Psychological Influences in Critical Care: Perspectives From Psychoneuroimmunology

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Despite increasing knowledge, including the recent breakthrough in gene mapping in the Human Genome Project, much is still unknown or not understood about the human body. Although hundreds, even thousands, of complex clinical problems might occur during a patient’s stay in a critical care unit, common problems occur on an on-going basis. Some of those problems have their roots in a neuroendocrine response to illness. Authors of epidemiological studies propose what many critical care nurses have known for some time: psychological stress is a component of many of these problems, including, among others, hypertension and hypotension, pain, cardiac disorders, dyspnea, respiratory diseases, fever, infections, and tachycardia. Data suggest a probable link between psychological states and host resistance, and substantial evidence indicates an association between psychological stress and the immune response.¹

Chronic stress may increase susceptibility to disease; however, large individual differences exist in psychological responses to stress. Psychoneuroimmunology, the study of the phenomena of bidirectional relationships between the brain, behavior, and the immune system, is an evolving scientific field. This discipline is also concerned with the subsequent effects of these interactions on the development and progression of disease and how these relationships moderate physical health and susceptibility to disease.²

Although studies have indicated the association between the immune response and stress,³ few prospective, randomized controlled clinical trials have been done to determine if psychosocial interventions can affect the immune system and the progression of medical disorders. Investigators have begun to establish that responses to specific stress situations can result in impaired immunity and that relaxation and cognitive-behavioral stress management have health benefits,⁴ so efforts in helping persons maintain the highest level of health possible have become even more important. Thus, advanced practice nurses, indeed all critical care nurses, provide a critical link between patients and the attainment of health or prevention of disease by incorporating these techniques into therapeutic interventions. In this article, I provide an overview of the immune system and its relationship to stress in the context of psychoneuroimmunology and offer suggestions for health-promoting management of patients experiencing stress.

Relationship Between the Immune System and Psychoneuroimmunology

The immune system is a collection of molecules, cells, and organs that under most conditions interact to protect a person from both outside invaders and the body’s own altered internal cells. The system involves an elaborate defense against various viral, bacterial, and other microbial infections that can act independently or in conjunction with each other.⁵ The immune system as a whole does not function independently; rather, the immune and
neurological systems communicate with each other in 2 principal ways: by means of hormones that the brain regulates and by means of nerve fibers that communicate with immune cells. More recently, the term psychoneuroimmune network has been used to describe this activity. This interconnectedness at the molecular level between the neuroendocrine system and the immune system has been linked to neuroendocrine hormones or neuropeptides and other mediators that influence immune responses. Neuropeptides assist with the movement of immunocytes, immunocytes in turn produce neuropeptides, and nerve cells produce immune-associated cytokines.

Acute stress can alter immunocompetence; conversely, immunological alterations can be associated with stress. Substantial data support the idea that stress may be one of the most important determinants in the higher rates of respiratory tract infections, malignant diseases, and resistance to metastasis. For example, cancer cells may affect T and B lymphocytes, and patients with cancer have decreased percentages of T-cell subpopulations. Psychoneuroimmunology is, in part, a multidisciplinary effort to determine if psychological factors have an impact on health due to their effect on immunocompetence.

Immunocompetence is provided and maintained by 2 cellular systems that involve lymphocytes (white blood cells). These 2 functionally distinct yet interactive parts consist of elements that are acquired (adaptive) and elements that are innate (nonadaptive) (Table 1). Lymphocytes are produced by the body’s primary (bone marrow and thymus) and secondary (lymph nodes and spleen) lymphatic organs. Lymphocytes are descendants of the bone marrow’s collection of stem cells. B cells (bursa-dependent or bone marrow–derived lymphocytes) mediate a circulating or humoral response, whereas T cells (thymus-dependent lymphocytes) mediate a cellular or cell-mediated response. However, the long-held view that the thymus produces T cells and that bone marrow produces B cells was recently challenged, as was the oversimplified view of the immune response as separate humoral and cell-mediated responses rather than the more accurate view of it as 2 parallel antigen-specific immune responses with distinct purposes.

<table>
<thead>
<tr>
<th>Type of immunity</th>
<th>Characteristics</th>
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<tr>
<td>Acquired</td>
<td>Response is specific&lt;br&gt;Distinguishes between foreign cells and self&lt;br&gt;Distinguishes one antigen from another antigen&lt;br&gt;Memory is induced&lt;br&gt;Makes immunization possible&lt;br&gt;Makes resistance to infection possible</td>
</tr>
<tr>
<td>Innate</td>
<td>Response is nonspecific&lt;br&gt;Cannot recognize invaders</td>
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Current research focuses on 2 different neurotransmitters that interact directly with immune cells: norepinephrine and substance P. Norepinephrine works on receptors on thymus-derived lymphocytes and enhances expression of chemicals that play a significant role in the modulation of immune responses. Norepinephrine also initiates the release of particular antibodies (IgM). However, although norepinephrine is an immune agonist, it also can inhibit the destruction of tumor cells and cells infected with herpes simplex virus.
Neurokinins are a newly identified neurotransmitter system composed of 3 related peptides. The most well known of these is substance P. Substance P is present in both the peripheral and the central nervous systems, where it is usually found with one of the other neurotransmitters, most commonly serotonin. It is hypothesized that substance P plays an active role in the regulation of pain, asthma, psoriasis, inflammatory bowel disease, emesis, migraine, schizophrenia, depression, and anxiety.\textsuperscript{10}

Lymphocytes and macrophages have receptors for substance P. Substance P helps lymphocytes move to areas of inflammation, triggers production of IgA antibodies, and promotes phagocytosis (digestion of foreign material and other debris) and chemotaxis (movement of immune cells toward, for example, a site of infection).

**The Immune System**

No matter how important any single part of the immune system might be, no part is effective without communication with the whole system. The synergy of the combined immune system, not the power of any one element, is what makes the system so effective a protector. Thus, although for descriptive purposes dividing the immune system into acquired and innate systems seems suitable, this division is somewhat artificial. Both systems influence each other and are in turn shaped by their environment.

**Acquired Immunity**

Acquired or adaptive immunity has 2 key attributes: specificity and memory. First, specificity enables the body to distinguish foreign cells from self and to distinguish one foreign antigen from another. Whereas a macrophage will overcome any foreign cell, the cells that mediate acquired immunity have mechanisms to select a precisely defined target. Second, the establishment of memory cells enables immunization and resistance to reinfection with the same microorganism for an extended period. Memory is an antigen-specific phenomenon. The ability of memory cells to respond to an antigen depends on previous exposure to the antigen; immunological memory of an antigen may persist for years to decades. The cells responsible for these extraordinary abilities are B and T lymphocytes. The life span of these cells varies from days to months or years, depending on the type and subtype of the cells.

**B Cells**

B cells, the cells associated with humoral immunity (Table 2\textsuperscript{•}), are created daily in the bone marrow and circulate throughout the bloodstream. B cells are responsible for the rapid response to extracellular and mucosal microorganisms, including some viruses and parasites (if the organisms spend part of their life cycle in extracellular fluid). When stimulated by antigen, B cells proliferate and differentiate into memory B cells and plasma cells. The plasma cells produce the circulating soluble factors known as antibodies or immunoglobulins. Stem cells differentiate and give rise to a population of precursor B cells. These cells acquire the ability to express immunoglobulin on their surfaces. Each fully mature B cell can synthesize immunoglobulin and can express different immunoglobulins on its surface. Because each B cell has a different immunoglobulin, each cell binds to a different antigen. However, most often a B cell will find nothing to bind to in its short life span and thus will be rapidly replaced by a new B cell.
Circulating antibodies or immunoglobulins such as IgG, IgM, IgA, IgD, and IgE provide an important defense mechanism against disease in healthy persons, but the humoral response can become hyperactive or hypoactive in a variety of disease states. Hyperactive responses or increased levels of immunoglobulins can occur in 2 ways: either acutely, as a reaction to a disease or inflammatory stimulus ("acute-phase" reaction) or chronically, as in autoimmune or immune-mediated diseases, chronic infections, and certain types of bone marrow and organ cancers. Hypoactive responses or decreased levels of immunoglobulins can be due to rare genetically based immunodeficiency states such as agammaglobulinemia or hypogammaglobulinemia and to the immunosuppression associated with chronic viral, bacterial, or parasitic infections; cancers; aging; genetic factors; malnutrition; drugs; toxins; pregnancy; childbirth; lactation; and stress.

T Cells
T cells act as coordinators and effectors of the immune system (Table 3). T cells serve 2 roles. First, they act as the coordinator of other acquired immune responses by producing a wide variety of cytokines and a variety of cell-surface polypeptides that serve as receptors to ensure appropriate cell-cell interactions. Second, they act as the primary responders to chronic intra-cellular infections. T cells are responsible for destroying infected or cancerous cells and for coordinating all acquired immune responses; T cell–mediated immunity is generally called cellular immunity. Cellular immunity can be further divided into the major histocompatibility complex (MHC) class I and CD8+ system and the MHC class II and CD4+ system.
Cell-mediated immunity involves the lymph nodes, thymus, spleen, intestine, and tonsils and a mucosal secretory component mediated by IgA. The numerous cytokines secreted by T cells and the molecules on the surface of the cells are critical for the control of all other immune elements. Some cytokines, including interferons, interleukins, colony-stimulating factors, tumor necrosis factor, and chemokines, are considered components of cellular immunity because they induce an antiviral state in other cells. Other cytokines play important roles in regulating the interactions of the immune system.

The 2 main types of T cells are killer or cytotoxic T cells (TC or CD8+ cells) and helper T cells (TH or CD4+ cells). Each cytotoxic T cell has a unique cell-surface molecule called a T-cell receptor. Mature CD8+ cells journey throughout the body searching for cells that bear complexes to which the T-cell receptor will bind; binding of the receptor to the complex leads to destruction of the complex-bearing cell. However, whereas immunoglobulins can recognize any type of antigen, T-cell receptors recognize only short amino acid chains or peptides displayed on the surface of cells in conjunction with MHC molecules. Most, if not all of the cells in the body constantly produce MHC molecules and attach small peptides to the molecules for expression on the cell surface. Cytotoxic T cells explore the surface of all cells for MHC-peptide complexes. Helper T cells are probably the most important of the immune cells, even though they do not directly destroy any diseased cells or microorganisms. Rather, they produce a surplus of chemical factors that regulate all other aspects of the immune system. Like cytotoxic T cells, helper T cells act by recognizing MHC-peptide complexes via T-cell receptors. Helper T cells recognize the presence of a foreign antigen and then stimulate production of antibodies and produce cytokines that "turn on" or activate other T cells. No acquired immune response could occur without the chemicals that helper T cells produce. The suppression or absence of an immune response, as may occur in infection with human immunodeficiency virus, results in a collapse of the immune system. Suppressor T cells function in an opposite manner to helper T cells. They act to reduce or "turn off" the immune response.

**Cooperation Between Immune Cells**

Finally, cooperation between the various subpopulations of T cells and between T and B cells is important in the normal humoral and cellular immune responses. Hyperactive cellular immune responses occur in autoimmune and other immune-mediated diseases whereas hypoactive
cell-mediated immunity causes immunosuppression and immunoincompetence. Although because of its specificity, acquired immunity is the focus of more research than is innate immunity, both acquired and innate immunity are inter-related and depend on each other for proper function.

**Innate Immunity**

Innate or nonadaptive immunity refers to immune elements that are nonspecific. These elements generally can distinguish between self and foreign tissues or organisms but cannot recognize a particular invader. Similarly, they respond to all foreign tissues and organisms in the same manner, and despite repeated exposure to the same antigen, they neither adapt nor improve their effectiveness against the antigen.

If an infectious organism cannot enter the body, an immune response to the organism is not needed, and the body maintains a healthy state. On the other hand, if an organism breaks through the body’s defensive mechanisms, an immune response occurs. The importance of the skin and mucosa in resisting infection cannot be overemphasized; they are the locations at which most microorganisms are stopped. Areas of broken skin are more susceptible to infection than is healthy intact skin. Similarly, the mucosal tissues of the eyes and the gastrointestinal and genitourinary tracts are not as effective as intact skin at resisting microorganisms. However, mucosal secretions contain a number of chemical elements, including enzymes such as lysozyme, that can prevent infections by destroying the outer surface of many bacteria. Nonmucosal tissue contains non-specific immune chemicals; one of the most important is a complex known as complement. Acting alone, a fragment of complement attracts various immune cells to the surface of foreign organisms. When multiple fragments are brought together, they produce destructive pores in the membranes of microorganisms. Cellular release of other chemicals, including kinins and histamine, in response to trauma or microbial invasion results in an inflammatory response.

**Relationship Between the Immune System and Stress**

The understanding of the role of emotional and immunological responses to stress has increased since the early 1980s when the relationship between the immune and the nervous systems became a field of study. Relationships between these 2 responses have been determined empirically; however, the importance of their effects has not been demonstrated, and so the evidence remains controversial. Studies indicate that stress seems to be related to changes in both the numbers of white blood cells in circulation and the quantity of antibody in the blood. For example, psychological stressors induce cell division among CD8+ cells, thereby increasing the number of these cells and suppressing immune function. Moreover, stress is associated with changes in the functioning of immune cells. Links between negative and psychological states such as anxiety, depression, hopelessness, and grief and the immune system have been explored. Results suggest that depressed and anxious mood states are associated with decreases in lymphocyte proliferation and the activity of natural killer cells and with changes in the number of white blood cells and the quantity of antibody circulating in the blood. In addition, a person’s ability to produce antibody to a specific substance seems to be related to the amount of anxiety he or she is experiencing. Greater anxiety is associated with a decrease in the amount of antibody produced after exposure to a potentially harmful substance. Further, a connection seems to exist between the duration and quality of the stress and the amount of immune change. For example, the longer the stress and the greater the degree of pessimism, the greater is the decrease in the number of specific types of lymphocytes. Stress is also associated with the activation of several systems, including the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Activation of these 2
pathways results in elevated blood levels of hormones, specifically cortisol and the catecholamines epinephrine and norepinephrine. Blood levels of these hormones are related to immune functioning. For example, acute increases in cortisol and epinephrine are related to decreases in the number of circulating white blood cells. The interpretation of changes in the immune system that are unequivocally due to stress is difficult. Nevertheless, stress clearly has an adverse effect on health, probably mediated at least in part by a person’s immune system. This effect is of particular relevance to nurses and the long-held belief in the connection between the mind and the body. Thus, critical care nurses must incorporate this knowledge into a management plan appropriate to the well-being of each patient and the patient’s family.

Management of Psychological Stress
Hans Selye\textsuperscript{16} concluded that the human body has a finite capacity for handling stress and that when that capacity is exhausted, the body can no longer fight off the effects of stress and dies. The multiple stressors associated with hospitalization, acute illness or injury (particularly, traumatic injury), chronic diseases, or even transplantation reduce a patient’s perceptions of control, resulting in a stress response. This increased stress response has been associated with altered immune function and decreased immunity.\textsuperscript{11,12,17} Under those circumstances, all the technology, pharmacological or herbal agents, or other well-intentioned interventions will prevent neither the cumulative effects of stress nor its ultimate outcome. However, the effect of stress can be reduced; that is, the stressors can be avoided whenever and wherever possible, and the tension released so that the harmful effects of stress are alleviated. More specifically, patients who are encouraged to use health-promoting behaviors in the management of stress may have a physiological benefit as well as the intended psychological benefit.\textsuperscript{18} Nurses can help patients manage psychological stress by doing the following.

Encourage Hope
Persons who consider themselves healthy have goals, aspirations, plans, and purpose that guide and focus their lives, providing them with hope, meaning, and substance. Hope is a dynamic internal process related to the experience of meaning and the realization of life’s possibilities. This realization allows a person to make satisfactory and significant life choices. Hope has also been described as an anticipation of a future that is good\textsuperscript{19} and can give a sense of internal peace and freedom. Hope is necessary for a person to set goals and anticipate a positive outcome. Yet, despite progress in the treatment and diagnosis of some illnesses such as infection with human immunodeficiency virus, many patients and their families—and healthcare providers—have an attitude of hopelessness and pity. It is important therefore for advanced practice nurses to foster hope through a sense of self and an anticipation of some degree of recovery among all participants in the process of achieving wellness.

Promote a Sense of Autonomy
Supporting a patient’s values means, inherently, advocating that patient’s personal decision making and choices or sharing the decision making instead of making unilateral judgments for the patient. However, shared decision making cannot occur without trust. Trust is one of those overarching principles that form the bond between nurses and patients. Patients need to feel safe in the environment of decision making. A person’s autonomy provides for freedom of choice to use various dynamic methods of maintaining health and preventing illness, with the person choosing what will be of most help or not. Nurses assess all a patient’s activities toward achieving health or a more positive state from the patient’s perspective. When these activities involve complementary or alternative methods, nurses must nonjudgmentally assess whether
these activities are harmful and whether the activities are being used to promote or maintain health or prevent illness.20

**Use Visualization, Imagery, and Biofeedback**

Visualization, imagery, and biofeedback are acceptable complementary therapies for care of patients with terminal illnesses.21 For example, many cancer centers follow a wellness model rather than a sickness model, with protocols designed to help restore or maintain the greatest level of health possible. The rationale is that the chance that cancer will take over the body is reduced when the body is healthy and functioning optimally. To this end, advanced practice nurses in critical care can take lessons from the wellness model and ensure that any management plan incorporates each aspect of the whole person—physical, emotional, cognitive, and spiritual. Participation in stress management; relaxation; and efforts to enhance immune functioning, psychological well-being, and empowerment play large roles in positive outcomes, and, in fact, are some of the dominant activities used by cancer survivors. Almost any patient can learn these techniques, which are used to enhance the goals of clinical psychoneuroimmunology.

Visualization and imagery are directed toward the specific healing process and are a vehicle for conscious and unconscious communication of psychological and physiological processes. An inextricable connection exists between visualization and biofeedback. In its most simple terms, visualization allows patients to see what their bodies must do, and biofeedback tells them how well the body has responded to those cues and instructions.

**Incorporate Strategies That Promote Sleep**

The disturbance of sleep is sometimes an inevitable outcome of acute care hospitalization. However, sleep is necessary for the body to recover from the effort and strain placed on it by a hypercatabolic state. Restlessness that prevents rapid-eye-movement sleep adversely affects sleep quality, and in general, sleep deprivation leads to immunosuppression.2 Typically, benzodiazepines have been the pharmacological agents of choice for the treatment of sleeplessness, but they should be used with caution in hospitalized patients. Rather, nonpharmacological interventions for insomnia, including sleep hygiene measures, should be used. It cannot be overemphasized that basic nursing interventions such as providing uninterrupted periods of sleep, promoting comfortable positioning, reducing environmental sounds and lights, incorporating a patient’s own presleep measures, using back rubs, encouraging relaxation techniques, and ensuring the patient’s privacy will immeasurably help a patient sleep.

**Consider the Use of Music**

For centuries, healing has been associated with the use of music because of the capacity of music to bring about mental, emotional, and physical calmness. Relaxing music in a quiet, restful environment can induce relaxation, thereby reversing the deleterious effects of the stress response. In particular, reductions in heart rate, respiratory rate, and myocardial oxygen demand can be significantly greater in persons who listen to music than in those who do not.22–24

**Alleviate Pain**

The role of pain control in disease has only recently been investigated, but the results suggest that pain itself is a detriment to recovery. Adequate pain relief not only is a primary concern in caring for patients who are experiencing pain but also may be a physiological necessity. Because pain can increase the stress response, alleviating or reducing pain is important. In addition to the use of pharmacological agents, cognitive-behavioral strategies are an important component in the management of pain25 and generally include relaxation training, self-monitoring of stressors, and cognitive coping strategies. These strategies are supported by the Agency for Health Care Research and Quality (formerly the Agency for Health Care Policy and Research) as adjuncts to
the traditional use of analgesics for the management of pain due to cancer. The strategies are used to mitigate the overwhelming stressful response and are directed toward changing a person’s belief about his or her pain.

**Recommend Use of Vitamins**

Certain vitamins are typically depleted in the body during prolonged periods of stress: vitamins C, B complex, and D. Specifically, ascorbic acid, thiamine (vitamin B₁), pyridoxine (vitamin B₆), pantethine (the active form of vitamin B₅) and methylcobalamin (vitamin B₁₂), the amino acid tyrosine, and other nutrients such as lipoic acid, phosphatidyl-serine, and plant sterol/sterolin combinations may help in sustaining an adaptive response and in minimizing some of the systemic effects of stress. Controversies abound about the effects of supplements, and supplements may not be necessary for patients who have an adequate diet. In the critical care setting, however, an adequate diet is often unlikely or not possible. Thus, ensuring that patients are provided adequate nutrition and supplements, if necessary, may help in the response to stress.

**Determine Need for Psychotropic Medications**

The stress of hospitalization, including the added stress of acute illness or injury, may lead to various responses, including anxiety, depression, and other coping difficulties. Psychotropic medications can be used judiciously as an adjunct to manage short-term emotional stress during hospitalization. Long-term use of psychotropics and use of these medications in patients who have preexisting psychiatric disorders or who were receiving psychotropic drugs at the time of admission require a referral to an appropriate healthcare provider. The most appropriate medications for short-term intervention fall into 3 general categories: antidepressants, anxiolytics, and sedatives/hypnotics (Table 4).
**Conclusion**

Research in psychoneuroimmunology has defined the role of stress in reducing the effectiveness of the immune system in combating infection and other stress-related disorders. Although anxiety and stress most probably interfere with recovery through behavioral and physiological mechanisms, the exact mechanism of interference is unclear. Awareness and interest in the health benefits of mind-body interventions, particularly the use of visualization, imagery, and biofeedback to ameliorate the effects of anxiety and stress, have increased. Research has provided undeniable evidence of the inter-connectedness of the mind and body, yet, for a variety of reasons, some healthcare providers are reluctant to use this knowledge as an adjunct to conventional therapy. At the very least, these complementary and adjunctive therapies may improve patients’ quality of life when cure is not possible.

**References**


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<table>
<thead>
<tr>
<th>Medications and examples</th>
<th>Uses</th>
<th>Precautions/comments*</th>
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</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td>Treat depression</td>
<td>Do not give antidepressants with monoamine oxidases</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>Promote sleep</td>
<td>May cause somnolence</td>
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<tr>
<td>Fluoxetine (Prozac)</td>
<td>Provide pain control</td>
<td>Monitor patients for bradycardia and sinus arrest, because SSRIs may interact with many cardiovascular drugs</td>
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<tr>
<td>Paroxetine (Paxil)</td>
<td>Effects generally require 7 days of treatment</td>
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<tr>
<td>Sertraline (Zoloft)</td>
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<td>Fluvoxamine (Luvox)</td>
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<td><strong>Tricyclic antidepressants</strong></td>
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<td>Imipramine (Tofranil)</td>
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<td>Desipramine (Norpramin)</td>
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<tr>
<td>Nortriptyline (Pamelor)</td>
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<tr>
<td><strong>Anxiolytics</strong></td>
<td>Treat acute anxiety</td>
<td>Do not give with monoamine oxidases</td>
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<tr>
<td>Benzodiazepine, short acting</td>
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<td>With all benzodiazepines, monitor patients for hypotension, respiratory depression, and rebound; use cautiously in patients with history of drug abuse</td>
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<tr>
<td>Alprazolam (Xanax)</td>
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<td>Benzodiazepines, intermediate acting</td>
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<td>Lorazepam (Ativan)</td>
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<td>Benzodiazepines, long acting</td>
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<td>Diazepam (Valium)</td>
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<td>Flurazepam (Dalmane)</td>
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<tr>
<td>Phenothiazine</td>
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<td>Promethazine</td>
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<tr>
<td>Prochlorperazine (Compazine)</td>
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<tr>
<td>Other</td>
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<td></td>
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<tr>
<td>Buspirone (BuSpar)</td>
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<tr>
<td><strong>Sedatives/Hypnotics</strong></td>
<td>Promote onset and continuity of sleep</td>
<td>Use short term (7-10 days)</td>
</tr>
<tr>
<td>Zolpidem tartrate (Ambien)</td>
<td></td>
<td>Monitor patients for orthostatic changes</td>
</tr>
<tr>
<td>Trazodone (Halcion)</td>
<td></td>
<td>Rebound insomnia may occur after cessation of drug</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td></td>
<td>Monitor blood and urine</td>
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*Use all drugs with caution in elderly persons.*


