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Atypical Antipsychotic Agents in the Treatment of Schizophrenia

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Atypical antipsychotic medications have documented benefits over the older typical antipsychotics and their use is rapidly becoming the standard of care for schizophrenia. This article summarizes the differences between typical and atypical agents, presents the characteristics of the four currently available atypicals and provides recommendations for the treatment of schizophrenia with these new agents.

Schizophrenia is a severe mental illness which affects approximately 1-1.5% of the population[1,2] and leads to suicide in 10% of affected patients.[1] It is a chronic disease with many patients requiring long-term support and care. Estimates of the costs of schizophrenia in the U.S. vary. In 1991 it was estimated that the direct costs of the disease were $19 billion and indirect costs were $46 billion.[2] Another analysis, which includes fewer indirect costs, found costs to be $34 billion in1990.[3] This study estimated that the direct costs of medical care were an average of $4,100 per patient per year. The most severely ill patients, who respond inadequately to conventional antipsychotic agents, required intensive institutional care costing approximately $90,000 per patient per year.[3,4]

The course of schizophrenia can be divided into three phases: the acute phase, the stabilization phase and the stable phase. The majority of patients alternate between the acute and stable phases. Some patients have a relatively stable course and others show progressive worsening that is associated with severe disability. Complete remission is not common.[5]

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Prevention Strategies for Post-Menopausal Osteoporosis

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Osteoporosis is a major public health problem in the U.S. Hip fractures are the 14th leading cause of death and cost approximately $10 billion per year to manage. As the average life expectancy and elderly population continues to grow, so does the prevalence of this disease. It is currently estimated at 9.4 million women. Despite continued research, available strategies for the management of osteoporosis do not restore bone to normal levels. Therefore, it is vital to utilize prevention strategies focusing on the identification of high-risk groups, the detection of early bone loss, the minimization of further bone loss, and ultimately, the prevention of fractures.[1,2]

Prevention strategies should optimally begin during childhood and adolescence.[2] Educational efforts should promote adequate calcium and Vitamin D intake, avoidance of tobacco, and regular weight-bearing exercise to aid in the attainment of optimal peak bone mass. After age 35, strategies should be altered to prevent the accelerated bone loss that occurs with menopause and to slow the insidious bone loss that occurs with aging.

Bone mineral density (BMD) testing, reported as T-scores, and careful risk-factor assessment serve to guide providers in the selection of prevention and treatment strategies for high-risk individuals. A BMD of 2.5 SD below the young adult mean (or a T-score of -2.5) is arbitrarily used to define osteoporosis and to serve as a threshold for therapeutic intervention.[1,2] Because BMD explains only half of an individual's fracture risk, reducing or eliminating additional modifiable risk factors is imperative.[1,3]

Several modifiable risk factors include inadequate calcium intake, tobacco and excessive alcohol use, and sedentary lifestyle. When assessing risk factors, it is prudent to perform a thorough environment and medication review to minimize additional fall risks. Medications that increase fall risk include psychotropics, sedatives, and antihypertensives. Medications that increase fracture risk through deleterious effects on BMD include chronic corticosteroids, anticonvulsants, and excessive thyroid replacement.

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During acute episodes patients typically exhibit severe positive psychotic symptoms such as delusions and/or hallucinations. They may also exhibit severe negative symptoms such as apathy, psychomotor retardation and social isolation. The stabilization phase may last for six months or more after the acute phase and is associated with less severe psychotic episodes. It may then be followed by a stable phase where symptoms are low in severity.[5]

The general goals of treatment are to decrease the frequency, severity and psychosocial consequences of acute episodes and to maximize psychosocial functioning between these episodes.[5] Positive symptoms are particularly responsive to treatment but negative symptoms often persist between episodes and can become more prominent throughout the course of the disease.[6]

Medications can have a major impact on the likelihood of hospitalization and the overall successful outcome of care, yet they have traditionally comprised a minor portion of total schizophrenia costs.[6] Older "typical" antipsychotics (e.g. haloperidol, chlorpromazine) are associated with side effects which can limit their use in some patients or lead to non-compliance and diminished quality of life of many others. When used at recommended doses, the new "atypical" antipsychotics have a decreased or absent propensity to cause extra-pyramidal side effects or movement disorders.[7]

There are currently four atypical antipsychotics approved for use in the treatment of schizophrenia in the U.S. An additional agent, ziprasidone is expected to be approved for use shortly. Clozapine, the first atypical to be approved by the FDA, has been shown to be effective in treatment-resistant patients and in the treatment of negative symptoms.[7] The "non-clozapine atypicals", risperidone, olanzapine and quetiapine are also effective in the treatment of negative symptoms. They have a safer and more tolerable side effect profile than clozapine but are less effective in treatment-resistant patients.[8]

The atypicals appear to be more effective at improving cognitive function, affective symptoms and functional status than typical antipsychotics. They demonstrate superior symptom control leading to reduced relapse rates compared with typical antipsychotics.[8] This has been reported to reduce hospitalization rates and health care costs.[1,6,8,9]

Evidence supports early use of atypical agents. A 14 member panel of psychiatrists, primary care physicians, pharmacists and a psychiatric nurse produced recommendations and treatment guidelines for the management of psychosis in Oregon in 1998.[8] Non-clozapine atypicals were recommended as preferred agents for the initial treatment of psychosis with clozapine recommended for use in treatment refractory patients.

A review of OMAP (Office of Medical Assistance Programs) prescription data in 1998 revealed a steady increase in the use of atypical antipsychotics over the year. By December, the monthly cost of atypical antipsychotics billed to OMAP reached more than $2 million with over 10,000 prescriptions. Olanzapine was prescribed more frequently for patients between 19 and 65 years of age while risperidone was prescribed more frequently for patients over 65 years and for patients under 19 years of age.

Choosing an atypical antipsychotic

Risperidone has been available in the U.S. since 1994, olanzapine since 1996 and quetiapine since 1997. The relative effectiveness of these agents is unknown. However, their pharmacological and side-effect profiles differ greatly. The choice of agent should be tailored to individual patients and be based on the preferred side effect profile, together with a consideration of the cost of therapy. Figure 1 illustrates the differences in the side-effect profiles of the atypical antipsychotics.[7,10-16]

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Figure 1

Drug	EPS	Anti-cholinergic effects	Sedation	Weight-gain	Prolactin increase	Orthostatic hypotension	Seizure risk
Clozapine	+	++++	++++	++++	+	++++	+++*
Risperidone	++ *	+	++	++	+++	++	+ to ++*
Olanzapine	+ *	+++*	+++	+++	+	+ to ++	+ to ++
Quetiapine	+	++	++ to +++	++	+	++	+ to ++
Chlorpromazine	+++	+++	++++	N/A	N/A	++++	N/A
Haloperidol	++++	++	++	++	N/A	++	N/A

Key

EPS	= extrapyramidal symptoms
+	= none to very low
++	= low
+++	= moderate
++++	= marked
*	= dose dependent effect
N/A	= not available

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Risperidone is associated with a low incidence of extra-pyramidal symptoms (EPS) between 2mg and 6mg daily. [12] Individual thresholds for EPS vary. At doses above 10mg daily, EPS with risperidone occur at a similar rate to typical antipsychotics. Risperidone also increases prolactin levels to a greater extent than other agents and as a result may cause breast tenderness, galactorrhea or menstrual disturbances. In practice only a few patients discontinue treatment because of these effects.[11]

A limitation of olanzapine therapy is its tendency to cause weight gain which may be associated with development of type II diabetes. [1,13] It is also associated with a relatively high incidence of anticholinergic effects (e.g. dry mouth, blurred vision, constipation or sinus tachycardia) which are dose dependent.[1]

Recommendations:

- Olanzapine or quetiapine may be preferred for patients with irregular menses or prolactin related disorders.
- Risperidone may be preferred for patients already on anticholinergic agents or for those with conditions aggravated by anticholinergic effects.
- Risperidone or quetiapine have a lower propensity to cause weight gain and may be preferred for patients who are obese.

Drug interactions may also affect the choice of agent used although generally doses can be adjusted to account for these effects. Interactions differ for each agent but many involve the cytochrome P450 isoenzymes, CYP2D6, CYP3A4 and CYP1A2. Drugs which are potent enzyme inducers (e.g. carbamazepine, phenytoin, rifampin) may lead to reduced antipsychotic plasma levels resulting in reduced antipsychotic effect. Enzyme inhibitors (e.g cimetidine, ciprofloxacin, erythromycin or fluoxetine) may increase antipsychotic drug levels resulting in increased severity or emergence of new adverse effects.[14]

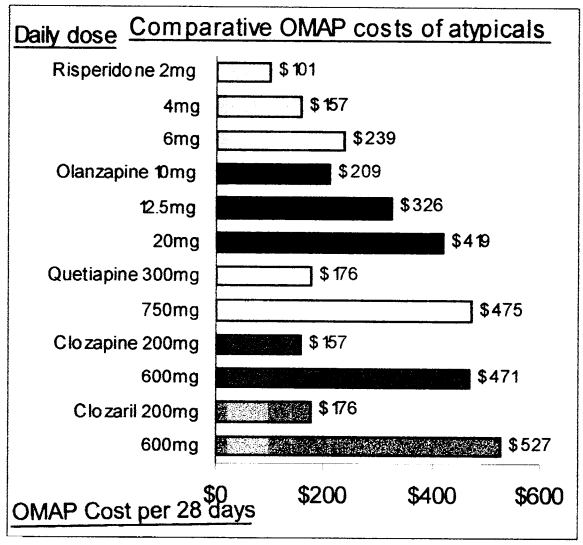
Fatal cardiorespiratory dysregulation has been reported with clozapine and benzodiazepines. This is thought to be a result of additive CNS depressant effects. Although this interaction does not seem to occur with other atypicals, caution is recommended, particularly with the structurally similar olanzapine.[14] Concomitant use of atypicals and medications with anticholinergic, orthostatic or sedative profiles should be avoided wherever possible due to increased adverse effects.[14]

There are substantial differences in the medication costs of the non-clozapine atypicals. At treatment doses the acquisition costs of risperidone are much lower than costs of olanzapine. Quetiapine costs are competitive when lower doses are used. (Figure 2) Since much is still unknown about the relative efficacy of the atypicals, new research is required before conclusions can be made in regard to total treatment costs.

Treatment Strategy

Primary care providers (PCPs) and psychiatrists need to work together to maximize the care of active or in-remission psychotic patients. A psychiatric consultation can be useful for an initial diagnosis, for development of a treatment strategy , and for ongoing follow-up. Close coordination between psychiatry and PCPs is needed when medications seem to be ineffective,

Figure 2



Mean doses used in Oregon 1998:
Olanzapine 12.5mg daily
Risperidone 3.5mg daily
Quetiapine 241mg daily
Prices are from the Red Book, May 1999 (AWP-11%)

side-effects become problematic or other situations arise that may indicate dose adjustments or combination therapies are required.

Once a therapeutic agent is selected, treatment should be initiated and titrated as recommended in manufacturers guidelines to minimize adverse effects. The severity and incidence of adverse effects generally increase with the dose, therefore the maximum recommended dose should not be exceeded without clinical justification.

Therapeutic trials should run for 5-8 weeks if the patient demonstrates no response, and up to 12 weeks if there is partial response to therapy (Figure 3, page 5).[8] A patient typically begins to respond to therapy within 3-5 weeks. If there is no improvement by this time, reconsider the diagnosis, co-morbidities, substance abuse and patient adherence to the treatment regimen. Once patient adherence is confirmed, the dose may be increased for a further 2-3 weeks. If the patient experiences partial but not complete response at this dose, it may be continued for a further 1-3 weeks.[8]

Monitor side-effects closely throughout therapy. Troublesome side-effects may be managed by reducing the antipsychotic dose, by adding additional drug therapies or by switching to a different antipsychotic agent.[5]

As there are a limited numbers of therapeutic options available, an antipsychotic should not be abandoned without an adequate opportunity for it to work. However, if there is a poor response to treatment after a reasonable trial period or if intolerable side-effects develop, then an alternative agent may be tried. Switching agents should be done over several days, weeks, or even months with clozapine. It is a complex process and requires very close monitoring.[8] Introduce the new agent slowly with a gradual increase in dose. Initially continue the old agent and then taper it to a low dose before discontinuing.

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LIVER TOXICITY WITH TROVAN®

Trovafloxacin and alatrofloxacin (the intravenous form of the drug) have been associated with the development of severe and unpredictable liver injury. Post-marketing surveillance reports of this new quinolone antibiotic associate its use with over 100 cases of liver damage since February 1998. There have been 14 cases of acute liver failure. Five patients died from liver related illness, four patients required a liver transplant (one patient died), three patients recovered without a liver transplant and the final outcome for two patients is pending.

The effects of trovafloxacin on the liver are unpredictable. Liver failure has been reported after just 2 days exposure to the drug and an increased risk of toxicity is associated when it is used for 14 days or more. Liver failure has also been reported after re-exposure to trovafloxacin.

In response to these reports the FDA has recommended that trovafloxacin should only be used where other antimicrobials are not effective or appropriate. Trovafloxacin use should be restricted to treatment of serious limb or life-threatening infections (e.g. nosocomial or community-acquired pneumonia, complicated intra-abdominal infections, skin or skin-structure infections or gynecologic/pelvic infections). Trovafloxacin use should only be initiated in an inpatient health care facility and its use should not be continued beyond 14 days. The physician must consider that the benefit of treatment outweighs the potential risks.

Prescribers are advised that any patients who develop clinical signs or symptoms of liver dysfunction should discontinue trovafloxacin therapy. Any suspected adverse events should be reported to the FDA via MedWatch, 1-800-FDA-1088. ■

Review of Muscle Relaxants Reveals Extended Use of Carisoprodol in Oregon

The Oregon Drug Use Review Board reviewed the skeletal muscle relaxant class at the May meeting. The review revealed that over 200 patients (36%) on carisoprodol continued therapy for more than 8 weeks. This is not a new trend, but is concerning because the risk of physical dependence to carisoprodol (Soma®) is well documented. The Substance Abuse and Mental Health Services Administration Drug Abuse Warning Network reports that episodes of non-medical use and overdose of carisoprodol have increased 164% from 1990 to 1996 (from 2,600 to 7000 episodes.)[1]

Skeletal muscle relaxants (i.e. carisoprodol, chlorzoxazone, metaxolone, methocarbamol and orphenadrine) are indicated for the relief of acute painful musculoskeletal conditions of local origin. There is limited evidence for the efficacy of these drugs and there are several reasons not to use them.[2,3] There is no evidence these drugs have direct skeletal muscle relaxation. Any efficacy is likely due to their sedative properties.

The abuse of skeletal muscle relaxants and specifically carisoprodol have been described in several case reports.[4-6] Carisoprodol is metabolized to meprobamate (Miltown®, Equanil®), a rarely used sedative-hypnotic. Generally, abusers of carisoprodol demonstrate signs of tolerance to meprobamate and suffer withdrawal symptoms of anxiety, tremors, insomnia and occasionally hallucinations or seizures. Acute overdose results in CNS depression, respiratory depression and potentially coma or death.

If skeletal muscle relaxants are prescribed, prescribers should keep in mind that published studies support the use of non-opioid analgesics (aspirin or acetaminophen) in combination with them. Short-term use (less than 2 weeks) is recommended since studies have not demonstrated long-term efficacy, and tolerance may develop rapidly. Carisoprodol is not recommended because of the significant potential for dependence and abuse. ■

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✦✦✦ DISPENSING REMINDER ✦✦✦

100 Day Supply

OMAP administrative rules allow pharmacists to dispense 100-day supplies of the following classes of chronic medicines when prescribers specify.

First Data Bank Drug Class Code	Description
36	Contraceptives, Topical
48	Anticonvulsants
55	Thyroid Preparations
63	Contraceptives, Oral
70	Rauwolfias
72	Vasodilators, Coronary
73	Vasodilators, Peripheral
74	Digitalis Preparations
75	Xanthine Derivatives

Life Threatening Infections Linked with New Treatment for Rheumatoid Arthritis

Etanercept (Enbrel®) a new treatment for moderate to severe rheumatoid arthritis, has been associated with the development of serious infections including sepsis. Six deaths have been reported to the FDA and to Immunex Corp. since its approval in November 1998.

Etanercept is a recombinant tumor necrosis factor (TNF) receptor and is the first biologic response modifier approved for the treatment of rheumatoid arthritis. TNF is thought to have a key role in inflammatory processes of rheumatoid arthritis and local inhibition of TNF is beneficial in the treatment of the disease. However, TNF also plays a pivotal role in the immune system and systemic inhibition may result in clinical syndromes such as septic shock.

Many patients who developed serious infections whilst on etanercept therapy had a history of chronic or recurrent infections, pre-existing infections, diabetes or other conditions predisposing them to infections. The product label, which warned against use of etanercept in patients with sepsis or serious infections has been extended following these reports. Etanercept should not be used in any patients with an active infection, including chronic or local infections. Caution should be used if considering prescribing etanercept to a patient with a history of recurrent infections, or with underlying conditions such as advanced or poorly controlled diabetes.

Although it is unclear at this time whether etanercept is truly the cause of these serious infections, physicians should be aware of these reports. Any patients who present with a new infection whilst on etanercept therapy should be closely monitored.
Any cases of serious infections or sepsis developing in patients on etanercept should be reported to the FDA via MedWatch (1-800-FDA-1088) ■

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Figure 3[8,15]

Choice of antipsychotic	First dose	Titrate dose to therapeutic range over first 7 days of treatment	Therapeutic range (adults)	Maximum recommended dose
Risperidone	1 mg HS or AM	Increase dose by 1 mg every 2-3 days	2-6 mg/day	No increased benefit above 6mg/day
Olanzapine	5-10 mg HS	Increase dose by 5mg per week	10-20 mg/day	No increased benefit above 20mg/day
Quetiapine	25 mg bid	Increase dose by 50 mg per day	300-750 mg/day	No safety data above 800mg/day

- Continue treatment for 5-12 weeks using a dose within the therapeutic range.
- Review at weekly intervals to monitor response and side- effects during the first 4 weeks.
- Reduce visits to every 2-3 weeks, then monthly when stabilized.
- Continue antipsychotic therapy for at least 6 months.

Generally, patients should not be on more than one antipsychotic other than during changes in treatment.[8] There are some reports of individuals responding well to combinations of atypical and typical antipsychotics which may be due to different receptor affinities. Mood stabilizers such as lithium, carbamazepine or valproate may also be useful in patients not completely responsive to treatment. Antidepressants may be beneficial for patients with post-psychotic depression and benzodiazepines may be useful for patients with persistent excitement or anxiety. If a second agent is introduced, physicians should monitor treatment closely to establish benefit. A return to monotherapy is recommended if there is no clear benefit.

Once a patient has improved on a particular medication and dose it should be continued for at least six months before dosing adjustment or discontinuation is considered.[5] Monitoring for side-effects to antipsychotic therapy should be done at every opportunity and at least every six months. Patients on quetiapine need regular eye examinations as there is a theoretical risk of cataract formation. It is recommended that a slit lamp examination of the lens be done at, or shortly after, initiation of quetiapine treatment and then at 6-month intervals during treatment.[10]

A trial of clozapine should be considered for patients with schizophrenia who have positive symptoms or violent behavior that does not fully respond to adequate trials of one or two antipsychotics.[5] It is thought that clozapine has a distinct 'anti-aggressive effect' in addition to its antipsychotic effects[8,17] and it also seems to have some additional mood stabilizing properties.[17] Clozapine may also be useful for patients who experience intolerable EPS with two or more antipsychotics from different classes. A trial of clozapine should be for at least 3 months using a dose of 200-600mg daily.[5]

Clozapine is associated with agranulocytosis and weekly WBC monitoring is required for all patients for the first six months of treatment. If no problems occur during this time the frequency of monitoring may be reduced to every two weeks. An analysis of all patients who received clozapine between 1990 and 1995 found the incidence of agranulocytosis with clozapine was 0.38%. The mortality rate was found to be dramatically lower than previous estimates at 0.012%.[18,19]

Prescribing in the Elderly

The prevalence of schizophrenia in the elderly is 1%, of whom 10% have late onset schizophrenia.[5] Late onset is more common in women and is typically paranoid schizophrenia. Positive symptoms are less severe while negative symptoms tend to increase.[5] Dementia is not considered an indication for antipsychotic therapy unless patients show psychotic symptoms or significant aggressive behavior.[8] Non-antipsychotic treatment of agitation with more benign drugs should be attempted first.

Caution should be used when prescribing antipsychotics for elderly patients as they show a greater variability of response and side effects tend to occur more frequently.[5] All agents may cause hypotension, tachycardia or a prolonged QT interval and these may be a problem in patients with pre-existing cardiovascular disorders. Confusion, memory impairment or hallucinations may result from increased sensitivity to anticholinergic effects. The use of antipsychotic agents with anticholinergic effects may also be a problem in patients with prostatic hypertrophy or glaucoma (Figure 1).

Patients with pre-existing Parkinson's symptoms may experience a worsening tremor and rigidity on antipsychotic therapy.[5] Although a first line treatment for psychosis in idiopathic parkinsonism, clozapine use should be restricted in the elderly due to its potential for agranulocytosis, its anticholinergic effects and its likelihood of causing seizures, hypotension and sedation.[5]

The starting doses of antipsychotic agents for elderly patients should be approximately 25% of those prescribed for young adults.[5] Due to increased sensitivity, elderly patients may show signs of EPS even when very low doses of antipsychotics are prescribed. Physicians should monitor all patients for development of EPS and reduce the dose or change therapy as appropriate. If patients experience sedation or a sudden decrease in blood pressure with a single daily dose, treatment may need to be given in divided doses throughout the day. If treatment is for night time agitation the dose should be given two hours before the disturbance usually occurs.[5]

Aging is often associated with an improvement in symptoms of schizophrenia. Complete remission of social deficits occurs in over 25% of patients while another 40% show a marked

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improvement particularly in positive symptoms. Due to the increased risk of treatment side-effects, particularly tardive dyskinesia, it may be that gradual withdrawal of therapy could be considered in some patients .[5]

Conclusions

Non-clozapine atypical antipsychotics are the preferred agents for the initial treatment of schizophrenia. It is not yet possible to recommend one agent over the others and independent studies are required to compare the effectiveness and total costs of treatment with the new atypicals. The choice of atypical antipsychotic should be based primarily on the most appropriate side-effect profile. Patients are much more likely to comply with treatment with antipsychotics if side-effects are minimized and this should lead to lower relapse rates. ◙

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Pharmacologic agents that slow bone loss and reduce fracture risks are available for patients that have osteoporosis or are at high risk for its development. Of these medications, sound fracture data is available only for estrogen replacement and alendronate (Fosamax®). Other agents that slow bone loss include calcitonin (Miacalcin®), and raloxifene (Evista®). There is continued research on therapies that promote bone formation such as fluoride, anabolic steroids, and parathyroid hormone. Future approaches will likely consist of combination regimens that slow bone loss and promote bone formation.

Ensuring adequate calcium intake of 1000 to 1500 mg daily is the foundation of every therapeutic plan. Diet remains the preferred source of calcium intake. It is recommended that an individual's dietary intake of calcium be estimated and then supplemented to meet NIH goals.

General Recommendations[1,2]

- Counsel all women on the risk factors for osteoporosis focusing on adolescents
- Recommend adequate calcium and vitamin D intake and supplement as needed
- Recommend regular weight-bearing and extensor muscle strengthening exercise to reduce the risk of falls and subsequent fractures
- Advise patients to eliminate risk factors such as tobacco smoking and alcohol
- Initiate prophylactic therapy in women with T-scores between -1.5 to -2.5 based on the presence of additional risk factors
- Consider treatment for all women who present with fractures and/or T-scores $\leq$ -2.5

Calcium supplementation is commonly provided with calcium carbonate or calcium citrate. Advise patients to supplement based on the amount of elemental calcium per tablet. Calcium carbonate is the least expensive agent and has the highest percentage (40%) of elemental calcium per tablet. This salt form requires gastric acid for dissolution and absorption. Calcium citrate is recommended for patients who are achlorhydric or on acid-suppressive therapy with an H2-antagonist or proton-pump inhibitor. The optimal administration of calcium is in small divided doses (e.g. tid) and with food to maximize absorption and minimize constipation.

The benefit of population-wide Vitamin D supplementation remains controversial. Reserve Vitamin D in doses of 400-800 IU per day for elderly patients with minimal intake of dairy or Vitamin D-fortified food products and minimal exposure to sunlight.[4,5]

The gold standard for post-menopausal women without contraindications continues to be estrogen replacement therapy (ERT).[2] ERT provides the greatest benefit relative to cost and has been demonstrated to increase BMD by 5-10% and decrease the risk of vertebral and hip fractures by 50% or more.[6-8] Randomized controlled trials assessing ERT in osteoporosis have documented the following: (1) the benefits are greatest on trabecular bone, (2) the optimal dose required is 0.625 mg qd conjugated estrogen or its equivalent, (3) initiation of ERT at the onset of menopause is ideal; however, initiation prior to age 70 produces substantial benefit, (4) the optimal duration of ERT is lifelong because fracture risk returns to baseline within 5-10 years after discontinuing use. ERT may possess other benefits including a reduction in the development of cardiovascular disease and Alzheimer's disease, and alleviation of vasomotor symptoms and urogenital atrophy. With the help of their health care providers, patients must be well-informed of their individual risk to benefit ratio.

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Alternatives to ERT: Selection of a second-line agent must be evaluated on an individual basis. The bisphosphonates produce the largest gains in BMD and are preferred in patients with severe bone loss.[2] Currently, alendronate (Fosamax®) is the only bisphosphonate approved for use in osteoporosis in the U.S. Additional products are approved for use in other countries (etidronate) and are in development (e.g. clodronate, tilundronate, and risedronate).[9]

Alendronate produces increases in BMD by 6-8% and decreases hip, wrist, and vertebral fracture incidence by up to 50%.[10-12] The benefits are dose-related and, like estrogen, are greatest on trabecular bone. Five mg per day is adequate for prevention and 10 mg per day is warranted for treatment. The optimal duration of use has not been established. Alendronate's clinical utility is often limited by poor oral absorption and adverse GI effects such as nausea, dyspepsia, and esophageal ulceration. Continual reinforcement and instruction to take alendronate with 6-8 oz. of water on an empty stomach and to remain upright for at least 30 minutes can help reduce the incidence of these events. Avoid its use in patients with impaired GI motility and who cannot comply with the administration requirements.

OSTEOPOROSIS INTERVENTION COST COMPARISONS

Therapy	Dose	OMAP Cost / Yr *
Conjugated estrogens (CE) (Premarin®)	0.625 mg po qd	$166
CE with medroxyprogesterone (MPA) (generic Provera®)	0.625 mg CE & 5 mg MPA po qd	$238
Micronized estradiol (generic Estrace®)	1 mg po qd	$105
Esterified estrogen (Estratab®, Menest®)	0.625 mg po qd	$159
Transdermal estradiol (Estraderm®, Climara®, Vivelle®)	0.05 mg TD (apply 1-2 x wk)	$126-561
Alendronate (Fosamax®)	5 mg po qd (prevention) 10 mg po qd (treatment)	$640
Raloxifene (Evista®)	60 mg po qd	$659
Salmon calcitonin (Miacalcin®)	200 IU IN qd (1 spray in 1 nostril qd)	$837

* Red Book, May 1999 (AWP-11%)

Raloxifene (Evista®) is a selective estrogen receptor modulator (SERM). This agent possesses estrogenic activity in the bone and liver and antiestrogenic activity in the breast and uterus. In general, the benefits of raloxifene on BMD are less than that seen with ERT. Clinical trials assessing the efficacy of raloxifene 60 mg per day demonstrated small increases in BMD of 2-3% in the spine and hip, values similar to low-dose (0.3 mg/day) conjugated estrogen.[13,14] Raloxifene also produces small decreases in LDL-cholesterol, however, it lacks the HDL benefits seen with estrogen. It is unknown if raloxifene reduces cardiovascular morbidity and mortality. Common adverse effects include increased vasomotor hot flashes and an increased risk of thromboembolic events.[15] The risk of thromboembolic events is comparable to ERT and is greatest during the first 4 months of use. The MORE (Multiple Outcomes of Raloxifene Evaluation) trial is currently evaluating fractures, cardiovascular events, and breast cancer. Meanwhile, due to its increased cost and unknown benefits relative to ERT, it is recommended to reserve the use of raloxifene for post-menopausal patients who decline ERT and alendronate.

Calcitonin is recommended for use as an alternative agent in patients that are not candidates for ERT and/or alendronate. The intranasal product (Miacalcin®) is the preferred formulation due to ease of administration. As evidenced in limited trials in post-menopausal women, calcitonin produces small increases in BMD from 1-3%.[16] Fracture data with this agent are limited and controversial. Calcitonin appears to be most effective in high-turnover bone loss seen with menopause and corticosteroids. The use of calcitonin may also be beneficial in patients with bone pain following a vertebral fracture. Administration consists of one 200 mcg spray in alternating nostrils daily. Common adverse effects such as nasal congestion and rhinitis are usually transient and abate with continued use.

In summary, the goals of therapy are to attain peak bone mass, slow bone loss, and prevent fractures. ERT is first-line therapy for the prevention or treatment of osteoporosis in post-menopausal women without contraindications to its use. The selection of a second-line agent should involve consideration of the patient's severity of bone loss or fractures with the drug's proven ability to prevent fractures, its adverse effect profile, and cost. Patients with severe osteopenia and/or those with previous fractures are good candidates for alendronate. For other patients who are not candidates for alendronate or ERT, calcitonin or raloxifene may be considered. ■

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We hope you found this issue of the Oregon Drug Use Review Board Newsletter useful as well as thought-provoking and interesting. We welcome your questions, concerns, comments or ideas regarding the newsletter. Address correspondence to the managing editor:

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