Anxiety disorders in family practice

Diagnosis and management

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SUMMARY

Anxiety disorders are common in family practice. Although not ideal, the DSM 3-R definitions of anxiety disorders provide a framework for diagnostic precision that assists physicians in choosing the best treatment. Assessing functional status helps determine the need for psychotherapeutic or pharmacologic intervention. We evaluate specific interventions and suggest the risks and benefits for each disorder.

RÉSUMÉ

Les troubles anxieux sont courants en médecine familiale. Bien que le DSM-III-R ne propose pas de définitions idéales des troubles anxieux, cet outil constitue néanmoins un cadre de travail pour préciser le diagnostic et pour aider les médecins à choisir le meilleur traitement. L'évaluation de l'état fonctionnel contribue à préciser le besoin d'intervention psychothérapeutique ou pharmacologique. L'article évalue certaines interventions spécifiques et discute de leurs risques et avantages dans chacun des troubles.

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ANXIETY IS A COMMON, IMPORTANT, and challenging problem that confronts every family physician. Workload surveys have demonstrated that anxiety and depression are two of the five most common practice problems, occurring in between 3% and 5% of all practice encounters.[1] Population-based surveys have found that between 25% and 30% of adults complain of at least one important life stress that causes symptoms of anxiety each year.[2,3] One practice survey found that 29% of middle-aged patients, who visited their family physicians during 1 year, had anxiety recorded as one of their presenting symptoms; another survey found 20% of all patients reported anxiety symptoms.[4,5]

Part of a family physician's ambivalence about dealing with anxiety symptoms arises from the perception that everyone experiences signs and symptoms of anxiety almost daily and that anxiety should be accepted as part of normal living. Thus, anxiety might not require the attention that "serious" health problems require. However, the importance of severe anxiety disorder is illustrated by an individual's deteriorating ability to function when suffering from unresolved grief, uncontrolled panic disorders, socially paralyzing agoraphobia or social phobias, or totally consuming obsessive-compulsive behaviour. More difficult to recognize, but possibly more common, are alcoholic or addicted individuals whose addiction can be attributed to self-medication as a means of controlling social phobia or panic disorder.

Even less easily quantified are the negative effects on the lives of spouses, children, or families in close contact with those suffering serious anxiety disorders. Few people are likely to pass through life without either personally suffering from a serious anxiety disorder or being in close contact with someone who is.

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Diagnosis

Both family medicine and psychiatric diagnostic classification systems provide a framework to help physicians decide when and how to intervene. The most common form of anxiety seen by family physicians has been called "acute situational disturbance."[6] This term is also found in the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM 3-R)[7] but

is not considered an anxiety disorder. The *International Classification of Primary Care* (ICPC)[6] defines acute situational disturbance as anxiety emerging from problems of living, including acute grief reaction brought on by a great loss or anxiety brought on by problem relationships with spouses, children, friends, relatives, and fellow workers.

The DSM 3-R defines problems at the extreme end of the continuum of anxiety where symptoms are the most severe and infrequently seen in family practice.[7] However, understanding the extreme forms of anxiety disorders assists family physicians to determine the therapeutic threshold for each individual. This should bring more precision to diagnosing anxiety disorders and should lead to more appropriate therapy.

Panic disorder. Panic disorder is characterized by discrete periods of intense fear or discomfort, usually lasting minutes and occurring unexpectedly. The onset of an attack is described as a feeling of sudden, intense fear or apprehension accompanied by many of the physical signs and symptoms of anxiety, such as shortness of breath, faintness, choking, dry mouth, sweating, nausea, flushing, palpitations, fear of dying, fear of losing self-control, and fear of losing bowel or bladder control. These symptoms often bring patients to the emergency room. Physicians must assess how much the fear of these episodes impairs an individual's function and quality of life, as well as how long and how often the episodes occur, so that they can judge when intervention is required.

Agoraphobia. Agoraphobia is fear of being in a place or situation from which escape might be difficult or embarrassing in the event of an anxiety attack. Fear leads patients to avoid or suffer anxiety symptoms while in the dreaded place or situation. Agoraphobia most commonly develops in 20- to 30-year-old women and leads to poor quality of life and impaired social function.

Panic disorder without agoraphobia. This disorder is less disabling than panic disorder with agoraphobia, which often devastates social and work functions. Panic is equally prevalent among men and women. The longer the symptoms last, the greater the risk of depression. Several years of panic attacks puts sufferers at high risk for alcohol and drug abuse and increased risk for suicide. Family physicians should be very sensitive to the use of self-medication to mask the symptoms of panic.

Minor social phobias. Such phobias, relatively common in the general population, involve fear of acting in a humiliating or embarrassing way in public. The phobia leads to avoidance behaviour and various forms of self-medication, characterized by the "stiff drink" before carrying out some dreaded social task. Individuals who suffer social phobias are at risk for alcohol or benzodiazepine abuse because both provide socially acceptable ways of controlling discomfort.

Simple phobias. Simple phobias involve the fear of an object or situation. Objects are usually animals, insects, or reptiles, and the fear could extend to buildings or places where encounters with the object might occur. This disorder is more common among women than men and is usually minimally disabling unless the feared object is very common.

Obsessive-compulsive disorder. This disorder involves an obsession with persistent ideas, thoughts, or impulses that are intrusive or senseless. Thoughts of violence, fear of bacterial contamination, or doubts as to one's own behaviour are characteristic of this disorder. A compulsion is a purposeful repetitive behaviour usually performed in response to an obsession. The behaviour is designed to neutralize the dreaded obsession. Depression is often present with these behaviours, and functional impairment can become quite severe. Sufferers are at high risk for alcohol and benzodiazepine abuse. Minimally disabling presentations of obsessive-compulsive disorder are commonly seen in family practice.

Posttraumatic stress disorder. This usually occurs after a violent or life-threatening trauma. The disorder is characterized by recurrent episodes of severe

anxiety symptoms when the individual recalls or is reminded of the trauma. Depression often accompanies posttraumatic stress disorder.

Generalized anxiety disorders. Generalized anxiety disorders are defined in the DSM 3-R as definite anxiety symptoms during most of each day for more than 6 months in response to irrational concerns. None of the previously defined anxiety disorders are present. Although one might expect generalized anxiety disorder to be common, it is rarely seen in family practice or psychiatry in the way it is described in the DSM 3-R. Acute situational disturbances are often mislabeled as generalized anxiety disorders.

Although not officially acknowledged in any classification, concurrent anxiety and depression are commonly seen by family physicians. Mixed anxiety and depression often exist in persons suffering from serious disease or chronic physical illness, or in individuals who feel trapped in an impossible situation.

Determining the type of therapy is a judgment ideally made by both physician and patient. To determine the threshold for therapy, physicians must consider the effect of anxiety on the patient's physical, emotional, social, and psychological function; the patient's quality of life, as perceived by the patient; and the duration and frequency of the episodes of anxiety.

Assessment of severity

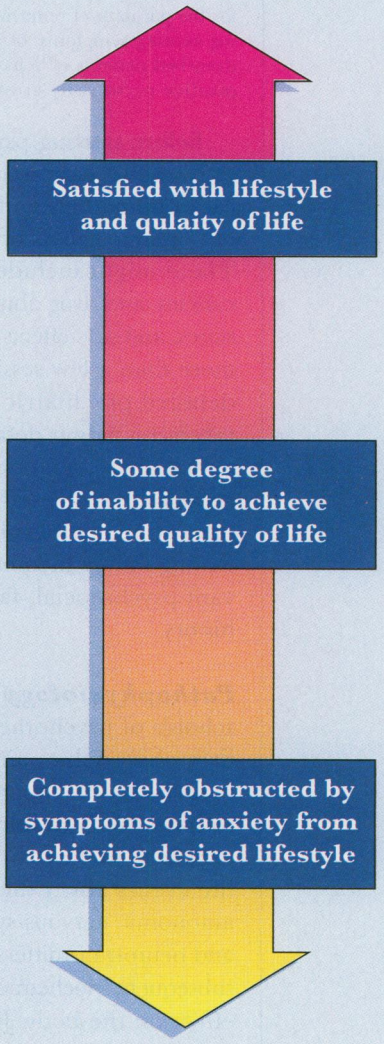
It is important for family physicians to consider the severity of anxiety symptoms (*Table 1*) on a continuum. At one end are most people (more than half of the population) who experience signs and symptoms of anxiety from time to time but are able to cope with life stresses in ways that do not really affect their function or quality of life. The further one moves along the continuum, the more disabled physically, emotionally, socially, and psychologically the patient is, and the poorer his or her quality of life (*Figure 1*).

The challenge for family physicians is to assess the functional status and quality of life of each patient and to determine when he or she has deteriorated to the

Table 1. **Assessment of severity:** *Physical, emotional, psychological, and social effects of the anxiety must be considered.*

SEVERITY	QUALITY OF LIFE
Mild	Patient can recall incidents in the past when, because of anxiety-related symptoms, some aspect of function was impaired.
Moderate	Function important to the individual was noticeably impaired on several occasions in the previous few months.
Severe	Several aspects of function important to the individual were seriously impaired each week during the last 3 months.

Figure 1. **Quality of life continuum:** *Quality of life, as perceived by the patient, can be measured along an analogue scale. The continuum might combine acceptance of physical limitations with the inability to achieve life goals or objectives.*



point where intervention is needed to control signs and symptoms.[8] Once the decision to intervene has been made, physicians must decide which therapy will potentially provide more benefit than harm.

The threshold for therapeutic intervention is influenced by each individual's values and life situation. Every diagnostic and therapeutic boundary is blurred by an individual's past and present circumstances and the social supports available. The quality of the physician-patient relationship also influences the decision as to when therapeutic intervention is indicated.

Managing anxiety with psychotherapy

The Ontario Health Insurance Plan fee schedule defines psychotherapy as:

> any form of treatment for mental illness, behavioural maladaptions that are assumed to be of an emotional nature, in which a physician deliberately establishes a professional relationship with a patient for the purposes of removing, modifying, or retarding existing symptoms, or attenuating or reversing disturbed patterns of behaviour, and of promoting positive personality growth and development.[9]

Before starting psychotherapy, physicians should carry out appropriate physical examinations and blood tests to rule out organic causes of anxiety symptoms. These might include hyperthyroidism, caffeine and drug abuse, drug withdrawal states, and side effects of medical drugs. If more than a few sessions are planned, a detailed psychiatric history should be taken, including details of physical and sexual abuse, abandonment, family disruptions, loss of loved ones, accidents and operations, mental health problems among family members, and other relevant psychosocial, family, and personal history.

Pathophysiology. There are many schools of psychotherapy, each with its own philosophies and techniques.[10] No matter what the approach, patients need to have the pathophysiology of anxiety explained to them. Stresses, traumas, and life events affect the body through the autonomic nervous system via hormones and neurotransmitters. Each feeling has a subsequent biochemical and physiological effect on the body. If these feelings are repressed, they can cause symptoms through the autonomic nervous system. Explaining the pathophysiology helps patients understand the connection between mind and body.

Relaxation. All family physicians should be able to teach a progressive relaxation exercise to their patients. This could be tape-recorded during a session tailored to the patient's problem. The patient should be encouraged to rehearse relaxation at each visit and to practise daily at home.[11] The relaxation exercise might include breathing awareness and progressive muscle relaxation, as well as a visualization or guided imagery of a comfortable, relaxing scene from the past with visual, auditory, and kinesthetic aspects.[12] This visualization could then be used as a hypnotic induction for desensitization for phobias, ego strengthening to build self-esteem, or age regression to reframe serious traumas of the past.

Creative listening. Many patients need someone to listen to them in a nonjudgmental, supportive, empathetic way. Even without any formal postgraduate training in psychotherapy, family physicians can still help patients deal with acute situational disturbances like the death of a loved one, marital break-up, loss of employment, or life's other transitions. You can be a good creative listener, "a big ear" playing back to the patient the essence of what is said, reflecting content and affect. Rogers and Stevens postulated "empathy", "unconditional regard", and "genuineness" as necessary conditions for psychotherapy.[13] Dr Stan Greben in his book, *Love's Labours. Twenty-five Years of Experience in the Practice of Psychotherapy*,[14] talks about six attributes that are important for a therapist: empathetic concern, respectfulness, realistic hopefulness, self-awareness, reliability, and strength. Asking sensitive questions, dealing with negative self-esteem, removing guilt, helping patients express feelings in constructive ways, uncovering past traumas, and helping patients to mobilize their own resources can help them over a crisis and strengthen them after the crisis has passed.

Behaviour therapy. Behaviour therapy suggests that anxiety is a learned habit that

has been environmentally reinforced. Through education, practical advice, problem solving, desensitization, progressive relaxation, and positive and negative reinforcements, symptoms are removed. A cognitive version is the technique of thought stopping. The patient is taught to identify and put into words the anxiety-producing thoughts and belief systems that create the anxious feelings. The false beliefs are then attacked and disputed, and new, more positive, sensible, and affirmative beliefs are practised. Encouragement, assertiveness, eliminating "shoulds," and reframing are emphasized. Biofeedback is still used in specialized centres to teach patients how to modify their symptoms physiologically. Asking patients to keep a journal of thoughts, feelings, and dreams can provide insight and awareness.

Experiential therapy. Experiential therapies develop the patient's own awareness of bodily sensations, postures, tensions, and movements with an emphasis on somatic processes.[15] Performing dreams, psychodrama, acting out fantasies, and entering into dialogues with parts of oneself are some of the techniques used to bring patients into moment-to-moment awareness of the here and now. Emphasis is on feelings, spontaneity, and getting patients to stop intellectualizing, which is often seen as a defence against feeling and experiencing.

Negative thinking. Sometimes catastrophizing is a habitual way of thinking passed on from a parent. Patients internalize their parent's critical, self-defeating, self-deprecating, severe, judgmental voice. Because they carry around this internalized degrading voice, they feel chronically anxious. Negative self-esteem is often central to anxiety disorders. Resolution of this persistent, negative self-image allows people to feel positive about themselves and the future.

Practical matters. A patient's motivation, resistance to intervention, and the transference and countertransference aspects of therapy are most important. Sometimes, working on his or her own psychological issues helps a clinician better understand and help someone else. Further training in the techniques of psychotherapy is often helpful.

Agoraphobia and obsessive-compulsive disorders often need longer-term specialized treatment. Phobias, panic disorders, and posttraumatic stress disorder can be managed well with hypnosis and behaviour therapy. Situational and generalized anxiety respond to relaxation, psychodynamic, and experiential therapy, as well as to creative listening. "Talking therapy" can be a rewarding and important part of treating anxiety.

Diet manipulation and exercise often assist in removing symptoms. A progressive exercise program involving brisk walking, cycling, swimming, dancing, aerobics, or racquet sports gets patients out of the house and helps release internalized frustrations. Eliminating alcohol, coffee, chocolates, colas, and sugar and eating regularly spaced meals sometimes improves symptoms.

Pharmacologic intervention

Effective drug treatment is available for anxiety. Anxiolytics in their primary role (benzodiazepines and buspirone) or antidepressants with anxiolytic properties in specific applications (monoamine oxidase inhibitors, tricyclic antidepressants, and serotonin reuptake inhibitors) can be given. The latter are not discussed here.

Primary anxiolytics. In animal studies, the basic evidence that a drug has anxiolytic properties is shown in its ability to inhibit avoidance response to conflict stimuli (normal anxiety response). These drugs are then tested on humans in controlled trials for specific disorders that represent what we consider "pathologic anxiety." It is useful to keep these seemingly opposite models in mind when choosing a drug for anxiety in family medicine. Sometimes, a distressing reaction to a life event or an acute situational disturbance justifies pharmacotherapy, even though the anxiety does not fit the classic criteria of a specific disorder.

Remember, too, that anxiolysis need not mean sedation. With the older drugs, such as barbiturates, small amounts of anxiolysis called for large amounts of sedation, if not toxicity. It is now possible to obtain a selective anxiolysis if sedation is

not wanted, although sedation is useful when anxiolytics are used to help sleep.

Benzodiazepines. Benzodiazepines, as a class, share myorelaxant and anticonvulsant properties. Onset of action is fast and drowsiness is the most noticeable side effect. Concerns exist about tolerance, physical dependence, and abuse. Tolerance to the effects of benzodiazepines is not supported by scientific evidence, except for the side effect of drowsiness (which lasts only a few weeks).[16] Physical dependence is likely to develop in proportion to the dose, potency, and length of time a particular benzodiazepine is used. Abuse, although not frequent, is a risk. Benzodiazepines cross-react with alcohol and should not be prescribed for patients with a personal or family history of alcohol or substance abuse.[17-19]

Common observations suggest that benzodiazepines have depressant properties. But researchers currently argue rather that they unveil underlying depression, if already present. On the other hand, alprazolam and adinazolam (not available in Canada) have antidepressant properties of their own. A distinction must be made between short-, intermediate-, and long-acting benzodiazepines because different advantages and disadvantages are linked to their kinetic patterns.

Short- and intermediate-acting benzodiazepines must be given three or four times daily if a steady state is desirable. Rebound anxiety and withdrawal symptoms appear early. Because they do not accumulate, they are safer for elderly patients. Long-acting benzodiazepines can be given once or twice daily. Accumulation of active metabolites could lead to subtle motor and cognitive impairment, but makes withdrawal easier to handle.

Buspirone. Buspirone, first of the azapirone family, has no sedative, myorelaxant, or anticonvulsant properties. Its very slow and subtle onset of action favours its use for more chronic anxiety. There is no cross-reaction with benzodiazepines or alcohol. No tapering is needed at the end of treatment, and antidepressant properties appear only in the higher dosage range. However, it cannot block panic attacks, and patient selection is critical because not everyone responds.

Prescribing. After the diagnosis is made, assessing the following will help decide whether drug treatment is appropriate and which drug should be used. Consider and discuss with the patient the severity of anxiety; toxicity and acceptability of side effects; other diagnoses (eg, personality disorder); expected duration of known stressors and planned duration of treatment; expectations about the goals of treatment; prior experience; and personal attitude about medication.

Panic disorder (with or without agoraphobia): Before prescribing any drug, give information on panic disorder and stop agents that cause panic, such as caffeine. Then advise the patient of the goal (suppression of attacks) and duration (longer than 6 months) of treatment.

If a patient's function is severely impaired, or if there is strong anticipatory anxiety or agoraphobia, you might immediately begin alprazolam or clonazepam, 1 to 8 mg daily until attacks cease. Try tapering, very slowly, after 6 or more months of treatment at the full dose.

If patients are willing to wait for benefit, or if depression is present, first-generation monoamine oxidase inhibitors are very effective, but are unpopular because of dietary restrictions. Tricyclics, usually imipramine, clomipramine, and desipramine, are well documented as being effective for controlling panic disorder.[20] Warn patients that they might feel more anxious in the first 2 or 3 weeks and that side effects of some tricyclics can be confused with panic symptoms.[21] Tricyclics should commence with very small doses, as little as 10 mg daily). Attacks are usually suppressed with doses between 50 mg and 150 mg daily. The controlling dose should be maintained for at least 6 months with reduction and monitoring for recurrence. Serotonin reuptake inhibitors are safe and effective, but have a different profile of side effects and are more expensive.

Social phobia: Monoamine oxidase inhibitors are effective for managing social phobias. Concern over dietary restrictions make it tempting to try β-blockers, such as propranolol and atenolol. Because β-blockers are not considered psychotropic

agents, patients accept them readily. Benzodiazepines are sometimes taken as required.

Obsessive-compulsive disorder: Clomipramine is currently the drug of choice for managing obsessive-compulsive disorder. Serotonin reuptake inhibitors have also been demonstrated effective.

Posttraumatic stress disorder: Every anxiolytic and antidepressant has been tried with various degrees of success for managing posttraumatic stress disorder. Using a case-by-case approach, you have to rely on your personal experience and clinical judgment.

Generalized anxiety disorder: Generalized anxiety disorder is best managed in the short term with benzodiazepines and in the longer term (more than 4 to 6 months) with buspirone. Tricyclic antidepressants, beginning with imipramine, have also been found effective.[22]

Adjustment disorders: Adjustment disorders, with anxious or depressed moods, are classified apart from anxiety disorders in the DSM 3-R. If the perceived stressor cannot be modified, it is reasonable to treat the actual mood of the patient, knowing that anxiety is usually the precursor of depression.

Mixed anxiety and depression: Although anxiety and depression as a rubric does not appear in either general practice or psychiatric classifications, we expect it to be classified in the fourth edition of the DSM. This is congruent with the links between anxiety and depression already observed in both clinical and pharmacologic practice. Anxiolytics with antidepressant properties (alprazolam and buspirone) or antidepressants with anxiolytic properties are useful and effective for managing this common problem.

Acute situational disturbances: Benzodiazepines have been used for up to 6 weeks for this unclassified problem. Buspirone should be considered if the reaction to a situation becomes chronic.

Drugs for the future: Drugs under development will act either selectively on particular benzodiazepine receptors or on the serotonin pathway of anxiety, as the search for selective anxiolysis without the risks of sedation and dependence intensifies. Selective agonists of the ω1 (limbic) benzodiazepine receptor and partial agonists have been developed (alpidem, bretazenil). Following buspirone, new agents include gepirone and ipsapirone in the azapirone family. Moclobemide, a reversible monoamine oxidase inhibitor, became available in Canada in October 1992 and could prove useful for treating panic disorders and social phobias; it does not require unpopular dietary restrictions. These new treatments hold promise, but require further evaluation.

Conclusion

Anxiety is one of the most common problems detected in family practice. Neither family medicine nor psychiatric classification systems have taken into account the spectrum of anxiety disorders seen by family physicians. Precision in both diagnosis and determination of adverse effects on function and quality of life provides clinicians with the information required for appropriate therapy.

When therapy is required, many psychotherapeutic and pharmacotherapeutic agents can be used. Specific psychotherapeutic and pharmacotherapeutic approaches are best used only for specific conditions. Psychotherapy alone can offer relief from most anxiety disorders. Both pharmacotherapy and psychotherapy should be used concurrently when more intensive treatment is required.

New pharmacologic agents currently being developed promise more specific therapeutic effects with fewer side effects and a lower risk of addiction. More precision in diagnosis, and resulting specificity in the management of anxiety disorders in family practice, should result in improved outcomes for the many people suffering from anxiety disorders. ■

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References

1. Rosser WW, Beaulieu M. Institutional objectives for medical education that relates to the community. *Can Med Assoc J* 1984;130: 683-9.
2. Mollinger GD, Balter MB, Manheimer DE, Cison IH, Parry HJ. Psychic distress, life crisis and use of psychotherapeutic medications:

national household survey data. *Arch Gen Psychiatry* 1978;35:1045-52.
3. US Department of Health, Education and Welfare. *Current estimates from the Health Interview Survey – United States 1975 to March 1977.* Washington, DC: Department of Health, Education and Welfare. National Health Survey Series 10:115.
4. Zung WWK. Prevalence of clinically significant anxiety in a family practice setting. *Am J Psychiatry* 1986;143:1471-2.
5. Rosser WW. Benzodiazepine prescription to middle-aged women; is it done indiscriminately by family physicians? *Postgrad Med* 1982;71(4):115-20.
6. Lamberts H, Woods M. *International classification of primary care.* Oxford: Oxford University Press, 1987.
7. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 3rd ed, revised. Washington, DC: American Psychiatric Association, 1987.
8. Baughman OL, Backerman IA, McGowan G. Azaperones and anxiety disorders: expanding roles in primary care. *Adv Ther* 1990;7(6):293-310.
9. Ontario Ministry of Health. *Schedule of benefits. Physician services under the Health Insurance Act.* Toronto: Ontario Ministry of Health, 1991:XV.
10. Karasu TB. Psychotherapies: an overview. *Am J Psychiatry* 1977;134:851-63.
11. Rapp MS, Thomas MR, Leith MG. Muscle relaxation techniques: a therapeutic tool for family physicians. *Can Med Assoc J* 1984;130:691-4.
12. Borins M. *An apple a day – a holistic health primer.* Toronto: Holistic Press, 1980:81-7.
13. Rogers C, Stevens B. *Person to person: problem of being human.* Lafayette, Calif: Real People Press, 1967:89-103.
14. Greben S. *Love's labours. Twenty-five years of experience in the practice of psychotherapy.* New York: Schoeken Books, 1984:18-45.
15. Stevens JO. *Awareness: exploring, experimenting, experiencing.* Lafayette, Calif: Real People Press, 1971:5-84.
16. American Psychiatric Association. *Benzodiazepine dependence, toxicity, and abuse.* Washington: American Psychiatric Association, 1990:116.
17. Jinks MJ. Insomnia and anxiety. In: Herfindal ET, Hirschman JL, editors. *Clinical pharmacy and therapeutics.* Baltimore: Williams and Wilkins, 1984:710-26.
18. Laux G, Puryear DA. Benzodiazepines – misuse, abuse and dependency. *Am Fam Physician* 1984;30(5):139-47.
19. Brown CS, Rakel RE, Wells BG, Downs JM, Akiskal HS. A practical update on anxiety disorders and their pharmacologic treatment. *Arch Intern Med* 1991;151:873-84.
20. Office of Medical Applications of Research. *Consensus development conference on the treatment of panic disorder.* Rockville, Md: National Institute of Health and National Institute of Mental Health, September 1991.
21. Lydiard RB, Ballenger JC. Antidepressants in panic disorder and agoraphobia. *J Affect Disord* 1987;13(2):153-68.
22. Kahn RJ, McNair DM, Lipman RS, Covi L, Rickels K, Downing R, et al. Imipramine and chlordiazepoxide in depressive and anxiety disorders. II. Efficacy in anxious outpatients. *Arch Gen Psychiatry* 1986;43:79-85.

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