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Side effects of antidepressants: An overview

ABSTRACT

Adverse effects of antidepressant drugs can decrease compliance and delay recovery. It is therefore crucial to consider potential side effects when choosing an antidepressant. Although there is no perfect antidepressant that works quickly and is completely free of adverse reactions, newer antidepressants are safer, better tolerated, and associated with a lower rate of noncompliance.

KEY POINTS

Although side effects can be idiosyncratic, most can be explained by the drug's mechanism of action.

Most antidepressant side effects subside within the first few days to weeks of therapy.

Sexual dysfunction is a side effect of all serotonin reuptake inhibitors, venlafaxine, and duloxetine. Bupropion and nefazodone have the lowest risk for sexual side effects.

The risk of suicide may be increased during the first month or so of antidepressant therapy; physicians, patients, and family members should be vigilant for signs of suicidal thoughts and behavior.

In elderly patients, serotonin reuptake inhibitors seem to be safer and better tolerated than tricyclic antidepressants. The choice should be made on the basis of side effect profile and drug interactions.

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CURRENT ANTIDEPRESSANT DRUGS are effective and generally well tolerated, but noncompliance remains worrisome. Up to 70% of patients taking antidepressants are noncompliant,[1,2] as a result of either missed doses or premature discontinuation. According to Lin et al,[1] 28% of patients stopped taking antidepressants in the first month of treatment, and 44% discontinued by the third month. Several reasons were identified for premature discontinuation, with side effects the most common. Dropout rates in studies of tricyclic antidepressants varied from 7% to 44%; in studies of serotonin reuptake inhibitors, the dropout rates were 7% to 23%.[3,4]

Physicians should educate and reassure their patients about potential side effects. Benign and transient side effects are more common than dangerous or irreversible effects, especially with the newer antidepressants. This knowledge can help in reducing the rate of medication discontinuation, which is important because even after a medication has produced the desired benefit, it needs to be continued to prevent relapses.

This article will focus on the adverse effects of antidepressants, with the goal of helping physicians to recognize and understand them, so that patients can undergo effective treatment.

SIDE EFFECTS ARE USUALLY PREDICTABLE

Medications are the mainstay of treatment of moderate to severe depression, often combined with psychotherapy.[5] In addition, antidepressants are used to treat other psychiatric illnesses and even medical illnesses (TABLE 1).

Although some side effects of antidepres-

TABLE 1

Other indications for antidepressant drugs

Anxiety disorders: phobic disorders, panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, post-traumatic stress disorder

Attention deficit and disruptive behavior disorders

Eating disorders: anorexia and bulimia

Gastrointestinal disorders: irritable bowel syndrome

Genitourinary disorders: enuresis

Pain syndromes: migraine headache, other chronic pain conditions

Psychotic disorders: schizoaffective disorder

Sleep disorders: insomnia, night terrors, sleep apnea, narcolepsy, functional enuresis

sant drugs are idiosyncratic, most can be explained by their effects at the synaptic level (TABLE 2).[6,7] Antidepressants typically block the reuptake of certain neurotransmitters (norepinephrine, serotonin, and dopamine) back into the nerve ending and block some of the other neurotransmitter receptors.[7–10] The most clinically relevant receptor blockade occurs at muscarinic (acetylcholine), histaminic (H1), alpha-1 adrenergic, dopaminergic (D2), and possibly serotonergic (5-HT2A) receptors.

Side effects are not always a disadvantage. For example, a patient with insomnia may benefit from a sedating antidepressant given at bedtime.

Serotonin reuptake inhibitors are metabolized by the P-450 system

SEROTONIN REUPTAKE INHIBITORS

Serotonin reuptake inhibitors have replaced the tricyclic antidepressants as the first-line treatment for depression and now account for most prescriptions for antidepressants in the United States. Fluoxetine (Prozac) was introduced in 1988 and was followed by sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro). All but fluvoxamine are approved by the US Food and Drug Administration (FDA) for treating depression; fluvoxamine is approved for obsessive-compulsive disorder.

Mechanism of serotonin reuptake inhibitors

Serotonin reuptake inhibitors selectively block serotonin reuptake at the presynaptic nerve terminal.

Citalopram and escitalopram have the most selective effect on serotonin reuptake, with little inhibitory effect on norepinephrine and dopamine reuptake and a low affinity for alpha 1 adrenergic receptors, muscarinic cholinergic receptors, and histamine H1 receptors.[11,12]

Other serotonin reuptake inhibitors have similar profiles, except that paroxetine has some anticholinergic properties, fluoxetine weakly inhibits norepinephrine reuptake, and sertraline weakly inhibits norepinephrine and dopamine reuptake.[7–9,11]

Pharmacokinetics of serotonin reuptake inhibitors

Serotonin reuptake inhibitors differ in their pharmacokinetics. Fluoxetine has the longest half-life, and its active metabolite (norfluoxetine) has a half-life of 7 to 15 days.[11] Paroxetine and fluvoxamine have relatively short half-lives (21 and 15 hours, respectively).

All serotonin reuptake inhibitors are metabolized in the liver by the cytochrome P-450 system.[11] Because they competitively inhibit these hepatic enzymes, serotonin reuptake inhibitors can increase the levels of other medications metabolized by these enzymes, possibly leading to toxic effects. The greater the P-450 inhibition, the greater the possibility of drug interactions. For example, giving desipramine (a tricyclic antidepressant) with a serotonin reuptake inhibitor such as fluoxetine can lead to as much as a fourfold increase in the plasma level of desipramine, which could lead to increased anticholinergic effects, sedation, seizures, and cardiotoxicity. Fluoxetine might interact with warfarin, with the possibility of an increased anticoagulant effect and an increased risk of bleeding.

Side effects of serotonin reuptake inhibitors

Serotonin reuptake inhibitors are generally well tolerated. However, approximately 15% of patients cannot tolerate certain side effects and therefore may stop taking the drug.

Sexual dysfunction. Although psychi-

atric illnesses in themselves can affect sexual desire and performance, so can the drugs used to treat the illness. Sexual dysfunction is the most common side effect of all serotonin reuptake inhibitors. Delayed ejaculation, anorgasmia, and decreased libido can occur in up to 60% of patients,[13,14] and the effects continue as long as the drug is taken.

The stimulation of serotonin 5-HT2 and 5-HT3 receptors is a proposed mechanism for the occurrence of sexual dysfunction due to serotonin reuptake inhibitors, so it has been suggested that adding medications that block those receptors might help with this adverse effect. The most common medications for counteracting this adverse effect fall into three groups: alpha-2 adrenergic receptor antagonists, serotonin 5-HT2 or 5-HT3 receptor antagonists (eg mirtazapine), and dopaminergic agents. Other strategies include decreasing the dose; adding bupropion, sildenafil, cyproheptadine, or buspirone; or switching to another antidepressant that has few sexual side effects, such as bupropion, mirtazapine, or nefazodone.[2,14]

Gastrointestinal effects. Sertraline and fluvoxamine may cause more gastrointestinal side effects than other serotonin reuptake inhibitors. Nausea and diarrhea are dose-related and usually resolve within the first 2 weeks of treatment. Starting the medication at a low dose and giving it with food usually alleviates nausea.

Constipation and dry mouth tend to be more common with paroxetine because of its anticholinergic activity.[6]

Anorexia is most common with fluoxetine and occurs early in the treatment.[8,14] It is probably related to activation of 5-HT2C receptors.[8] However, with time this suppressant effect on appetite is lost. Indeed, serotonin reuptake inhibitors have the potential to cause weight gain, possibly due to desensitization and down-regulation of the serotonin receptors associated with appetite control.

Central nervous system side effects include anxiety, insomnia, sedation, nightmares,[6,14] and extrapyramidal symptoms. Patients may experience increased anxiety, most commonly early in treatment.

Sleep disturbances, either insomnia or somnolence, have been reported in about

TABLE 2

Adverse effects of antidepressant drugs, based on mechanism of action

Norepinephrine transporter blockade
- Anxiety
- Augmentation of pressor effects of sympathomimetic amines
- Diaphoresis
- Tachycardia
- Tremor

Serotonin reuptake inhibition
- Anorexia early in the treatment and weight gain later
- Dose-dependent increase or decrease in anxiety
- Ejaculatory disturbances, anorgasmia, and decreased libido
- Extrapyramidal side effects
- Interaction with monoamine oxidase inhibitors and tryptophan
- Nausea, vomiting, and diarrhea.
- Sedation or insomnia
- Serotonin syndrome

Dopamine reuptake inhibition
- Activation and aggravation of psychosis
- Parkinsonism
- Psychomotor activation

Alpha-1 adrenergic receptor blockade
- Postural hypotension and dizziness
- Potentiation of the antihypertensive effect of other medications
- Reflex tachycardia

Dopamine D2 receptor blockade
- Extrapyramidal side effects: akathisia, dystonia, parkinsonism, tardive dyskinesia
- Endocrine effects; prolactin elevation

Histamine H1 receptor blockade
- Drowsiness
- Falls in the elderly
- Orthostatic hypotension
- Sedation
- Weight gain

Muscarinic acetylcholine receptor blockade
- Blurred vision
- Central effects: memory and cognitive impairment, delirium in severe cases
- Gastrointestinal effects: decreased salivation, dry mouth, decreased peristalsis, constipation
- Precipitation of narrow-angle glaucoma
- Sinus tachycardia
- Urinary hesitancy and retention

ADAPTED FROM RICHELSON E. INTERACTION OF ANTIDEPRESSANTS WITH NEUROTRANSMITTER TRANSPORTERS AND RECEPTORS AND THEIR CLINICAL RELEVANCE. J CLIN PSYCHIATRY 2003; 64(SUPPL 13):5–13; AND RICHELSON E. PHARMACOLOGY OF ANTIDEPRESSANTS. MAYO CLIN PROC 2001; 76:511–527.

25% of patients taking serotonin reuptake inhibitors. Fluoxetine is more likely to cause insomnia than is paroxetine, which is more likely to cause sedation. Others tend to lead equally to somnolence or insomnia. Insomnia can be treated with trazodone, benzodiazepines, or other sedative medications.[14]

Headache, nightmares, and vivid dreams have been reported in a minority of patients. These side effects often resolve within a few weeks and rarely lead to a change in medication.

In rare cases, serotonin reuptake inhibitors can cause extrapyramidal side effects, including akathisia (motor restlessness; constant movement).[6] Such adverse effects are not due to dopamine receptor blockade but rather to increased serotonin at the synaptic levels, mediating inhibition of the release of dopamine through one of the presynaptic serotonin receptor subtypes. The rate of seizures with serotonin reuptake inhibitors is 0.1% to 0.2%, which is not significantly different from that with placebo.[15,16]

Orthostatic hypotension is unlikely in patients treated with serotonin reuptake inhibitors because they do not block alpha-1 adrenergic receptors significantly.[6,15]

Serotonin reuptake inhibitors should be tapered to avoid the discontinuation syndrome

These drugs have minimal effects on histamine H1 receptors and therefore they are less sedating than tricyclic antidepressants.

Bleeding. Serotonin reuptake inhibitors inhibit platelet function and may prolong bleeding. Several reports have indicated an association between the use of these drugs and bleeding disorders ranging from bruising and epistaxis to more serious conditions such as gastrointestinal bleeding.[17]

Hyponatremia has been reported in rare cases.[18]

Serotonin syndrome is serious.[15,19] Resulting from hyperstimulation of serotonin receptors, it is characterized by nausea, diarrhea, restlessness, extreme agitation, hyperreflexia, autonomic instability, myoclonus, hyperthermia, rigidity, delirium, seizure, and status epilepticus. In severe cases, it can result in cardiovascular collapse, coma, and death.

This syndrome can occur when a monoamine oxidase inhibitor is given with a serotonin reuptake inhibitor, pentazocine, or L-tryptophan. Therefore, it is mandatory to wait at least 2 weeks after stopping a serotonin reuptake inhibitor before starting a monoamine oxidase inhibitor, and at least 5 weeks if switching from fluoxetine, in view of this drug's long half-life.

Discontinuation syndrome can occur if a serotonin reuptake inhibitor with a short half-life such as paroxetine or fluvoxamine is abruptly stopped.[14,15,20] Patients may experience dizziness, nausea, weakness, insomnia, anxiety, irritability, and headache. These symptoms tend to be transient and resolve spontaneously within a week. Slowly tapering serotonin reuptake inhibitors over a couple of weeks can help prevent this syndrome. Fluoxetine is less likely to cause this syndrome because of its long half-life. Indeed, fluoxetine has been used to treat the discontinuation syndrome caused by other serotonin reuptake inhibitors.

VENLAFAXINE

Venlafaxine (Effexor) was first released in an immediate-release form. An extended-release form (Effexor XR) was approved by the FDA in 1997.

Venlafaxine inhibits serotonin and norepinephrine reuptake and is a weak inhibitor of dopamine reuptake.[8] It is not active at the muscarinic, nicotinic, histaminergic, or adrenergic receptors.

The most common side effects are **nausea, dizziness, insomnia, somnolence,** and **dry mouth**. Gastrointestinal side effects are less common with the XR preparation.

Sexual dysfunction can occur, as with serotonin reuptake inhibitors.[13]

Discontinuation syndrome, with nausea, somnolence, insomnia, and anxiety, can result if venlafaxine is abruptly stopped.[21] To prevent this syndrome, venlafaxine XR should be tapered over several days to weeks.

Hypertension can occur with venlafaxine XR,[22] especially in higher doses. Physicians should be cautious when prescribing this medication to patients with preexisting hypertension. Blood pressure should be monitored regularly, especially when using venlafaxine XR at doses of 225 mg or more per day.

MIRTAZAPINE

Mirtazapine (Remeron) is a presynaptic alpha 2 adrenergic receptor antagonist and a potent antagonist of serotonin 5-HT2 and 5-HT3 receptors.[8,23] It has very little effect on 5-HT1 receptors. Therefore, mirtazapine directly increases norepinephrine release and, indirectly, serotonin release. It also blocks histamine receptors and has minimal affinity for muscarinic and alpha-1 adrenergic receptors.

Sedation is the most common side effect. Giving the medication at bedtime can minimize sedation. Nighttime sedation could be an advantage in depressed patients with sleep disturbances, but on the other hand, undesirable daytime sedation could occur.

Weight gain. Mirtazapine can increase appetite and carbohydrate craving.[14] This may lead to significant weight gain if not monitored closely. It may also increase cholesterol and triglyceride levels. Patients should be educated and advised to monitor their weight and to exercise regularly at the time of prescribing this medication.

Liver function tests, especially alanine aminotransferase, can be mildly elevated.

Neutropenia has developed in rare cases in patients treated with mirtazapine.[15] This hematologic condition is more likely to occur in patients with other risk factors for neutropenia.

Dizziness, dry mouth, constipation, increased appetite, and **disturbing dreams** have also been reported.

Mirtazapine does not tend to cause sexual dysfunction.[14]

BUPROPION

Bupropion (Wellbutrin) is a unique antidepressant that has few sexual side effects and tends not to cause an increase in appetite or weight gain.[2,13,14] Besides depression, it is used in smoking cessation.

Bupropion is thought to work by inhibiting norepinephrine reuptake and dopamine neurotransmission. It also has an active metabolite that mediates antidepressant efficacy by blocking reuptake of norepinephrine and dopamine.[8]

Insomnia, headache, tremors, and **nausea** are common side effects of bupropion. **Increased irritability** and **agitation** may also occur.

Seizures. The extended-release formulation carries a seizure risk of about 0.4% at a dose of 400 mg per day. Physicians should avoid prescribing this medication to patients with a history of seizure, epileptiform discharges on electroencephalography, heavy alcohol use, or eating disorders; or with benzodiazepine withdrawal, head trauma, or organic brain syndrome.

Bupropion does not cause orthostatic hypotension, daytime drowsiness, or anticholinergic side effects.

Caution should be used in patients with renal or liver diseases because these conditions could result in elevated plasma levels of bupropion.

DULOXETINE

Duloxetine (Cymbalta), the newest approved antidepressant, is an inhibitor of serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake.[24] It has no significant affinity for adrenergic, cholinergic, or histaminergic receptors.

Nighttime sedation may be desirable in depressed patients with sleep disturbances

The most common side effects reported in placebo-controlled clinical trials were **nausea, dry mouth, constipation, fatigue, decreased appetite,** and **sweating.**[24] The overall dropout rate due to side effects was 10%, with nausea as the most common adverse event.

Sexual dysfunction was more common with duloxetine than with placebo.[25] However, the rate appears to be less than with serotonin reuptake inhibitors.

Initial insomnia, irritability, anxiety, nervousness, and **restlessness** were also reported.

Duloxetine was associated with an increased risk of **mydriasis** and should be used with caution in controlled narrow-angle glaucoma.

Treatment with duloxetine was associated with **increased blood pressure**. Therefore, one should measure blood pressure before starting duloxetine and periodically monitor it throughout treatment.[26]

Duloxetine should not be used in combination with monoamine oxidase inhibitors

and can be used only at least 14 days after stopping one of these drugs.

If duloxetine is stopped, it should be tapered gradually to avoid **discontinuation side effects**.

TRICYCLIC AND TETRACYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants were introduced shortly after monoamine oxidase inhibitors. They were the drugs of choice for depression in the 1980s, but they are not as widely used now because less toxic and more selective medications are available.

These medications block reuptake of norepinephrine and serotonin. They are also competitive antagonists at the muscarinic, histaminergic, and alpha 1 and 2 adrenergic receptors, which results in their characteristic side effect profile.[8] Amitriptyline, imipramine, and doxepin have the most anticholinergic activity, whereas nortriptyline and desipramine are less anticholinergic.[6,15]

Anticholinergic side effects include dry mouth, constipation, urinary retention, blurred vision, confusion, and delirium. Narrow-angle glaucoma can be aggravated.

Renal or liver diseases can elevate bupropion levels

Cardiac effects. Tricyclic antidepressants may slow cardiac conduction, causing intraventricular conduction delay, atrioventricular block, flattened T waves, depressed ST segments, and prolonged QT intervals.[27] All tricyclic antidepressants can cause tachycardia, which is one of the most common reasons for stopping them. Nortriptyline is the least likely to cause orthostatic hypotension.

Because of cardiotoxicity, an overdose of as little as 1 week's worth of medication can be fatal.

Sedation is the most common side effect of tricyclic antidepressants and is a result of anticholinergic and antihistaminergic effects.[28] Doxepin has the highest antihistaminergic activity among tricyclic antidepressants.

Weight gain and **sexual side effects** are also common.[14]

A discontinuation syndrome[28] is mostly related to cholinergic and serotonergic rebound. After prolonged treatment, tricyclic antidepressants should be tapered gradually over several weeks.

Drug interactions are significant. Serotonin reuptake inhibitors may raise the plasma levels of tricyclic antidepressants. There is a possibility that phenytoin levels increase with tricyclic coadministration. Valproic acid can increase levels of tricyclics, and carbamazepine may decrease them.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors are very effective antidepressants, but dietary restrictions and the risk of hypertensive crises limit their use.

These drugs irreversibly inactivate the enzyme monoamine oxidase in the central nervous system, platelets, liver, and gastrointestinal tract, the last of which may cause an increase in tyramine absorption.

Monoamine oxidase inhibitors were discovered in the early 1950s. The first drug of this class was iproniazid, but serious side effects, particularly hypertensive crisis and hepatic necrosis, prevented its use.[15,29] Currently available are phenelzine (Nardil), isocarboxazid (Marplan), tranylcypromine (Parnate), and selegiline (Eldepryl). Reversible monoamine oxidase inhibitors require few dietary restrictions but are not available in the United States; these include moclobemide (Manerix) and befloxatone.

Orthostatic hypotension, the most frequent side effect, is secondary to alpha-1 adrenergic blockade. The exact mechanism is not known but likely involves elevated norepinephrine at presynaptic alpha-2 receptors. **Dizziness** and **reflex tachycardia** may also occur.

Antihistaminergic activity might lead to **weight gain** and **sedation**.

Hypertensive crises are usually induced by consuming food rich in tyramine or by medications with sympathomimetic activity. Headache, stiff neck, sweating, nausea, and vomiting characterize the prodromal phase. This could be followed by autonomic instability, elevated blood pressure, cardiac arrhythmia, coma, and death.

Sexual dysfunction, hepatotoxicity, and **pyridoxine deficiency** have been reported.

Drug interactions are numerous, including problems with over-the-counter medications such as pseudoephedrine. Serotonin syndrome can occur when monoamine oxidase inhibitors are combined with serotonin reup-

take inhibitors, tricyclic antidepressants, or carbamazapine. Coadministration with opioids, especially meperidine, may lead to autonomic instability, delirium, and death. Caution should be taken when using monoamine oxidase inhibitors with antihypertensive agents, due to an increased likelihood of hypotension.

TRAZODONE

Trazodone is effective in treating depression, but it is not often used for this indication because other antidepressants with a more benign side effect profile are available.

Trazodone is a weak inhibitor of serotonin reuptake and a potent antagonist of serotonin 5-HT2A and 5-HT2C receptors.[8] The side effects of trazodone are mostly attributed to antihistaminic and alpha-1 adrenergic blockade.

Sedation. Trazodone has been often used for treating insomnia because it has sedative qualities. However, in a recent review, Mendelson[30] found that data are lacking to support its use in this way.

Trazodone can cause significant **orthostatic hypotension, dizziness,** and **headache**. In rare cases, it can cause **priapism** in the absence of sexual stimuli. This serious side effect usually occurs during the first 4 weeks of treatment, and it is not dose-dependent.

ANTIDEPRESSANTS AND SUICIDE RISK

The relationship between antidepressants, especially serotonin reuptake inhibitors, and suicidal ideation and behavior has received considerable public attention lately. The use of these drugs in children and adolescents has been of particular concern.[31]

In October 2004, the FDA issued a warning about the increased risk of suicidal thoughts and behavior in children and adolescents being treated with antidepressant medications. The agency has asked pharmaceutical manufacturers to add a "black box" warning statement to the label for all antidepressant medications to describe the risk and emphasize the need for close monitoring of patients started on these medications.

The risk was identified in a combined analysis of short-term (lasting up to 4 months), placebo-controlled trials of the serotonin reuptake inhibitors fluoxetine, citalopram, paroxetine, fluvoxamine, and sertraline, as well as bupropion, nefazodone, mirtazapine, and venlafaxine XR, in children and adolescents with major depressive disorder and other psychiatric disorders.[32] The analysis showed a twofold greater risk of suicidal thoughts and behavior during the first few months of treatment in those receiving antidepressants—an average of 4%—compared with the rate with placebo.

Of note: although this analysis suggests that the incidence of suicide may be higher in patients taking serotonin reuptake inhibitors, no definitive link has been made. There were no reported cases of suicide in these studies.[32]

If there is an increased risk of suicide, a possible explanation is that serotonin reuptake inhibitors and some other antidepressants can cause anxiety, agitation, and activation, particularly at the start of treatment. In someone with lowered mood, new aversive symptoms might further worsen mood and increase the risk of suicide.[33]

The FDA recognizes that depression and other psychiatric disorders can have significant consequences if not appropriately treated. The new warning does not prohibit the use of antidepressants, but it warns of the risk of suicidal thoughts and behavior and encourages clinicians to balance this risk with clinical need and to closely monitor patients, especially at the start of treatment. This issue remains a concern and a topic of continuing scientific debate.

Tricyclic antidepressants can cause tachycardia

Suicide is a significant public health problem. Each year there are approximately 30,000 suicides in the United States and 1 million worldwide.[34,35] Suicide is the eighth leading cause of death in the United States, and major depression is a factor in about 50% of suicides.[36]

The suicide rate has actually been declining over the last 10 to 15 years, coinciding with the introduction of serotonin reuptake inhibitors and increases in antidepressant prescriptions.[37–39] Furthermore, most of those who commit suicide and carry the diagnosis of major depressive disorder at the time of death are either untreated or receiving subtherapeutic doses of antidepressants,[37,39] indicating the

need for better recognition and adequate treatment of patients at risk.

It is important to educate patients about their illness and available treatment options. They should be informed about the current controversy regarding the use of serotonin reuptake inhibitors as a part of the process of obtaining informed consent. They need to be instructed to watch for any signs of activation, agitation, or suicidal ideation, and inform the prescribing physician immediately.

It is also reasonable to schedule more frequent follow-up visits at the beginning of treatment to monitor more closely for emergence of these side effects. Patients at higher risk for suicide may be given limited amounts of the medication, just enough until the next follow-up visit. Any reports of suicidal ideation need to be taken seriously, and hospitalization should be considered.

Patients need to be referred for psychiatric consultation if one or more antidepressants fail or produce only a partial response, or if they have major depression with psychotic features.

ANTIDEPRESSANTS IN THE ELDERLY

The risk of suicide during antidepressant therapy remains a topic of debate

Medication dosages need to be altered in older age because of physiological changes. Aging and concomitant medical problems affect the pharmacodynamics and pharmacokinetics of medications. In addition, many elderly patients use a number of medications, and caution should be given to potential drug interactions.[40]

No important differences in efficacy have been found between classes of antidepressants in the elderly. The choice of antidepressant in the elderly should be based on its side effect profile and drug interactions.[41]

Serotonin reuptake inhibitors appear to be safer and better tolerated than tricyclic antidepressants. Common side effects of serotonin reuptake inhibitors in the elderly are nausea, insomnia, and sedation. Citalopram and sertraline have the fewest, if any, drug interactions. Paroxetine can cause more sedation and anticholinergic side effects.

Tricyclic antidepressants should be started with very low doses. Alpha-1 adrenergic blockade leads to orthostatic hypotension, which can cause dizziness and falls in the elderly. Histaminic effects can cause sedation and weight gain. Blood levels of tricyclic antidepressants should be monitored, as should their electroencephalographic, blood pressure, and cardiac effects.

Mirtazapine may be a useful alternative to tricyclic antidepressants in the elderly because it promotes sleep and causes minimal orthostasis.

IMPORTANCE OF PATIENT EDUCATION

Education and reassurance of patients about side effects will enhance compliance and improve treatment outcome. Providing patients with contact information might decrease their anxiety and help in reporting any adverse event. It is also very helpful to provide patients with literature explaining the potential side effects. Patients should be encouraged to contact their provider about any troublesome side effect that does not resolve.

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