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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

   HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

   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 contents of articles in much more detail.

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.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* DECEMBER 2006

Vaccinating The Staff Protects The Residents

12-1 EFFECTIVENESS OF AN INFLUENZA VACCINE PROGRAMME FOR CARE HOME STAFF TO PREVENT DEATH, MORBIDITY, AND HEALTH SERVICE USE AMONG RESIDENTS.

Vaccination of residents of care-homes against influenza can be effective in preventing respiratory illness, admissions to hospital, and death. The immune response in the elderly, however, is reduced. Protection against flu is only 50% to 70%. Residents are vulnerable to flu outbreaks even when vaccination rates are high.

These investigators hypothesized that vaccination of the *staff* would reduce transmission to *residents*, and therefore reduce residents' influenza-like illness, and associated deaths and health service use.

Randomized controlled trial followed 44 large private-chain UK elder-care homes during 2 flu seasons—2003-04 and 2004-05 (Total residents = 2604; total staff = 1703.) All residents had been routinely offered flu vaccine. The homes had not routinely offered vaccination to staff members.

Randomized to: 1) intervention homes, and 2) matched control homes.

Vaccination for flu was offered to the staffs of the intervention homes, but not to control homes.

	Vaccine coverage of full time staff	Vaccine coverage of part-time staff
Intervention homes	48%	21%
Control homes	6%	4%

All-cause mortality was less in the residents of intervention homes by 5 per 100 residents. Consultations for flu-like illness 7 per 100 less in intervention homes. Admissions to hospital for flu-like illness less by 2 per 100.

Conclusion: Vaccinating the staff against influenza can prevent deaths, and lower health care service use and flu-like illness among the residents of elder-care homes.

The Healthcare Infection Control Practices Advisory Committee, and the Advisory Committee on Immunization Practices recommend influenza vaccination for health care personnel.

I do not know how the general health and age of "care home" residents in the UK compares with that of residents of "retirement homes" in the USA. Many elderly in the USA homes remain in good health and continue to be active. Most receive flu vaccine every year. Many residents are also receiving assisted care and nursing care. I would judge that, overall, immune response to flu vaccine is attenuated.

"This Result Was Somewhat Unexpected"

12-2 PREVENTION OF ANTIGENICALLY DRIFTED INFLUENZA BY INACTIVATED AND LIVE ATTENUATED VACCINES

The efficacy of flu vaccines may decline during years when the circulating viruses have antigenically drifted from those included in the vaccine.

The vaccine to be given later in the year 2004-05 was formulated in February of 2004. By the winter of 2004, the strains of circulating virus had antigenically drifted from the viruses included in the vaccine:

Vaccine	Nationally circulating virus
Type A/New Caledonia /20/99 (H1A1)	

Type A/Wyoming/3/2003 (H3N2)	Type A California/072004-like strain (H3N2)
Type B/Shanghai/361/2002-like strain (Yamagata lineage)	Type B Hawaii/33/2004-like strain (Victoria lineage)

This study determined efficacies of both the traditional killed vaccine and the newer attenuated live vaccine and compared them with placebo in preventing symptomatic, laboratory confirmed flu.

Immune response to vaccine was much more robust for the killed vaccine.

Efficacy favored the killed vaccine.

Absolute difference (%) between killed vaccine and placebo:

For types A and B combined	5.5 %	NNT = 18 *
For type A	3.1 %	NNT = 32

Absolute difference (%) between live vaccine and placebo:

For types A and B	2.4 %	NNT = 42
For type A	2.1%%	NNT = 48

(* Number of subjects needed to treat to prevent one laboratory-confirmed case of flu.

My calculations from their data RTJ)

Absolute difference (%) between killed vaccine and placebo:

For type B	2.8 %	NNT = 47

Absolute difference (%) between live vaccine and placebo:

For type B	1.7%	NNT = 59

In the year 2004-05 when antigenically drifted type A (H3N2) influenza and an additional type B virus were circulating, the killed vaccine worked well. “This result was somewhat unexpected, given the problems reported in past years when antigenically drifted viruses were circulating.”

The live attenuated vaccine appeared to be protective, particularly against type A influenza, although the absolute efficacy estimates were not (*statistically*) significant.

Conclusion: In the 2004-2005 flu season, when most circulating viruses were dissimilar to those included in the vaccine, the killed vaccine was efficacious in preventing laboratory confirmed symptomatic influenza in healthy adults. The live attenuated vaccine was less efficacious.

This certainly suggests that we should provide vaccine for everyone every year. Even if the virus and the vaccine do not match, the killed vaccine may provide some protection in adults. This news is encouraging as we enter the era of universal vaccination against flu. Note that the general type H3N2 did not drift. I wonder if vaccine would give any protection if the drift were greater, and a completely new viral type became epidemic (eg, H5N1). I doubt it. The news about the attenuated live vaccine is not reassuring, at least for adults.

See the following abstract concerning children.

Evidence Of A Herd Immunity Effect

12-3 EFFECTIVENESS OF SCHOOL-BASED INFLUENZA VACCINATION

Children are important vectors for the spread of influenza. Focusing efforts on flu vaccination of healthy children may be an effective and practical method of reducing the burden of flu in the *community*.

This study assessed the effect of a school-based vaccination program on *households* of children attending schools. (A herd immunity effect.)

Selected 11 intervention schools (total students = 5840; mean age = 8) and 17 matched control schools (total students = 9451) in 4 states representing geographically and demographically diverse regions. Offered live attenuated vaccine at no charge to all healthy children age 5 years and older in the intervention schools.

Outcomes:	Intervention schools	Control schools	Absolute difference
Children %			(Adjusted)
Any fever or flu-like illness	40	52	11
Fever + cough or sore throat	17	26	8
Adults in households %			
Any fever or flu-like illness	32	44	11
Fever + cough or sore throat	8	13	4

Conclusion: Incidence of flu-like illness was lower in households of children who received the live attenuated vaccine than households of children who did not receive the vaccine.

The study is provocative, not definitive. "Flu-like illness" is not necessarily influenza.

Note the benefit was evident despite an antigenic drift. (See the previous abstract.)

This is another indication that more generalized use of flu vaccines can promote "herd" immunity.

"Lifestyle Counseling And Metformin Should Be Started At The Same Time"

12-4 MANAGEMENT OF HYPERGLYCAEMIA IN TYPE 2 DIABETES

The authors present an algorithm to achieve good glycemic control:

Lifestyle counseling and metformin

Add sulfonylurea or thiazolidinedione or basal insulin

HbAic 7% and above

Metformin	Metformin	Intensify insulin
+	+	
sulfonylurea	thiazolidinedione	
+	+	
basal insulin	sulfonylurea	
	OR	
	metformin	
	+	
	thiazolidinedione	

+

basal insulin

HbAic still 7% and above

Intensify insulin + metformin + or - thiazolidinedione

Treatment of hyperglycemia in DM2 is complex. Combinations of glucose lowering drugs are often needed to achieve and maintain blood glucose at target levels. Development of new drugs has increased treatment options, and has contributed to the uncertainty surrounding new therapeutic approaches.

The traditional approach to lowering blood glucose consists of an ordered sequence: lifestyle modifications; oral monotherapy; oral combination therapy; and finally insulin (with or without oral drugs). This strategy usually results in recurrent failure because patients are allowed to become hyperglycemic before the next step is considered. "The aim should be to keep glycemic levels as near to normal as possible."

Metformin is widely accepted as the first line drug. It is relatively effective, safe, and cheap. It may be associated with a decrease in cardiovascular disease in obese persons with DM2. It does not cause weight gain, and may be associated with weight loss.

Conclusion: The burden of DM2 can be prevented by stringent control of hyperglycemia and other cardiovascular disease risk factors. Treatment needs to focus on maintaining blood glucose values as close to the non-diabetic range as possible, with early initiation of effective drugs (combinations of oral drugs and insulin). And prompt adjustment of treatment when HbA1c is above target.

This is an eminently practical clinical review, I wish for more like it.

Newer compounds are not included because of limited evidence and high costs.

The new therapies made available over the years to treat DM2 have been amazing. I believe most primary care clinicians will stick to the old standbys. And await further experience to tell if any newer drugs provide better control and more favorable outcomes than the old standards.

We can now do much to reduce the devastating complications of diabetes with control of other cardiovascular risk factors and glycemia. This is a major challenge for primary care.

A New Drug Class for Treatment of Type 2 Diabetes.

12-5 THE INCRETIN SYSTEM: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND DIPEPTIDYL PEPIDASE-4 INHIBITORS IN TYPE 2 DIABETES

This article reviews the action of glucagon-like peptide (**GLP**). GLP is a normally produced incretin—a human gut-derived hormone that:

1) Stimulates insulin production and suppresses glucagon secretion

2) Inhibits gastric emptying

3) Reduces appetite and food intake

Drugs have been developed to enhance GLP action:

1. GLP receptor agonists. (Termed incretin mimetics)

2. Inhibitors of the enzyme which degrades GLP, and prolongs GLP action. (Incretin enhancers)

I abstracted the article briefly to introduce a newly FDA-approved inhibitor of the enzyme which degrades GLP and thus increases its activity (Januvia; sitagliptin phosphate; an incretin enhancer; Merck). Januvia is being advertised. It is a once-a-day orally effective agent approved as mono-therapy for type 2 diabetes, and as an add-on to other drugs.

The recommended dose is 100 mg once a day with or without food. It works only when blood glucose in elevated, It enhances insulin production by the pancreas, and reduces uncontrolled production of glucagon and thus decreases glucose output from the liver.

Adverse effects are similar to placebo. The most common are stuffy or runny nose, sore throat, upper respiratory infection, and headache.

Used as an add-on to metformin, Januvia led to a greater reduction in HbA1c than metformin alone. It also reduced post meal glucose levels and fasting blood glucose.

Treatment was not associated with weight gain or increased risk of hypoglycemia.

This information comes from a press release by Merck. I would not prescribe Januvia at this time. I believe it adds little benefit above that of well established antidiabetes drugs. Several more years of use by the general public are required to establish effectiveness and safety

"May Increase The Potential For Improving Glycemic Control In The Diabetes Population"

12-6 EFFICACY AND SAFETY OF INHALED INSULIN THERAPY IN ADULTS WITH DIABETES MELLITUS: *A Meta-Analysis*

The FDA approved inhaled insulin one year ago for use in non-smokers, and in patients without pulmonary disease. Because of its pharmacokinetic profile it has been studied as a pre-meal alternative to injections of regular or rapid-acting insulin.

Comparisons:

Inhaled insulin vs subcutaneous insulin:

Small difference in decrease in HbA_{1c} favored subcutaneous insulin. (Mean difference = 0. 08%)

No difference in proportion of patients achieving the goal of HbA_{1c} under 7%. (25% vs 27%)

Inhaled insulin vs oral agents:

Three studies showed a large difference in HbA_{1c} favoring inhaled insulin (mean difference = 1.45%)

Two studies showed only a small difference (0.20%) favoring inhaled insulin. These trials included more subjects, and were of longer duration.

Subjects with DM2 taking inhaled insulin were more likely to achieve HbA_{1c} under 7%. (31% vs 17%).

Safety:

A. Severe hypoglycemia:

Inhaled insulin vs subcutaneous insulin:

Patients with DM1 patients in both groups experienced more episodes of severe hypoglycemia than patients with DM2. Little difference between inhaled and injected

	Inhaled	Injected

DM1	75%	78%
DM2	16%	18%

Severe hypoglycemia was more commonly reported in patients using inhaled insulin vs oral agents:

Inhaled 9% Oral 4%

B. Pulmonary safety:

The most common pulmonary symptom was a nonproductive cough (17%). Cough occurred within seconds to minutes. It was mild and not associated with changes in pulmonary function. Cough diminished over time.

FEV1 decreased from baseline (mean reduction = 0.03 L). FEV1 decreased slowly over 6 months, but was stable thereafter.

A few discontinued inhaled insulin because of respiratory events.

Conclusion: Inhaled insulin had slightly less efficacy in glycemic control than subcutaneous regular insulin. Patient-acceptance was increased. "Until long-term safety data are available, inhaled insulin should be reserved for nonpregnant adults with diabetes who are opposed to injections and who would otherwise delay appropriate and timely therapy with insulin."

All trials comparing inhaled insulin vs subcutaneous insulin included injected long-acting insulin in addition to inhaled insulin in the inhaled insulin group.

And the majority of trials comparing inhaled insulin vs oral agents included continuation of oral agents in the treatment group.

Administration of inhaled insulin is not simple. There must be a learning curve. It may take some weeks before dose is titrated to obtain maximum efficacy and safety.

COST: At my pharmacy a starter kit containing an inhaler, a replacement chamber, 180 1-mg blisters (equivalent to 3 U regular insulin) , and 90 3-mg blisters (equivalent to 8 U regular insulin) costs $188.00

Please read the full abstract !

Continued Treatment For An Additional 5 Years Increased BMD

12-7 EFFECTS OF CONTINUING, OR STOPPING, ALENDRONATE AFTER 5 YEARS OF TREATMENT The FLEX Trial

Alendronate (*Fosamax; Merck*) is a potent bisphosphonate which decreases bone turnover, increases bone mineral density (**BMD**), and decreases risk of fracture in women with osteoporosis. The optimum duration of treatment of women with postmenopausal osteoporosis is uncertain.

This study compared the effects of discontinuing alendronate after 5 years vs continuing for 10 years. (At baseline, all had received alendronate for 5 years.)

Randomized 1100 postmenopausal women to: 1) alendronate 5 mg daily; 2) 10 mg daily, or 3) placebo. (The study combined outcomes of 5 and 10 mg because there were small BMD differences noted between them.)

Mean change in BMD after an additional 5 years:

	Placebo (%)	Combined 5 mg and 10 mg (%)
Total hip	-3.38	-1.02
Femoral neck	-1.48	+0.46
Trochanter	-3.25	-0.08
Lumbar spine	+1.52	+5.26
Total body	-0.27	+1.01

Those who continued alendronate had a statistically significant lower risk of clinically recognized vertebral fractures (2.4% for alendronate vs 5.3% for placebo).

No significant differences between groups for serious adverse events, including upper g.i. events.

Conclusion: Compared with 5 years of therapy, continuation of alendronate (either 5 or 10 mg daily) for a total of 10 years maintained BMD and reduced bone remodeling. The risk of clinically evident vertebral fractures was lower in those who continued alendronate.

Practical Pointers has abstracted many studies about osteoporosis. All have reported the effects of drugs on patients with established osteoporosis—ie, treatment of the disease, not prevention. I await a study which begins treatment at menopause (likely with low dose bisphosphonates + calcium and vitamin D supplements) to prevent or retard development of osteoporosis. I judge this would be a more effective clinical method to prevent the devastating effects of osteoporosis much more effectively than treatment after osteoporosis has developed.

Associated With An Increase In Hip Fracture.

12-8 LONG-TERM PROTON PUMP INHIBITOR THERAPY AND RISK OF HIP FRACTURE

Millions of people are taking PPIs continuously, and long –term. PPI use leads to hypochlorhydria, particularly among elderly people who may have decreased PPI clearance. Hypochlorhydria could lead to calcium malabsorption, low bone mineral density, and increased risk of fracture.

This case-control study compared users of PPI and non-users, all over age 50.

Cases—patients with incident hip fracture (n = 13 556).

Controls—matched to cases (n = 135 000).

Compared PPI use in cases vs controls. Main outcome = risk of hip fracture associated with PPI use.

The adjusted odds ratio for hip fracture associated with more than 1 year of PPI use was 1.4.

The strength of the association rose with duration of PPI use:

PPI use	1 year	2 years	3 years	4 years
Odds ratio	1.2	1.4	1.5	1.6 (Adjusted for some possible confounders)

The risk of hip fracture was markedly increased among *long-term* users of *high-dose* PPI as compared with non-users of acid-suppression. (Odds ratio = 2.7)

Gastric acid may be important for absorption of insoluble calcium. Calcium malabsorption secondary to acid suppression by PPI therapy may potentially explain the association.

Conclusion: Long-term PPI therapy, particularly at high doses, was associated with an increase in hip fracture.

I believe this is a valid clinical point. Patients fitting these criteria should receive calcium and vitamin D supplementation long-term, and more liberal recommendations for use of bisphosphonates.

"Might Be Associated With Exaggerated Liver Injury In Some Individuals."

12-9 PARACETAMOL (ACETAMINOPHEN; *TYLENOL*); *Are Therapeutic Doses Entirely Safe?*

Acetaminophen (eg, *Tylenol*) is thought to be safe in recommended doses (up to 4 grams daily in adults). It is currently the most widely used analgesia and antipyretic drug worldwide.

It is hepatotoxic and nephrotoxic at doses greater than 4 g a day. It has become an important cause of acute liver failure. The most severe cases may require liver transplant. Mortality may be high.

In recent years, unintended overdoses, rather than those that are intentional, have been the main cause of acetaminophen-induced acute liver failure in the USA. The dose leading to liver failure may be as low as 7 grams a day.

A recent study was designed to determine why abnormal liver function tests were observed during studies of clinical development of a new combination of an opioid (hydrocodone) and acetaminophen. Participants were randomly assigned to placebo, acetaminophen-alone 4 g a day, or a combination of 4 g acetaminophen with one of three opioids. Duration of observation = 14 days. Although trough acetaminophen concentrations did not exceed therapeutic limits in any group, up to 44% of participants in the acetaminophen groups (including those given acetaminophen alone) had concentrations of alanine aminotransferase (ALT) more than three times the upper limit of normal (suggesting liver injury). No participant given placebo had an increase to this level. In 27% of participants ALT levels were increased to more than 8 times normal. The investigators concluded that the acetaminophen content was associated with ALT elevations.

Concomitant administration of opioids did not seem to increase ALT levels.

Awareness of possible toxicity is particularly important for people who are likely to be at high risk for hepatotoxicity—those dependent on alcohol, chronic users of acetaminophen, the severely malnourished, smokers, and those with acute liver disease.

I believe this is a valid clinical point. Primary care clinicians should be alert to possible acetaminophen toxicity. Note the rapid development of transferase elevations (within 14 days). I wonder—Why, considering the vast usage of acetaminophen, has this toxicity not been reported and disseminated before? My Goodman and Gilman "Pharmacological Basis of Therapeutics" does not mention liver toxicity from usual doses of acetaminophen, only from excessive doses.

Prevalence of impaired liver function is high in the US. This includes many elderly persons otherwise in good health..

The prevalence of non-alcoholic steatosis and steatohepatitis is increasing with the obesity epidemic. Are these patients more susceptible to toxic effects of acetaminophen?

ABSTRACTS DECEMBER 2006

Vaccinating The Staff Protects The Residents

12-1 EFFECTIVENESS OF AN INFLUENZA VACCINE PROGRAMME FOR CARE HOME STAFF TO PREVENT DEATH, MORBIDITY, AND HEALTH SERVICE USE AMONG RESIDENTS.

Vaccination of residents of care-homes against influenza can be effective in preventing respiratory illness, admissions to hospital, and death. The immune response in the elderly, however, is reduced. Protection against flu is only 50% to 70%. Residents are vulnerable to flu outbreaks even when vaccination rates are high.

These investigators hypothesized that vaccination of the *staff* would reduce transmission to *residents*, and therefore reduce residents' influenza-like illness, and associated deaths and health service use.

Conclusion: Vaccination of staff reduced mortality of residents, and incidence of flu-like illness.

STUDY

1. Randomized controlled trial followed 44 large private-chain UK elder-care homes during 2 flu seasons—2003-04 and 2004-05 (Total residents = 2604; total staff = 1703.) All residents had been routinely offered flu vaccine. The homes had not routinely offered vaccination to staff members.
2. Randomized to: 1) intervention homes, and 2) matched control homes.
3. Vaccination for flu was offered to the staffs of the intervention homes, but not to control homes.
4. Main outcomes = all-cause mortality among residents. Secondary outcomes = influenza-like illnesses, and health service use by the residents.

RESULTS

1. In the 2003-04 year:
   A The national influenza rates were higher
   B.

	Vaccine coverage of full time staff	Vaccine coverage of part-time staff
Intervention homes	48%	21%
Control homes	6%	4%

   C. All-cause mortality was less in the residents of intervention homes by 5 per 100 residents.
   D. Consultations for flu-like illness 7 per 100 less in intervention homes.
   E. Admissions to hospital for flu-like illness less by 2 per 100.
2. The influenza rates were much lower in the milder 2004-05 season. The direction of the effect was the same in both years, but much less in the 2004-05 year.

DISCUSSION

1. Vaccinating retirement home staff against influenza can prevent deaths in residents, and morbidity and use of health care services.
2. "The reduction is equivalent to preventing five deaths, two admissions to hospital with influenza-like illness,

seven general practitioner consultations for influenza-like illness, and nine cases of influenza-like illness per 100 residents during influenza activity."

3. These results were seen despite high levels of vaccination of residents. (Poor immune response to vaccine in elderly people can leave them vulnerable). The 4% higher uptake of vaccine among residents in intervention homes could not have accounted for the 25% decrease in mortality, or a halving of flu-like illness.
4. "Achieving higher vaccine uptake could also have increased effectiveness, but is notoriously difficult in health care workers."
5. "This study provides strong evidence to support influenza vaccination of care home staff even when vaccine uptake by residents is high."

CONCLUSION

Vaccinating the staff against influenza can prevent deaths, and lower health care service use and flu-like illness among the residents of elder-care homes.

BMJ December 16, 2006; 333: 1241-44 Original investigation, firs author Andrew C Hayward, University College, London, UK

"This Result Was Somewhat Unexpected"

12-2 PREVENTION OF ANTIGENICALLY DRIFTED INFLUENZA BY INACTIVATED AND LIVE ATTENUATED VACCINES

The efficacy of flu vaccines may decline during years when the circulating viruses have antigenically drifted from those included in the vaccine.

The vaccine to be given later in the year 2004-05 was formulated in February of 2004. By the winter of 2004, the strains of circulating virus had antigenically drifted from the viruses included in the vaccine:

Vaccine:	Nationally circulating virus
Type A/New Caledonia /20/99 (H1A1)	
Type A/Wyoming/3/2003 (H3N2)	Type A California/072004-like strain (H3N2)
Type B/Shanghai/361/2002-like strain (Yamagata lineage)	Type B Hawaii/33/2004-like strain (Victoria lineage)

The study determined efficacies of both the traditional killed vaccine and the newer attenuated live vaccine and compared them with placebo in preventing symptomatic, laboratory confirmed flu.

Conclusion: Despite the viral drift, the traditional killed vaccine (given by injection) was efficacious in preventing laboratory confirmed, symptomatic flu. The live attenuated virus vaccine (given by nasal inhalation) was also efficacious, but less so than that of the inactivated vaccine, especially for type B.

STUDY

1. Randomized, double-blind placebo-controlled trial entered 1247 healthy adults; mean age 27. All provided a preintervention blood specimen. About half had received flu vaccine before.
2. Randomized to: 1) the traditional killed vaccine given by injection, 2) the new attenuated live vaccine given by nasal inhalation, or 3) placebo injection or saline inhalation
3. By the fall of 2004, the circulating type A H3N2 virus had drifted, and the circulating virus now included a type B Victoria lineage strain not included in the vaccine.
4. Influenza activity began in January 2005. Primary endpoint = number of cases of symptomatic flu (type A or Type B) laboratory confirmed by either isolating the virus, or by rise in antibody titer by a factor of 4 or more. A secondary endpoint = symptomatic flu determined by culture or PCR.

RESULTS

1. Immune response to vaccine was much more robust for the killed vaccine:

Serum antibody titer for influenza: components increased by a factor of four or more:

	Killed vaccine	Live vaccine
Influenza A H3 component	67%	21%
Influenza A H1 component	70%	9%
Influenza B component	85%	14%

2. Cumulative incidence of flu:	Inactive vaccine (%)	Live vaccine (%)	Placebo (%)
Types A and B combined	(N = 367)	(N = 363)	(N = 146)
Culture or serologic positive	2.7	5.8	8.2

The absolute difference between killed vaccine and placebo for types A and B = 5.5%; number needed to treat to prevent one case of flu = 18.

The absolute difference between live vaccine and placebo for types A and B = 2.4%, Number needed to treat with live vaccine to prevent one case of flu = 42

3. Cumulative incidence:	Killed vaccine (%)	Live vaccine (%)	Placebo (%)
Type A flu:	(N = 522)	(N = 519	(N = 206)
Culture or PCR positive	1.3	2.3	4.4

The absolute difference between killed vaccine and placebo for type A = 3.1%. Number needed to treat to prevent one case of type A flu = 32

The absolute difference between live vaccine and placebo for type A = 2.1%. Number needed to treat to prevent one case of type A flu = 48

4. Cumulative incidence:	Killed vaccine (%)	Live vaccine (%)	Placebo (%)
Type B flu			
Culture or PCR positive	0.6	1.7	3.4

The absolute difference between killed vaccine and placebo for type B = 2.8%, Number needed to treat with inactive vaccine to prevent one case of type B flu = 47

The absolute difference between live vaccine and placebo for type B = 1.7%. Number needed to treat to prevent one case of type B flu = 59

5. Adverse effects (active vs placebo);

Inactive vaccine; Only arm soreness was significantly associated.

Live vaccine: Runny nose and congestion, headache, muscle aches.

DISCUSSION

1. When a circulating virus antigenically drifts from the strain in the vaccine, the efficacy of the inactive vaccine is believed to decline.
2. In the 2004-05 season, the type A H3N2 virus had antigenically drifted. This led to concern that the efficacy of the inactivated vaccine would be low given the genetic differences between the two viruses.
3. Two markedly different type B viruses (Yamagata, and Victoria) had been circulating for a number of years. One or the other had typically predominated. In the winter of 2004-05, when the Yamagata strain was selected for the vaccine, viruses of both lineages were in circulation. (Ie, no immunization for Victoria.)
4. In the year 2004-05 when antigenically drifted type A (H3N2) influenza and an additional type B virus were circulating, the killed vaccine worked well. "This result was somewhat unexpected, given the problems reported in past years when antigenically drifted viruses were circulating."
5. The live attenuated vaccine appeared to be protective, particularly against type A influenza, although the absolute efficacy estimates were not (*statistically*) significant.
6. Among cases of flu confirmed by cell culture or PCR, the killed vaccine provided good protection against both type A and type B. virus. The live attenuated vaccine protected poorly against type B.
7. The authors make several comments about use of live virus:

In children, the live vaccine has been consistently shown to be efficacious, even against antigenically drifted strains. There seemed to be high rates of seroconversion in children.

Some adults may not become infected by the live vaccine viruses because of past infections with influenza.

Even if the live virus is not as efficacious as the killed virus in adults, its intranasal route of administration might still be an advantage as the United States moves toward a recommendation for universal use of flu vaccine.

The live virus vaccine could also be useful in a pandemic, given that the population would have no preexisting antibodies to the newly emerging virus.

CONCLUSION

In the 2004-2005 flu season, when most circulating viruses were dissimilar to those included in the vaccine, the killed vaccine was efficacious in preventing laboratory confirmed symptomatic influenza in healthy adults.

The live attenuated vaccine was less efficacious.

NEJM December 14, 2006; 355: 2513-22 Original investigation, first author Suzanne E Ohmit, University of Michigan School of Public Health, Ann Arbor

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Evidence Of A Herd Immunity Effect

12-3 EFFECTIVENESS OF SCHOOL-BASED INFLUENZA VACCINATION

Children are important vectors for the spread of influenza. Focusing efforts on flu vaccination of healthy children may be an effective and practical method of reducing the burden of flu in the *community*.

This study assessed the effect of a school-based vaccination program on *households* of children attending schools. (A herd immunity effect.)

Conclusion: Incidence of flu-like illness was lower in households of children who received the live attenuated vaccine than households of children who did not receive the vaccine.

STUDY

1. Selected 11 intervention schools (total students = 5840; mean age = 8) and 17 matched control schools (total students = 9451) in 4 states representing geographically and demographically diverse regions.
2. Offered live attenuated vaccine at no charge to all healthy children age 5 years and older in the intervention schools. The vaccine was formulated in early 2004. By the fall, the circulating virus had antigenically drifted. *(See preceding abstract.)*
3. After the predicted peak week of flu, all households received a questionnaire including questions about demographics and vaccination status among household members. And incidence of "flu-like illness".

RESULTS

1. Only about half of the students in intervention schools received the vaccine. The majority had not received vaccine before.

2. Outcomes:	Intervention schools	Control schools	Absolute difference
Children %			(Adjusted)
Any fever or flu-like illness	40	52	11
Fever + cough or sore throat	17	26	8
Adults in households %			
Any fever or flu-like illness	32	44	11
Fever + cough or sore throat	8	13	4

3. Use of outpatient health care, emergency department care, prescription medications, and over-the-counter medications was lower in children the intervention schools and in their households.
4. School absences were lower in children in the intervention schools. Fewer paid workdays were missed by adults in homes of children attending the intervention schools.
6. Adverse effects: "In surveys taken after vaccination, students had significantly elevated rates of symptoms

of influenza-like illness and use of nonprescription medicines and humidifiers than in surveys taken before vaccination"

DISCUSSION

1. "This school-based vaccination intervention resulted in influenza-related outcomes in household members of children attending intervention schools."[1] (Even when only half of the students received vaccine.)
2. The study was designed to compare the effects of school-based vaccination of school children and their household members regardless of the vaccination status of individual students.

CONCLUSION

"School-based immunization against influenza directly and indirectly reduces outcomes related to influenza-like illness."

NEJM December 14, 2007; 355: 2523-32 Original investigation, first author James C King, Jr. University of Maryland, Baltimore.

Study supported by MedImmune, maker of the live attenuated vaccine. *FluMist*

1 I believe this is slightly misleading. There was no firm indication that the illnesses were indeed influenza-related.

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"Lifestyle Counseling And Metformin Should Be Started At The Same Time"

12-4 MANAGEMENT OF HYPERGLYCAEMIA IN TYPE 2 DIABETES

Strict glycemic control can reduce micro-vascular complications of diabetes.

Recent trials also indicate that intensive therapy aimed at normoglycemia has beneficial effects in reducing risk of cardiovascular (macro-vascular) disease in patients with type 2 diabetes (**DM2**) as well as in type 1.

Treatment of hyperglycemia in DM2 is complex. Combinations of glucose lowering drugs are often needed to achieve and maintain blood glucose at target levels. Development of new drugs has increased treatment options, and has contributed to the uncertainty surrounding new therapeutic approaches.

This clinical review presents a management guideline designed to help primary care clinicians treat patients with DM2.

What level of glycemic control should we aim for?

Ideally the HbA1c should be as close to normal as possible, without imposing a high risk of severe hypoglycemia. The upper limit in the Diabetes Control and Complications trial was 6.1%. The American Diabetes Association states that "An HbA1c of 7% or greater should serve as a call to action to initiate or change therapy with the goal of achieving a level as close to the non-diabetic range as possible".

How do I establish and sustain glycemic control?

The clinical course of DM2 is characterized by a gradual decline in beta-cell function. Treatment needs to be adjusted regularly.

The traditional approach to lowering blood glucose consists of an ordered sequence: lifestyle modifications; oral monotherapy; oral combination therapy; and finally insulin (with or without oral drugs).

This strategy usually results in recurrent failure because patients are allowed to become hyperglycemic before the next step is considered. “The aim should be to keep glycemic levels as near to normal as possible.”

Lifestyle change an option?

The potentially most effective (but most difficult) step is to change patients’ lifestyles, and to achieve a clinically meaningful and lasting weight loss. Evidence for a successful and durable lifestyle modification is lacking.

Weight loss with bariatric surgery is the most effective and durable treatment. But relatively modest weight loss may be clinically effective. Drugs subsequently prescribed may be more effective if a lower body mass index is maintained.

Is metformin still the first line drug?

It is widely accepted as such. It is relatively effective, safe, and cheap. It may be associated with a decrease in cardiovascular disease in obese persons with DM2. It does not cause weight gain, and may be associated with weight loss.

Lifestyle counseling and metformin should be started at the same time. “This advice goes against the usual approach where metformin is added if lifestyle changes do not improve DM2 control.”

Other drugs will be needed if target values of blood glucose are not maintained.

Which drugs after metformin?

Sulfonylureas, thiazolidinediones, and insulin are the most widely used.

Sulfonylureas are potent stimulators of insulin secretion. Their glucose-lowering potency is similar to that of metformin. Main side effects are weight gain and severe hypoglycemia, particularly for elderly people taking long-acting sulfonylureas.

Thiazolidinediones sensitize adipose tissue, liver and muscle to insulin. They are less effective in lowering glycemia. Their putative beneficial action on lipids and inflammation may contribute to lowering risk of cardiovascular disease. They are more expensive. Their main adverse effect is fluid retention, which may increase risk of heart failure.

Glucosidase inhibitors, meglitinides, and pramlintide are less widely prescribed, possibly because of limited efficacy, g.i. side effects, higher costs, and need for multiple daily administrations.

A sulfonylurea, a thiazolidinedione, or insulin is the preferred option to add to metformin. The choice should be based on the degree of hyperglycemia. Insulin is the most effective glucose-lowering agent. It

should be used when HbA1c is high (8.5% and above). Insulin therapy can be started at any time in the course of DM2. It can correct almost any degree of hyperglycemia, provided adequate doses are used. This can be done safely only when guided by self-monitoring blood glucose. When the HbA1c is more than 1.5% above target, insulin or a sulfonylurea is the best choice. A thiazolidinedione may be prescribed when glucose values are neared to target.

And then? Three oral agents, insulin as add-on, or insulin alone?

A combination of 3 oral agents for lowering blood glucose should be considered only when patients are already close to target, and when circumstances make it difficult to use insulin. The combination of three oral agents is more expensive than using insulin + metformin, and no greater benefit has been shown.

If target HbA1c levels are not achieved by dual oral therapy, the next step is to start basal insulin. Intermediate or long acting insulin taken at bedtime is a good first choice. Injections of short acting insulin before meals may be used if treatment needs intensification. Sulfonylureas should be gradually stopped. Preprandial insulin and sulfonylureas do not work well together.

Inhaled insulin has been approved, but long-term experience is limited.

The goal should be to maintain HbA1c as close as possible to 6% or lower.

Conclusion: The burden of DM2 can be prevented by stringent control of hyperglycemia and other cardiovascular disease risk factors. Treatment needs to focus on maintaining blood glucose values as close to the non-diabetic range as possible, with early initiation of effective drugs (combinations of oral drugs and insulin). And prompt adjustment of treatment when HbA1c is above target.

BMJ December 9, 2006; 333; 1200-1204 "Clinical Review", first author R J Heine, University Medical Centre, Amsterdam, Netherlands.

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A New Drug Class for Treatment of Type 2 Diabetes.

12-5 THE INCRETIN[1] SYSTEM: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND DIPEPTIDYL PEPIDASE-4 INHIBITORS IN TYPE 2 DIABETES

This "New Drug Class" article reviews the action of glucagon-like peptide (**GLP**). GLP is a normally produced incretin—a human gut-derived hormone that:

1) Stimulates insulin production and suppresses glucagon secretion
2) Inhibits gastric emptying
3) Reduces appetite and food intake

Drugs have been developed to enhance GLP action:

1. GLP receptor agonists. (Termed incretin mimetics)
2. Inhibitors of the enzyme (a peptidase;) which degrades GLP, and prolongs GLP action. (Termed incretin enhancers)

Clinical trials report that exenatide (a GLP mimetic) reduces fasting and postprandial glucose concentrations, and HbA1c levels. It is given by injection twice a day. Weight loss is associated. Mild nausea is the most common adverse event.

New orally administered GLP inhibitors reduce HbA1c with few adverse events and no weight gain.

Long term clinical studies are needed to determine the benefits of targeting the incretin axis for treatment of DM2.

Lancet November 11, 2006; 368: 1696-1705 first author Daniel J Drucker, University of Toronto, Ontario, Canada.

1 Incretin is the generic name for all insulinotropic substances originating in the g.i. tract in response to ingestion of glucose.

This long article describes GLP mimetics and enhancers in detail. Consult the original.

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"May Increase The Potential For Improving Glycemic Control In The Diabetes Population"

12-6 EFFICACY AND SAFETY OF INHALED INSULIN THERAPY IN ADULTS WITH DIABETES MELLITUS: ***A Meta-Analysis***

Achievement to glycemic goals in patients with diabetes mellitus (**DM**) is far from adequate. Fewer than half of adults with DM attain HbA_{1c} under 7%.

Insulin effectively lowers hyperglycemia. But, there is resistance to its use, primarily because of the need for injections. Patients may defer initiating insulin therapy for long periods. They may accept insulin if made available in a less invasive method of administration.

The FDA approved inhaled insulin[1] one year ago for use in non-smokers, and in patients without pulmonary disease. Because of its pharmacokinetic profile it has been studied as a pre-meal alternative to injections of regular or rapid-acting insulin.

This systematic review examined the efficacy, safety and patient acceptability of inhaled insulin in non-pregnant patients with DM. It included randomized, controlled trials (of at least 12 weeks duration) that compared inhaled insulin (+ long acting insulin by injection) with subcutaneous insulin and oral agents. The reviewers found 16 open label trials (over 4000 patients) which met their inclusion criteria. The trials included patients with both DM1 and DM2 and compared HbA_{1c} outcomes.

A. Seven trials compared inhaled insulin vs subcutaneous insulin in patients with type DM1:

Treatment group	Control group
Inhaled insulin TID with meals	Subcutaneous regular insulin BID or TID with meals
Plus long acting insulin by injection	Plus long acting insulin

B. Four trials compared inhaled vs subcutaneous insulin in patients withDM2

Inhaled insulin TID with meals	Subcutaneous regular insulin BID to TID
Plus long acting insulin	Plus long acting insulin

C. Five trials compared inhaled insulin vs oral agents in patients withDM2:

Inhaled insulin TID with meals Oral agents

Plus oral agent(s) in 3 trials

(Note that only two trials of 16 [both in comparison with oral agents] concerned inhaled insulin alone.)

Inhaled insulin was administered with meals, and titrated to study-specific glucose goals.

Comparisons:

Inhaled insulin vs subcutaneous insulin:

Small difference in decrease in HbA_{1c} favored subcutaneous insulin. (Mean difference = 0. 08%)

No difference in proportion of patients achieving the goal of HbA_{1c} under 7%. (25% vs 27%)

Inhaled insulin vs oral agents:

Three studies showed a large difference in HbA_{1c} favoring inhaled insulin (mean difference = 1.45%)

Two studies showed only a small difference (0.20%) favoring inhaled insulin. These trials included more subjects, and were of longer duration.

Subjects with DM2 taking inhaled insulin were more likely to achieve HbA_{1c} under 7%. (31% vs 17%).

Safety:

A. Severe hypoglycemia:

Inhaled insulin vs subcutaneous:

No difference between the 2 groups reporting at least one episode of severe hypoglycemia:

Patients with DM1 patients in both groups experienced more episodes of severe hypoglycemia than patients with DM2:

	Inhaled	Injected
DM1	75%	78%
DM2	16%	18%

Severe hypoglycemia was more commonly reported in patients using inhaled insulin vs oral agents:

Inhaled 9% Oral 4%

B. Pulmonary safety:

All trials excluded patients with a history of recent smoking or underlying pulmonary disease.

All had normal chest X-ray and pulmonary function tests.

The most common pulmonary symptom was a nonproductive cough (17%). Cough occurred within seconds to minutes. It was mild and not associated with changes in pulmonary function. Cough diminished over time.

FEV1 decreased from baseline (mean reduction = 0.03 L). FEV1 decreased slowly over 6 months, but was stable thereafter.

A few discontinued inhaled insulin because of respiratory events.

C. Patient-reported outcomes:

All trials reported increased overall patient satisfaction with inhaled insulin. Areas of improvement included: ease of administration, comfort, convenience, mealtime flexibility, and ease of taking many times a day.

Two trials reported improvement in overall quality-of–life.

Patients randomized to inhaled insulin were more likely to continue taking it rather than switching back

to injected insulin.

DISCUSSION

1. “Inhaled insulin is comparable to subcutaneous regular insulin in lowering glycemia in adults with type 2 diabetes.”
2. Compared with oral agents, inhaled insulin yielded a greater reduction in glycemia than fixed doses of oral agents.
3. Inhaled insulin was associated with dry cough and a mild nonprogressive decrease in pulmonary function.
4. Inhaled insulin was preferred by patients over subcutaneous insulin.
5. There was no difference between the proportion of patients receiving inhaled insulin or subcutaneous insulin who achieved the HbA1c target less than 7%. (~ 25%). However, these proportions are much lower than those achieved with intensive subcutaneous insulin therapy in the Diabetes Control and Complications Trial.
6. “However, without having shown the superiority of inhaled insulin, it is important to avoid having patients replace their current subcutaneous insulin therapy with inhaled insulin and expect the same degree of glycemic control.”
7. The finding that inhaled insulin improves glycemia more than fixed doses of oral agents is consistent with previous observations that have reported a higher efficacy of insulin versus oral therapy in terms of achieving glycemic control.
8. Dose adjustments with available inhaled insulin devices have yet to be perfected for the finer, small-increment dosing needed to avoid hypoglycemia.
9. A major concern is the potential for pulmonary toxicity because of the immunogenic and growth-promoting properties of insulin, especially for long-term administration. Longer-term studies are required.
10. Smoking increases the rate of absorption and bioavailability of inhaled insulin. Changes in smoking habits rapidly alter the pharmacokinetics of inhaled insulin. “Patients who smoke may represent up to a quarter of the diabetes population in the United States.”
11. There are no data on the pharmacokinetics of inhaled insulin during lower respiratory infections. Because patients with diabetes are at greater risk for chronic lung conditions and acute respiratory infections, a better characterization of efficacy and safety is warranted in patients with pulmonary disease.
12. Patients are more satisfied with inhaled insulin and prefer it to subcutaneous insulin. Patients with poorly controlled DM2 were more likely to choose and accept inhaled insulin therapy if offered. This increases the potential for improving glycemic control in the diabetes population.

CONCLUSION

Inhaled insulin had slightly less efficacy in glycemic control than subcutaneous regular insulin. Patient-acceptance was increased. “Until long-term safety data are available, inhaled insulin should be reserved for nonpregnant adults with diabetes who are opposed to injections and who would otherwise delay appropriate and timely therapy with insulin.”

Annals Int Med November 7, 2005; 145: 665-75 Review article, first author Lisa Ceglia, Tufts-New England Medical Center, Boston Mass.

Supported by the National Institutes of Health

1 *Exubera* (Pfizer; recombinant DNA origin)

Data from the Exubera web site accessed through GOOGLE:

Inhaled insulin should be administered immediately before meals.

All patients with type 1 diabetes should also receive longer acting insulin by injection.

For patients with type 2 diabetes, inhaled insulin may be used alone, or combined with oral agents or long-acting insulin.

All patients should have pulmonary function assessed prior to initiating therapy. Function should be monitored periodically thereafter.

Blisters come in two sizes which allow individualization of dosage: 3-mg equivalent to 8 IU of subcutaneous regular human insulin 1 mg equivalent to 3 IU regular human insulin.

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Continued Treatment For An Additional 5 Years Increased BMD

12-7 EFFECTS OF CONTINUING, OR STOPPING, ALENDRONATE AFTER 5 YEARS OF TREATMENT The FLEX Trial

Alendronate (*Fosamax; Merck*) is a potent bisphosphonate which decreases bone turnover, increases bone mineral density (**BMD**), and decreases risk of fracture in women with osteoporosis. The optimum duration of treatment of women with postmenopausal osteoporosis is uncertain.

This study compared the effects of discontinuing alendronate after 5 years vs continuing for 10 years.

Conclusion: Continued treatment for an additional 5 years increased BMD, but did not decrease incidence of fractures.

STUDY

1. Randomized, double-blind trial entered 1099 postmenopausal women (mean age = 73). All had previously received alendronate for 5 years in the Fracture Intervention Trial (FIT).
2. Randomized to: 1) alendronate 5 mg daily; 2) 10 mg daily, or 3) placebo. Subjects also received a daily supplement of 500 mg calcium and 250 mg vitamin D.[1] (The study combined outcomes of 5 and 10 mg because there were small BMD differences noted between them.)
3. Primary outcome = total hip bone BMD. Secondary outcomes = BMD at other sites, and biochemical markers of bone remodeling.
4. Follow-up = 5 years.

RESULTS

1. Mean change in BMD after an additional 5 years:

	Placebo (%)	Combined 5 mg and 10 mg (%)

Total hip	-3.38	-1.02
Femoral neck	-1.48	+0.46
Trochanter	-3.25	-0.08
Lumbar spine	+1.52	+5.26
Total body	-0.27	+1.01

2. No statistical difference between 5 and 10 mg except for total body BMD.
3. Continuing alendronate for an additional 5 years maintained. or increased BMD after a first 5-years of therapy. BMD gradually decreased in the placebo group.
4. Bone turnover markers (type 1 collagen, and bone-specific alkaline phosphatase) decreased in the placebo group; remained close to baseline in the alendronate groups.
5. After 5 years, cumulative risk of non-vertebral fractures did not differ between groups. (19% vs 18.9%)
6. Those who continued alendronate had a statistically significant lower risk of clinically recognized vertebral fractures (2.4% for alendronate vs 5.3% for placebo).
7. No significant reduction in morphometric (determined by X-ray screening) vertebral fractures (9.8% vs 11.3%).
8. No differences in height loss between groups.
9. Safety: No significant differences between groups for serious adverse events, including upper g.i. events.

DISCUSSION

1. Bisphosphonates remain in bone for many years. The terminal half-life of alendronate is similar to that of bone mineral—about 10 years.
2. When bone containing a bisphosphonate is resorbed, some of the drug recirculates locally and binds again to bone surfaces. The drug continues to inhibit bone resorption long after active treatment stops, although to a lesser extent than with continued treatment.
3. Women who continued to take alendronate for an additional 5 years (during mean ages 73 and 78) maintained higher BMD than subjects assigned to placebo.
4. Some residual beneficial effects of alendronate were noted in the placebo group after the additional 5-years.
5. The decline in BMD following discontinuation of alendronate was much lower than that seen after discontinuation of estrogen, raloxifene, or intermittent parathyroid hormone therapy. Discontinuation of these agents is associated with immediate and substantial decreases in BMD.
6. “The decreased risk of clinical vertebral fracture in those continuing alendronate, suggests that continuing treatment for 10 years does not have adverse effects on bone strength. “
7. The absolute benefit of continuing alendronate was larger in women with existing vertebral fractures, and for those with low baseline BMD.

CONCLUSION

Compared with 5 years of therapy, continuation of alendronate (either 5 or 10 mg daily) for a total of 10 years maintained BMD and reduced bone remodeling.

The risk of clinically evident vertebral fractures was lower in those who continued alendronate.

JAMA December 27, 2006; 296: 2927-38 Original investigation by the Fracture Long-term Extension Intervention Trial (FLEX), first author Dennis M Black, University of California, San Francisco.

1 An inadequate dose

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Associated With An Increase In Hip Fracture.

12-8 LONG-TERM PROTON PUMP INHIBITOR THERAPY AND RISK OF HIP FRACTURE.

The advent of potent acid suppressors such as proton pump inhibitors (**PPIs**) has revolutionized the treatment of acid-related diseases such as gastroesophageal reflux disease. Millions of people are taking PPIs continuously, and long –term.

PPI use leads to hypochlorhydria particularly among elderly people who may have decreased PPI clearance. Hypochlorhydria could lead to calcium malabsorption, low bone mineral density, and increased risk of fracture.

Calcium absorption decreases with age and urinary excretion increases with age. This causes a negative calcium balance in late adulthood. Any additional calcium deficit due to stomach acid suppression would increase risk.

This study determined the association between long-term PPI therapy and risk of hip fracture.

Conclusion: PPI therapy was associated with increased risk of hip fracture.

STUDY

1. Case-control study based on the General Practice Research Database of the UK (1987-2003). The study compared users of PPI and non-users, all over age 50. (Mean baseline age = 77.)
2. Cases—patients with incident hip fracture (n = 13 556).
   Controls—matched to cases (n = 135 000).
3. Compared PPI use in cases vs controls. Main outcome = risk of hip fracture associated with PPI use.

RESULTS

1. The adjusted odds ratio for hip fracture associated with more than 1 year of PPI use was 1.4.
2. The strength of the association rose with increasing duration of PPI use:

PPI use	1 year	2 years	3 years	4 years
Odds ratio	1.2	1.4	1.5	1.6 (Adjusted for some possible confounders)

3. The risk of hip fracture was markedly increased among long-term users of high-dose PPI as compared with non-users of acid-suppression. (Odds ratio = 2.7)
4. The positive association between PPI use and hip fracture was stronger in men than in women. (Odds ratio = 1.8 vs 1.4)

DISCUSSION

1. "We found a significantly increased risk of hip fracture associated with long-term PPI therapy, particularly among long-term users of high-dose PPI."
2. Gastric acid may be important for absorption of insoluble calcium. Calcium malabsorption secondary to acid suppression therapy may potentially explain the association. An acidic environment in the stomach facilitates the release of ionized calcium from insoluble calcium salts. Both gastrectomy and pernicious anemia (which are associated with more profound levels of acid suppression than PPI therapy) are associated with increased risk of osteopenia and fracture.[1]
3. Acid suppression related to regular-dose PPI or histamine blockers is likely more modest than with high-dose PPI.
4. "We were unable to fully determine whether receiving calcium supplementation influenced the primary association because we did not have information on over-the-counter calcium supplement use."
5. The authors suggest that increased calcium intake should be advised in long-term PPI users, preferably from a dairy source. Insoluble calcium supplements should be taken with meals.

CONCLUSION

Long-term PPI therapy, particularly at high doses, was associated with an increase in hip fracture.

JAMA December 27, 2006; 296: 2947-53 Original investigation, first author Yu-Xiao Yang, University of Pennsylvania School of Medicine, Philadelphia, PA

1 Now add bariatric surgery

The higher risk in men is interesting, No explanation by the authors.

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"Might Be Associated With Exaggerated Liver Injury In Some Individuals."

12-9 PARACETAMOL (ACETAMINOPHEN; *TYLENOL*); *Are Therapeutic Doses Entirely Safe?*

Acetaminophen (eg, *Tylenol*) is thought to be safe in recommended doses (up to 4 grams daily in adults).

It is available over-the-counter, and is currently the most widely used analgesia and antipyretic drug worldwide.

It is hepatotoxic and nephrotoxic at doses greater than 4 g a day. It has become the important cause of acute liver failure. The most severe cases may require liver transplant. Mortality may be high.

In recent years, unintended overdoses, rather than those that are intentional, have been the main cause of acetaminophen-induced acute liver failure in the USA. The dose leading to liver failure may be as low as 7 grams a day. Nevertheless, the FDA Office of Drug Safety has concluded that no change is needed in how the drug is sold.

A recent study[1] was designed to determine why abnormal liver function tests were observed during studies of clinical development of a new combination of an opioid (hydrocodone) and acetaminophen. Participants were

randomly assigned to placebo, acetaminophen-alone 4 g a day, or a combination of 4 g acetaminophen with one of three opioids. Duration of observation = 14 days. Although trough acetaminophen concentrations did not exceed therapeutic limits in any group, up to 44% of participants in the acetaminophen groups (including those given acetaminophen alone) had concentrations of alanine aminotransferase (ALT) more than three times the upper limit of normal (suggesting liver injury). No participant given placebo had an increase to this level. In 27% of participants ALT levels were increased to more than 8 times normal. The investigators concluded that the acetaminophen content was associated with ALT elevations. Concomitant administration of opioids did not seem to increase ALT levels.

Three other studies lend support to the idea that therapeutic doses of acetaminophen might be associated with liver injury in some patients. For patients with severe acute viral hepatitis, recent ingestion of therapeutic doses of acetaminophen was associated with higher aminotransferase levels and greater prolongation of prothrombin times compared with patients who did not receive acetaminophen.

In a preliminary study from France, 52% of patients with biochemical and clinical evidence of acute liver disease while on antituberculosis drugs had a history of recent acetaminophen ingestion.

For patients who present with acute liver injury, with markedly elevated serum aminotransferase, and who have a history of recent acetaminophen ingestion, physicians should consider acetaminophen hepatotoxicity as a cause and consider treatment with acetylcysteine.

For patients on long-term acetaminophen therapy who develop signs of liver toxicity, acetaminophen should be considered a possible cause.

"Use of acetaminophen might be associated with exaggerated liver injury in some individuals." We should be aware that administration of acetaminophen in doses that are thought traditionally to be safe might lead to raised transaminases, suggesting some degree of liver injury. Awareness of possible toxicity is particularly important for people who are likely to be at high risk for hepatotoxicity—those dependent on alcohol, chronic users of acetaminophen, the severely malnourished, smokers, and those with acute liver disease.[3]

"However, these findings should not be taken out of context because unnecessary anxiety may encourage patients to switch to potentially more toxic alternatives."

Lancet December 23/30, 2006; 368: 2195-96 Commentary, first author Rajiv Jalan, University College London, UK

1 "Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily" JAMA 2006; 296: 87-93 Watkins PB et al.

2 Acetaminophen is converted by the cytochrome P450 system in the liver to a metabolite that is detoxified by glutathione (a sulfhydryl [–SH] -containing molecule). Acetaminophen does not cause hepatotoxicity until the glutathione content of the liver is depleted. Factors which increase the activity of the P450 system increase toxicity of acetaminophen. N-acetylcysteine (*Mucomyst*) supplies –SH to replenish hepatic glutathione. This does not explain why usual doses of acetaminophen cause toxicity.

3 The prevalence of non-alcoholic steatosis and steatohepatitis is increasing along with the epidemic of obesity. Are these patients more susceptible to toxic effects of acetaminophen?

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