

PRACTICE GUIDELINE FOR THE PHARMACOLOGICAL TREATMENT OF ANXIETY DISORDERS IN THE ELDERLY

Chittaranjan Andrade¹, Saifuddin Kharawala²

INTRODUCTORY NOTES

1. Guidelines should be evidence-based. As the available evidence on the pharmacological treatment of anxiety disorders in the elderly almost exclusively addresses generalized anxiety disorder, this guideline will concentrate on making recommendations for this diagnosis. However, as guidance on the pharmacotherapy of other anxiety disorders in the elderly is also necessary, this guideline will provide broad suggestions for the pharmacotherapy of certain other anxiety disorders, as well; such suggestions are based on the general principles of pharmacotherapy in elderly patients (see Tables), on extrapolations from findings in younger adults, and on clinical experience.
2. Guidance on the following anxiety disorders is specifically excluded from the purview of this document: specific phobia, because it is generally agreed that behavioral approaches are the treatment method of choice; obsessive-compulsive disorder, because this disorder is already the subject of a previous guideline; posttraumatic stress disorder, because this is a disorder which is clinically substantially different from the other anxiety disorders considered in this document.
3. In view of the paucity of literature in the field, this guideline will also indicate areas in which research is required.

INTRODUCTON

Psychiatric disorders in the elderly

Anxiety and depressive disorders are among the most common psychiatric conditions in the elderly (Kessler et al, 2005). In general, however, the prevalence of these conditions is lower in the elderly than in younger subjects. There are at least two relatively obvious reasons for this lower prevalence:

1. The elderly are more settled in life; in contrast, younger persons are exposed to higher levels of stress and expectation.
2. Individuals with anxiety and depressive disorders, particularly those in whom the disorder is more severe, may have a lower life expectancy; those who survive into old age, therefore, may have greater adaptative competence and, hence, emotional stability.

The above notwithstanding, old age is associated with medical disorders, departure of offspring, demise of same-age friends and family members, retirement, and other relatively unique stresses; these increase the risk of anxiety and depressive disorders at an otherwise relatively quiescent time of life.

Anxiety disorders

Anxiety is a normal human emotion. In moderation, anxiety stimulates an anticipatory and adaptative

1. MD Professor, 2. DPM Research Officer, Department of Psychopharmacology National Institute of Mental Health and Neurosciences.

response to challenging or stressful events. In excess, anxiety destabilizes the individual and a dysfunctional state results. Anxiety is considered excessive or pathological when it arises in the absence of challenge or stress, when it is out of proportion to the challenge or stress in duration or severity, when it results in significant distress, and when it results in psychological, social, occupational, biological, and other impairments.

The DSM-IV (American Psychiatric Association, 1994) includes the following major categories of anxiety disorders: panic disorder (with or without agoraphobia), agoraphobia without panic, social phobia (social anxiety disorder), specific phobia, generalized anxiety disorder (GAD), acute stress disorder, posttraumatic stress disorder, obsessive compulsive disorder, and anxiety disorder not otherwise specified. DSM-IV also lists anxiety occurring as an adjustment disorder, or secondary to substance abuse or a general medical condition. Finally, anxiety not amounting to a psychiatric diagnosis may occur situationally in normal persons, or as a symptom of another psychiatric disorder.

Epidemiology of anxiety in the elderly: Western studies

An issue that is generally overlooked is that anxiety research in the elderly often employs instruments and criteria that have not been validated for this population (Fuentes and Cox, 1997). In consequence, much of the data presented below may lack validity and may underestimate the occurrence of anxiety in the elderly.

Population-based surveys indicate that anxiety disorders are among the most frequent psychiatric disorders, with 1-year prevalence rates of 12.6-17.2% (Regier et al, 1988; Kessler et al 1994). These figures are generally lower in the elderly. The Epidemiologic Catchment Area (ECA) study (Regier et al, 1988) reported on the 1-month prevalence of panic disorder, phobias, and obsessive-compulsive disorder in 18,571 noninstitutionalized adults from five sites across the United States. Of these, 5,702 subjects were 65 years of age or older. In this study, the overall prevalence of anxiety disorders in the elderly subjects was 5.5% as compared to 7.3% in subjects of all ages. The prevalences of phobic disorder, panic disorder and obsessive-compulsive disorder in the elderly were 4.8%, 0.1%, and 0.8% respectively as compared to 6.2%, 0.5% and 1.3% in subjects of all ages.

Flint (1994) reviewed the epidemiology and comorbidity of anxiety disorders in 8 random-sample community surveys of anxiety disorders in persons 60 years of age or older. Most studies showed that anxiety disorders were less common in the elderly than in younger adults. GAD and phobias accounted for most of the cases of anxiety in late life. Although any of the anxiety disorders could arise for the first time in old age in the context of another psychiatric or medical disorder, agoraphobia appeared to be the only primary anxiety disorder that may begin to any significant degree in late life.

A study of 3,107 older adults (age 55-85 years) in the Netherlands found the prevalence of anxiety disorders to be 10.2%. The common disorders were GAD (7.3%) and phobic disorders (3.1%). The incidence of panic disorder was 1.0%, and that of obsessive-compulsive disorder was 0.6% (Beekman et al, 1998).

Schaub and Linden (2000) examined 516 German subjects aged 70 years and older. They found that the weighted overall prevalence of anxiety disorders was 4.5%. They observed that anxiety disorders in the elderly did not appear much different from those in younger subjects. Interestingly, although anxiety symptoms were an almost daily experience, their relative contribution to the spectrum of mental disorders (in the elderly) seemed to decrease, rather than increase, with age.

Jorm (2000) reviewed epidemiological studies across the adult life span and found that the commonest trend was for an initial rise in the prevalence of anxiety disorders across age groups; this was followed by a drop. Interestingly, when other risk factors were statistically controlled for, a different pattern emerged: most studies showed a decrease in anxiety, depression, and distress with increase in age. This decrease was not accounted for by the exclusion of the institutionalized elderly from epidemiological surveys, or by selective mortality of people with anxiety or depression. Possible explanations suggested for this finding included decreased emotional reactivity with age, increased emotional control, and psychological immunization to stressful experiences.

Samuelsson et al (2005) described a longitudinal cohort study of 192 healthy subjects aged 67 years at first assessment; these subjects were followed up for up to 34 years. The cumulative probability for the development of clinical anxiety during follow up was 6%. No significant risk factor for anxiety was found.

Flint (2005) reviewed the epidemiology of GAD in the elderly and concluded that, when present alone, this disorder has a period prevalence of about 1% in community-dwelling older people; GAD that is comorbid with another psychiatric disorder has a period prevalence of approximately 4%. Pure GAD in late life is a fairly even mix of chronic cases that began earlier in life, and cases of first onset in later life. A frequent and consistent finding is that late-life generalized anxiety is commonly comorbid with major depression.

In the National Comorbidity Survey Replication, 9282 English-speaking adult American subjects were interviewed. Among all disorders, DSM-IV anxiety disorders showed the highest lifetime prevalence: 28.8 % overall, and 15.3 % in the elderly. Elderly subjects had a lower prevalence for each of the anxiety disorders relative to the rest of the population. The overall lifetime prevalences in the whole sample and in the elderly subjects, separately, were 5.7% and 3.6% for GAD, 4.7% and 2.0% for panic disorder, 1.4% and 1.0% for agoraphobia without panic, 12.5% and 7.5% for specific phobia, 12.1% and 6.6% for social phobia, 6.8% and 2.5% for posttraumatic stress disorder, and 1.6% and 0.7% for obsessive-compulsive disorder (Kessler et al, 2005).

Epidemiology of anxiety in the elderly: Indian studies

After 1985, 6 Indian studies addressed psychiatric and anxiety disorders in subjects aged 60 and above. Whereas other studies had been published earlier, these are not reviewed in this guideline because they were not accessible to these reviewers, and perhaps do not reflect contemporary diagnostic practice.

Bhogale and Sudarshan (1993) described the diagnostic profile of 238 elderly outpatients attending the psychiatric clinic of two general hospitals in Karnataka. They observed that anxiety reaction accounted for 3% of subjects, and that obsessive-compulsive disorder formed <1% of the sample.

Prasad et al (1996) studied 265 elderly outpatients at a tertiary care mental hospital in Bangalore. They observed that neurotic disorders accounted for 17% of the sample; some of these patients may have had anxiety disorder, though the number was not specified.

Pereira et al (2002) studied 698 geriatric patients attending a psychiatric hospital in Goa. They observed that nearly 9% of the patients had neurotic, stress-related, and somatoform disorders (ICD-10, World Health Organization, 1992); of these, a little over a third were diagnosed with mixed anxiety and depression.

Singh et al (2004) described 181 geriatric outpatients presenting at the psychiatric clinic of a teaching general hospital in Chandigarh. They found that nearly 16% of patients had ICD-10 neurotic, stress-related, and somatoform disorders; there was no mention of the proportion of subject with specific anxiety disorders.

Tiple et al (2006) described the psychiatric morbidity in patients in Varanasi. They found that nearly 5% of geriatric patients (n=84) in the psychiatry outpatient department of a general hospital had GAD; the corresponding figures for subjects in other categories were reported, but could have been of doubtful reliability because of the very small sample sizes in the respective groups.

A limitation of these data is that none were population based, and hence all could have been biased by factors which discouraged presentation at outpatient services. Severity of illness is one example of a biasing factor; anxiety disorders are less alarming to patients and caregivers than depressive, psychotic, or dementing disorders, and are therefore less likely to result in a psychiatric consultation.

The only population-based study was reported by Tiwari and Srivastava (1998). These authors identified 488 elderly subjects in a rural region of Uttar Pradesh. Nearly 9% of the subjects were diagnosed with ICD-9 (World Health Organization, 1977) anxiety neurosis. These data may contain unknown biases because over 42% of the geriatric population was assigned a psychiatric diagnosis; in contrast, less than 4% of nongeriatric subjects had an ICD-9 psychiatric diagnosis.

It should be kept in mind that anxiety is a result of inadequate coping and inadequate support in the face of stress; therefore, as stress is low and support is high in elderly subjects in the average Indian household, the prevalence and magnitude of anxiety disorders in the elderly may be lower in India than in the West. More epidemiological data from the general population are, however, required, as also data from specific populations, such as the medically ill, or those who have been recently bereaved.

Management of anxiety disorders in the elderly

The early diagnosis and treatment of anxiety disorders in the elderly is an important concern because the elderly are frail and may deteriorate rapidly if, as a result of a psychiatric condition, they neglect their diet or their medical care.

Anxiety disorders, in general, have been poorly studied in the elderly. There is no information about the treatment of anxiety in elderly Indian subjects. As a result, the recommendations in this guideline are largely based on extrapolations of data obtained from Western studies, most of which were conducted in younger or more general populations; this guideline, however, takes into consideration the pharmacodynamic, pharmacokinetic, and practical circumstances peculiar to the elderly.

PHARMACOLOGICAL TREATMENT OF ANXIETY DISORDERS IN THE ELDERLY

A note is made here that, unless specified otherwise, clinical trials that are referenced are double-blind and placebo-controlled.

International literature

Most clinical trials specifically exclude children, adolescents, and the elderly from the sample; as a result, there is very little empirical research on the safety and efficacy of drugs in the treatment of anxiety disorders in the elderly. Only a few studies on the subject could be identified; these examined either exclusively or predominantly patients with GAD; some did not state the study diagnostic criteria explicitly but merely included 'anxious' patients. The studies are briefly considered here.

Clobazam is structurally different from the other benzodiazepines and is therefore claimed to result in less sedation and a lower risk of dependence (Beaumont 1995). In a double-blind, non-placebo controlled trial, de Souza et al (1981) randomized 30 anxious patients aged 65 years and above (mean, 77 years) to receive lorazepam (1 mg thrice a day) or clobazam (10 mg thrice a day) for 4 weeks. Afterwards, patients were abruptly switched to placebo for a further 2 weeks. Only 20 patients completed the study: 9 on lorazepam and 11 on clobazam. Both groups showed similar, substantial improvement which progressively increased and peaked at 4 weeks; both groups, especially that treated with lorazepam, experienced rebound anxiety upon drug discontinuation. Immediate memory for common objects was more impaired with lorazepam than with clobazam. Dependence and withdrawal were not formally assessed. The small sample size, the high drop out rate, the thrice daily dosing schedule and the absence of a placebo control group mean that this study cannot be used to reliably guide clinical practice.

Robinson et al (1988) reported data from a 4-week open, multicenter study of buspirone (15 mg/day) in 6574 nonpsychotic patients with clinically manifest anxiety requiring anxiolytic treatment. There were 605 patients aged 65 years and older. The older and younger patients achieved similar relief of anxiety within four weeks. Most patients (80%) in both groups reported no adverse effects. The adverse effect profile of buspirone in the older patients differed little from that in the younger patients. Levine et al (1989) also reported that buspirone was safe and effective in octogenarians with anxiety.

Feighner (1987) described a multicenter, 12-month, open-label follow-up study of 700 patients who had been treated with buspirone. All patients had DSM-III (American Psychiatric Association, 1980) GAD. There were 42 patients aged 65 years old and older. Buspirone was effective and well tolerated; the efficacy and adverse effect profile of the drug was similar in the older and younger groups. Drop out due to inefficacy or adverse effects was rare after 3 months of treatment. Dosing (15-30 mg/day) was also similar in older and younger patients.

Bohm et al (1990) recruited 40 primary care patients, aged >65 years, with a primary anxiety disorder (n=20) or anxiety secondary to neurotic depression (n=20). All patients were receiving concomitant medication for chronic medical conditions. These patients were randomized to receive either buspirone (5-30 mg/day; mean, 18 mg/day) or placebo. At the end of the 4-week study, buspirone was superior to placebo in the attenuation of scores on the Hamilton rating scales for anxiety and depression (HAM-A and HAM-D) and the Clinical Global Impression (CGI) scale. Buspirone was very well tolerated, and was associated with a placebo level of adverse effects.

Fratolla et al (1992) randomized 40 patients, aged 65-80 years and diagnosed with an anxiety disorder, to receive either alpidem (25-50 mg thrice daily; modal dose, 75 mg/day) or placebo. At the end of the 3-week study, alpidem was found to be superior to placebo in effecting improvement on HAM-A, the State-Trait Anxiety Inventory (STAI-X1), a visual analog scale (VAS), and the CGI; benefits were evident from day 7, itself. Formal assessment of psychomotor functioning and immediate memory identified no deficits with alpidem in either domain.

Katz et al (2002) conducted a secondary analysis of data from 5 randomized, double-blind, placebo-controlled clinical trials of extended release venlafaxine (37.5-225 mg/day) in 1,839 adult outpatients with a DSM-IV diagnosis of GAD; all patients were at least moderately anxious (HAM-A of at least 18). Three trials were of 8 weeks duration, and 2 lasted 24 weeks. In these trials, 10% of subjects were at least 60 years old. Venlafaxine was superior to placebo in the elderly subgroup, with CGI

response rates of 66% vs 41% for venlafaxine vs placebo, respectively. Benefits were apparent at both 8 weeks and 24 weeks. Overall drop out and drop out due to adverse events did not differ much between the two groups (23% vs 31% and 15% vs 14% for venlafaxine vs placebo, respectively).

In a small, open study, Morinigo et al (2005) recruited 15 elderly (age >65 years) patients with various anxiety disorders. All patients had moderate to severe illness and had failed treatment with antidepressant drugs and benzodiazepines. These patients were treated with risperidone (approximately 1 mg/day) augmentation of their ongoing medications. After 3 months, 13 patients showed good response, and 14 patients tolerated the medication well.

Lenze et al (2005) recruited 34 patients, aged 60 years and older, diagnosed with a DSM-IV anxiety disorder. Almost all patients had GAD, and all patients were at least moderately anxious (HAM-A of at least 17). These patients were randomized to receive either citalopram (n=17) or placebo (n=17). Response was defined as a global rating of much or very much improved, or as at least 50% attenuation of HAM-A ratings. At 8 weeks, the response rates for citalopram vs placebo were 65% vs 24%, respectively. Sedation was the most common adverse effect of citalopram; otherwise, the drug was very well tolerated.

Schuermans et al (2006) conducted the only randomized controlled comparison of pharmacotherapy with CBT in elderly subjects with anxiety disorders. The sample was mixed, and comprised 84 patients, aged 60 years and over, diagnosed with DSM-IV GAD, panic disorder, agoraphobia, or social phobia. These patients were randomized to 15 sessions of CBT, or sertraline (up to 150 mg/day), or a waiting list control group. Only 52 patients completed the study. CBT and sertraline both conveyed significant improvement in anxiety, worry, and depressive symptoms at treatment endpoint as well as at a 3-month follow up; sertraline was superior to CBT in the attenuation of worry symptoms (only). Effect size estimates for CBT were in the small to medium range at both treatment endpoint (mean d, 0.42) and 3-month follow up (mean d, 0.35); in contrast, effect sizes with sertraline were all large (mean d, 0.94 and 1.02, respectively). There was virtually no change in ratings in the waiting list controls (mean d, 0.03).

In an open study, Blank et al (2006) treated 30 subjects, aged 60 years and older, with citalopram. Almost all patients were diagnosed with DSM-IV GAD. The duration of the study was 32 weeks. There were 13 drop outs: 5 due to nonresponse, 3 due to adverse effects, and 5 due to other reasons. Thus, only 57% of the sample completed the 32-week study. Response, defined as a HAM-A score <10, was obtained in 60% of the sample. Treatment completers experienced significant improvement in sleep, social functioning, vitality, mental health, and role difficulties due to emotional problems.

An important finding in the pooled analysis of Katz et al (2002) was that there were no main effects for age nor any significant age by treatment interactions for any of the many primary and secondary outcome variables at either 8 or 24 week endpoints. The results for early treatment discontinuation were similar. Earlier, Robinson et al (1988) had also reported that older and younger patients responded similarly to buspirone, and displayed a similar profile of adverse effects. These findings suggest that the response of anxiety to venlafaxine and buspirone is independent of age; one may therefore hope that responses may be independent of age with other drugs, as well.

Indian literature

There are no published Indian studies on the use of any drug in elderly patients with any anxiety

disorder.

Summary

1. Buspirone, alpidem, citalopram, sertraline, and venlafaxine are effective and well tolerated in the treatment of GAD in the elderly.
2. Sertraline may be superior to CBT in the short- to intermediate-term, including at a 3-month follow-up. Long-term data on the differences between the two treatments are, however, unavailable.
3. Benefits of pharmacotherapy are evident for up to 32 weeks; studies of longer duration are unavailable.
4. Larger studies, more rigorously-designed studies, more recent studies, and studies on antidepressant drugs are associated with higher drop out rates.
5. The venlafaxine and buspirone data suggest that elderly patients with anxiety respond no differently from younger patients with anxiety; this implies that responsiveness to anxiolytic medication may be independent of age.
6. No data are available to guide the duration of therapy. There are no Indian data on the subject.

TREATMENT ISSUES: OVERVIEW

The treatment of anxiety disorders in the elderly, as with treatment of any psychiatric disorder in any age group, should be based on a complete medical and psychiatric evaluation followed by the prescription of appropriate pharmacotherapy, psychotherapy, and/or self-help.

Pharmacotherapy may be more important than either psychotherapy or self-help in the elderly because drug therapy is easy to institute and maintain; in contrast, psychological interventions require intact cognitive abilities, and the willingness of the patient to make the efforts necessary in therapy. Psychological interventions also require to be available, accessible, acceptable, and affordable, qualifiers which cannot always be assured in India.

Tables 1 and 2 describe factors that may be expected to influence medication adherence, pharmacodynamics, and pharmacokinetics in the elderly. Table 3 lists considerations which may influence the choice of medication used for the treatment of anxiety in the elderly. General guidelines for psychopharmacological intervention in elderly patients are presented in Table 4

TREATMENT ISSUES: SPECIFIC DRUGS

Drugs used in the treatment of anxiety disorders include the following:

1. Benzodiazepines
2. Antidepressants
3. Major tranquilizers
4. Others (buspirone, pregabalin, antihistamines, propranolol, tiagabine, anticonvulsants, alpidem, herbal treatments, etc.)

Each of these is considered in turn.

BENZODIAZEPINES

Efficacy

Benzodiazepines are among the best-established drugs for the treatment of anxiety; diagnoses for which benzodiazepines have proven efficacy include GAD and panic disorder. Benzodiazepines are also effective for situational anxiety and anxiety due to adjustment disorder. The greatest advantage of benzodiazepines is their rapid onset of action. Benzodiazepines may also reduce free-floating anxiety in obsessive-compulsive disorder, posttraumatic stress disorder, agoraphobia, social anxiety disorder, and specific phobia; however, the role of benzodiazepines in these conditions is adjunctive only (Andrade, 2005; Salzman, 2005).

In addition to being anxiolytic, benzodiazepines have sedative, hypnotic, and muscle relaxant properties. The sedative and hypnotic effects are beneficial in restless and insomniac patients; however, as tolerance rapidly develops, these benefits are best appreciated during short-term treatment. The muscle relaxant property is useful in patients with headache, pain in the neck and/or pain in the low back that can be attributed to heightened muscle tension. The profile of anxiolysis, hypnosis, and muscle relaxation potency varies from benzodiazepine to benzodiazepine (Andrade, 2005).

Although efficacy has been demonstrated chiefly for drugs such as diazepam (Jacobson et al, 1985; Ross et al, 1987; Rickels et al, 1993), clobazam (Judd et al, 1989), alprazolam (Elie and Lamontagne, 1984), and clonazepam (Davidson et al, 1993; Rosenbaum et al, 1997), the benefits are likely a class action with some variations in the profile of symptom efficacy, as referred to above.

Adverse effects

The commonest and most important adverse effect of benzodiazepines is sedation. Sedation may result in an early morning hangover, daytime drowsiness, psychomotor slowing (with incoordination, at higher doses), and cognitive impairments (with confusion, at higher doses). The psychomotor and cognitive effects may result in decreased quality of life, inefficiency, or even accidents. A particularly important concern is the risk of falls and fractures. Alcohol and other central nervous system depressants can potentiate these untoward effects of benzodiazepines (Andrade, 2005; Salzman, 2005).

Another serious and unwanted consequence of regular benzodiazepine use is the development of dependence. Dependence is a function of drug, dose, and duration of therapy, and is more likely with high potency benzodiazepines, high doses, and prolonged treatment. Evidence of dependence may become apparent after a period as brief as a week or two: tolerance develops to the sedative effects of the drug, and withdrawal symptoms appear after abrupt discontinuation. These withdrawal symptoms most commonly include psychic and somatic manifestations of anxiety, restlessness, and insomnia. Symptoms usually begin within a day, and may last for as long as a week; these are generally delayed and milder with long-acting benzodiazepines. In rare cases, withdrawal convulsions and delirium may occur (Andrade, 2005).

Withdrawal reactions are more common with drugs that have shorter half-lives, such as lorazepam and alprazolam, and less common with those that have longer half-lives, such as clonazepam and diazepam. This is because, even with abrupt withdrawal, blood levels of drugs with long half-lives fall slowly, as in a gradual taper. Withdrawal problems can be minimized by tapering the dose over a period that is proportionate to both dose and duration of therapy, and by switching from a benzodiazepine with a short half-life to one with a long half-life. Certain symptoms of withdrawal can be attenuated by the use of other drugs such as zopiclone or imipramine (Andrade, 2005).

Tolerance does not develop to the anxiolytic effect of benzodiazepines. It may be added that benzodiazepine abuse and dose escalation is uncommon amongst patients who receive the drugs for therapeutic purposes (Woods and Winger, 1995).

In patients with aggressive tendencies and other undesirable behaviors, benzodiazepine use can result in a reduction of inhibitions and a consequent unmasking of the undesirable behaviours (Salzman, 2005).

Benzodiazepines are generally safe in overdose, unless combined with other central nervous system depressants, including alcohol (American Psychiatric Association, 1990).

Common drugs and dosing

Amongst the benzodiazepines, alprazolam (0.5-2.0 mg/day), clonazepam (0.5-2.0 mg/day) or diazepam (5-10 mg/day) are generally preferred for the management of uncomplicated anxiety. Alprazolam, clonazepam, and diazepam are very effective in patients with panic disorder at doses that may be 2-3 times higher than those used in uncomplicated anxiety.

Preparations and administration

Sustained-release formulations of diazepam and alprazolam have been commercially marketed. The former is patently unnecessary, given the long half-life of the drug. Sustained-release alprazolam is, however, a welcome preparation because the duration of alprazolam anxiolysis is briefer than the half-life of the drug suggests (Alexander, 1995). Benzodiazepines with long half-lives are best administered once-nightly, or, at the most, twice a day; sustained-release alprazolam is best administered once each morning. The timing and frequency of administration of other benzodiazepines should be based on the half-life of the drug (and its metabolites), and on the indication for which the drug is being used.

Highlights

The advantages of benzodiazepines in the treatment of anxiety can be summarized as follows:

1. Rapid onset of action and high efficacy
2. Efficacy against restlessness and muscle tension
3. Low risk of pharmacokinetic drug interactions
4. Low risk of fatality in overdose

The risks associated with the use of benzodiazepines in the elderly can be summarized as follows:

1. Problems related to sedation: decreased quality of life; impaired cognition, with confusion at higher doses; slowed psychomotor reflexes, and hence an increased risk of falls and fractures; potentiation of sedation by other drugs
2. Drug dependence

Recommendations for the use of benzodiazepines to treat anxiety disorders in the elderly

Benzodiazepines can be used as primary treatment for GAD, or as an adjunctive treatment for GAD or other anxiety disorders; in the latter event, they can be used in low doses to treat specific symptoms, such as free-floating anxiety in patients with posttraumatic stress disorder. It may be inadvisable to use benzodiazepines as a primary treatment for panic disorder because elderly patients may not tolerate the higher doses that are required for this indication.

As sedation and dependence with benzodiazepines are important concerns, the use of these drugs should be restricted to

1. Patients in whom rapid anxiolysis is required.
2. Those in whom the treatment duration is likely to be short (and in whom, therefore, the risk of dependence is low). Such patients include those affected by acute stress or an adjustment disorder, those who are symptomatic during the period that it takes an antidepressant drug to effect anxiolysis, and those who experience antidepressant-induced jitteriness or heightened anxiety early during therapy.
3. Those who may not be disturbed by the sedative effects of the drugs, such as patients who are terminally ill.
4. Those who have failed to show adequate response to other classes of anxiolytics.

There is no evidence that any one benzodiazepine is superior to the rest; therefore, the choice of drug is driven primarily by safety concerns. Important recommendations are to choose a drug with a shorter half-life, to use the lowest effective doses, and to prefer nighttime dosing in order to minimize daytime sedation.

Prefer drugs with long half-lives only if once-daily dosing is an important criterion, if missed doses are likely (which will reduce efficacy and precipitate withdrawal when short-acting drugs are used), and if drug discontinuation is being attempted.

Adequate counselling should be provided about the risks associated with sedation and falls. This is especially important when treating patients who frequently require to void urine during the night.

ANTIDEPRESSANTS

Efficacy

Antidepressant drugs have proven efficacy in GAD, panic disorder, and social anxiety disorder. A particular asset of antidepressant drugs in the treatment of anxiety disorders is that these drugs are also effective in treating depression, which is frequently comorbid with anxiety.

Antidepressant drugs which have been found effective in the treatment of GAD are imipramine (Rickels et al, 1993), venlafaxine (Davidson et al, 1999; Gelenberg et al, 2000; Algulander et al, 2001; Rickels et al, 2000 & 2004), paroxetine (Rocca et al, 1997; Pollack et al, 2001; Liebowitz et al, 2002; Stocchi et al, 2003), escitalopram (Davidson et al, 2004; Goodman et al, 2005; Stein et al, 2005), mirtazapine (Gambi et al, 2005), sertraline (Steiner et al, 2005) and others.

Antidepressant drugs which have been found effective in the treatment of panic disorder are phenelzine (Buiges and Vallejo, 1987), imipramine (Cross-National Collaborative Panic Study, 1992), brofaromine (van Vliet et al, 1993 & 1996), paroxetine (Lecrubier et al, 1997; Ballenger et al, 1998), fluoxetine (Michelson et al, 1998), sertraline (Pohl et al, 1998), mirtazapine (Sarchiapone et al, 2003), escitalopram (Stahl et al, 2003), venlafaxine (Bradwejn et al, 2005), and others.

Antidepressant drugs which have been found effective in the treatment of social phobia are phenelzine (Liebowitz et al, 1992), moclobemide (Versiani et al, 1992), brofaromine (van Vliet et al, 1992; Lott et al, 1997), paroxetine (Stein et al, 1998), sertraline (Van Ameringen et al, 2001), escitalopram (Lader et al, 2004; Kasper et al, 2005), venlafaxine (Algulander et al, 2004; Stein et al, 2005), and others.

There is stray evidence to suggest that some antidepressant drugs may be more effective than

others in the treatment of anxiety disorders; for example, Baldwin et al (2006) found that 10 mg/day (but not 20 mg/day!) of escitalopram was superior to paroxetine in the treatment of GAD. Different drugs may also differ in efficacy against comorbid anxiety; for example, in patients with depression, paroxetine was superior to moclobemide for comorbid panic but not comorbid GAD (Pini et al, 2003). Finally, as could be expected, different antidepressant drugs would differ in their tolerability profile.

It is likely that the efficacy of antidepressant drugs in the anxiety disorders is a class action. If the recent research is heavily biased in favor of the SSRIs and certain other newer antidepressants, it is only because these drugs are better tolerated than the classical tricyclic antidepressants, and because these drugs were under patent at the time of study, thereby spurring research.

Monoamine oxidase inhibitors are also effective in the treatment of anxiety and panic. Moclobemide, however, may be ineffective in panic disorder with agoraphobia (Loerch et al, 1999).

Adverse effects

Adverse effects of antidepressant drugs which are of concern in the elderly are as follows (Andrade, 2005):

1. Muscarinic anticholinergic activity with the tricyclic antidepressants may result in urinary retention in elderly males with enlargement of the prostate. Anticholinergic activity can also compromise cognitive functioning. Blurred vision and constipation are other adverse effects that could be particularly poorly tolerated by the elderly.
2. Antiadrenergic activity (at alpha-1 receptor sites) with the tricyclic antidepressants may result in orthostatic hypotension, and hence falls and fractures.
3. Antihistaminic (at H1 receptor sites) and antiserotonergic (at 5-HT₂ receptor sites) activity with drugs such as the tricyclic antidepressants and mirtazapine may result in increased appetite and sedation. The former can worsen comorbid medical conditions such as diabetes mellitus, hypercholesterolemia, and osteoarthritis. The latter can cause daytime drowsiness, impairment of cognition, and impairment of psychomotor reflexes, with consequences already discussed in the section on benzodiazepine drugs.
4. Heightened serotonergic tone at 5-HT₂ receptors with drugs such as the SSRIs, venlafaxine, and duloxetine can result in anorexia and insomnia, both of which could be problematic in patients who already have difficulties with maintaining nutrition and the regularity of sleep.
5. Cardiac conduction abnormalities induced by tricyclic antidepressants could pose especial risks to patients who have existing heart disease.
6. Abrupt discontinuation can lead to an unpleasant SSRI discontinuation syndrome with drugs such as the SSRIs, mirtazapine, venlafaxine, and duloxetine. Abrupt discontinuation of tricyclic drugs can lead to cholinergic rebound.

Common drugs and dosing

Common drugs used in the treatment of GAD include sertraline (50-200 mg/day), paroxetine (10-50 mg/day), fluvoxamine (50-200 mg/day), citalopram (20-60 mg/day), escitalopram (5-20 mg/day), venlafaxine (37.5-225 mg/day), mirtazapine (7.5-30 mg/day), duloxetine (30-60 mg/day), and the tricyclic agents (25-150 mg/day).

Preparations

Paroxetine, venlafaxine, and clomipramine are available as controlled release preparations; these may be better tolerated than the immediate release formulations.

Recommendations for the use of antidepressant drugs to treat anxiety in the elderly

There is no convincing evidence to suggest that any one antidepressant is superior to any other antidepressant in anxiety disorders; therefore, the choice of antidepressant should be driven by considerations of safety and tolerability.

In general, the SSRIs are effective in all the anxiety disorders under consideration, and have the most favorable adverse effect profile; these drugs should hence be considered as first-line agents. Among the SSRIs, escitalopram carries the least risk for drug interactions (Andrade, 2005); this is important because elderly patients often receive several drugs for various comorbid illnesses. Escitalopram may also be better tolerated than paroxetine in GAD (Bielski et al, 2005). Sertraline and citalopram, specifically, have been associated with a low risk of drug interactions in the elderly (Spina and Scordo, 2002). The tricyclic antidepressant drugs are likely to be the least well tolerated, and should be avoided, or used in the lowest possible doses.

A benzodiazepine may need to be prescribed in low doses during the initial days of treatment with an antidepressant in case the patient requires rapid relief of anxiety, and in case antidepressant-induced anxiety, agitation, or jitteriness develops.

PREGABALIN

Pregabalin has recently been studied, and found effective, in patients with GAD (Feltner et al, 2003; Pohl et al, 2005). It is as effective as venlafaxine for this indication and is associated with an earlier treatment response (Montgomery et al, 2006). The onset of benefit is evident from the first week, itself. Insomnia is also attenuated with this drug. Pregabalin appears to have all the advantages of the benzodiazepines without the chief disadvantage: dependence. Abrupt discontinuation of pregabalin does not result in withdrawal symptoms (Feltner et al, 2003).

Adverse effects

Pregabalin is very well tolerated except for adverse effects related to sedation. Tolerance appears to develop to sedation with pregabalin.

Dosing

A dose of 75-300 mg/day may be used in 2 divided doses.

Recommendations

The recommendations for the use of pregabalin are the same as those for the benzodiazepines with the exception that, because of the absence of risk of dependence, pregabalin may be preferred over the benzodiazepines. Pregabalin, however, does not have muscle relaxant properties and may therefore have a more limited spectrum of symptomatic efficacy.

BUSPIRONE

The only anxiety disorder for which buspirone has demonstrated efficacy is GAD (Jacobson et al, 1985; Ross et al, 1987). Buspirone is also effective in anxious patients with coexisting depression (Gammans et al, 1992). Buspirone is however ineffective in panic and social anxiety disorders (Sheehan et al, 1990; van Vliet et al, 1997).

In GAD, the efficacy of buspirone may be less in patients who have previously received benzodiazepines (Schweizer et al, 1986). Buspirone may also be less effective if somatic anxiety is marked; this could be because 1-PP, a metabolite of buspirone, blocks alpha-2 presynaptic adrenoceptors, thereby increasing noradrenergic neurotransmission through increased activity of the presynaptic neuron (Andrade, 2005)..

Special adverse effects in the elderly

Buspirone is very well tolerated. Anorexia and insomnia are the only adverse effects that may be of concern in the elderly (Goldberg, 1994).

Dosing

Treatment with buspirone is best started at 10-15 mg/day in 2-3 divided doses; this dose can be increased, if required, to a target of 15-30 mg/day in 2-3 divided doses. Rarely, higher doses, of up to 45-60 mg/day, may be needed.

Recommendation

Buspirone may be preferred when anxiety is mild, when psychic anxiety dominates the clinical picture, and when a nonsedating drug is desired. A practical limitation of buspirone is the need for twice- to thrice-daily dosing.

ANTIHISTAMINES

Limited, short-term data suggest that hydroxyzine is effective in GAD (Lader and Scotto, 1998; Llorca et al, 2002). It is however unclear whether the benefits are primary or consequent upon the sedative effect of the treatment. An advantage of hydroxyzine is that it does not produce dependence (Natens, 1992).

Special adverse effects in the elderly

Sedation and increased appetite are the only adverse effects that may be of concern in the elderly.

Dosing

Hydroxyzine may be used in the dose of 50-100 mg/day (in divided doses) to treat uncomplicated anxiety.

Recommendation

The evidence base for the efficacy of antihistamines is limited. Data on long-term safety and efficacy are unavailable. These drugs are therefore best avoided in favor of the other drugs for which greater evidence of safety and efficacy is available. However, these drugs may be useful when the duration of treatment is likely to be limited to a few weeks, and when a sedative or hypnotic drug is desired. In this regard, hydroxyzine may be preferable to a benzodiazepine or a tricyclic antidepressant.

MAJOR TRANQUILLIZERS

Conventional anxiolytics were formerly classified as minor tranquillizers whereas antipsychotics were classified as major tranquillizers; both were so regarded because of their efficacy in anxious or agitated patients. Low doses of trifluoperazine (2-6 mg/day) have been found to be superior to placebo in the treatment of GAD (Mendels et al, 1986). Other typical antipsychotics have also been found to be superior to placebo, or as effective as benzodiazepines, in patients with GAD and other anxiety disorders; however, few of these studies have been well conducted (Gao et al, 2006). Drugs

occasionally used include prochlorperazine (Goldberg and Finnerty, 1979) and flupenthixol (Bjerrum et al, 1992).

Risperidone (0.5-3.0 mg/day) has been found to be useful as an adjunct in patients with GAD (Brawman-Mintzer et al, 2005; Simon et al, 2006). Olanzapine has been found effective in monotherapy for social anxiety (Barnett et al, 2002) and as augmentation of fluoxetine in refractory GAD (Pollack et al, 2006; mean dose, 9 mg/day). Olanzapine (5 mg/day) was also effective in an open label augmentation study of patients with panic disorder (Sepede et al, 2006). In another open label study, quetiapine was found effective in patients with social anxiety (Schutters et al, 2005).

It should be kept in mind that antipsychotic drugs are associated with numerous cognitive, behavioral, and other adverse effects; these could be expected to be more problematic in the elderly. An expert panel did not recommend using antipsychotics in GAD and panic disorder (Alexopoulos et al, 2004).

Special adverse effects in the elderly

The neuroleptics are associated with a risk of extrapyramidal symptoms, including tardive dyskinesia. Most or all major tranquilizers are sedating, impair cognition, and increase appetite and weight.

Recommendations

The use of this class of medication should be restricted to patients in whom other treatments fail. Effective doses are likely to be lower than those necessary for the treatment of psychosis.

BETA-BLOCKERS

Drugs such as propranolol have been used to attenuate palpitations, tremor, and other autonomic symptoms of anxiety. Despite their wide-spread use in social anxiety, studies do not show superiority of the beta-blocker atenolol over placebo (Liebowitz et al, 1992; Turner et al, 1994). Findings of benefits for performance anxiety in musicians (James et al, 1983; James and Savage, 1984) may not be validly generalized to other categories of patients.

Special adverse effects in the elderly

Beta-blockers may be associated with postural hypotension. Whereas they may be beneficial in certain types of cardiac disease, they may also worsen heart block, or increase the risk of cardiac failure.

Dosing

Propranolol is the most commonly used drug, in doses such as 10-40 mg/day.

Recommendations

The use of beta-blockers is, at best, adjunctive in anxious patients, and can be used to attenuate symptoms of autonomic system hyperactivity.

ANTICONVULSANTS

Anticonvulsants drugs, such as carbamazepine, valproate, lamotrigine, and gabapentin, have shown efficacy in preliminary studies and require further research.

Small, open label studies have found valproate effective in social anxiety disorder (Kinrys et al, 2003) and panic disorder (Primeau et al, 1990; Keck et al, 1993; Woodman et al, 1994; Baetz et al, 1998). Carbamazepine was effective in panic disorder in one (Tondo et al, 1989) but not another (Uhde et al, 1988) open study. In a small, placebo-controlled trial, gabapentin was found effective in patients with

social phobia (Pande et al, 1999); in a larger, placebo-controlled study, gabapentin was found effective in patients with panic disorder, but only in the more severely ill patients; not in the whole sample (Pande et al, 2000). The use of anticonvulsants in anxiety disorders was reviewed by van Ameringen et al, (2004).

Recommendation

Until data from double-blind, placebo-controlled studies become available, these drugs are best considered experimental in the treatment of anxiety.

ALTERNATE SYSTEMS OF MEDICINE

A small, Indian, short-term, double-blind, placebo-controlled study found Ashwagandha effective in the treatment of GAD (Andrade et al, 2000). Unpublished Indian data suggest that other (proprietary) herbal formulations may also be effective in GAD (Andrade; unpublished data). St. John's wort was found ineffective in an Indian study (Andrade, unpublished data).

Kava-kava extract may not have significant anxiolytic properties (Connor et al, 2006). Homeopathy was ineffective in one controlled study (Bonne et al, 2003).

Dosing

Ashwagandha may be initiated in the dose of 1-2 g/day in 2-3 divided doses. The target dose is 2-6 g/day.

Special adverse effects in the elderly

Ashwagandha appears to be associated with a placebo level of adverse effects.

Recommendation

In India, legal strictures prohibit cross-prescriptions across systems of medicine. Therefore, no recommendations are made herein. The information provided herein is for the guidance of patients who express a preference for herbal medicine.

OTHER TREATMENTS

Tiagabine is effective in GAD (Pollack et al, 2005); however, this drug has been associated with new-onset seizures and should therefore not be used for anxious patients (Suppes et al 2002).

5-HT₃ antagonists have been studied in patients with generalized anxiety. In general, drugs such as lesopitron (Sramek et al, 1996; Fresquet et al, 2000), zatosepron (Smith et al, 1999), ondansetron (Freeman et al, 1997), and tropisetron (Lecrubier et al, 1993) have shown modest or no efficacy.

Deramciclone, a camphor derivative, blocks 5-HT_{2A} and 5-HT_{2C} receptors. It was found effective in GAD, with placebo-level adverse effects and no withdrawal reaction on abrupt discontinuation at 8 weeks (Naukkarinen et al, 2005).

Opipramol blocks D₂, 5-HT₂, H₁, and sigma-1 and -2 receptors and has shown efficacy in treating generalized anxiety (Moller et al, 2001).

Recommendation

Until data on safety and efficacy are available, none of these drugs are recommended for the treatment of anxious patients.

SCOPE FOR FUTURE RESEARCH

1. There is a need for population-based studies to determine the prevalence of different anxiety disorders in different age groups in India. There is also a need for purposive sampling of the elderly to determine the prevalence of the anxiety disorders: important subpopulations include community-dwelling subjects; those in old age homes; those with general medical and, more specifically, cardiac and surgical ailments; those with other psychiatric disorders in whom anxiety disorders may be comorbid; those who have recently been bereaved, etc.
2. There is an urgent need to empirically establish the short- and long-term safety and efficacy of different anxiolytic medications in the elderly, especially those with medical comorbidity. Indian studies are particularly necessary because, at present, none have been published.

RECOMMENDATIONS FOR THE PHARMACOTHERAPY OF ANXIETY DISORDERS IN THE ELDERLY

1. Drugs for which modest empirical data on safety and efficacy (in elderly subjects) are available: citalopram, sertraline, venlafaxine, buspirone (Group A drugs).
2. Drugs for which efficacy and safety can be inferred from empirical data obtained from younger adults: escitalopram, paroxetine, fluoxetine, mirtazapine, phenelzine, brofaromine, moclobemide (Group B drugs).
3. Drugs which have been found effective in the elderly, but which may not be well-tolerated by the elderly: clobazam, alpidem (Group C drugs).
4. Drugs which have not been studied in the elderly, which have shown efficacy in younger adults, and which, for reasons of poorer tolerability in elderly subjects, are best reserved for use in special circumstances: benzodiazepines, pregabalin, tricyclic antidepressants (Group D drugs).
5. Other possibly effective drugs which may be used in special circumstances: beta-blockers, Ashwagandha (Group E drugs).
6. Drugs to be considered in exceptional circumstances, only: risperidone, olanzapine, other atypical and typical antipsychotics (Group F drugs).
7. Effective drugs the use of which is specifically discouraged: tiagabine (Group G drugs).
8. Experimental treatments, the use of which is discouraged: anticonvulsants, 5-HT₃ inhibitors, opipramol, deramciclane, etc. (Group H drugs).

Note: Alpidem and brofaromine are not commercially available.

FLOW CHART

Step 1: Use any drug from Group A.

Step 2: Use any drug from Group A or B, preferably one belonging to a pharmacological class different from that tried in Step 1.

Step 3: Consider a drug from Group C or D.

Step 4: Consider another drug from Group C or D, preferably one belong to a pharmacological class different from that tried in Step 3; consider a benzodiazepine if not already tried.

Step 5: Consider olanzapine, risperidone, or other atypical or typical antipsychotics.

Practical notes

1. The choice of drug, dosing instructions, and related issues should be guided by the notes in Tables 1-4, and by the discussions on specific drugs in the specific sections of this guideline.
2. Time lines to decide upon the efficacy of a dose are usually 2-3 weeks, and to decide upon the efficacy of a drug are usually 2-6 weeks. The wide variation in deciding on whether or not a drug is effective is because, whereas drugs such as the benzodiazepines and pregabalin usually show efficacy within the first week of treatment, the antidepressants take 2-6 weeks to demonstrate efficacy, particularly for conditions such as panic disorder.
3. Benzodiazepines may be used in Steps 1 or 2 if specifically indicated, such as due to the severity of anxiety, the need for rapid anxiolysis, the lack of risk of problems related to sedation (as in bedridden patients) or dependence (as in terminally ill patients), or the development of anxiety or jitteriness during the early weeks of treatment with an antidepressant drug.
4. Beta blockers may be used as augmenting agents during any of the steps described in the flow chart above. The use of beta blockers should be driven by the prominence of somatic symptoms of anxiety.
5. Other combination therapies may be considered only if specifically indicated; for example, the use of a low dose of a tricyclic antidepressant to treat insomnia associated with anxiety in patients who are receiving a selective serotonin reuptake inhibitor.

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Table 1: Factors that may influence medication adherence in the elderly.

1. Doctor-patient relationship
2. Patient education; identification and dispelling of myths
3. Efficacy of the medication, and the perceived benefit
4. Adverse effects of the medication
5. Availability, accessibility, affordability, and acceptability of the medication
6. Complexity of the prescription
7. Medical and psychiatric comorbidity
8. Cognitive capacity
9. Availability of family support
10. Cultural beliefs
11. Regularity of follow up

Table 2: Pharmacodynamic and pharmacokinetic considerations in the elderly.

1. There may be impaired absorption due to age-related changes in the gastrointestinal environment.
2. Albumin levels may be lower. As a result, at a given dose, drugs with high protein binding may be characterized by a larger free fraction. This could result in increased dose-dependent adverse effects.
3. There is a decrease in the volume of body fat, especially in elderly men, and hence a decrease in the storage of lipophilic drugs in fat reservoirs. This increases the risk of dose-dependent adverse effects with drugs such as the benzodiazepines.
4. There is a decreased volume of brain tissue and hence neuronal targets; hence, there could be a decreased dose requirement, and an increased sensitivity to drug-induced adverse effects.
5. Homeostatic responses are diminished; hence, there could be an increased sensitivity to adverse effects such as postural hypotension.
6. There is a decreased capacity of the liver and kidneys to metabolize and excrete drugs; this could result in the accumulation of drugs, especially those with long half-lives.

7. There is decreased cardiac output, and hence further decrease in liver metabolism and renal excretion.
8. There is an increased risk of drug interactions because of medical co-medications.

Table 3: Considerations which may influence the choice of medication in the elderly.

1. Considerations related to efficacy, with especial reference to previous treatment response and the presence of comorbid illness (e.g. depression)
2. Considerations related to adverse effects, with especial reference to medical comorbidity
3. Considerations related to drug interactions, with especial reference to concurrent medical treatments
4. Considerations related to treatment adherence.

Table 4: General guidelines for psychopharmacological intervention in the elderly.

1. Monotherapy is desirable; polypharmacy should be resorted to only if there is a specific need.
2. Start with the drug which has the best efficacy-adverse effect profile, and with which compliance is most likely.
3. Start at a low dose and increase the dose gradually so as to minimize the adverse effect burden and allow adaptation to the adverse effects.
4. Prefer once-daily dosing, wherever feasible, to improve compliance; split the dose only if adverse effects emerge at dose peaks.
5. Use a controlled-release preparation, wherever available and wherever necessary, to reduce adverse effects associated with dose peaks. Controlled-release formulations are particularly helpful in reducing adverse effects with drugs such as alprazolam and paroxetine.
6. Schedule frequent visits to assess the efficacy-adverse effect profile of the prescription.
7. If there is no benefit after 2-6 weeks at the maximum tolerated dose, taper (where relevant) and withdraw the drug and switch to an alternate drug preferably from a different medication class; keep in mind the risk of pharmacodynamic and pharmacokinetic drug interactions during the cross-taper.
8. Repeat the procedure until a drug is identified which adequately treats the anxiety disorder.
9. At all stages, counsel the patient and the caregiver about time-lines to efficacy, adverse effects to be watchful for, and other issues related to treatment.
10. At all stages, to the extent feasible, include psychosocial interventions to enhance coping, decrease illness burden, improve compliance, and specifically address symptoms of the disorder.
11. Especially in the elderly, there are no data available to guide the duration of treatment. Therefore, treat for as long as it is considered that the patient is at risk of relapse if the medication were to be discontinued. Otherwise expressed, withdraw treatment only when there is mutual confidence that the patient will be reasonably symptom-free when off drugs. In general, patients with generalized anxiety disorder are best treated until they have been well for at least 6 months.
12. Discontinuation of medication after successful treatment should generally be effected through a slow taper to minimize the risk of withdrawal symptoms, rebound anxiety, or frank relapse of the anxiety disorder.