressants and calcium antagonists, sedation, cardiovascular and mood-related symptoms with beta blockers, gastric irritation with NSAIDs, and so on.

Comment. Prophylactic pharmacotherapy is generally used only in those patients in whom the severity or frequency of headaches is sufficient to warrant the inconvenience and long-term side effects of daily medication.

Behavioral and Physical Therapies

Benefits. Relaxation training with or without thermal biofeedback, EMG biofeedback, and cognitive-behavioral therapy are all somewhat effective in preventing migraines (Classes A and B).

Harms. The committee is aware of no major adverse effects of these modalities.

Relaxation training, thermal biofeedback combined with relaxation training, EMG biofeedback, and cognitive-behavioral therapy are all somewhat effective in preventing migraine when compared with controls. Given the evidence reviewed, no conclusions can be made regarding equivalence or superiority among specific behavioral treatments or for specific behavioral treatments relative to other specific preventive

pharmacological therapies. Therefore, relaxation training, thermal biofeedback combined with relaxation training, EMG biofeedback, and cognitive-behavioral therapy may be considered as treatment options for prevention of migraines (Grade A). Specific recommendations regarding which of these to use for specific patients cannot be made.

Behavioral treatments have been directly compared and integrated with drug treatments as preventive therapy for migraines. The addition of propranolol conferred additional clinical benefits when added to (1) thermal biofeedback plus relaxation plus cognitive-behavioral therapy, (2) thermal biofeedback plus relaxation, and (3) EMG biofeedback (amitriptyline also proved beneficial in a later trial). Therefore, behavioral therapy (i.e., relaxation, biofeedback) may be combined with preventive drug therapy (i.e., propranolol, amitriptyline) for patients to achieve additional clinical improvement for migraine relief (Grade B).

The empirical evidence pertaining to treatment of migraines with acupuncture is limited and the results are mixed. Very limited evidence evaluates hypnosis, TENS, cervical manipulation, occlusal adjustment, and hyperbaric oxygen as preventive or acute therapy for migraine. Therefore, evidenced-based treatment recommendations are not yet possible regarding the use of hypnosis, acupuncture, TENS, cervical manipulation, occlusal adjustment, and hyperbaric oxygen as preventive or acute therapy for migraines. For hyperbaric oxygen treatment, even if further studies confirmed the efficacy results presented above, the lack of availability would limit practical clinical application of this treatment (Grade C).

Practice Issues

A physician's treatment of patients with primary headache includes pharmacological management of acute attacks, prophylactic pharmacological management, and behavioral management. Tables 5-6, 5-7, and 5-8 summarize conclusions regarding relative efficacy and side effects for each class of drug.

Each patient should be actively engaged in his or her own management decisions (e.g., discuss treatment/medication preferences), and in each instance treatment must be tailored to the individual's needs (e.g., based on severity of illness, comorbidity/coexisting conditions, prior response to medications). When creating and maintaining a partnership, realistic patient expectations need to be established. General principles of management include:

1. *Educate* migraine sufferers about their condition and its treatment and encourage them to participate in their own management.
2. *Use migraine-specific agents* (triptans, DHE, ergotamine) in patients

with more severe migraine and in those whose headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen plus caffeine. *Despite the lack of evidence that headaches of different type and severity respond to specific agents*, strong clinical impression suggests that this is true. Failure to use an effective treatment promptly may increase pain, disability, and the impact of a headache.

3. *Select a nonoral route of administration* for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex.

4. *Consider a self-administered rescue medication* for patients with severe migraine who do not respond well to (or fail) other treatments.

5. *Guard against medication-overuse headache.* (The terms “rebound headache” or “drug-induced headache” are sometimes used interchangeably with “medication-overuse headache.”)

6. *When choosing specific agents*, in addition to a consideration of the demonstrated efficacy and side effects of that agent, it is important to consider the strength of the evidence supporting use of that drug (i.e., Class A data). However, for many effective drugs, optimal studies have not been performed, often because closely related agents are known to be effective and there has been little incentive to study these additional agents. Therefore, in many instances (DHE, calcium antagonists, specific tricyclics) agents are widely used and are considered effective, despite the absence of Class A studies.

Recommendations

For Gulf War veterans with chronic headache not associated with underlying pathology (e.g., tumors, vascular abnormalities), the committee recommends the following treatments:

- **pharmacological management of acute episodes, using agents listed in Table 5-6, taking into consideration the clinical effectiveness and potential side effects, as listed;**
- **prophylactic pharmacological management for headaches that occur frequently or are disruptive to the patient’s functioning, as listed in Tables 5-7 and 5-8, taking into consideration the clinical effectiveness and potential side effects, as listed;**
- **use of behavioral and physical treatments, including relaxation training, thermal biofeedback combined with relaxation training, EMG biofeedback and cognitive-behavioral therapy, or behavioral therapy combined with preventive drug therapy.**

IRRITABLE BOWEL SYNDROME

Introduction

Irritable bowel syndrome (IBS) is a common clinical condition that affects 10–20% of adults. Epidemiological studies indicate a high prevalence in the general population; 14 to 24% of women and 5 to 19% of men (Drossman et al. 1997; Jailwala et al. 2000). Reports indicate that IBS accounts for 12% of visits to primary care providers and 28% of visits to gastroenterologists and that patients with IBS have poorer quality of life and higher health care utilization than persons without the disorder (Drossman 1993; Whitehead et al. 1996; Jailwala et al. 2000). Community-based studies have provided data to demonstrate that patients with IBS have greater disability, threefold higher absenteeism from work, and two-fold higher average health care costs than do healthy controls (Talley et al. 1995a, b; Jailwala et al. 2000).

The Rome II Criteria, revised in 1999 by an international consensus group, is an established standard for the diagnosis of IBS (see Table 5-9).

There are no structural or biochemical markers for IBS. A diagnosis established utilizing the Rome Criteria and thorough physical examination should be followed by further evaluation as appropriate for the specific age group and clinical setting. Performing extensive laboratory, radiological, or endoscopic procedures does not establish a diagnosis of IBS; it is often unnecessary and may be harmful (*Functional GI Disorders 2000*).

TABLE 5-9 Rome II Diagnostic Criteria for Irritable Bowel Syndrome

Abdominal discomfort or pain that has two of these features:

- Relief with defecation
- Onset associated with change in stool frequency
- Onset associated with change in form (appearance of stool)
- Symptoms for at least 12 weeks in the preceding 12 months (need not be consecutive weeks)

The following symptoms, while not essential, increase the diagnostic confidence with their presence:

- Abnormal stool frequency (>three/day or <three/week)
 - Abnormal stool form (lumpy/hard or loose/watery)
 - Abnormal stool passage (straining, urgency, feelings of incomplete evacuation)
 - Passage of mucus
 - Bloating or feeling of abdominal distention
-

SOURCE: Thompson et al. 1999. Reprinted with permission from BMJ Publishing.

Evaluation of Therapies

Beneficial

- Antispasmodic agents, tricyclic antidepressants, and cognitive-behavioral therapy appear to be efficacious in the treatment of IBS.

Likely to Be Beneficial

- Fiber supplements are likely to be beneficial when constipation is the predominant symptom of IBS. If diarrhea is the predominant symptom, opiates (loperamide, diphenoxylate HC with atropine sulfate) are likely to be beneficial. Loperamide does not cross the blood-brain barrier and is therefore preferable to other narcotics such as codeine or diphenoxylate.

Unknown Efficacy

- Many pharmacotherapeutic approaches discussed in this report have not been sufficiently investigated, and therefore evidence of their true effectiveness remains unknown. These include SSRIs (selective serotonin reuptake inhibitors), prokinetic agents, oral prostaglandins, complementary alternative medicine approaches, and other newer antidepressants and anxiolytics.

Pharmacological Therapies

Treatment strategies must be individualized and based on the severity of symptoms. A comprehensive electronic search of MEDLINE (1966 to 1999), EMBASE (1980 to 1999), PsycINFO (1967 to 1999), and the Cochrane controlled trials registry was undertaken to identify randomized, double-blind, placebo-controlled, parallel, or cross-over trials of a pharmacological intervention for adult patients who reported outcomes of improvement in global or irritable bowel-specific symptoms in order to evaluate the efficacy of pharmacological agents for IBS (Jailwala et al. 2000) (see Table 5-10). A manual search of the bibliographies from all retrieved publications was also conducted by these same investigators.

A trial had to satisfy the following six criteria for inclusion:

- address treatment of IBS;
- study adult patients;
- administer a pharmacological intervention to more than 10 patients for at least two weeks;
- include a placebo-control group;

TABLE 5-10 Efficacy of Pharmacological Interventions in the Treatment of IBS

Intervention	Global or Symptom Improvement		Global Improvement		Balance of Evidence and Recommendations
	Total Trials	Positive Trials	Total Trials	Positive Trials	
Bulking agents					
All trials	13	4	11	4	Efficacy not clearly established
High-quality trials	7	3	7	3	
Smooth-muscle relaxants					
All trials	16	13	12	9	Beneficial for abdominal pain
High-quality trials	7	7	5	4	
Prokinetic agents					
All trials	6	2	5	2	Evidence inconclusive for domperidone; <i>Cisapride removed from market</i>
High-quality trials	4	1	3	1	
Loperamide					
All trials	4	4	2	2	Beneficial for diarrhea
High-quality trials	2	2	1	1	
Psychotropic agents					
All trials	7	7	5	5	Evidence inconclusive; more high-quality trials are needed
High-quality trials	1	1	1	1	
Peppermint oil					
All trials	3	1	2	0	Efficacy not clearly established
High-quality trials	1	1	0	0	
5-Hydroxytrypta-mine-receptor antagonists					
All trials	3	3	3	3	Evidence suggestive; further study required
High-quality trials	2	2	2	2	

SOURCE: Jaiwala et al. 2000. Reprinted with permission from the American College of Physicians.

- report an outcome measure of global status or individual symptoms (or both) of IBS; and
- use a randomized double blind, parallel group or cross-over design.

These inclusion criteria were independently applied by all three authors to a subset of studies to assess interrater variation. Criteria for high-quality trials were established. A summary of 28 high-quality trials of pharmacotherapy for IBS was listed, and efficacy of pharmacological interventions in the treatment of IBS was detailed.

To be noted is that although four smooth-muscle relaxants (cimetroprium, pinaverium, otilonium, and trimetubutine) were consistently shown to be efficacious in high-quality trials, none of these agents is currently approved for treatment of IBS in the United States (Jailwala et al. 2000).

Antimuscarinic agents are frequently prescribed in the United States for symptoms of IBS specifically for abdominal pain and associated distention. Relief is probably associated with reduction in the contractility of the gut due to precipitating factors such as specific food intake, stress, or other inciting agents. In a study meta-analysis of smooth-muscle relaxants in IBS (Poynard et al. 1994), this class of drugs was significantly better than placebo for global assessment (62 to 35% improvement) and abdominal pain (65 vs. 45%). Similar findings were noted in a 1997 study of IBS. This study reviewed 15 randomized well-controlled studies of at least two weeks' duration (Camilleri and Choi 1997).

Practice Issues

Several psychological treatments have been studied in patients with IBS, including psychodynamic/interpersonal psychotherapy, cognitive-behavioral treatment, hypnosis, relaxation, biofeedback, and meditation. "These seem to be effective in reducing abdominal pain and diarrhea but not constipation, and they also reduce anxiety and other psychological symptoms. It is not known whether the improvement in irritable bowel symptoms relates to changes in gastrointestinal physiology or in the psychological interpretation of enteroceptive sensation. A positive response is associated with patients who relate symptom exacerbations to stressors and have a waxing and waning of symptoms rather than chronic pain. There are no comparative data to determine which treatments are superior, and additional studies are needed to determine the relative efficacy of psychological treatments for various subgroups of patients" (Drossman et al. 1997).

Practice Issues are outlined in Table 5-11. Antidepressants are usually used in smaller doses for IBS patients than for depression. See Table 5-12.

TABLE 5-11 Practice Issues/Considerations

Class	Example	Principal Use	Dosage
Antispasmodics	Hyoscyamine	Pain predominant	0.125–0.250 mg q4 hours
	Dicyclomine		1–40 mg qid
Opiates	Loperamide	Diarrhea predominant	2–4 mg qid
	Diphenoxylate HCL with atropine sulfate		1–2 tablets qid
Bile acid sequestrant	Cholestyramine	Diarrhea predominant	4–24 gm qd in divided doses
5-HT ₃ antagonist	Alosetron*	Diarrhea predominant in female patients	1 mg bid
Fiber supplement	Psyllium, methycellulose, Ca polycarbophil	Constipation predominant	Titrate to regular BMs (20–30 gm qd)
Isosmotic electrolyte solution	PEG 3350	Constipation predominant	Titrate to regular BMs (17–34 gm qd-bid)
Oral prostaglandin	Misoprostil	Constipation predominant	200–400 mg qd-tid

*Recent voluntary withdrawal from market due to adverse effects.

SOURCE: *Functional GI Disorders: New Visions*. 2001. Monograph. Foundation for Digestive Health and Nutrition, created by the American Gastroenterological Association. p. 12. Reprinted with permission of the American Gastroenterological Association.

A randomized controlled trial supporting the efficacy of psychodynamic psychotherapy appeared in the literature (Guthrie et al. 1993), as did controlled studies generally supportive of cognitive-behavioral therapy (Blanchard et al. 1981; Bennet and Wilkinson 1985; Neff and Blanchard 1987; Lynch and Zamble 1989; Corney et al. 1991; Runsey 1991; Shaw et al. 1991; Greene and Blanchard 1994; Payne and Blanchard 1995; VanDulmen et al. 1996; Toner et al. 1998).

A randomized double-blind placebo-controlled trial of 116 patients who fulfilled the Rome Criteria was conducted during 1996–1997 utilizing Chinese herbal medicine (Bensonssan et al. 1998). Patients were randomly allocated to one of three treatment groups; *individualized* Chinese herbal formulations, a *standard* Chinese herbal formulation, or placebo.

TABLE 5-12 Antidepressants for IBS Gastrointestinal Disorders

Class	Example	Principal Use	Dosage
TCAs	Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline	Treatment of Pain, Nausea, and Nonspecific Symptoms	Low-Dose Range (e.g., 25–75 mg qd)
SSRIs	Fluoxetine, Fluvoxamine, Paroxetine, Sertraline	Treatment of Symptoms of Concurrent Anxiety and Depression	Usual Psychiatric Dosage
Other newer Antidepressants and Anxiolytics	Amoxapine, Bupropion, Maprotyline, Mirtazapine, Nefazodone, Trazodone, Venlafaxine	Treatment of Symptoms of Concurrent Anxiety and Depression	Usual Psychiatric Dosage

SOURCE: *Functional GI Disorders New Visions*, Monograph. 2001. Foundation for Digestive Health and Nutrition, created by the American Gastroenterological Association. p.14. Reprinted with permission of the American Gastroenterological Association.

Initially, patients in the active treatment groups had significant improvement in bowel symptom scores as compared to *placebo*. However, on follow-up 14 weeks after completion of treatment only the individualized complementary and alternative medicine (CAM) treatment group maintained improvement. Further trials designed to study individual herbs in the various manifestations of IBS will be required to demonstrate consistent therapeutic efficacy of CAM therapy.

The conclusion noted in the American Digestive Health Foundation monograph, *Functional GI Disorders* (2000), is most useful in treating patients with IBS: “A therapeutic program that concentrates more on ‘health’ than on ‘illness,’ that teaches coping strategies rather than promises a cure, is, in the end, far more likely to maximize the value (both economic and medical) of the intervention and provide relief for patients suffering from this still mysterious debilitating disorder.”

Recommendations

For Gulf War veterans who meet the diagnostic criteria for IBS, the committee recommends that:

- **cognitive-behavioral therapy, tricyclic antidepressants (TCAs), and smooth-muscle relaxants be considered in appropriate age-specific, carefully selected clinical settings and**
- **results of treatment studies should be monitored to clearly establish therapeutic effectiveness of these agents in the various subgroups of patients diagnosed with IBS.**

PANIC DISORDER

Introduction

Panic disorder consists of recurrent, unexpected panic attacks accompanied by at least one month or more of persistent concern about having another attack, worry about the implications of having an attack, or significant behavioral change related to the attack. At least four of 13 characteristic symptoms must occur during the attacks, such as shortness of breath, dizziness, palpitations, and trembling or shaking (American Psychiatric Association 2000). The clinician will have determined that the attacks are not induced by a substance (e.g., caffeine) or a medical illness (e.g., hyperthyroidism) and that the anxiety is not better accounted for by another mental disorder. Table 5-13 contains the DSM-IV definition of panic attacks. Table 5-14 provides the DSM-IV criteria for panic disorder without agoraphobia.

TABLE 5-13 DSM IV-TR Criteria for Panic Attack

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes:

1. Palpitations, pounding heart, or accelerated heart rate
 2. Sweating
 3. Trembling or shaking
 4. Sensations of shortness of breath or smothering
 5. Feeling of choking
 6. Chest pain or discomfort
 7. Nausea or abdominal distress
 8. Feeling dizzy, unsteady, lightheaded, or faint
 9. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
 10. Fear of losing control or going crazy, fear of dying
 11. Paresthesias (numbness or tingling sensations)
 12. Chills or hot flushes
-

SOURCE: Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders*, 1994, Fourth Edition, Text Revision, copyright 2000, American Psychiatric Association, p. 395.

TABLE 5-14 *DSM-IV* Criteria for Panic Disorder Without Agoraphobia

A. Both 1 and 2:

1. Recurrent unexpected panic attacks.
2. At least one of the attacks has been followed by at least one month (or more) of one (or more) of the following: (a) persistent concern about having additional attacks; (b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy"); or (c) a significant change in behavior related to the attacks.

B. Absence of agoraphobia.

C. The panic attacks are not due to the direct physiological effects of a substance (e.g., drug of abuse, medication) or a general medical condition (e.g., hyperthyroidism).

D. The panic attacks are not better accounted for by another mental disorder such as social phobia (e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to the phobic situation), obsessive-compulsive disorder (e.g., exposure to dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives).

SOURCE: Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, copyright 2000. American Psychiatric Association, p. 402.

It is estimated that 2 to 3% of women and 0.5 to 1.5% of men have panic disorder (Robins et al. 1984). Panic disorder has an onset in the mid-20s, although age of onset may vary. One-third to one-half of panic patients develop agoraphobia, a condition in which they experience anxiety and avoidance of places or situations where escape or help may be unavailable if panic symptoms occur (Weissman et al. 1997). Situations eliciting agoraphobia include traveling on buses, subways, or other public transportation and being on bridges, in tunnels, or far from home.

Panic attacks vary in frequency and intensity (American Psychiatric Association 1998). They generally have a sudden onset, peak within minutes, and last 5 to 30 minutes. It is not uncommon for individuals to experience numerous moderate attacks for months at a time or to experience frequent attacks daily for a short period, with months separating subsequent periods of attack.

Among individuals with panic disorder, the lifetime prevalence of major depression is 50 to 60% (Lesser et al. 1989). For individuals with both panic disorder and major depression, the onset of major depression precedes the onset of panic disorder in one-third of cases. Subjects with panic symptoms or disorder are frequent users of emergency medical services and are more likely to be hospitalized for physical problems.

Patients with panic disorder, especially with comorbid depression, are at higher risk for suicide attempts, impaired social and marital functioning, use of psychoactive medication, and substance abuse.

Panic disorder is generally considered chronic and lifelong (American Psychiatric Association 1998). Although total remission is uncommon, research suggests that 50 to 70% of patients will show some amount of improvement with time. Family studies show that the risk of panic disorder is eight times as high among first-degree relatives of probands with panic disorder as among relatives of control subjects (Knowles and Weissman 1995).

Evaluation of Therapies

The care of patients with panic disorder involves a comprehensive array of approaches designed to reduce the frequency and severity of panic attacks, reduce morbidity, and improve patient functioning (American Psychiatric Association 1998). For most patients, treatment is conducted on an outpatient basis. Once the diagnosis is made, a treatment plan should be developed taking into account the specific needs of the patient and the unique factors that may affect the expression of the patient's panic disorder, including developmental factors, psychosocial stressors and conflicts, social supports, and general living situation.

According to the American Psychiatric Association (1998), elements of clinical management for patients with panic disorder include (1) establishing and maintaining a therapeutic alliance; (2) educating and reassuring the patient concerning panic disorder; (3) evaluating particular symptoms and monitoring them over time; (4) evaluating types and severity of functional impairment; (5) identifying and addressing comorbid conditions; (6) working with other health professionals; (7) educating family members and enlisting their help when appropriate; (8) enhancing treatment compliance; and (9) working with the patient to address early signs of relapse.

There are three classes of medication known to be effective in treating panic disorder: SSRIs, TCAs, and BZPs. Medications from all classes have roughly comparable efficacy (American Psychiatric Association 1998; Sheehan 1999). Most medication studies have focused on the value of the drugs in stopping or reducing the frequency of panic attacks, but medication also reduces anticipatory anxiety, phobic avoidance, and depression and improves global functioning.

Beneficial Therapies

- SSRIs
- TCAs

- BZPs
- CBT
- Maintenance therapy to prevent reoccurrence

Likely to Be Beneficial

- MAOIs
- Newer antidepressants (venlafaxine, nefazodone, trazodone)
- Valproate
- Group therapy

Unknown Effectiveness

- Beta blockers
- Psychodynamic psychotherapy
- Marital and family therapy

Cognitive-Behavioral Therapy (CBT)

Benefits. CBT has been found to be effective in RCTs for the treatment of panic disorders. Randomized controlled trials of CBT for panic disorder have been conducted with treatment length varying from 4 to 16 weeks. In a summary of 12 studies, the response rate using an intent-to-treat analysis was 66% (American Psychiatric Association 1998). Using completer analysis, the response rate was 78%. Control treatments produced response rates ranging from 8 to 78%.

Harms. The committee is aware of no major adverse effects of CBT, which is generally considered safe. Patients are informed that the therapy is voluntary and that they may drop out at any time. The therapy is time limited, typically lasting 12–20 sessions.

Comment. CBT encompasses a range of treatments each consisting of several elements, including psycho-education, continuous panic monitoring, development of anxiety management skills, cognitive restructuring, and in vivo exposure. The efficacy of CBT for the treatment of panic disorder is supported by extensive evidence (Barlow 1997; Shear and Weiner 1997; American Psychiatric Association 1998).

CBT requires considerable time and discipline on the part of the patient, as well as the availability of a trained therapist. Exercises must be practiced daily, and monitoring must be done continuously. In addition, patients must be willing to confront feared situations. Approximately 10 to 30% of patients are unwilling or unable to complete these requirements (American Psychiatric Association 1998). CBT is less effective for these patients.

Group Therapy

Benefits. There is some evidence for the effectiveness of CBT administered in group settings for the treatment of panic disorder (Telch et al. 1993; Neron et al. 1995). Other types of group therapy have more limited evidence for benefit.

Harms. Some patients may be uncomfortable in group settings, and maintaining confidentiality may be a concern.

Comment. Group therapy can be an efficient way to help many patients at once.

Psychodynamic Therapy

Benefits. There is no evidence for the effectiveness of psychodynamic psychotherapy in the treatment of panic disorder.

Harms. Psychodynamic psychotherapy may be associated with difficulty in terminating treatment because of the attachment the patient forms with the therapist.

Comment. Psychodynamic psychotherapy and related therapies by their very nature are not amenable to clinical trials to assess efficacy.

Marital/Family Therapy

Benefits. Marital/family therapy has no demonstrated benefit in treating panic disorder. These therapies are usually directed toward changing behaviors in the marriage or family to improve these relationships, which may, as a by-product, reduce symptoms of anxiety.

Harms. The committee is not aware of adverse consequences associated with marital/family therapy.

Comment. Marital and family therapies are usually not administered for the treatment of panic disorder but may be beneficial when marital/family problems are involved in the presentation of the disorder.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Benefits. Five SSRIs are now available in the United States: citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. RCTs show that each is effective in treating panic disorder (American Psychiatric Association

1998). Paroxetine and sertraline both have a Food and Drug Administration (FDA) indication for the treatment of panic disorder; it is likely that all of the SSRIs are effective in treating it. The database for SSRI therapy of panic disorder is extensive, and there are sufficient controlled trials to conclude that these medications have demonstrated short-term efficacy in treating panic attacks. A recent analysis of 27 studies involving 2,348 patients in randomized perspective, double-blind, placebo-controlled trials suggested that the effect size for improvement with SSRIs and panic disorder is significantly greater than for alprazolam or imipramine (Boyer 1995).

Harms. SSRIs may cause a disruption of sleep, loss of weight, sexual dysfunction, and agitation. In general, however, the side effects are fewer and less severe than with the tricyclic antidepressants. Because elimination of SSRIs involves hepatic metabolism, doses need to be carefully adjusted for patients with liver disease.

Comment. SSRIs are safe and effective; they are not lethal in overdose and have few serious effects on cardiovascular function. These agents are now considered first-line therapy for panic disorder. They are widely used but tend to be expensive.

Tricyclic Antidepressants (TCAs)

Benefits. TCAs are effective in treating panic and have been used for nearly 40 years for that purpose (American Psychiatric Association 1998). Controlled trials have been conducted with imipramine, desipramine, and clomipramine. Studies show that following treatment with TCAs, 45 to 70% of patients are panic-free compared to 15 to 50% of those receiving placebo.

Harms. Adverse effects of TCAs include dry mouth, constipation, urinary hesitancy, sweating, sleep disturbance, orthostatic hypotension, fatigue and weakness, weight gain, and sexual dysfunction. Dosages must be carefully titrated, and higher doses are associated with greater dropout rates. Overdoses can lead to significant cardiac toxicity and fatality; TCAs should not be prescribed to patients with narrow-angle glaucoma or significant prostatic hypertrophy. Caution should be exercised in prescribing TCAs to patients at risk for falls due to the potential for orthostatic hypotension. Due to their potential for lethality with overdose, TCAs should be prescribed in limited quantities to patients who may pose a suicide risk.

Comment. TCAs are used less frequently for treating panic disorder than the newer SSRIs because of their many side effects, although they are equally efficacious.

Benzodiazepines (BZPs)

Benefits. BZPs are effective in reducing the intensity and frequency of panic attacks and anticipatory anxiety (Davidson 1997; American Psychiatric Association 1998). Alprazolam has been studied more extensively than the other BZPs and is FDA approved for the treatment of panic disorder. Controlled trials involving more than 1,000 patients have shown alprazolam to be superior to placebo in the treatment of panic attacks. Other benzodiazepines, including diazepam, clonazepam, and lorazepam, given in equivalent doses, are probably as effective as alprazolam in the treatment of panic disorder.

Harms. The adverse effects of BZPs include sedation, fatigue, ataxia, slurred speech, memory impairment, and weakness. BZPs have a potential to induce drug dependency and should be avoided in patients with substance abuse disorders. Discontinuation of these drugs can be difficult. Abrupt discontinuation of BZPs can lead to seizures.

Comment. BZPs should never be used as first-line therapy for panic disorder due to their tendency to cause habituation.

Beta Blockers

Benefits. Beta blockers are widely prescribed in primary care settings to treat panic disorder and other anxiety syndromes. Research suggests that they are probably more effective than placebo but are less effective than antidepressants or BZPs.

Harms. Beta blockers are well tolerated but provide incomplete symptomatic relief.

Comment. Beta blockers should not be prescribed as a first-line treatment for panic disorder but may be helpful in alleviating peripheral manifestations of the condition, such as heart palpitations.

Monoamine Oxidase Inhibitors (MAOIs)

Benefits. MAOI therapy is probably effective in treating panic disorder, but much of the evidence was collected before the diagnosis was introduced in *DSM-III* in 1980 (American Psychiatric Association 1998).

Harms. While the MAO inhibitors are not anticholinergic, their side effects often resemble the tricyclic medications. A major concern with MAOIs is the risk of hypertensive crisis secondary to ingestion of tyramine. Patients taking MAOIs must adhere to a low-tyramine diet. Persons unable to follow the diet should not take MAOIs. Potentially serious drug-drug interactions can occur with SSRIs, sympathomimetic amines, decongestants, dextromethorphan, and meperidine. These drugs should not be used with MAOIs. In addition, at least two weeks is recommended between discontinuation of the MAOIs and use of anesthetics for electroconvulsive therapies.

Comment. Because of the dietary restrictions involved in their use, MAOIs are infrequently used to treat patients with panic disorder and are considered second-line therapies.

Newer Antidepressants

Benefits. Venlafaxine, nefazodone, and trazodone may be effective for persons with panic disorder, based on evidence from open-label or small RTCs (Mavissakalian et al. 1987; De Martinis et al. 1996; Pollack et al. 1996).

Harms. These medications are generally safe and well tolerated, though venlafaxine carries with it the rare possibility of inducing hypertension.

Comment. More data are necessary before any specific recommendations can be made about their use.

Valproate

Benefits. At least one small open-label trial suggests that valproate may be effective in treating panic disorder (Woodman and Noyes 1994).

Harms. This mood stabilizer is generally well tolerated, although it may be associated with transient nausea, weight gain, and tremor.

Comment. More information is needed before specific recommendations can be made about its use.

Maintenance Therapy

Benefits. RCTs have found that continuing antidepressant drug treatment for patients with panic disorder reduces the risk of relapse (American Psychiatric Association 1998).

Harms. Adverse effects are those reported for the specific treatments listed above.

Comment. It is unclear from the literature how long maintenance therapy should last, although most psychiatrists recommend continuation of pharmacotherapy for at least 6–12 months following response to medication.

Practice Issues

CBT and specific medications have been found to be effective treatments for panic disorder (Barlow 1997; Davidson 1997; Jefferson 1997; Shear and Weiner 1997; American Psychiatric Association 1998; Sheehan 1999;). An emerging body of data suggests that patients do best when receiving a combination of CBT and medication (American Psychiatric Association 1998).

Recommendation

For Gulf War veterans who meet the criteria for panic disorder, the committee recommends treatment with antidepressant medication and cognitive-behavioral therapy.

POSTTRAUMATIC STRESS DISORDER

Introduction

Posttraumatic stress disorder (PTSD) occurs in persons who have experienced a traumatic occurrence that has involved experiencing, witnessing, or being confronted with an event that involves actual or threatened death, serious physical injury, or a threat to one's physical integrity. Examples include combat situations, physical assault, rape and other forms of sexual assault, and disasters such as home fires. The three major elements of PTSD are (1) reexperiencing the trauma through dreams or recurrent and intrusive thoughts; (2) emotional numbing, such as feeling detached from others; and (3) symptoms of autonomic hyperarousal such as irritability and exaggerated startle response (American Psychiatric Association 2000). Two subtypes are specified in the *DSM-IV*: acute, when the duration of symptoms is less than three months, and chronic, when symptoms last three months or longer. Table 5-15 provides the *DSM-IV* definition of PTSD.

The prevalence of PTSD in the general population is estimated at about 0.5% in men and 1.2% in women (Helzer et al. 1987). Most men with the disorder have experienced combat situations. For women the most

TABLE 5-15 *DSM-IV* Criteria for Posttraumatic Stress Disorder

A. The person has been exposed to a traumatic event in which both of the following have been present:

1. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others.

2. The person's response involved intense fear, helplessness, or horror.

Note: In children, it may be expressed instead by disorganized or agitated behavior.

B. The traumatic event is persistently reexperienced in at least one of the following ways:

1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. *Note:* In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.

2. Recurrent distressing dreams of the event.

Note: In children there may be frightening dreams without recognizable content.

3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated).

Note: In young children, trauma-specific reenactment may occur.

4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

5. Physiological reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by at least three of the following:

1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma.

continued

frequent precipitating stressor is a physical assault or rape. The disorder can occur in persons of any age, and even young children have been observed to develop it (American Psychiatric Association 2000).

PTSD can begin within hours or days of the stressor but can be delayed for months or years. The disorder is chronic for many. Symptoms fluctuate but typically worsen during stressful periods. Rapid onset of symptoms, good premorbid functioning, strong social support, and the absence of psychiatric or medical comorbidity are factors associated with a good outcome (Choy and de Bosset 1992; Davidson and Conner 1999; American Psychiatric Association 2000). Typically, the more severe the stressor, the greater the likelihood of developing PTSD. In wartime situations certain experiences are linked to the development of PTSD, including witnessing a friend killed in action, witnessing wartime atrocities, or

TABLE 5-15 *Continued*

-
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma.
 3. Inability to recall an important aspect of the trauma.
 4. Markedly diminished interest or participation in significant activities.
 5. Feeling of detachment or estrangement from others.
 6. Restricted range of affect (e.g., unable to have loving feelings).
 7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, or children, or a normal life span).
- D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by at least two of the following:
1. Difficulty falling or staying asleep.
 2. Irritability or outbursts of anger.
 3. Difficulty concentrating.
 4. Hypervigilance.
 5. Exaggerated startle response.
- E. Duration of the disturbance (symptoms in B, C, and D) is more than one month.
- F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: If duration of symptoms is less than three months

Chronic: If duration of symptoms is three months or more

Specify if:

With delayed onset: If onset of symptoms is at least six months after the stressor

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participating in them (Breslau and Davis 1987). The person's age, history of emotional disturbance, level of social support, and proximity to the stressor are all factors that affect the likelihood of developing PTSD (Smith et al. 1990).

Many patients with PTSD develop comorbid major depression, other anxiety disorders, alcohol and drug abuse, anger and irritability, and poor impulse control (Mellman et al. 1992; American Psychiatric Association 2000).

Evaluation of Therapies

The care of patients with PTSD involves a comprehensive array of approaches designed to reduce the frequency and severity of PTSD symp-

toms (Davidson and Connor 1999). For most patients with PTSD, treatment can be conducted on an outpatient basis. A careful assessment should precede treatment to rule out medical causes for the symptoms. The assessment should take into account the individual's developmental factors, psychosocial stressors and conflicts, social supports, and general living situation.

Similar to the clinical management of panic disorder, clinicians working with patients who have PTSD should include:

1. establishing and maintaining a therapeutic alliance to educate and reassure the patient concerning the PTSD,
2. evaluating the particular symptoms and monitoring them over time;
3. evaluating types and severity of functional impairment;
4. identifying and addressing comorbid conditions;
5. working with other health professionals;
6. educating family members and enlisting their help when appropriate;
7. enhancing treatment compliance; and
8. working with the patient to address early signs of relapse.

Cognitive-behavioral therapy (CBT) and medication have both been shown to be effective treatments for PTSD. The choice between psychotherapy and medication depends upon an individualized assessment of efficacy, benefits, and risks of each modality and the patient's personal preferences.

Beneficial Therapies

- SSSRIs
- CBT

Likely to Be Beneficial

- TCAs
- MAOIs
- BZPs
- Group therapy
- Maintenance therapy to prevent reoccurrence

Unknown Effectiveness

- Psychodynamic psychotherapy
- Marital/family therapy

Cognitive-Behavioral Therapy (CBT)

Benefits. CBT has been found effective in the treatment of PTSD in a randomized clinical trial that compared prolonged exposure and stress inoculation. CBT is symptom oriented and involves psycho-education, anxiety management, cognitive restructuring, and exposure to feared cues. These techniques are effective in the management of PTSD and may ameliorate many of the symptoms associated with it (Foa 1997). Early treatment may prevent the development of chronic PTSD in some patients.

Harms. The committee is aware of no major adverse effects of CBT, which is generally considered safe. Patients are informed that the therapy is voluntary, they may drop out at any time, and the therapy is time limited, typically lasting 12–20 sessions.

Comment. CBT requires considerable time and discipline on the part of the patient, as well as the availability of a trained therapist.

Group Therapy

Benefits. There is no evidence for the effectiveness of group therapy in the treatment of PTSD.

Harms. Some patients may be uncomfortable in group settings, and maintaining confidentiality may be a concern.

Comment. Group therapy can be an efficient way to help many patients at once.

Psychodynamic Therapy

Benefits. There is limited evidence for the effectiveness of psychodynamic psychotherapy in the treatment of PTSD (Brom et al. 1989).

Harms. Psychodynamic psychotherapy may be associated with difficulty in terminating treatment because of the attachment the patient forms to the therapist.

Comment. Psychodynamic psychotherapy and related therapies by their very nature are not amenable to clinical trials to assess efficacy.

Marital/Family Therapy

Benefits. Marital/family therapy has no demonstrated benefit in treating PTSD. These therapies are usually directed toward changing behaviors in the marriage or family to improve these relationships, which may, as a by-product, reduce symptoms of anxiety.

Harms. The committee is not aware of adverse consequences associated with marital and family therapies.

Comment. Marital and family therapies are usually not administered for the treatment of PTSD but may be beneficial when marital/family problems are involved in the presentation of the disorder.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Benefits. Sertraline was recently approved by the FDA for the treatment of PTSD and is safe and effective in reducing its symptoms (Brady et al. 2000). It is currently the only FDA-approved medication for PTSD. A small RCT of fluoxetine showed a marked reduction in overall PTSD symptoms (van der Kolk 1994) compared to placebo. Open-label trials and case reports have also shown benefit for fluoxetine, sertraline, and fluvoxamine (Friedman 1998). These drugs have a broad range of effects and reduce hyperarousal symptoms, anxiety, insomnia, and depression.

Harms. SSRIs may cause a disruption of sleep, loss of weight, sexual dysfunction, and agitation. In general, however, the side effects are fewer and less severe than with the tricyclic antidepressants. Because elimination of SSRIs involves hepatic metabolism, doses need to be carefully adjusted for patients with liver disease.

Comment. SSRIs are safe and effective; they are not lethal in overdose and have few serious effects on cardiovascular function. These agents are now considered first-line therapy for PTSD. They tend to be expensive.

Tricyclic Antidepressant (TCAs)

Benefits. There have been several case reports, open-label trials, and small RCTs in the treatment of PTSD, producing statistically significant but generally modest benefits with TCAs (Friedman 1998). Drugs studied include amitriptyline, nortriptyline, imipramine, and desipramine.

Harms. Adverse effects of TCAs include dry mouth, constipation, urinary hesitancy, sweating, sleep disturbance, orthostatic hypotension, fatigue

and weakness, weight gain, and sexual dysfunction. Doses must be carefully titrated, and higher doses are associated with greater dropout rates. Overdoses can lead to significant cardiac toxicity and fatality. TCAs should not be prescribed to patients with narrow-angle glaucoma or significant prostatic hypertrophy. Caution should be exercised in prescribing TCAs to patients at risk for falls due to the potential for orthostatic hypotension. Due to their potential for lethality with overdose, TCAs should be prescribed in limited quantities to patients who may pose a suicide risk.

Comment. TCAs are used less frequently for treating PTSD than the newer SSRIs.

Benzodiazepines (BZPs)

Benefits. BZPs are effective in reducing symptoms of anxiety. Their effectiveness in treating PTSD is uncertain, although a small RCT of alprazolam and open-label trials of alprazolam and clonazepam suggest benefit (Friedman 1998).

Harms. The adverse effects of BZPs include sedation, fatigue, ataxia, slurred speech, memory impairment, and weakness. BZPs have a potential to induce drug dependency and should be avoided in patients with substance abuse disorders. Discontinuation of these drugs can be difficult. Abrupt discontinuation can lead to seizures.

Comment. BZPs may be helpful as an adjunctive therapy for short-term treatment of anxiety associated with PTSD but should not be used as a first-line therapy.

Monoamine Oxidase Inhibitors (MAOIs)

Benefits. Phenelzine produced reduction of PTSD symptoms in a small RCT (Kosten et al. 1991), but results have been mixed in other studies (Friedman 1998).

Harms. A major concern of MAOIs is the risk of hypertensive crisis secondary to ingestion of tyramine. Patients taking MAOIs must adhere to a low-tyramine diet. Persons unable to follow the diet should not take MAOIs. Potentially serious drug-drug interactions can occur with SSRIs, sympathomimetic amines, decongestants, dextromethorphan, and mepiridine. These drugs should not be used with MAOIs.

Comment. Because of the dietary restrictions involved in their use, MAOIs are rarely used to treat patients with PTSD.

Maintenance Therapy

Benefit. Patients with PTSD may benefit from continuing antidepressant drug treatment.

Harms. Adverse effects are those for the specific treatments listed above.

Comment. It is unclear how long maintenance therapy should last, but it is generally continued for 12 months following improvement (Davidson and Connor 1999).

Practice Issues

CBT and SSRIs have been found to be effective treatments for PTSD (Foa 1997; Davidson and Connor 1999; Brady et al. 2000). An emerging consensus among clinicians is that patients do best when they receive a combination of CBT and medication (Foa et al. 1999; Ballenger et al. 2000).

Recommendation

For Gulf War veterans who meet the criteria for PTSD and with no contraindications, the committee recommends treatment with antidepressant medication and cognitive-behavioral therapy.

MEDICALLY UNEXPLAINED PHYSICAL SYMPTOMS

Introduction

As described in Chapter 2, many Gulf War veterans experience symptoms that correspond closely to symptoms experienced by people in other populations that have recognized diagnoses of unknown etiology, such as chronic fatigue syndrome. The committee recognizes that studies of the treatment of persons with these diagnoses could inform veterans and their health care providers regarding effective treatments for their symptoms. The major focus of this report has, therefore, been upon these conditions. Yet, in addition to those veterans whose symptoms are similar to conditions with unknown etiologies, there remain a number of Gulf War veterans with symptoms for which there is no readily identifiable diagnosis. These individuals have been categorized as experiencing medically

unexplained physical symptoms or MUPS (Engel and Katon 1999). Many who experience MUPS visit health care providers. A 1987 IOM report noted, “[F]or the patient and the health professional, such encounters can be frustrating because the symptom is often so very difficult to diagnose and treat. The absence of a diagnosable disease does not mean the absence of abnormalities, disturbances, or alterations in bodily functions. Thus, severe illness, illness behavior, and suffering can exist in the absence of a diagnosable disease. Effective treatment of patients with chronic pain [symptoms] requires that health care professionals view illness broadly and not only in terms of a narrow disease model” (IOM 1987: 3).

Engel and Katon described MUPS as arising from a four-part process. First, an individual must experience the symptom. Second, the person having the symptom must believe it has medical significance. Third, the symptomatic and concerned individual must behave in a way that indicates his or her suspicion of serious illness or disease (e.g., he or she seeks health care). Fourth, the clinician must determine that the symptoms are unexplained or partly explained by medical problems. Of course, persons who qualify for the diagnosis of chronic fatigue syndrome or fibromyalgia, for example, would meet the criteria for MUPS. Yet others who do not fall into the diagnosis categories reviewed previously in this report also fall into this category.

As noted by Wessley et al. (1999), patients seek help from doctors for symptoms and doctors diagnose diseases to explain them. One common way to explain these symptoms is to disaggregate them into a series of diagnostic categories. Wessley et al. argue, that the existence of specific syndromes such as chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome is largely an artifact of medical specialization and that similarities between these syndromes outweigh the differences. They suggest, instead, a dimensional classification. The intricacies of the debate between investigators who propose to aggregate these medically unexplained physical symptoms and those who propose to disaggregate them is beyond the scope of this report. Nevertheless, the debate is relevant because, to the degree that overlap across these diagnoses exists, the way is opened to more general strategies and services for their management.

The evidence of efficacy of some of the therapies for diagnoses reviewed previously may also be applicable to MUPS. Because there are no published reports to date of RCTs for the treatment of MUPS, however, direct evidence of efficacy is currently lacking. Despite the absence of RCTs for MUPS (apart from the above diagnoses), a general approach to the patient, as developed by health care providers who work with these patients, has evolved.

Practice Approach²

Conservative diagnostic testing. Clinicians are often aware at the time of initial history and physical that diagnostic testing offers a low yield or that anxiety or depression are important exacerbating factors. Most evidence suggests that ordering medically unnecessary tests to reassure patients does not work (Kidd et al. 1993; McDonald et al. 1996). It may also promote a passive patient mindset (e.g., “the doctor’s in charge” and will “find it and fix it”) that is counter to behavioral activation goals and the shifting of responsibility for wellness to the patient. One alternative to running new tests is for doctor and patient to carefully review past testing together, an approach that promotes clinician-patient collaboration and patient understanding. It is important, however, that both the clinician and the patient recognize that MUPS is not a diagnosis and that they continue to explore, without excessive testing at each visit, the possibility that new evidence indicates the emergence of a specific disease entity.

Judicious medication use. Medications are no substitute for person-centered care that addresses patient concerns and disability. Central nervous system depressants such as sedative-hypnotics, “muscle relaxers,” and anxiolytics are usually inappropriate unless insomnia is acute, related to a clearly identifiable stressor, and expected to abate within a short time. These medications and narcotic analgesics usually do more harm than good, since they typically slow cognition, cause sedation, and reduce overall functioning and levels of physical activity.

In contrast, antidepressants may reduce MUPS among patients with chronic pain, panic disorder, dysthymic disorder, and major depressive disorder and can result in improved activity levels among depressed or anxious patients. It is important to carefully explain the rationale for psychotropic medications prescribed for MUPS or else patients may assume “the doctor thinks that the symptoms are in my head.” All patients with MUPS should receive a complete and careful explanation of medication side effects, so that if they occur the clinician’s credibility is enhanced and the chance of continued adherence is maximized.

Reassurance strategies. Comforting patients with MUPS often entails reassurance. This means more than simply telling them that their symptoms are not serious, a strategy that many patients will experience as

²The section is taken from a report prepared for the committee by Charles C. Engel, Jr., M.D., M.P.H., and Wayne J. Katon, M.D.

patronizing. Reassurance involves elucidation of the patient's beliefs about their illness (beliefs about cause, prognosis, and treatment) and providing education and advice that address those beliefs.

Clinicians can learn the phrases that people with MUPS find belittling and avoid them. Similarly, they can learn some phrases that "join" the clinician and patient in a collaborative dialogue. For example, most individuals with MUPS describe their distress as secondary to symptoms. It is best to adopt the patient's words and views regarding causation, no matter how faulty the clinician may think they are. Patients with MUPS understandably react negatively to physician statements such as "There's nothing physiologically wrong." This is an unempathetic statement that runs contrary to the patient experience of physical distress. It is important to convey that the clinician believes that the patient is hurting and will work collaboratively with them to maximize functioning and quality of life. The clinician may have to prepare the patient for a shift in emphasis from a solely diagnostic and curative approach to a rehabilitative emphasis.

Collaborative goal setting. Reducing disability requires specific changes in patient behavior. It requires patients to take an active, collaborative role in their treatment. Clinician-patient collaboration and negotiation of behavioral goals will usually prove to be more rewarding than striving for elusive cures. Goals must be specific, incremental, realistic, and achievable, and they should center on observable or reportable behaviors. First and foremost, goals must be negotiated with the patient to provide the patient with a feeling of ownership of his or her goals. Productive goal-setting areas include occupational, household, or social tasks, physical activation, sleep hygiene, or medication adherence. Clinicians should shift the responsibility for change to the patient but avoid blaming the patient for his or her predicament.

Physical and role reactivation. Regular exercise in tolerable doses helps patients with MUPS discharge distress, increase stamina, and improve functioning. A physical therapist is seldom necessary to initiate reactivation strategies. Instead, activation goals can be negotiated in the primary care setting. The goal here is to start at low levels of exertion and gradually increase exercise in a stepwise fashion to build aerobic capacity and functional reserve. Patients may also need encouragement to remain gainfully employed and active in supportive relationship roles. This reduces dependence and improves morale, self-confidence, and ability to meet expectations.

Involvement of social supports. Clinicians should encourage participation of support systems in nearly all aspects of care, provided that the

patient approves of this. Involving family or friends can enhance rapport and help clarify concerns, illness beliefs, symptoms, and deficits in functioning.

Coordination of care. In the absence of well-coordinated and centralized care, patients with multiple MUPS are likely to bounce from specialist to specialist, receive many unnecessary diagnostic procedures, and end up on multiple unnecessary medications. The key elements of coordinated care include:

1. establishment of a relationship with a single primary care provider;
2. appointments at regular, time-contingent intervals of about every four to six weeks;
3. a brief physical examination at each visit to address new physical concerns; and
4. limits on patient-initiated visits for an exacerbation of otherwise chronic symptoms.

Introducing specialty mental health consultation. Psychiatric referral is frequently appropriate for those with MUPS, especially for patients who request it, have suffered a recent stressor, have a treatment-refractory psychiatric disorder, or describe suicidal or other clinically worrisome issues. However, *most patients with MUPS do not require psychiatric treatment or psychological testing*. Some patients may be alienated by a psychiatric referral and become less cooperative. Evidence suggests that a surprisingly large proportion of patients with MUPS receive mental health referrals without an adequate explanation as to why they are needed (Kouyanau et al. 1997).

In some cases, there is little doubt that a clinician desires psychiatric referral primarily in order to reject a difficult patient. Not surprisingly, this message is seldom lost on the patient. Clinicians should not wait until potential medical causes are “ruled out” before introducing psychiatric referral to patients with MUPS. To prevent patients from experiencing mental health referral as rejection, it is usually best for clinicians to anticipate the potential need and introduce it early in a nonthreatening way. Clinicians should see patients again after completion of mental health consultation to reduce any patient concerns over personal rejection or abandonment. Primary care clinicians can ask patients how they experienced the consultation and contact the consultant directly for recommendations if possible. Close collaboration between the primary care physician and the mental health consultant is optimal to decrease misunderstandings and support treatment goals.

Collaborative Primary Care Management

Collaborative, behaviorally oriented health care programs that are based in primary care settings are the next step in an appropriate continuum of population-based health care for MUPS. Such programs can enhance patient adherence to behavioral approaches initiated in primary care. In addition, on-site consultation reduces stigma by presenting it as a routine part of the primary care experience rather than something mysterious and remote. On-site collaboration also provides primary care providers with satisfying opportunities to work closely with specialists.

Several groups have looked at primary care-based psychosocial interventions for persons with MUPS, psychiatric disorders, or both. Strategies have most commonly involved screening (Ormel and Giel 1990; Ormel et al. 1990, 1991), physician and patient education (Andersen and Harthorn 1990), primary care-based mental health consultation (Kates 1988), interdisciplinary treatment teams (NIH 1979), and psychotherapy techniques adapted for primary care use (Catalan et al. 1991). Researchers (Smith et al. 1990; Kashner et al. 1992; Rost et al. 1994) have found replicable reductions in the cost of care and even small improvements in health-related quality of life for patients with the most severe forms of MUPS (i.e., patients with somatization disorder) simply by sending a set of short, codified recommendations to patients' primary care providers with advice on how to manage them.

Katon and colleagues (1992b) completed a randomized trial of psychiatric consultation for "distressed high utilizers of primary care" at a health maintenance organization. Distressed high utilizers (the top 10% of ambulatory care utilizers over the year prior to study who were identified as distressed either by their primary care physicians or by high scores on a validated paper-and-pencil measure) accounted for approximately one-third of all outpatient visits, 26% of all prescriptions, and one-half of all inpatient hospital days. The intervention consisted of a structured psychiatric research interview followed by a 30-minute collaborative patient interview and treatment planning session involving the generalist, psychiatrist, and patient. Patients in the control group received usual primary care. Improvements in mental status or service utilization of intervention patients over that of controls could not be demonstrated. In retrospect, the intensity of the intervention was low, perhaps serving notice that MUPS involve many complex factors that are not responsive to a brief one-time intervention that targets mainly psychiatric disorders. Prescription practices were marginally better for the intervention group, but subsequent antidepressant regimen adherence was generally poor for patients in both groups. There was no formalized mechanism for interdisciplinary collaboration after the initial consultation and no way of subse-

quently enhancing primary care clinicians' effectiveness or their adherence to the original collaborative care plan (Katon et al. 1992b).

More recently, primary care approaches to physically symptomatic and distressed primary care patients have focused on "multimodal" or "multifaceted" interventions. These are best administered in steps, so that the most intensive, expensive, or burdensome treatments are held in reserve for those who are otherwise treatment refractory. Components have included screening; on-site mental health consultation; cognitive-behavioral and problem-solving therapies aimed at medication adherence, depression, MUPS, physical activation, and relapse prevention; videotapes, pamphlets, and other educational materials on self-care; structured follow-up strategies; and standardized written primary care instructions. Other efforts to enhance primary care clinicians' ability to tackle the multiple needs of their patients have employed "academic detailing," feedback to clinicians from their patients' automated pharmacy or health care utilization records, and case management.

Katon and colleagues (1996) used a multifaceted approach to assist depressed primary care patients, an approach that can serve as a model for similar primary care-based MUPS interventions. Elements of their intervention targeted the patient, the physician, and the process of health care delivery. Elements that targeted patients were reading materials on depression, antidepressants, simple self-administered cognitive-behavioral techniques for managing depression, and a videotape on similar topics for viewing with spouses. Elements that targeted primary care physicians were didactics on antidepressants and behavioral treatment of depression, case-based consultation for each depressed patient, and ongoing interaction and feedback between the psychologist and primary care physicians.

Elements that targeted the process of care were extensive and manualized. These included behavioral therapy conducted in the primary care setting and aimed at teaching patients depression self-management skills, improving medication regimen adherence, and preventing future relapses. Psychologist contacts were scheduled and occurred in the primary care setting. These contacts involved skills training, education, and homework. Relaxation training, assertiveness training, problem-solving training, and collaborative psychologist-patient development of a relapse prevention plan were done. Additional telephone contacts with the psychologist occurred after completion of primary care-setting contacts. Symptom monitoring occurred by a standardized measure and a checklist. The psychologist screened and documented antidepressant side effects, dosing, and adherence.

During weekly interdisciplinary team meetings, a psychiatrist reviewed antidepressant-related information and overall treatment progress. The psychiatrist would advise medication alterations as indicated,

and the psychologist communicated these recommendations to the primary care physician, who would carry them out. This integrated process of care was carefully monitored for integrity by using a numerical rating system. These integrity ratings were monitored and used to provide regular clinician feedback.

Katon and co-workers (1996) compared this collaborative interdisciplinary intervention to usual care for depressed primary care patients using a randomized controlled design. As long as four months after completion of the intervention, intervention patients with major depression reported greater satisfaction with care, adherence to the medication regimen, and improvement in depressive symptoms than major depression patients receiving usual care. The results of the intervention were less clearly favorable among patients with minor depression (significantly improved antidepressant regimen adherence and perceived antidepressant helpfulness, but there were no significant differences between the groups regarding depression symptoms or satisfaction with depression care; Katon et al. 1996). Other analyses of these data have found evidence of improvements in physical symptoms. Analyses of cost-effectiveness found that the intervention was more costly than usual care for patients with both major and minor depression. However, for the major depression patients, the multifaceted intervention offered significantly greater cost-effectiveness than usual primary care (Von Korff et al. 1998).

Given the added expense associated with collaborative models, it may be that they are best focused on patients for whom routine primary care management strategies for MUPS fail. When a patient's symptoms reach some threshold of extended duration, more intensive collaborative efforts may be proactively introduced. For example, Katon et al. (1999) found that compared to usual care, an intensified collaborative approach for primary care patients with persistent symptoms of depression significantly improved adherence to antidepressant therapy, satisfaction with care, depressive symptoms, and the likelihood of full recovery at three- and six-month follow-up (Katon et al. 1999). A similar stepped intensity of care may also benefit people at elevated risk of poor outcomes due to MUPS.

Specialized Intensive Multimodal Care

There are several examples on which to model tertiary prevention programs for patients with MUPS who fail to improve in response to collaborative primary care approaches. These programs are multimodal and multidisciplinary, occur in specialized (i.e., nonprimary care) settings, and involve either a three- to four-week inpatient or intensive outpatient program or a 10- to 15-week program of weekly or biweekly individual or group visits. These programs emphasize carefully planned

psychosocial elements that address the chronic nature of reduced functioning and the factors that reinforce it. Evidence-based criteria for these programs have yet to be applied.

Usually, psychosocial and medical care is combined with a highly structured and generally supervised physical activation or exercise plan. These programs view disability as a behavior amenable to modification regardless of its biomedical etiology. Engel and colleagues (1998) have described such a program for Gulf War veterans with MUPS. The intervention, called the Specialized Care Program (SCP), is a three-week intensive outpatient program modeled directly after the University of Washington's Multidisciplinary Pain Center (Loeser and Egan 1989). Preliminary data suggest that treated patients make mild-to-moderate gains in multiple domains, including functional status and health-related quality of life, psychosocial distress, physical symptoms, and physical health concerns (Engel et al. 2000).

Bonica at the University of Washington was among the first to apply a multidisciplinary approach to the treatment of chronic pain patients in the late 1950s (Loeser and Egan 1989). Since then, the approach has gained relatively wide acceptance for work-impaired chronic pain patients, especially those with back pain and fibromyalgia. A recent meta-analysis of 65 controlled studies of multidisciplinary interventions for chronic pain patients noted improvements in return-to-work rates, pain, mood, and health care utilization (Flor-H. et al. 1992). The authors were cautious in their conclusions, noting that the level of methodological rigor for most studies was low.

Recommendations

Given the lack of efficacy and effectiveness studies focused on treatments for patients with MUPS, the committee is unable to recommend specific treatments. However, research conducted to date and described above has demonstrated that there are approaches to treating MUPS that show promise and should be further researched.

Therefore, for Gulf War veterans with unexplained symptoms, the committee recommends that:

- **for the purposes of treatment efficacy and effectiveness studies, explicit criteria for medically unexplained physical symptoms (apart from chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome) be developed and used uniformly in treatment studies and**
- **treatment studies of antidepressant medications, cognitive-behavioral therapy, and a stepped intensity-of-care program be implemented for MUPS.**

6

Conclusion

Despite the fact that the Gulf War was short in duration with 148 combat deaths, health consequences linger 10 years after the fighting ended. Military personnel who served in the Gulf have a significantly higher risk than those who were not deployed to Southwest Asia of suffering symptoms of fatigue, memory loss, difficulty concentrating, pains in muscles and joints, headache, depression, and anxiety. Symptoms range in severity from the barely detectable to completely debilitating, and no single accepted case definition or etiology has been identified that describes or explains this cluster of symptoms.

Numerous research efforts addressing Gulf War veterans' health have attempted to answer many different questions. What health effects might be attributable to service in the Gulf? Are ill veterans receiving appropriate care? How can the federal government be better prepared to meet future obligations to protect the health of military personnel? In fulfilling its charge and responding to a congressional mandate, this committee and its report focused on answering two questions:

1. Are there effective treatments for some of the difficult-to-diagnose, ill-defined, or unexplained health problems experienced by Gulf War veterans?
2. In the future, what approach should be used to assess treatment effectiveness?

The committee found that symptoms experienced by Gulf War veterans are similar to those experienced by patients in other circumstances

who have conditions of unknown etiology, including *chronic fatigue syndrome* (fatigue, headache, cognitive dysfunction, and other symptoms), *depression* (fatigue, loss of memory and other general symptoms, cognitive dysfunction, and sleep disturbances), *fibromyalgia* (joint pain, sleep disturbances, fatigue), and *irritable bowel syndrome* (diarrhea, constipation, abdominal pain, nausea, vomiting, and other gastrointestinal symptoms). Other symptoms reported by Gulf War veterans correspond to the diagnoses of headache and panic disorder. Because of its prevalence in veterans' populations and for purposes of completeness, posttraumatic stress disorder is also included in this report, even though the Department of Veterans Affairs is an acknowledged leader in the treatment of posttraumatic stress disorder. The committee examined treatments for these diagnoses to learn what might be borrowed from these conditions to apply to the treatment of Gulf War veterans. Treatment recommendations are based on demonstrated efficacy in randomized controlled trials.

In addition to these diagnoses, the committee examined approaches to the treatment of individuals with medically unexplained symptoms. No randomized controlled trials have been conducted on treatments for medically unexplained symptoms; therefore, no specific treatment recommendations could be made. However, the committee explored current theories and research on treatment and has recommended a patient-centered approach to care that is appropriate for both those with medically unexplained symptoms and those who receive a diagnosis.

Veterans of conflicts as far back as the Civil War reported health problems similar to those experienced by Gulf War veterans (Hyams et al. 1996). Research into the consequences of war-related illnesses and deployment-related health effects is beginning to examine ways to prevent or at least mitigate such problems. While research proceeds, we are faced with the task of providing effective treatments to Gulf War veterans who are suffering from difficult-to-diagnose, ill-defined, or unexplained illnesses. The committee hopes that the findings and recommendations contained in this report will aid in treating ill Gulf War veterans and in helping devise approaches to assessing the effectiveness of other treatments for these veterans.

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Appendixes

Appendix A

Coalition Forces and Force Strength

Total U.S. forces deployed—697,000. Peak personnel strength—541,400.
Total other coalition forces—259,700 at peak personnel strength.

Country	Number	Country	Number
Afghanistan	300	Norway	50
Argentina	300	Oman	6,300
Australia	700	Pakistan	4,900
Bahrain	400	Philippines	unknown
Bangladesh	2,200	Poland	200
Belgium	400	Qatar	2,600
Canada	2,000	Romania	unknown
Czechoslovakia	200	Saudi Arabia	100,000
Denmark	100	Senegal	500
Egypt	33,600	Sierra Leone	unknown
France	14,600	Singapore	unknown
Germany	unknown	South Korea	200
Greece	200	Spain	500
Hungary	50	Sweden	unknown
Italy	1,200	Syria	14,500
Japan	unknown	Thailand	unknown
Kuwait	9,900	Turkey	unknown
Morocco	13,000	UAE	4,300
Netherlands	600	UK	45,400
New Zealand	unknown	United States	697,000
Niger	600	Zaire	unknown

Appendix B

Workshop Summary

The Institute of Medicine's Committee on Identifying Effective Treatments for Gulf War Veterans' Health Problems held an information-gathering workshop and public hearing on August 14, 2000. The purpose of this meeting was to obtain information that would assist the committee in accomplishing its charge. Dr. Bernard Rosof, committee chair, reviewed the three main tasks of the committee charge. These are (1) to identify and describe methods for evaluating treatment effectiveness, regardless of disease or condition; (2) to identify illnesses and conditions prevalent among Gulf War veterans, including medically unexplained physical symptoms; and (3) to identify valid models of treatment for such illnesses (to the extent that they exist) or identify new approaches, theories, or research on management of patients with these conditions if validated treatment models are not available. The following is a summary of material presented during this workshop and public testimony.

IRRITABLE BOWEL SYNDROME

Howard Spiro, M.D., spoke about diagnosing irritable bowel syndrome (IBS). He defined it as beginning in adolescence and consisting of abdominal pain related to, relieved by, or worsened by bowel movements. A person who develops a change in his or her bowel habits later in life does not, according to Dr. Spiro, have IBS. In the case of later life changes in bowel habits, one must search for a cause for the change, for the disordered bowel. For example, it is possible that infection can lead to

chronic diarrhea in people who never before had that problem, or malignancy can be responsible for a change in bowel habits.

Therapy for irritable bowel depends on symptoms and other contributing factors. If the problem is due to lactose intolerance, one ceases to ingest lactose-containing products. Antimuscarinic agents are used to reduce spasm. Small doses of antidepressants are used for patients who have abdominal pain that one cannot characterize; antidiarrheal agents are used for those with diarrhea. It may be that in some cases the physician will recommend hypnotism or psychotherapy, depending on his or her concept of the cause.

GULF WAR VETERANS IN THE UNITED KINGDOM

Col. John Graham, M.D., spoke about the British experience with the Gulf War. The British government deployed about 50,000 troops. During deployment, health concerns focused on infectious, communicable, and diarrheal diseases as well as battle casualties. There was also a great deal of concern about the possible use of chemical and biological warfare agents.

Dr. Graham reported that veterans' health concerns in the United Kingdom following the Gulf War could be divided into two time frames: before a 1993 British Broadcasting program about illnesses in U.S. Gulf War veterans, and after. Before the program, concerns in the U.K. focused on health effects of exposure to smoke from burning oil wells and to depleted uranium and on treatment for posttraumatic stress disorder (PTSD). Following the program, veterans' concerns coalesced into what became known as Gulf War illnesses and underfinancing of the medical assessment program.

About 3000 veterans have been referred to the British medical assessment program. Symptoms reported are very similar to those reported by U.S. Gulf War veterans. British soldiers do, however, have a higher rate of diagnosed PTSD than that reported in the United States. A research program was commissioned to determine if there was an excess of ill health in the veteran community, to find if such ill health could be related to exposures in the Gulf, and to come up with treatment and preventive strategies. A study by Simon Wessley found that British Gulf veterans report the same kinds of symptoms that British Bosnian veterans do but at two to three times the rate. Nicholette Cherry's study of mortality did not find any statistically significant differences between the Gulf veteran cohort and the Erie group (veterans deployed to Northern Ireland), although there was a slight excess in the number of deaths due to external causes (e.g., automobile accidents) in the Gulf veteran group. These findings mirror the findings of Han Kang's study in the United States.

Simon Wessley has conducted a second-phase study where ill veterans and ill controls are brought in for clinical evaluation. Dr. Wessley

found that about 40% of the veterans who reported themselves as being unwell in Phase I of the study report that they are better in Phase II.

MEDICALLY UNEXPLAINED PHYSICAL SYMPTOMS

A recent article by Craig Hyams, M.D., reviewed the medical literature from the U.S. Civil War through the present. He found that concern about medically unexplained physical symptoms (MUPS) has occurred following every war. According to Dr. Engel, disease is something that is identified by biological indices or exam findings. When we find symptoms but no biological indices or examination findings, then these symptoms are unexplained. This does not, however, mean that they do not have an explanation. But it is not necessary to know the cause of symptoms to treat them.

Dr. Engel stated that a problem in caring for patients with MUPS is “medicine as usual,” that is, the physician takes a history, listens to how the patient feels, examines the patient, then does some laboratory testing with the idea of identifying a diagnosis and a treatment. If the physician is unable to diagnose the problem, several things might happen—treatment may end; there may be further testing, retesting, and referral; the patient may be given pills; or there is surgical intervention. For patients with MUPS, this may result in more harm than good. Certain diagnostic tests have important morbidities associated with them. Additionally, over-testing conveys to the patient the message that he or she has to prove his or her illness, that it is necessary for a test to show something to validate the patient’s problem.

It is also possible that if symptoms are unexplained, many physicians will describe them as somatization or psychological in nature. However, according to Dr. Engel, the first step in caring for patients with MUPS is to legitimize the patient’s illness. Disability already exists; it only becomes worse if it is not acknowledged. Acknowledging the illness allows the patient and the physician to proceed to devising strategies for treating the symptoms. There are multiple levels at which intervention can occur, ranging from the intensive kind of program at Walter Reed for those with severe disability, to much less intensive strategies at the primary care level aimed at preventing patients from developing such severe problems that they require the specialty care approach.

At Walter Reed’s intensive program, the goal for treating MUPS is to improve outcomes through structured care targeting behavior and knowledge, to prevent disability in people with MUPS. The approach advocated is collaborative; that is, the patient and the physician collaborate and negotiate exact and explicit behavioral goals. Many patients are defeated by symptoms they view as out of control. It is the job of the health professional to help the patient become more activated, both physically

and psychologically, to find ways that the patient can help himself or herself to some degree. Progress is monitored by using outcomes the patients have decided are important (e.g., symptom reports, quality of life estimates, or capacity to function and fulfill roles) rather than use of strict biological indices that involve tests.

Dr. Engel stated that, in his opinion, postdeployment symptoms will continue to exist and the best approach is to address them through veteran-centered care that acknowledges illness, rather than disease-centered care that demands diagnosis.

TREATING U.S. GULF WAR VETERANS

About 1800 Registry examinations have been completed at the Seattle VA since the program began in 1993, and the Gulf War Veterans Clinic (established in 1994) is designed to provide long-term follow-up care for veterans. The team of health care providers in the clinic includes a physician, clinical psychologist, nurse practitioner, nurse researcher, female physician for women who prefer a female provider, and specialty consultants and support service providers (physical therapy, dietary, SW, C&P, occupational and vocational therapy). The clinic provides primary care and follow-up, compensation pension examinations, and outreach services, and it conducts research.

The top three symptoms of patients being seen at the Seattle clinic are feeling tired, joint pain problems, and problems of concentration or cognitive difficulties. The average number of symptoms these patients report is five. Data show that these patients have a great deal of distress, as noted by elevated scores on almost all psychiatric self scales. Upon closer examination, the Gulf clinic patients are even more distressed than other Gulf War veterans who are not using the clinic. The SF-36 is administered to determine patient level of functioning, and findings show that on all subscales the clinic's patients fall in the considerably impaired range. Patients report physical symptoms as well as psychiatric difficulties. Approximately 14% of male and 15% of female veterans using the clinic have symptoms consistent with the diagnosis of PTSD.

When veterans at the clinic are asked whether they believe their symptoms will go away on their own, almost 70% indicate strong disagreement; to the statement that "my symptoms are permanent," over 60% express very strong agreement. About 40% of veterans agree they need some type of psychiatric intervention, but more than 80% believe that they need a medical or biomedical intervention to treat their symptoms.

A survey was conducted of internal medicine providers and mental health providers at three Northwest VA hospitals. This survey asked the

providers to indicate what they believe to be the cause of Gulf War veterans' illnesses. About 50% of those surveyed (both internal medicine and mental health providers) responded that they believed the conditions experienced by Gulf War veterans had both biological and psychological aspects with regard to etiology and required treatment consisting of both biological and psychological interventions. The remaining 50% of the mental health providers were more likely to believe that the problems were physical in nature, whereas the remaining half of the internal medicine providers were more likely to believe that the problems are psychological or psychiatric in nature. These same mental health providers were significantly more likely to endorse biological interventions, while the internal medicine providers were more likely to endorse psychological interventions.

It was frequently the case that a Gulf War veteran would go to a medicine clinic, tests would be run but would show no definitive cause or abnormality, and the veteran would be referred for mental health services. Mental health would do a work-up, perhaps identify a psychiatric diagnosis, but the focus would still be on the veteran's symptoms so the veteran would be referred again to the medicine clinic, resulting in a frustrated veteran, frustrated clinicians, and an ineffective treatment model. Therefore, a new treatment model was developed for patients seen at the Seattle Gulf War Veterans Clinic. For patients with medically unexplained physical symptoms we shift from a biomedical management model to a model that emphasizes self-management. In this approach the patient's symptoms are recognized as chronic and the physician and patient work together to define strategies that will help the patient minimize the symptoms' negative impact. The focus is shifted from the cause of the symptoms to the effects of the symptoms. The goal is not necessarily to make the symptoms disappear but to diminish their impact on the patient's life and to increase function. Therapies used include cognitive-behavioral therapy, diet and exercise programs, vocational rehabilitation training, developing coping skills, and referral for compensation and benefit examination. Patient's beliefs about their illness and its causes are examined, and integrated physical and mental health care are provided.

The goal of the program is to maximize health and overall function, not just to diagnose an illness. The focus is on health, not disease, on clear, open communication and access, and on continuity in providers of care. Regularly scheduled visits are important, as is ongoing care. The philosophy driving the care at the Seattle VA Gulf War Veterans Clinic is that we do not have to fully understand the cause of the symptoms the veterans are experiencing to provide treatment that might be helpful.

PUBLIC TESTIMONY

Seventeen individuals testified during the period of public testimony. Of those, 10 are Gulf War veterans, one is the wife of a Gulf War veteran, one is a civilian experiencing the same kinds of problems reported by Gulf War veterans, two are physicians who have treated Gulf War veterans with health problems, one represents a veterans' service organization, one is a physician involved in research, and one is the director of a testing laboratory.

Seven presenters called for more extensive testing to arrive at appropriate diagnoses, although the kinds of tests desired varied among presenters and included tests for activation of coagulation and concomitant hereditary risk factors, bone density, ANA, creatinine, hyperalbumin, spec scans, viral screens, and specialized MRIs and tests for *streptococcus* and *staphylococcus*, peripheral nerve dysfunction, upper motor neuron dysfunction, dysautonomia, brain stem dysfunction, and cranial nerve dysfunction. Several presenters put forward the idea that massive doses of intravenous antibiotics were effective treatments for reducing the severity of symptoms, which they believed were due to infections. Others stated that they believe symptoms are due to immune suppression, autoimmunity, and coagulation activity. Suggested treatments varied based upon laboratory findings. The diagnosis of a genetically mutated strain of leishmaniasis was suggested as a cause of severe symptoms in Gulf War veterans. One presenter stated that cognitive-behavioral therapy and aerobic exercise had helped tremendously in managing pain and anxiety and in getting along with others.

A common theme among those testifying was the call for more responsive service from the VA. Many emphasized that they felt the providers encountered did not believe they were ill, did not understand the circumstances that Gulf War veterans faced during deployment, and were unsympathetic to the impairments and diminished quality of life experienced. It was pointed out that there is a catch-22 for those wishing to receive compensation benefits from the VA. That is, if a Gulf War veteran has an undiagnosed illness, he or she is eligible to receive compensation from the VA. But if the veteran receives a diagnosis, he or she must prove service connection before being allowed compensation.

One presenter stated that enormous amounts of time, money, and effort have been expended to find answers to the questions surrounding the health problems of Gulf War veterans. He suggested that agencies need to better coordinate with each other, that there should be a central repository for blood samples and tissue data, and that there should be a central database and national archives where researchers and others could consolidate their records and make information available to others in

order to enable more efficient examination and analysis of what we know and what we need to find out.

CONCLUDING REMARKS

Dr. Rosof, M.D., chair, thanked those who had provided testimony to the committee. He reviewed the committee charge and reminded those present that while the committee greatly appreciated the information provided, some of the issues raised were beyond the scope of the committee's charge and could not be addressed within the bounds of the current study. Dr. Rosof then concluded the public meeting.

**COMMITTEE ON IDENTIFYING EFFECTIVE TREATMENTS FOR
GULF WAR VETERANS' HEALTH PROBLEMS**

August 14, 2000

WORKSHOP AGENDA

- 9:00 Welcome and Introduction
Bernard Rosof, MD, Chair
- 9:15 Treating U.S. Gulf War Veterans—Presentation and
Discussion
Stephen Hunt, MD
Ralph Richardson, PhD
- 10:00 Gulf War Veterans' Health in the United Kingdom—
Presentation and Discussion
Col. John Graham, British Liaison Officer (Gulf Health)
- 10:30 BREAK
- 10:45 Irritable Bowel Syndrome—Presentation and Discussion
Howard Spiro, MD
- 11:30 Medically Unexplained Physical Symptoms
Charles Engel, MD
- 12:15 Concluding Discussion
- 12:30 LUNCH
- 1:30–1:40 Introduction—Bernard Rosof, MD, Chair
- 1:45–1:55 David Berg, MS
Director, Hemex Laboratories, Inc.
- 2:00–2:10 Janyce E. Brown, BFA
Editor/Publisher, The Surface Report

- 2:15–2:25 Edward J. Bryan, veteran
Health Care Liaison, VA-Boston University
Advisory Group
- 2:30–2:40 Kathleen Hannan, MD, Radiologist
Osceola Regional Hospital, Orlando, Florida
- 2:45–2:55 Edward Hyman, MD, FACP
- 3:00–3:10 James Johnson, US Army (Ret.)
- 3:10–3:30 BREAK
- 3:35–3:45 Kirt Love (Venus Hammack presenting)
Desert Storm Battle Registry
- 3:50–4:00 Mark Colins Maryan
Gulf War veteran
- 4:05–4:15 Ruth McGill, MD
- 4:20–4:30 Kevin G. Messer
Staff Sergeant, USMC Ret.
- 4:35–4:45 Harold Nelson
Staff Sergeant, US Army
- 4:50–5:00 Denise Nichols, Vice Chairman
National Vietnam and Gulf War Veterans Coalition
- 5:05–5:15 Michael Oldaker
USMC, Ret. Medical
- 5:20–5:30 Lawrence Plumlee, Co-President
National Coalition for the Chemically Injured
- 5:35–5:45 Frank Sauer, Sergeant Major
US Army Ret.
- 5:50–6:00 Steve Smithson, Assistant Director for Veterans' Affairs
and Rehabilitation, American Legion
- 6:00 Closing Remarks, Dr. Bernard Rosof, Chair

Appendix C

Unique Considerations in Chronic Fatigue Syndrome

Although fatigue is a common symptom, it is also one that is vague, imprecise, and nonspecific. One of the essential problems in the study and measurement of fatigue, either as a singular entity or as a component of a more well-defined disorder, is the failure to differentiate various types of fatigue. In *Chronic Fatigue and Its Syndromes* (Wessely et al. 1998), the authors challenge the reader to try a “thought experiment” that clearly illustrates the dilemma encountered in defining and assessing fatigue. Below, their experiment has been expanded and modified; however, the message regarding the problems encountered in defining fatigue remains intact.

- You run 5 miles under adverse conditions; even before starting you feel weak and daunted at the prospect. After completing only a portion of the course, you stop; the next day you are sore and tired.
- You are asked to carefully check the references for a 600-page book on fatigue. You feel overwhelmed and really just want to ride your bike. After a few hours your eyes hurt, you are weary, your concentration diminishes, and you are making many mistakes.
- It’s flu season and you are feeling achy and weak. Your nose is running, your throat is sore, and all you want to do is go to bed.
- You have just been up for two days finishing a grant proposal, then had to take a “red eye” and deliver the application in person to make the grant deadline.
- You have been driving in your car for an hour. The landscape is

boring and you can hardly keep your eyes open. All you want to do is sleep. You also often feel like this when at home watching TV.

- Climbing stairs has become progressively, though subtly, more difficult over the last two years.
- Although at first, exertion is not bothersome, after 10–15 minutes, you experience constant cramping in your extremities.

These examples illustrate the multidimensionality of fatigue. Fatigue can occur in anticipation of a task and be influenced by both physical (e.g., the length of the run) and psychological factors (e.g., how rewarding it will be). Fatigue can also be interpreted as a sense of effort needed to perform a task, and both physical and mental tasks may result in fatigue. In conjunction with the sensation or perception of fatigue, the effort associated with a task may be manifested as a change in behavior, especially a decrement in performance (e.g., information processing declines when one feels tired). Fatigue is also most often acute, and in such cases typically resolves after completion of the task. In cases in which fatigue is more chronic and pervasive, it is frequently associated with illness, stress, and sleep disturbances. Finally, as the last two vignettes illustrate, fatigue must be distinguished from sleepiness or drowsiness and true muscle weakness since these symptoms are associated with a different array of conditions, usually primary sleep and muscle disorders.

Thus, it is clear that a simple question regarding “fatigue” is not likely to be very informative or precise. Yet elements of fatigue can be ascertained if care is taken in questioning an individual or in constructing an instrument. However, complicating matters even more is the fact that patients often have additional meanings for fatigue. Sometimes, the word fatigue is used as a synonym for other complaints while at other times it becomes a general term to encompass an array of symptoms that occur together.

Patients will often equate fatigue with weakness, dizziness, lack of coordination or stamina, feeling “spacey,” poor concentration/cognitive abilities, having “rubber legs,” boredom, lack of motivation, malaise, or feeling blue or depressed. Despite the further ambiguity introduced by these descriptors, it is clear that fatigue has distinct physical and mental aspects that must be considered in measurement.