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Update on Anxiolytics and Hypnotics

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Update on anxiolytics and hypnotics

Goal

The goal of this article is to educate pharmacists on the newer anxiolytic and hypnotic agents.

Objectives

After reading this article, the pharmacist should be able to:

- Discuss the advantages of the new hypnotics and anxiolytics over previous agents.
- Discuss possible adverse effects and drug interactions of the new hypnotics and anxiolytics.
- Recommend one of the newer agents as an alternative to more conventional therapy when appropriate.

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History

Agents to produce sleep, called hypnotics, have been around thousands of years. Evidence shows that poppy plants were used as the first hypnotics some two-thousand years ago. The oldest hypnotic agent is chloral hydrate. Its popularity waned when the barbiturates came along but has become more popular in the last few decades.[1] It is less effective than flurazepam and tolerance to its effects develops rapidly.[2]

The bromides were introduced in the mid-1800s. Problems with these agents include their extremely long half-life of about 12 days, their low therapeutic index and irritation to the GI system.[1]

Early in the 20th century, barbiturates were introduced and quickly became popular hypnotic agents. These agents have numerous adverse reactions such as respiratory depression, nausea and vomiting, circulatory collapse and severe depression of the CNS. Barbiturates have become associated with abuse and overdose, and drug withdrawal can also be a serious problem. A chronic user of barbiturates, upon withdrawal, may experience irritability, insomnia and, in serious cases, convulsions and death.[1]

Other nonbarbiturate-nonbenzodiazepines include piperidinediones such as glutethimide and methyprylon, ethchlorvynol, methaqualone and meprobamate. All of these agents have problems similar to those of the barbiturates, specifically physical dependence and overdose potential.[1,3]

Benzodiazepines were a major breakthrough in sedative-hypnotics and have become the most frequently prescribed drugs in the U.S. Their main advantage over previous agents are their higher therapeutic index. Taken alone, these agents rarely cause death and produce little respiratory depression.[1,3] Physical dependence has become their major problem, however.[1]

Drug therapies of anxiety states are a

fairly recent development. Although anxiety states were recognized in the 19th century, most therapy revolved around psychotherapy.[4] A variety of drugs in different pharmacological classes are now used to treat the anxiety disorders. Alcohol is commonly used to self-treat situational anxiety; however, it is never a treatment of choice,[5] and alcoholism has become a complication of many anxiety disorders.[2]

When barbiturates came along, they were not only used as hypnotics, but also used to treat anxiety.[2] Barbiturates are not, however, specific anxiolytics and have the disadvantages discussed earlier.

Antihistamines are used occasionally and are especially good for patients with a high propensity for drug abuse.[5,6] The anticholinergic effects of these agents are their primary disadvantage, especially in the elderly in whom central effects such as confusion and hallucinations may also occur.[5]

Beta-adrenergic blocking agents are used primarily to alleviate the physical symptoms of stress. These agents are nonspecific and rarely are helpful in psychiatric patients.[4] Clonidine is also used to treat anxiety; however, its side effects of hypotension, depression and fatigue have limited its use.[5]

Antipsychotics were used more frequently for anxiety attacks in the past. They are less commonly used for that purpose now because of their questionable efficacy and their high potential for adverse effects such as tardive dyskinesia and extrapyramidal effects.[4,6]

Antidepressants, however, continue to be used and have shown efficacy in certain anxiety states. In the early 1960s monamine oxidase inhibitors (MAOIs) were found to be effective for panic disorder.[6] Phenelzine is most commonly used, and studies have proven its effectiveness in panic disorder.[5] Side effects include orthostatic hypotension, weight gain, sexual dysfunction, edema and hypertensive crisis, which can occur when the patient on an MAOI eats food rich in tyramine (aged cheese, red wine, sherry, beer, smoked meats or fish, etc.) and uses sympathomimetics or stimulants. Another disadvantage is that it takes weeks for a noticeable effect to occur.[5]

Imipramine is the tricyclic antidepressant (TCA) most commonly used for treating panic disorder, while other TCAs such as desipramine are occasionally used.[5] Like the MAOIs, weeks of therapy are required before a response occurs. Their anticholinergic side effects are more pronounced than with the MAOIs and may cause psychotic reactions, especially in the elderly.[2,5] TCAs can also cause orthostatic hypotension, tachycardia and decreased cardiac conduction.[2,5] Toxicity is another serious problem with these patients, and a few week's supply can easily cause death.

Benzodiazepines, as mentioned earlier, are the most commonly prescribed drugs in the U.S. Anxiety syndromes make up a large percentage of those prescriptions, and benzodiazepines can be used in all different types of anxiety disorders. Their advantages and disadvantages are mentioned above in the discussion on hypnotics.

The need for newer agents

Although the above-mentioned agents are effective against anxiety and insomnia, each has its own problems. The major disadvantage for all the hypnotics and for most of the anxiolytics is their potential for physical dependence. For those anxiolytics without addictive potential, the primary problems are adverse effects and toxicity. Therefore, the search goes on for drugs with specific actions, few side effects, a high therapeutic index and no addictive potential.

Buspirone (Buspar®)

Buspirone is a relatively new drug which is unique from the benzodiazepines in its chemical and pharmacologic properties. It was first introduced in 1985 in West Germany and is the first drug developed primarily as an anxiolytic.[4]

Pharmacology. Unlike the benzodiazepines, buspirone actually increases noradrenergic activity. Buspirone's mechanism of action is not completely understood, but it apparently does not involve action on the benzodiazepine-gamma aminobutyric acid-chloride (BZ-GABA-Cl) ionophore complex. It binds selectively to 5-HT_{1A} receptors, and this is most likely where the majority of its anxiolytic activity is produced.[7] These receptors are localized in areas of the CNS which may explain its more favorable adverse effect profile versus the benzodiazepines. Buspirone does not share the anticonvulsant and muscle relaxant properties of the benzodiazepines and exhibits anxiolytic effects only.[7]

The major disadvantage for all the hypnotics and for most of the anxiolytics is their potential for physical dependence. For those anxiolytics without addictive potential, the primary problems are adverse effects and toxicity.

Pharmacokinetics. Buspirone is absorbed rapidly and completely from the GI system. After undergoing first-pass metabolism only 4% of the drug reaches the systemic circulation.[5] The onset of action of buspirone is considerably de-

layed and occurs sometime during the first three weeks of therapy; therefore, it cannot be used for short-term or as-needed treatment. The distribution of buspirone is not completely known. The apparent volume of distribution is about 5.3 L/kg.[7] It is 95% bound to plasma proteins,[5] mostly to albumin and a 1-acid glycoprotein. The elimination half-life is about four hours in healthy patients while it is prolonged with renal impairment and hepatic cirrhosis. Buspirone is metabolized in the liver, primarily by oxidation, into several metabolites. The major active metabolite is 1-pyrimidinyl-piperazine (1-PP). It has about 20-25% of the anxiolytic activity of buspirone;[7] however, it is unclear how much it adds to buspirone's action. Both buspirone and its metabolites are excreted primarily in the urine although less than 0.1% is excreted as unchanged drug.[7]

Adverse effects. Adverse effects which have been reported include gastrointestinal complaints (nausea and vomiting), dizziness and headache. Each of these side effects were reported in less than 10% of patients. Sedation is reported in 10% of patients, which is the same incidence as with placebo. There are slightly more reports of adverse effects in the elderly.[4] Also, there are few reports of psychomotor impairment. Another unique feature of buspirone is its inability to potentiate the effect of alcohol and lack of addiction potential.[4]

There is little information on the toxicity of buspirone. Because dysphoria may occur at higher doses of 20-40 mg,[7] there is low potential for abuse. There also is little evidence that withdrawal occurs with sudden discontinuation of the drug. For acute toxicity, there are no specific antidotes and treatment usually involves supportive care. The lethal dose in humans is unknown.[4]

Drug interactions. Drug interactions include elevated blood pressure in patients with concurrent MAOI use. Therefore, it is not recommended to give both concomitantly, and there should be a 10-day washout after MAOI use before buspirone therapy is initiated.[8] There have been reports of elevations in ALT concentrations with concomitant buspirone and trazodone use. However, this remains unconfirmed in studies. As long as liver function tests are monitored, the manufacturer claims that the two may be used together.[8] When haloperidol and buspirone are used together, elevations occur in haloperidol concentration. This probably occurs through competition resulting in the inhibition of the metabolism of haloperidol.[8] It is not recommended that both be used concurrently until more information is obtained on this interaction.[8] Buspirone does not appear to interact with benzodiazepines; however, it is still recommended that they not be given together.[8]

Indications. Indications for buspirone include generalized anxiety disorders.

The side effect profile of buspirone is a definite advantage over the benzodiazepines. There is little sedation, making it an alternative for patients in whom the sedation and psychomotor impairment are intolerable.

Studies have shown that buspirone is as effective as benzodiazepines for these disorders.[8] In severe anxiety, however, buspirone is less effective than lorazepam and diazepam.[5] Previous treatment with benzodiazepines is often associated with disappointment in buspirone therapy.[5,7] This is probably due to its long onset of action and because buspirone does not alleviate the withdrawal symptoms of benzodiazepines.

Dosing and administration. Buspirone is only available orally. The starting dose is 10-15 mg/d in two or three divided doses. It can be given with or without food. Increases of 5 mg/day every two to four days can be made after one week of therapy at 15 mg/day. The usual maximum dose is 60 mg/day. Optimal effects may not occur for as long as six weeks.[5] It has not been determined how to adjust doses in hepatic and renal impairment. Some have suggested a 25-50% reduction in patients that are anuric.

The side effect profile of buspirone is a definite advantage over the benzodiazepines. There is little sedation, making it an alternative for patients in whom the sedation and psychomotor impairment are intolerable. It would also be indicated in patients who may have a history of drug dependence. The disadvantage is its long onset of action. In patients with symptoms requiring immediate alleviation, buspirone may not be ideal.

Clomipramine (Anafranil®)

Clomipramine is a tricyclic antidepressant used for more than 20 years in Europe and Canada which has more recently been used for various anxiety disorders.[9] It is so far the only agent approved for obsessive-compulsive disorder (OCD) and is marketed in the U.S. for this indication.

Pharmacology. Clomipramine inhibits reuptake of serotonin and norepinephrine like the other tricyclic antidepressants and is the most potent serotonin reuptake blocker in its class.[10] The activity of clomipramine is thought to be due to its inhibitory effect on serotonin. This activity increases serotonin levels, and long-term treatment may lead to a down regulation of the serotonin receptors. However, its exact mechanism is unknown.[9,10]

Pharmacokinetics. Absorption is rapid and complete from the GI system, but the drug undergoes first pass effect. Systemic bioavailability is about 50%.[11] The distribution pattern has yet to be completely determined. The mean apparent volume of distribution is 12 L/kg.[11] It is 98% protein bound to plasma proteins.[9,11] Clomipramine is extensively metabolized to a variety of metabolites. Demethylclomipramine, the major metabolite and a result of first pass demethylation, is active. Approximately 50-60% of the oral dose is found in the urine and the rest is in the feces. The mean elimination half-life of clomipramine is 32 hours while demethylclomipramine's mean half-life is 69 hours.[12]

Adverse effects. Clomipramine has the same adverse effect profile as the other tricyclic antidepressants.[9] The anticholinergic effects are most prominent and include dry mouth, constipation, sweating, blurred vision and urinary retention.[9] Cardiac effects include orthostatic hypotension, syncope, palpitations and tachycardia.[9] Seizures have been reported at an incidence of 0.7% and were more common with high doses (>300 mg/day) and with intravenous administration.[9] One particularly disturbing problem to patients is sexual dysfunction, although normal function returns with discontinuation of the drug.[9] Weight gain can also be a problem.[9] It is essential to counsel patients about these two side effects. In some trials there is a dropout rate of up to 28%.[9]

Acute toxicity with clomipramine is similar to those of other tricyclic antidepressants. Symptoms include severe anticholinergic effects. In extreme cases, hypotension, coma, cardiac abnormalities, convulsions and respiratory arrest may occur. Treatment involves the usual treatment of tricyclic antidepressant toxicity. The guidelines can change; therefore, a poison center should be called for updated information.[12]

Indications. Clomipramine, unlike most of the other tricyclic antidepressants, is used to treat obsessive compulsive disorder and panic disorder. Early studies have shown that clomipramine is superior to other tricyclic antidepressants in treating OCD.[9,10]

Dosing and administration. The starting dose for clomipramine in OCD is 25 mg two to three times daily.[10] The dose should be increased slowly depending on response and tolerance of side effects, up to 100-150 mg, although 250 mg has been used. Drug effect can take as long as five to six weeks to manifest.[9] Once symptoms have been alleviated the dose should be brought down to the lowest effective level.

Quazepam (Doral®)

Quazepam is a benzodiazepine introduced in 1990. The action of quazepam, like other benzodiazepines, revolves around its actions on GABA. Quazepam and one of its metabolites, 2-oxoquazepam (OQ), have selectivity for type 1 benzodiazepine receptors.[13] This is a unique quality which is shared by only one other benzodiazepine, halazepam. The significance of this selectivity is yet to be elucidated.[14]

Pharmacokinetics. Quazepam is absorbed rapidly and its bioavailability is approximately 80%.[8] There is, however, extensive first pass metabolism in animals which has not been quantified in humans. Quazepam is distributed into most tissues and body fluids, and the apparent volume of distribution is 5 L/kg when given at bedtime and 8.6 L/kg when given in the morning.[14] Both quazepam and OQ distribute quickly into the CNS and are more than 95% bound to plasma proteins.[13] Quazepam is extensively metabolized to OQ and N-desalkyl-2-oxoquazepam (DOQ), which is identical to N-desalkylflurazepam. Both metabolites have similar activity to the parent drug. The half-life of quazepam and OQ is about 40 hours.[13,14] The half-life of DOQ is about 70-75 hours.[13] In the elderly, the most significant change in half-life is in DOQ, which can increase to 190 hours.[14] Both metabolites are metabolized ultimately via conjugation with glucuronide formation. Quazepam is excreted both in urine and feces with very little in its original form.

Adverse effects. Adverse effects of quazepam are similar to other benzodiazepines. These include CNS depression and physical dependence. Quazepam may cause more daytime sedation than other benzodiazepines with shorter half-lifes. Sedation is also more of a problem at the higher dose of 30 mg.[13] Side effects are usually most pronounced in the first few days and may diminish with time or with decreases in dosage. At one week and four weeks of therapy, there appears to be little daytime drowsiness.[15] There have been rare reports of confusion and psychotic-like symptoms at the 30 mg dose, but none are reported at the 15 mg dose.[14] Rebound insomnia is not a problem with quazepam due to the long half-life of DOQ.[13] With respect to dependence, quazepam appears to have a low potential for abuse due to its carryover effects and decreased incidence of rebound insomnia. No definitive statements can be made though until larger numbers of patients use this drug and more studies are done.[14]

When compared with temazepam, quazepam appears to be more effective with short-term use, and there also seems to be less tolerance development when quazepam is used longer term.

Drug interactions. Drug interactions include additive CNS effects with other CNS depressants, anticonvulsants and alcohol. If drugs from both classes need to be used together, reductions in doses will be required to prevent overdosage. Administration of disulfiram and benzodiazepines which undergo oxidative metabolism may result in a decreased metabolism of the benzodiazepine.[8] Since quazepam is one of the these agents, patients taking both these agents should be watched for a greater response to quazepam. This is also the case with concomitant cimetidine administration. Cimetidine may inhibit the clearance of quazepam; therefore, response must again be monitored and dosage reductions made as necessary.[8]

Indications. Quazepam is used primarily as a hypnotic. It shares a similar pharmacokinetic profile as flurazepam and is very comparable in terms of efficacy and side effect profile. Flurazepam may have better long-term effectiveness, however.[14] When compared with temazepam, quazepam appears to be more effective with short-term use, and there also seems to be less tolerance development when quazepam is used longer term.[13,14]

Dosing and administration. Quazepam is available in oral form and given only a bedtime. The starting dose is 15 mg in most adults. In some people, 7.5 mg may be enough. The higher dose of 30 mg is sometimes used, but there is generally more daytime sedation at that dose. Quazepam and flurazepam share the same active metabolite and will therefore share many of the same properties. Quazepam may have advantages over temazepam and triazolam, but seems to have little over flurazepam.

Estazolam (ProSom®)

Introduced in 1991, Estazolam is another new benzodiazepine.

Pharmacology. Like other benzodiazepines, estazolam's actions are due to its effects on GABA. It is unknown whether estazolam has selectivity for either benzodiazepine type 1 or 2 receptors.

Pharmacokinetics. Estazolam is both rapidly and well-absorbed from the GI tract. The bioavailability is approximately 98%. It distributes widely into most tissues and fluids, and it appears to cross the blood-brain barrier.[8] The half-life ranges from 8-31 hours.[2] Estazolam is metabolized hepatically, and its metabolites have little activity. The two principal ones are 4-hydroxyestazolam and 1-oxo-estazolam. Both estazolam and its metabolites are primarily excreted in urine with a small percent excreted in feces.

Adverse effects. The side effect profile is essentially the same as that for quazepam, as is the drug interaction profile. In a study looking at long-term administration, no tolerance was seen during the six weeks of therapy.[16] The same study showed that rebound insomnia could occur with sudden withdrawal, but that this was just temporary.[16]

Drug interactions. Estazolam is oxidatively metabolized; therefore, there is again the potential for its increased activity when given with cimetidine or disulfiram. Doses should be adjusted when given concomitantly with these agents.

Indications. Estazolam is used, as are other benzodiazepines, as a hypnotic. Estazolam has an intermediate half-life which makes it less likely to cause daytime sedation than those with long half-lives. It is also less likely to cause the rebound insomnia seen when discontinuing benzodiazepines with short half-lives. Early studies show that estazolam has fewer side effects than flurazepam and is equally efficacious as a hypnotic.[17]

Dosing and administration. Estazolam is available in oral form only. The starting dose of estazolam in adults is 1 mg at bedtime. The dose then may be slowly increased to 2 mg. In elderly patients, the dose should be started at 0.5 mg at bedtime. When patients have been on therapy for long periods, they should be tapered slowly to avoid withdrawal. Estazolam has an intermediate half-life and would be expected to be similar to other benzodiazepines with similar half-lives such as temazepam. This agent is not expected to have any obvious advantages. Estazolam has only been available for a year. Until there is more widespread use of the drug, we will not know if there are any clear advantages or disadvantages.

Conclusion

Although new anxiolytics and hypnotics continue to appear on the market, very few of them have any significant advantage over previous agents. Buspirone appears to be a breakthrough in that it is significantly different from previous agents. It has specific effects, low incidence of side effects and little, if any, addiction potential. However, its long onset of action is a disadvantage. Clomipramine also has some advantages in that it has increased efficacy over imipramine in the treatment of OCD; however, it has many of the same side effects. The two newer benzodiazepines appear to have little advantage over the older agents. Perhaps with continued use, more advantages and/or disadvantages will be revealed. It appears that the search for the perfect anxiolytic and hypnotic will have to continue.

About the authors

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