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Mirtazapine: A Newer Antidepressant

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Mirtazapine is a newer antidepressant that exhibits both noradrenergic and serotonergic activity. It is at least as effective as the older antidepressants for treating mild to severe depression. Sedation is the most common side effect. Although agranulocytosis is the most serious side effect, it is rare (approximately one in 1,000) and usually reversible when the medication is stopped. Mirtazapine is relatively safe in overdose. Many clinicians consider mirtazapine a second-line or even third-line antidepressant, to be used when older antidepressants are not tolerated or are ineffective. Physicians who are concerned about the risks of elevated lipid levels and agranulocytosis may choose to reserve mirtazapine as a third-line choice. It is particularly useful in patients who experience sexual side effects from other antidepressants. Mirtazapine is also a good choice in depressed patients with significant anxiety or insomnia. Although mirtazapine has been used successfully in Europe for a number of years, its place in the care of patients with depression in the United States has not yet been established.

Antidepressants remain the cornerstone of treatment of depression by primary care physicians.[1,2] As new antidepressants are introduced to the market, physicians need to determine their place. *Table 1* compares selected antidepressants in terms of dosages and costs. A recent antidepressant introduced to the U.S. market is mirtazapine (Remeron).

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TABLE 1
Comparison of Selected Antidepressants

ANTIDEPRESSANT	*DAILY DOSAGE RANGE*	*COST**
Bupropion (Wellbutrin)	300 to 400 mg	$75 to 100
Fluoxetine (Prozac)	20 to 80 mg	75 to 290
Mirtazapine (Remeron)	15 to 30 mg	59 to 61
Nefazadone (Serzone)	200 to 600 mg	29 to 87
Paroxetine (Paxil)	10 to 40 mg	60 to 67
Sertraline (Zoloft)	50 to 200 mg	65 to 132

**—Estimated cost to the pharmacist based on average wholesale prices, for one month's therapy at the lowest usual dosage level, in Red book. Montvale, N.J.: Medical Economics Data, 1998. Cost to the patient will be higher, depending on prescription filling fee.*

As with any new drug, mirtazapine's place in the treatment of depression is not yet clear. Selective serotonin reuptake inhibitors (SSRIs) have become the drugs of choice in the treatment of depression.[3] Generally, either the older tricyclic antidepressants or the newer antidepressants are used for second-line therapy.[4] During the first few years of introduction to the U.S. market, it is reasonable for an antidepressant such as mirtazapine to be reserved for use in patients who do not tolerate or do not respond to initial therapy with SSRIs.

Pharmacology

Mirtazapine is a tetracyclic piperazinoazepine, which has a different structure from any other currently used antidepressant. It enhances central noradrenergic and serotonergic activity by blocking alpha$_2$ receptors and selectively antagonizing 5HT$_2$ and 5HT$_3$ receptors.[5–7] Thus, it is being classified as a noradrenergic and specific serotonergic antidepressant and referred to as an NaSSA.[8–10]

Mirtazapine is well absorbed without regard to food intake. It demonstrates linear kinetics over its usual dosage range and reaches peak plasma level approximately two hours after an oral dose.[11] The elimination half-life is 20 to 40 hours, so a steady state is reached in approximately five days. Mirtazapine is metabolized in the liver via the P450 cytochrome oxidase pathway, inhibiting cytochromes 2D6, 1A2 and 3A4. It is excreted in the urine. Clearance of the drug is diminished in the presence of liver or renal impairment. Therefore, a lower dosage is recommended in elderly patients and those with liver or renal dysfunction.

Mirtazapine is currently approved for use in adults. Because it is unknown if mirtazapine is secreted in breast milk, it should be used with caution in breast-feeding mothers. The U.S. Food and Drug Administration has labeled mirtazapine as a pregnancy category C drug.[12]

Efficacy

In the treatment of depression, as measured by Hamilton Depression rating scales, mirtazapine is clearly superior to placebo.[13–15] Several studies have shown mirtazapine to be at least as effective as amitriptyline (Elavil), trazodone (Desyrel) and fluoxetine (Prozac).[11,16,17] Mirtazapine has been used successfully in the treatment of mild to severe depression.[18]

Mirtazapine is especially helpful in patients with depression who are anxious; this drug has been shown to reduce anxiety and has even been used to relieve preoperative anxiety and insomnia in patients having gynecologic surgery.[13,19,20] Depressed patients with insomnia generally experience significant improvement while taking mirtazapine, including decreased sleep-onset latency, deeper sleep and fewer awakenings.[5,20] As with other antidepressants, mirtazapine has a delayed onset—although antidepressant effects may be noticeable after just one week.[11,14,18]

Side Effects

The most common side effects of mirtazapine are dose-dependent drowsiness (54 percent), dry mouth (25 percent), increased appetite (17 percent), weight gain (12 percent) and dizziness (7 percent). These side effects tend to improve with time.[3,7,12,18] Mild to moderate elevations in cholesterol, triglyceride and alanine aminotransferase (ALT: formerly known as SGPT) levels may also occur. The most serious side effect is agranulocytosis, which occurs in approximately one in 1,000 patients. This incidence is no higher than the incidence of other antidepressants. To date, all patients with this complication have recovered completely when the medication was stopped.[21] Routine laboratory monitoring is not recommended. A complete blood count and ALT measurement may be obtained if symptoms or signs suggest a need.

Mirtazapine has few, if any, cardiac effects and causes very little orthostatic hypotension.[3,21–23] Unlike the SSRIs, mirtazapine is associated with a very low incidence of sexual dysfunction, so it may be a good choice for use in patients who have experienced this side effect with other antidepressants.[9,10,24]

Information about overdose of mirtazapine in suicide attempts is limited because the drug is so new. However, to date no deaths have been recorded, and seizures and cardiotoxicity have not been noted in case reports. Excessive sedation appears to be the main effect of an overdose of mirtazapine.[18,21]

Drug-Drug Interactions

Multiple hepatic pathways are used in the metabolism of mirtazapine, so clinically significant drug-drug interactions are unlikely to occur.[3,25] However, little is actually known about drug-drug interactions in the clinical setting.[25] Because of its sedative effects, alcohol should not be taken with mirtazapine and excessive sedation may result when it is used with other sedating drugs, such as benzodiazepines.[3,26] Mirtazapine should not be used within 14 days of the use of a monoamine oxidase inhibitor because of the possibility that a hypertensive crisis will be triggered.[12]

Dosage

The usual starting dosage is 15 mg, with a usual dosage range of 15 to 30 mg per day.[18] Because of its common sedative effect, it is usually recommended that mirtazapine be taken at bedtime. It is available in 15-mg and 30-mg scored tablets.

The Author

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