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This document is divided into two parts:

1) The *Highlights* section contains brief comments patterned after the "abstract" placed on the first page of many studies reported in journals. *Highlights* condenses the content of studies, and allows a quick review of pertinent points of each article.

   The *Editorial Comments* are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of *Practical Pointers*.

2) The main *Abstracts* section is designed as a reference. It presents structured summaries of the content of articles in much more detail.

An *Index* containing all the Highlights is published twice a year. In an evening or two, the reader can refresh memory of the entire content of practical points abstracted from 6 major journals over the 6-month period.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 5 years can be accessed at www.practicalpointers.org

Richard T. James Jr, M.D.
Editor/Publisher.

HIGHLIGHTS AND *EDITORIAL COMMENTS* AUGUST 2005

CPGs Give Little Guidance For Care Of Older Patients.

8-1 CLINICAL PRACTICE GUIDELINES AND QUALITY OF CARE FOR OLDER PATIENTS WITH MULTIPLE COMORBID DISEASES: Implications for Pay-for-Performance

As the population ages, the prevalence of patients with multiple chronic medical conditions increases. Previous studies reported that up to half of Medicare patients aged 65 and older have at least 3 chronic medical conditions. One fifth has 5 or more. Difficulties rise as the number of diseases increases.

Physicians who care for older adults with multiple diseases must strike a balance between following CPGs and adjusting recommendations for individual patients' circumstances.

This study evaluated the applicability of 9 CPGs to the care of older individuals. Only 4 of The 9 CPGs included in the study addressed older individuals with comorbidities. Many did not discuss the quality of evidence underlying the recommendations for older patients.

None of the CPGs discussed the burden of comprehensive treatments on patients and caregivers. None discussed balancing short- and long-term goals such as when short-term quality of life is better without a treatment even if that treatment might lengthen life.

The authors generated a possible treatment schedule that would result if all the recommendations of the CPGs were followed in patients with 5 or more comorbid conditions. Developing a treatment plan for a hypothetical patient in accordance with CPGs would result in treatment with multiple drugs with a high complexity of administration. This could increase risks of medication errors, adverse drug events, drug interactions, and hospitalizations. Independent self-management and adherence would be difficult. The treatment burden might be unsustainable.

"CPGs do not provide an appropriate, evidence-based foundation for assessing quality of care in older adults with several chronic diseases." Although they provide detailed guidance for managing a single disease, they fail to address the needs of older patients with complex comorbid illnesses. CPGs rarely address treatment of patients with 3 or more chronic diseases—a group that includes half of the population over the age of 65.

This is not to say that CPGs are not valuable—only that their value is restricted.

I believe that elderly patients take too many drugs. Many continue to take drugs which have outlived their benefit. As we get old and older, the benefit/harm-cost ratio of drugs and interventions changes. The probability of benefits falls; the probability of adverse effects increases; and costs may become more burdensome.

I believe that some elderly persons, especially the very elderly, who feel reasonably well and cherish each day of the "precious few" that remain, would opt to be left in peace, and not risk being subjected to tests, examinations, surgical interventions, and drugs and treatments with adverse effects that might undermine their present quality of life. There is a trade-off between maintaining the present quality-of-life by comfort care only versus interventions which may lengthen life at the risk of decreasing present quality of life. This is a personal decision.

Realizing that the remaining days of my life are limited, I would not trade one day of quality-life at age 85 for 50 days of poor health at age 95 likely to be associated with increasing dependency, dementia, and loss of dignity.

At present, much of daily medical practice addresses the indications for treatment of a single disease or symptom. Many older patients expect and request a "pill for every ill". They should understand that this may lessen their present quality of life. It may be preferable to bear some of the symptoms and go on with daily living.

Healthy life-styles should continue.

Primary care clinicians must understand the choices and goals of each individual patient. The goal is to extend days-of-quality-life, not days-of-life.

The "art" of medicine must continue unabated.

A Review of Newer Pharmacological Agents

8-2 CHRONIC INSOMNIA

	Duration of action	Half-life (hr)	Dose (mg)	Indications
1) *Restoril* (tamezepam)	Intermediate	8-15	7.5-30	Sleep maintenance

May be tried for insomnia associated with difficulty in maintaining sleep. The greatest effect is on total sleep time. May soon be supplanted by *Lunesta*. Tolerance, measured by deterioration in sleep measures over time, has not been noted after use for 8 weeks. Daytime sleepiness, dizziness, and incoordination may occur with the intermediate-acting agents, but are not common.

The FDA has approved use for up to 10 days

2) *Lunesta* (eszopiclone)	Intermediate	5-7	1-3	Sleep maintenance

A 6-month study of *Lunesta* showed a 50% reduction in sleep-latency (onset of sleep) and a 65% reduction in wake time after onset of sleep. The greatest effect was on total sleep time. After 6 months, a sustained beneficial effect without development of tolerance was reported. Daytime sleepiness, dizziness, and incoordination may occur with the intermediate-acting agents, but are not common.

(I was unable to find any limitations by the FDA for duration of use.)

3) *Ambien* (zolpidem)	Short	3	5-10	Sleep onset

Studies of *Ambien* used intermittently (3 to 5 times a week) report effectiveness in chronic insomnia, with sustained benefits on nights the drug is taken, and sleep that is no worse than baseline on nights without medication. No rebound insomnia was reported after discontinuation. The greatest effect is on sleep latency. (Difficulty in going to sleep.) Short-term tolerance has not been noted after continuous use for 4 weeks, and intermittent use for 12 weeks. Amnesia, including that associated with sleep-related eating, has been described rarely. Adverse effects (drowsiness, dizziness, and incoordination) are less frequent with use of short-acting drugs and generally occur only after high dose.

The FDA has approved use for up to 10 days

4) *Sonata* (zaleplon)	Ultra short	1	5-20	Sleep onset and maintenance

Sonata may have effects in reducing the time to go to sleep, but may have no significant effect on total sleep time. Because of its very short half-life, it may be given on awakening during the night.

Administered 3.5 hours after lights out, with 4 hour more sleep permitted, it did not result in any daytime drowsiness or cognitive impairment. No rebound insomnia reported. Use for 6 months showed a sustained benefit without development of tolerance. Adverse effects (drowsiness, dizziness, and incoordination) are less frequent with use of short-acting drugs and generally occur only after high dose.

The FDA has approved use for up to 10 days

I believe these newer sleep medications will be increasingly prescribed by primary care clinicians.

To fit the drug to the sleep difficulty, we should ask the patient whether they have difficulty in sleep onset, or difficulty in sleep maintenance. Sonata may be a useful first choice for the former, and Lunesta of the latter.

Several of the author's comments interested me: 1) Use for secondary insomnia when elimination of the cause is not achievable. 2) "Off label" use (over ten days) for Ambien and Sonata. 3) Many sleep specialists recommend long-term use of pharmacological therapy in a subgroup of patients who do not respond to cognitive behavioral therapy This would also include patients for whom cognitive behavioral therapy is simply not an available means of therapy—ie, most patients consulting primary care clinicians.

I believe many primary care clinicians prescribe "sleeping pills" freely and for periods longer than approved. Clinical judgment is required. Several different drugs may be prescribed on a trial-and-error basis. We can now fit the pill to the patient. Intermittent therapy is preferable. I wonder. .. Would switching periodically from one to another be advantageous?

Bone Turnover Increases with Teriparatide; Decreases with Alendronate. Both Lead to Increased BMD.

8-3 OPPOSITE BONE REMODELING EFFECTS OF TERIPARATIDE AND ALENDRONATE IN INCREASING BONE MASS

Imbalances in the bone remodeling process affect mechanical properties related to bone strength, including bone geometry and microarchitecture. When bone resorption exceeds bone formation, osteoporosis results, and the risk of fracture increases.

Therapies can preferentially modulate 1) bone resorption (eg, alendronate) or 2) bone formation (eg, teriparatide; human recombinant parathyroid hormone). Both correct the imbalances in the bone remodeling process.

This study compared the biochemical effects of both drugs and their effects on bone mineral density (**BMD).**

Alendronate *suppressed* bone turnover. It inhibited bone resorption after one month and inhibited formation at 3 months. A new steady state was achieved and persisted through 12 months. The effect on inhibition of resorption continued and more than compensated for the reduction in formation. As a result, BMD increased modestly in the spine and proximal femur.

Teriparatide *increased* bone turnover. It increased the formation of bone which persisted for at least 12 months. Bone resorption also increased modestly for up to 12 months. The increase in bone formation more than overcame the rate of resorption. As a result, BMD increased.

Why should we be concerned about the detailed metabolic effects of these drugs? Because, since they act differently, their beneficial effect in increasing BMD and bone strength may be additive. Would use of both drugs,

concomitantly or in sequence, increase BMD and bone strength compared with use of either alone? See the following abstract.

One Year Of Parathyroid Hormone Followed By One Year Of Alendronate An Effective Means Of Increasing BMD

8-4 COMBINATION AND SEQUENTIAL THERAPY FOR OSTEOPOROSIS

Bisphosphonates produce a steady increase in bone mineral mass averaging about 1% a year for up to 8 to 10 years. And once-daily parathyroid hormone given subcutaneously increases central bone mass by 8% to 10% per year for up to 2 years.

Combinations of PTH + bisphosphonates appear to increase central bone mass, but to a lesser extent than with PTH alone.

When PTH is used alone, in the months after PTH is discontinued, some or all of the bone gained appears to be lost.

Administering bisphosphonates *after* a course of PTH appears to conserve the bone gained, and adds a further increase in its own right, roughly similar in magnitude to the short-term effect of bisphosphonates given to previously untreated patients.

The term "osteoporosis" denotes not only defects in bone mass, but also defects in "bone quality". The latter may be as important as the former in promoting weakness of bone. Both drugs improve "bone quality".

An accompanying article "One Year of Alendronate after One Year of Parathyroid Hormone (1-84) for Osteoporosis." NEJM August 1, 2005; 353: 555-65 reports:

1) One year of PTH followed by one year of placebo:

   Patients receiving PTH for one year gained BMD. During the 2nd year, when receiving placebo, much of the gain was lost. (Apparently PTH must be continued to maintain the gain in BMD.)

2) One year of PTH followed by one year of alendronate:

   Patients receiving PTH for one year gained BMD. During the 2nd year of alendronate-alone therapy, BMD continued to increase.

3) One year of alendronate + PTH followed by one year of alendronate alone:

   During the first year of combined therapy, there was no advantage over PTH alone. Over 2 years, BMD increased, but at somewhat lower rate than those receiving PTH for one year followed by alendronate.

4) One year of alendronate followed by a second year of alendronate:

   BMD increased over 2 years, but not as much as in the group receiving 1-year of PTH followed by 1-year of alendronate.

"Thus, from a clinical perspective, one year of parathyroid hormone followed by one year of alendronate would seem to be an effective means of increasing bone mineral density while minimizing the use of parathyroid hormone."

Note that 2-years of PTH was not used as a comparator.

More observation is required to determine the most favorable use of combinations. There seems to be some advantage.

Most of the studies of osteoporosis I have abstracted thus far concern treatment of the established disease. Prevention is much more important. Making sure that calcium and vitamin D intakes are adequate during all

periods of life is a start. Would very low-dose bisphosphonate, given perhaps once monthly, starting at the time of menopause, and continued for years, prevent the disease.?

Should Primary Care Clinicians Prescribe This Therapy?

8-5 WARFARIN PLUS ASPIRIN AFTER MYOCARDIAL INFARCTION OR ACUTE CORONARY SYNDROME: Meta-analysis with Estimates of Risk and Benefit.

After acute coronary events, a marked thrombin generation state persists for months. This suggests a role for anticoagulation beyond the initial use of low-molecular-weight heparin.

This study quantified the risks and benefits of warfarin + aspirin vs aspirin alone after acute coronary syndromes **(ACS).** Patients considered at high risk of major bleeding from warfarin therapy were excluded.

Outcomes per 1000 patients per year:

	Warfarin + aspirin	Aspirin alone	Absolute difference	NNT (2 y)
MI	22	41	19	53
Ischemic stroke	4	8	4	250
Major bleeding	1.5	0.6	0.9	1100
Death	No difference			

I included this abstract mainly to point out why many primary care clinicians will, with good reason, resist prescribing warfarin in addition to aspirin for patients with ACS . I believe primary care clinicians should rarely, if ever, prescribe warfarin for this indication..

1. *The NNT to benefit one patient is high. No benefit for mortality. The cited risk of major bleeding (~ 1 in 1000 per year) is unrealistically low when applied to primary care. Non-major bleeding will commonly occur and create anxiety, inconvenience, and additional costs.*
2. *Patients in primary care differ substantially from those in trials: They will be at higher risk for bleeding. Exclusion criteria may not be strictly applied. Patients will be less adherent to laboratory control; they will be less carefully followed; they may use OTC drugs that are contraindicated when warfarin is used; they may be more likely to eat foods which can increase risk of bleeding. Costs and inconvenience may be too high.*
3. *Many patients in primary care are elderly, medically indigent, and medically illiterate. Warfarin therapy is not suitable for these groups.*

Primary care clinicians will still apply the many other drug and lifestyle measures which reduce risk of recurrence of ACS

This is a good example of the "Catch 22" of interventions in primary care—benefits are often hidden, harms are evident. Physicians and patients would have no way of knowing which 19 patients of the 1000 treated are the ones that avoided an MI. On the other hand, patient and physician alike would be painfully and dramatically aware of bleeding.

Describing a New Dog Vector for One of the Most Virulent Human Infections Ever Identified.

8-6 ROCKY MOUNTAIN SPOTTED FEVER – Changing Ecology And Persisting Virulence

Rocky mountain spotted fever **(RMSF)** is one of the most virulent human infections ever identified. Up to 10% of persons infected will die. Many more will require intensive care, and have sequelae such as amputation and permanent learning impairment. This is despite the availability of a simple and highly effective treatment (doxycycline).

Diagnosis is difficult because of the non-specific presentation of the disease. Symptoms include fever, headache, myalgia, and (usually after 3 to 5 days) rash. The rash evolves from macular to macro-papular, to petechial. Organ-specific symptoms (nausea, vomiting, abdominal pain, and cough) confound diagnosis by distracting attention from systemic manifestations. Serologic analysis is not useful during an active infection.

Early clinical suspicion and empirical therapy are essential. Severe illness and death are associated with a delayed diagnosis, which may occur because of absence of a rash or presentation during a season with a low level of tick activity.

An accompanying study describes a new vector for RMSF—the brown dog tick which differs from the American dog tick. The brown dog tick is intimately related to households.

"No longer can we consider RMSF a disease of only rural and southern venues; it has emerged and re-emerged again. "

This is a caution aimed mainly at primary care clinicians. They should maintain a high degree of suspicion about the possibility of RMSF. On consultation by an acutely and seriously ill, previously well patient (especially a young patient with a rash), asking about ticks in the environment and tick bites should be routine.

As a public health measure, if ticks are prevalent, measures to eliminate them should be taken.

Since there is no confirmatory test immediately available, empiric treatment with antibiotic (doxycycline) is justifiable because the stakes are high. The outcome of unrecognized RMSF may be disastrous.

RMSF is defined as an infection caused by R rickettsii. But R rickettsii is not the only rickettsia carried by arthropods which can cause disease. Correspondence in this issue (NEJM August 1, 2005 pp 626-27) lists 6 different species. More unnamed species may exist.

ABSTRACTS AUGUST 2005

CPGs Give Little Guidance For Care Of Older Patients.

8-1 CLINICAL PRACTICE GUIDELINES AND QUALITY OF CARE FOR OLDER PATIENTS WITH MULTIPLE COMORBID DISEASES

As the population ages, the prevalence of patients with multiple chronic medical conditions increases. Previous studies reported that up to half of Medicare patients aged 65 and older have at least 3 chronic medical conditions. One fifth has 5 or more. Difficulties rise as the number of disease increases.

Clinical practice guidelines **(CPGs**) are based on clinical evidence and expert consensus to help decision making about treating specific diseases. Most CPGs address single disease in accordance with modern medicine's focus on evidence, based on randomized controlled trials. However, physicians who care for older adults with multiple diseases must strike a balance between following CPGs and adjusting recommendations to individual patient's circumstances.

This study evaluated the applicability of CPGs to the care of older individuals with several comorbid diseases. Data sources included a national survey which identified the most prevalent chronic diseases and a National Guideline Clearinghouse to locate evidence-based CPGs for each chronic disease.

The authors analyzed 7 of the most common chronic conditions: heart failure, stable angina, atrial fibrillation, diabetes, osteoarthritis, chronic obstructive pulmonary disease, and osteoporosis. These are usually managed in primary care. They chose CPGs promulgated by national medical organizations for each condition.

They abstracted data about applicability of the CPGs to individuals aged 65 and older with multiple comorbid diseases. This included indications for treatment, feasibility of treatment, and duration of therapy necessary to achieve benefit in the context of life expectancy. They considered the patient-centered aspects of decision making including effects of quality of life, physical functioning, pain, differentiation between short- and long-term effects, and goals of treatment (cure, arresting progression, preventing complications, managing symptoms). They considered patient preferences, shared decision making, and the burden of following recommendations (both by the patient and by care givers),

A hypothetical patient was considered—a 79-year old female with osteoporosis, osteoarthritis, diabetes, hypertension, and chronic obstructive pulmonary disease. They abstracted recommendations for each condition from 9 CPGs, and assembled a comprehensive treatment plan using explicit instructions from relevant CPGs. They tried to reduce complexity of the program and chose the least expensive medications with the fewest adverse effects.

RESULTS

Applicability of CPGs:

Only 4 of 9 CPGs addressed older individuals with comorbidities. Many did not discuss the quality of evidence underlying the recommendations for *older* patients. Only the diabetes CPGs discussed the relationship between life expectancy and the time needed to treat to achieve benefit.

Inclusion of patient-centered domains in CPGs:

None of the CPGs discussed the burden of comprehensive treatment on patients and caregivers. None discussed balancing short- and long-term goals such as when short-term quality of life is better without a treatment even if that treatment provides long-term benefits.

Applying CPGs to the hypothetical patient:

The authors generated a possible treatment schedule that would result if all the recommendations of the CPGs were followed. The patient would take 12 separate medications. This would require 19 doses per day, taken at 5 different times. In addition, the program would include 14 different non-pharmacological activities (educational, nutritional, rehabilitative, monitoring, and visiting specialists). Concurrent adherence to all CPGs would result in potential interactions between drugs, and between food and medications. Some recommendations contradicted each other. The cost of drugs would exceed $400 a month (almost $5000 a year).

DISCUSSION

"CPGs do not provide an appropriate, evidence-based foundation for assessing quality of care in older adults with several chronic diseases." Although they provide detailed guidance for managing single diseases, they fail to address the needs of older patients with complex comorbid illnesses. CPGs rarely address treatment of patients with 3 or more chronic diseases—a group that includes half of the population over the age of 65.

Developing a treatment plan for a hypothetical patient in accordance with CPGs may result in treatment with multiple drugs with a high complexity of administration. This could increase risks of medication errors, adverse drug events, drug interactions, and hospitalizations. Independent self-management and adherence would be difficult. The treatment burden might be unsustainable.

CPGs are designed largely by specialty-dominated committees for managing single diseases.

The use of CPGs to evaluate the quality of care given by individual clinicians, and to determine physician reimbursement through pay-for-performance measures could create inappropriate incentives for care.[1] CPGs are not designed for use in quality assessment. Transforming CPGs into performance standards and applying these standards to care of older patients with chronic conditions is problematic. CPGs are based on varying levels of evidence and assume application of clinical judgment and patient preference—both of which would be difficult to measure.

Quality indicators must balance scientific evidence against what is practical and feasible.

Measurement of quality of care should place emphasis on weighing burden, risks, and benefits of complex therapies—and on sharing decision making with patient and family.

Standards for developing CPGs note the importance of improving adherence by both physicians and patients, identifying the target population, and incorporating quality of life and patient preferences. The CPGs examined in this study did not give explicit guidance on how to do this.

JAMA August 10, 2005; 294: 716-24 "Special Communication" original investigation, first author Cynthia M Boyd, Center on Aging and Health, Baltimore MD.

1 The Medicare Payment Advisory Commission has recommended that Medicare adopt a pay-for-performance for physician reimbursement. The authors consider this ill-advised.

An editorial in this issue of JAMA by Patrick J O'Connor, Healthpartners Research Foundation, Minneapolis, Minn comments:

The National Guideline Clearinghouse (sponsored by the Agency for Healthcare Research and Quality) now lists over 1650 active CPGs—386 for diabetes alone. Most are based on studies limited to a single clinical intervention.

For the many individuals who have multiple medical problems, following the guidelines proposed for each problem leads to complex drug treatment schedules, multiple physician visits, high costs, and disruption of daily routines—all of which invite non-adherence.

There is much redundancy and significant variation in recommendations across multiple CPGs. CPGs are often embedded in lengthy documents that are not easily accessible at the point of care. "The most onerous problems that physicians who use CPGs now face include: too many evidence-based recommendations, recommendations that are sometimes inappropriate in particular clinical situations, and recommendations that often are not ranked in terms of their clinical value."

Benefits documented in clinical trials are "average" benefits. Even within the trials, the degree of benefit received from an intervention depends on many patient-specific factors. Practicing physicians care for patients with greater patient-specific variation than the subjects in clinical trials on which CPGs are based. The trials require restrictive eligibility criteria.

All recommendations are not of equal clinical value to all individual patients. Benefit estimates should take into account patient-specific factors such as age, estimated life expectancy, baseline risk of complications, and the complexity of a therapeutic regimen. "This is especially important for frail elderly patients with multiple chronic conditions, who may be unable or unwilling to tolerate, afford, or adhere to a large number of pharmacological and lifestyle interventions over long periods."

"Holding physicians accountable for hundreds of process and outcome measures could divert clinical attention from the few key interventions that are of most potential benefit to a patient, and might multiply costs of care with minimal positive effect on health."

Despite their limitations, evidence-based CPGs remain an important and necessary tool in the effort to improve health care quality. Customization of care in complex clinical scenarios respects the individuality of patients and the professional judgment of highly skilled physicians and minimizes the problem of overtreating patients most susceptible to drug interactions, drug adverse effects, and medical error.

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A Review of Newer Pharmacological Agents

8-2 CHRONIC INSOMNIA

Clinical studies adopt arbitrary definitions of insomnia. In practice, the patient's subjective judgment of sleep quality and quantity is a more important factor.

Chronic insomnia (lasting over one month) has a prevalence of 10% to 15%. It is more common in women and the elderly. It may have adverse consequences—fatigue, mood disturbances, problems with interpersonal relationships, occupational difficulties, and reduced quality of life.

Studies suggest that patients with *primary* insomnia differ from controls—increased global cerebral glucose metabolism on PET scan, differences in electroencephalographic patterns, increased 24-hour metabolic rate, and higher levels of secretion of adrenocorticotropic hormone and cortisol.

Insomnia *secondary* to other causes is more common than primary insomnia. (Eg, psychosocial stress, poor sleep hygiene, psychiatric disorders, medical conditions, and insomnia related to use of other drugs.) However. . . "If insomnia persists despite treatment of secondary causes, then therapy for primary insomnia should be instituted."

Pharmacological therapy:

The article presents a useful list of select FDA-approved medications for insomnia in table 3, page 806. Restoril is a benzodiazepine. The others, while technically not benzodiazepines (their chemical structures differ) are termed benzodiazepine-receptor agonists. All act by binding to the gamma aminobutyric-acid receptor. Some are relatively new.

	Duration of action	Half-life (hr)	Dose (mg)	Indications
1) *Restoril* (tamezepam)	Intermediate	8-15	7.5-30	Sleep maintenance

May be tried for insomnia associated with difficulty in maintaining sleep. The greatest effect is on total sleep time. May soon be supplanted by *Lunesta*. Short-term tolerance, measured by deterioration in sleep measures over time, has not been noted after use for 8 weeks. Daytime sleepiness, dizziness, and incoordination may occur with the intermediate-acting agents, but are not common.

The FDA has approved use for up to 10 days

2) *Lunesta* (eszopiclone)	Intermediate	5-7	1-3	Sleep maintenance

A 6-month study of *Lunesta* showed a 50% reduction in sleep-latency (onset of sleep) and a 65% reduction in wake time after onset of sleep. The greatest effect was on total sleep time. After 6 months, a sustained beneficial effect without development of tolerance was reported. Daytime sleepiness, dizziness, and incoordination may occur with the intermediate-acting agents, but are not common.

(I was unable to find any limitations by the FDA for duration of use. RTJ)

3) *Ambien* (zolpidem)	Short	3	5-10	Sleep onset

Studies of *Ambien* used intermittently (3 to 5 times a week) report effectiveness in chronic insomnia, with sustained benefits on nights the drug is taken, and sleep that is no worse than baseline on nights without medication No rebound insomnia was reported after discontinuation. The greatest effect is on sleep latency. (Difficulty in going to sleep.) Amnesia, including that associated with sleep-related eating, has been described rarely. Adverse effects (drowsiness, dizziness, and incoordination) are less frequent with use of short acting drugs and generally occur after high dose. Short-term tolerance, measured by deterioration in sleep measures over time, has not been noted after continuous use for 4 weeks, and intermittent use for 12 weeks.

The FDA has approved use for up to 10 days

4) *Sonata* (zaleplon)	Ultra short	1	5-20	Sleep onset and maintenance

Sonata may have effects in reducing the time to go to sleep, but may have no significant effect on total sleep time. Because of its very short half-life, it may be given on awakening during the night, and may not result in any daytime drowsiness or cognitive impairment, Studies report a 50% reduction in sleep latency. Administered 3.5 hours after lights out, with 4 hours more sleep permitted, it did not

result in any daytime drowsiness or cognitive impairment. No rebound insomnia reported.
Use for 6 months showed a sustained benefit without development of tolerance. Adverse effects (drowsiness, dizziness, and incoordination) are less frequent with use of short acting drugs and generally occur after high dose.

The FDA has approved use for up to 10 days

Many trials have shown the efficacy of these drugs in relieving short-term insomnia. A meta-analysis demonstrated significant improvements in sleep latency, total sleep time, number of awakenings, and sleep quality, compared with controls, A high percentage of patients fell asleep faster, slept longer, woke less often, and reported better sleep quality.

The relatively short duration of studies has been problematic. None have extended beyond 6 months. The short-acting agents have the greatest effect on sleep latency; intermediate- and long-acting have the greatest effect on total sleep time.

All are contradicted in pregnancy. They should not be combined with alcohol. Use lower doses in the elderly and in debilitated patients.

All may have adverse effects—drowsiness, dizziness, incoordination—less commonly associated with short acting drugs. Withdrawal effects, especially rebound insomnia, tend to be mild after the discontinuation of the intermediate-acting drugs. Marked rebound insomnia has been reported after discontinuation of triazolam (*Halcion*), a short acting benzodiazepine. Anterograde amnesia the day after has also been reported.

Non-prescription products marketed for treatment of insomnia include melatonin and the sedating histamine antagonists [eg, diphenhydramine (*Benadryl*), doxylamine (*Unisom*)]. Use of these drugs is not supported by rigorous data. The histamine-receptor antagonists may improve sleep subjectively, but conclusions are limited by a small number of subjects, a short duration of administration, and lack of objective measurements. Morning sedation is a side effect. Studies of melatonin have reported conflicting results.

The benzodiazepines, flurazepam (*Dalmane*; generic) and quazepam (*Serax*) are also approved by the FDA for treatment of insomnia, but because of their long half-life, they are generally not recommended.

Sedating tricyclic antidepressants [trazodone (*Desyrel*) and doxepin (*Sinequan*)] have been increasingly used for chronic insomnia for treatment of insomnia in depressed patients. There is a paucity of studies to support their use. Adverse effects are common.

A new melatonin-receptor agonist has been approved— *Rozerem* (ramelteon). More time will be needed to determine its place in management.

The author spends considerable time discussing cognitive behavioral therapy for treatment of insomnia. Primary care clinicians will find application of cognitive behavior therapy difficult to apply in the busy flow of practice. Referral to specialists (if available) may be considered. “Although long-term data are lacking, most sleep specialists recommend long-term use of pharmacologic therapy in a subgroup of patients with chronic primary insomnia who do not respond to cognitive behavioral therapy.”

"For insomnia that is predominantly associated with onset of sleep, off-label use of *Ambien* and *Sonata* (ie, longer than 10 days) should be considered." For insomnia that is predominantly associated with maintenance of sleep, intermediate-acting drugs (eg, *Restoril*) can be tried. But these drugs may soon be supplanted by *Lunesta*.

There is little role for use of long-acting benzodiazepines in management of insomnia unless a coexisting anxiety disorder is present.

NEJM August 25, 2005; 353: 803-10 "Clinical Practice" review article by Michael H Silber, Mayo Clinic College of Medicine, Rochester, Minn.

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Bone Turnover Increases with Teriparatide; Decreases with Alendronate. Both Lead to Increased BMD.

8-3 OPPOSITE BONE REMODELING EFFECTS OF TERIPARATIDE AND ALENDRONATE IN INCREASING BONE MASS

Imbalances in the bone remodeling process affect mechanical properties related to bone strength, including bone geometry and microarchitecture. When bone resorption exceeds bone formation, the risk of fracture increases.

Therapies can preferentially modulate 1) bone resorption (eg, alendronate) or 2) bone formation (eg, teriparatide). Both correct the imbalances of the bone remodeling process which occur in osteoporosis.

This study compared the biochemical effects of both drugs and their effects on bone mineral density (**BMD).**

Conclusion: Two distinct options for the management of osteoporosis lead to increases in BMD by opposite mechanisms of action.

STUDY

1. Randomized, parallel, double-blind study followed over 200 postmenopausal women with osteoporosis for 18 months. (Mean age = 66; T score -2.5 to -4.0 at the lumbar spine and femoral neck.) All received supplementary calcium and vitamin D.
2. Randomized to: 1) teriparatide (*Forteo*, recombinant human parathyroid hormone 1-34; 20 mg daily subcutaneously), or 2) alendronate (*Fosamax*, a bisphosphonate; 10 mg daily by mouth).
3. Compared effects on bone turnover of alendronate vs teriparatide by measuring:
   A. Two biochemical markers of bone turnover: 1) a marker of bone formation, and 2) a marker of bone resorption. (*See text*)
   B. Bone mineral density **(BMD)** by both:
      1. Area (grams per square centimeter) by dual-energy X-ray absorptiometry, and
      2. Volume (per cubic centimeter) by quantitative computed tomography—a measure of trabecular BMD.).

RESULTS

1. Biochemical markers of bone turnover (at 12 months):

Alendronate *decreased* bone turnover. It decreased both markers.—formation as well as resorption. The effect on impeding resorption overbalanced the effect on inhibiting formation. BMD increased modestly.

Teriparatide *increased* bone turnover. It increased both markers—formation and resorption. The rate of formation overbalanced the effect on resorption. BMD increased.

2. Bone mineral density (means at 18 months):	Alendronate	Teriparatide
Lumbar spine		
Area BMD	+ 5%	+10%
Trabecular BMD	+ 4%	+ 19%
Femoral neck		
Area BMD	+ 3.9%	+ 3.5%
Trabecular volumetric BMD	+ 2.2%	+ 5%
Cortical volumetric BMD	+ 8%	- 1%

3. Adverse effects: Both were safe and well tolerated. Withdrawals were about equal. One interesting difference—more patients in the alendronate group reported new or worsening back pain during treatment (39% vs 26%). [The authors offer no explanation.]

DISCUSSION

1. The improvement in BMD from the two drugs is mediated by distinct and opposite effects on bone cell activity. Biochemical markers of bone turnover reflect the different mechanisms of action:
   - Alendronate was associated with a *reduction* in biochemical markers of both bone resorption. and formation. The effect on reducing resorption outweighed the effect on reducing formation. BMD increased.
   - Teriparatide was associated with an *increase* in biochemical markers of both bone formation and bone resorption. The effect on increasing bone formation outweighed the effect on increasing bone resorption. BMD increased.
2. A greater increase in trabecular BMD was observed with teriparatide. Cortical BMD in the femoral neck increased more with alendronate.
3. These results do not provide evidence about the comparative fracture-protection effectiveness of the two drugs. Previous studies reported a benefit in reducing risk of fracture.

CONCLUSION

The two drugs accomplish their benefits by different and opposite effects on bone metabolism. Bone turnover increases with teriparatide, and decreases with alendronate. Both lead to increased BMD.

Archives Int Med August 8-22 2005; 165: 1762-68 Original investigation, first author Michael R McClung, Osteoporosis Center, Providence Portland Medical Center, Portland Oregon.

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One Year Of Parathyroid Hormone Followed By One Year Of Alendronate An Effective Means Of Increasing BMD

8-4 COMBINATION AND SEQUENTIAL THERAPY FOR OSTEOPOROSIS

Over the past 10 years, five agents have been approved for the treatment or prevention of osteoporosis. As a group, these drugs have revolutionized the management of osteoporosis.

They fall into 2 broad categories:

1) Agents that reduce exaggerated bone remodeling by impeding bone resorption.
   Eg, bisphosphonates
2) Agents that stimulate bone formation.
   Eg, parathyroid hormone (PTH 1-34—the FDA approved drug— limited by the FDA to two years of use.)

Bisphosphonates produce a steady increase in bone mineral mass averaging about 1% a year for up to 8 to 10 years. And once-daily parathyroid hormone given subcutaneously increases central bone mass by 8% to 10% per year for up to 2 years. (The duration of time for which data are available.)

As monotherapy, both classes of agents are effective in reducing risk of fracture.

It has not been established whether these drugs enhance each other's effects if given together or in certain sequences. Two articles in this issue of NEJM **[1,2]** provide important, but incomplete and preliminary information about the effects of combinations and sequences of drugs:

1) Combinations of PTH + bisphosphonates appear to increase central bone mass, but to a lesser extent than PTH alone.
2) When PTH is used alone, in the months after PTH is discontinued, some or all of the bone gained appears to be lost.
3) Administering bisphosphonates *after* a course of PTH appears to conserve the bone gained, and adds a further increase in its own right, roughly similar in magnitude to the short-term effect of bisphosphonates given to previously untreated patients.
4) PTH appears to maintain its anabolic effect in patients previously treated with a bisphosphonate.

The authors note that these conclusions reflect the effects of the drugs on bone mass alone. There are strong reasons to conclude that the antifracture efficacy of both classes of agents derives, in part, from effects distinct from mass changes. In addition to producing a small increase in bone mass, bisphosphonates reduce the number of active remodeling loci on bone surfaces. A reduction in the number of these loci produces a prompt decrease in bone fragility, independent of their effect on bone mass. In addition to increasing trabecular bone volume, PTH also increases the periosteal diameter at critical bone sites.

Defects in "bone quality" probably equal or even outweigh the mass defect in bone implied in the term "osteoporosis".

Osteoporosis is a multifactorial disorder, unlikely to be controlled by any single class of medication.

NEJM August 11, 2005; 353: 624-25 Editorial, first author Robert P Heaney, Osteoporosis Research Center, Creighton University, Omaha, Nebraska.

1 "One Year of Alendronate after One Year of Parathyroid Hormone (1-84) for Osteoporosis." NEJM August 1, 2005; 353: 555-65, original investigation, first author Dennis M Black, University of California, San Francisco.

The FDA limits use of PTH for treatment of osteoporosis to two years. Should antiresorptive therapy follow PTH therapy?

The trial considered 4 groups of women:

1) One year of PTH followed by one year of placebo:

Patients receiving PTH for one year gained BMD. During the 2nd year, when receiving placebo, much of the gain was lost. (Ie, apparently PTH must be continued to maintain the gain in BMD.)

2) One year of PTH followed by one year of alendronate:

Patients receiving PTH for one year gained BMD. During the 2nd year of alendronate-alone therapy, BMD continued to increase.

3) One year of alendronate + PTH followed by one year of alendronate alone:

During the first year of combined therapy, there was no advantage over PTH alone. Over 2 years, BMD increased, but at somewhat lower rate than those receiving PTH for one year followed by alendronate.

4) One year of alendronate followed by a second year of alendronate:

BMD increased over 2 years, but not as much as in the group receiving 1-year of PTH followed by 1-year of alendronate.

"Thus, from a clinical perspective, one year of parathyroid hormone followed by one year of alendronate would seem to be an effective means of increasing bone mineral density while minimizing the use of parathyroid hormone."

BMD is a secondary endpoint. The important primary endpoint is the effect on fracture—not reported in this study.

A previous trial by the same investigators reported that the combination of alendronate + PTH during one year did not provide a clear advantage over either one given alone.

2 "Daily and Cyclic Parathyroid Hormone in Women Receiving Alendronate" NEJM August 11, 2005; 353: 566-75 Original investigation, first author Felicia Cosman, Helen Hayes Hospital, West Haverstraw, NY.

This study concerned women who had taken alendronate for one year.

Randomized for an additional 15 months to 1) continued alendronate; 2) continued alendronate + PTH (1-34) given daily; or 3) continued alendronate + PTH given cyclically three months on, three months off.

In both PTH groups, BMD in the lumbar spine rose more than in the alendronate-alone group. BMD rose comparably in both PTH groups. Many women with osteoporosis previously treated with alendronate, who are at continued risk of fracture, may benefit from PTH.

The authors concluded that both continuous and cyclic PTH combined with alendronate increase BMD. Cyclic administration may be less costly.

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Should Primary Care Clinicians Prescribe This Therapy?

8-5 WARFARIN PLUS ASPIRIN AFTER MYOCARDIAL INFARCTION OR ACUTE CORONARY SYNDROME: Meta-analysis with Estimates of Risk and Benefit.

Several interventions are beneficial in the secondary prevention of myocardial infarction **(MI)**: beta-blockers, ACE inhibitors, statin drugs, and aspirin.

After acute coronary events, a marked thrombin generation state persists for months. This suggests a role for anticoagulation beyond the initial use of low-molecular-weight heparin.

Evidence for use of warfarin in this context has been conflicting. Warfarin use has not been widely adopted, perhaps because of fear of increased risk of bleeding, or belief that benefits are small compared with costs and inconvenience.

This study quantified the risks and benefits of warfarin + aspirin *vs* aspirin alone after acute coronary syndromes **(ACS).**

Conclusion: For patients with ACS who are at low or intermediate risk of bleeding, benefits of warfarin outweigh risks

STUDY

1. MEDLINE search yielded 10 randomized trials (over 5900 patients; 11 000 patient-years) comparing 1) warfarin therapy (INR > 2.0) plus aspirin vs 2) aspirin alone after ACS. No patient had received a stent.
2. The authors calculated risks of bleeding from a validated Outpatient Bleeding Risk Index which predicted risk of bleeding from warfarin based on 5 independent risk factors: age over 65; history of stroke, history of GI bleeding, a specific co-morbid condition (eg, renal insufficiency, severe anemia, recent myocardial infarction, and atrial fibrillation). If three or more of these factors are present, the risk of bleeding is high—30% in the first year. These patients were excluded from the meta-analysis. For patients with 1 or 2 risk factors risk of major bleeding is 7%; for patients with none, risk is 1%. These patients were included.
3. Many of the trial patients had at least one risk factor for bleeding (MI) placing them in an intermediate risk category.

RESULTS

1. Compared with aspirin alone, warfarin plus aspirin was associated with a decrease in the risks.
2. Outcomes per 1000 patients per year:

	Warfarin + aspirin	Aspirin alone	Absolute difference	NNT
MI	22	41	19	53
Ischemic stroke	4	8	4	250
Major bleeding	1.5	0.6	0.9	1100
Death	No difference			

DISCUSSION

1. The authors state that, although the risk of major bleeding is increased with warfarin + aspirin compared with aspirin alone (about 1 per 1000 per year in this meta-analysis), the benefits outweigh the risks for many patients as long as patients with high risk of bleeding from warfarin are excluded.
2. Benefits are greater in the first 3 months. Nevertheless, the curves for the combined endpoints continue to diverge for at least 5 years. The length of therapy is a clinical judgment.
3. “On the basis of our analysis, the benefits (*of warfarin + aspirin vs aspirin alone*) should

outweigh the harms for most patients." Cardiovascular events are usually more serious than bleeding events.

CONCLUSION

For patients with ACS at low or intermediate risk for bleeding, the benefits of warfarin outweighed the risk of bleeding.

Annals Int Med August 16, 2005; 143: 241-50 Original investigation, meta-analysis. First author Michael B Rothberg, Baystate Medical Center, Springfield, Mass.

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Describing a New Dog Vector for One of the Most Virulent Human Infections Ever Identified.

1 ROCKY MOUNTAIN SPOTTED FEVER – Changing Ecology And Persisting Virulence

Rocky mountain spotted fever **(RMSF)** is one of the most virulent human infections ever identified. Up to 10% of persons infected will die. Many more will require intensive care, and have sequellae such as amputation and permanent learning impairment. This is despite the availability of a simple and highly effective treatment (doxycycline).

Infections are sporadic, but persistent. Only small proportions of vectors are infected.

RMSF occurs when *Rickettsia rickettsii* in the salivary glands of a vector tick is transmitted into the human dermis, spreads, replicates in endothelial cells, and elicits widespread vasculitis. Vascular permeability results, leading to hypoperfusion and end-organ damage—most dangerous in the brain and lung.

Diagnosis is difficult because of the non-specific presentation of the disease. Symptoms include fever, headache, myalgia, and (usually after 3 to 5 days) rash. The rash evolves from macular to macro-papular, to petechial. Organ-specific symptoms (nausea, vomiting, abdominal pain, and cough) confound diagnosis by distracting attention from systemic manifestations. Serologic analysis is not useful during an active infection.

Early clinical suspicion and empirical therapy are essential. Severe illness and death are associated with a delayed diagnosis, which may occur because of absence of a rash or presentation during a season with a low level of tick activity.

In the USA, *R rickettsii* is predominantly transmitted by the American dog tick and the Rocky Mountain wood tick. An article in this issue of NEJM [1] describes transmission from a new vector—the brown dog tick. This tick feeds predominantly on dogs in peridomestic habitats. It is important in the transmission of RMSF to humans. This presents a threat owing to unique epidemiological features which differentiate it from the American dog tick. The brown dog tick lives along with humans in the household environment.

Other tick vectors, with specific ecological features and hosts determine the prevalence and incidence of RMSF in Mexico and South America.

The disease may occur more frequently than reported. Deaths from RMSF are at least 4 times the reported number. Severe sequellae may be unreported.

"The reasons for the under-recognition of RMSF falls squarely on physicians and the system that educates and reeducates them." Far too few physicians consider the diagnosis or take the time to inquire about tick bites or exposures.

"No longer can we consider RMSF a disease of only rural and southern venues; it has emerged and re-emerged again. "

NEJM August 11, 2005; 353: 551-53 "Perspective", first author J Stephen Dumler, Johns Hopkins University School of Medicine, Baltimore, MD

1 "Rocky Mountain Spotted Fever from an Unexpected Tick Vector in Arizona." NEJM August 11, 2005; 353: 587-94 Original investigation, first author Linda J Demma, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.

This study describes an outbreak of RMSF in communities in rural eastern Arizona transmitted by a tick not previously identified as a vector. Most of the patients were children. Two died. (They had not been treated with doxycycline, or treatment was late.) All patients had contact with tick-infested dogs. Only 4 had a history of tick bite. Fifteen of the 16 had rash during the course of the illness—13 of which involved the palms and soles. **1** Common laboratory findings included elevated liver enzymes, hyponatremia, and thrombocytopenia.

The communities had large populations of dogs. Dense populations of the brown dog tick were found feeding on dogs in the yards of patients. Ticks were also found in crawl spaces under houses, in discarded upholstered furniture, and in cracks in the stucco on the walls of houses. Only the brown dog tick was found.

The brown dog tick (which differs ecologically from the American dog tick) has not previously been reported to be a natural vector for RMSF in the USA. It is found worldwide, and is widely distributed across North America. It feeds primarily on dogs. The domestic habitat and broad distribution of the brown dog tick in the Western Hemisphere are a cause of concern about human exposure to this vector, and the introduction of RMSF into areas where it has not previously been recognized.

The principle vectors of *R rickettsii* are the American dog tick (eastern and central USA—the most common tick associated with RMSF commonly feeds on dogs.), and the Rocky Mountain wood tick (western USA). Both feed on small mammals which may harbor *R rickettsii.*

1 *The rash of RMSF commonly appears on the distal areas of the extremities. Appearance on the palms and soles is often described as a diagnostic feature. However, many cases occur without rash on the palms and soles. Indeed, waiting for this sign may delay treatment. RTJ*