



Answers to your questions
from our medical experts

1. Are estrogen patches safe?

? Is there any evidence that estrogen patches are safer than conjugated estrogen tablets?

Submitted by:
Gisele Viens, MD
St. Claude, Manitoba

The amount of estrogen that enters the blood stream from estrogen-containing products (pills, patches, vaginal creams and rings) can have varying effects depending on the specific product and how it is used.

Most of the safety data on the long-term health effects of estrogen comes from large studies involving estrogen and progestin oral tablets. A small head-to-head study found that oral estrogen pills increased heart disease risk factors, while transdermal estrogen patches (which avoid the first hepatic pass) did not.¹ This was linked to the finding that only oral estrogen increased the level of C-reactive protein, which is associated with higher risks of heart disease.

Until there are incontrovertible data that show otherwise, postmenopausal women who take any type of estrogen or progestin should be similarly counselled about health risks associated with hormone therapy.

Resources

1. Vongpatanasin W, Tuncel M, Wang Z, et al: Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women. *J Am Coll Cardiol* 2003; 41(8):1358-63.

Answered by:
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This month's topics:

1. Are estrogen patches safe?
2. Switch or augment an antidepressant?
3. Pregnancy and *candida*-positive urine cultures
4. LBD & PDD co-existence
5. Metformin vs. TZD
6. Prophylactic bisphosphonate and long-term steroid therapy
7. Can men be tested for HPV?
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10. Cholesterol-lowering agents and children

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2. Switch or augment an antidepressant?



For resistant depression, is switching to a different antidepressant vs. augmenting or combining with another antidepressant recommended?

Submitted by:
M. Cheng, MD
Ottawa, Ontario

Standards of practice suggest that when faced with a major depression, an antidepressant will be prescribed to the patient. Its dose will be gradually increased until it reaches the recommended therapeutic dose. If no improvement is obtained after an appropriate interval of time (usually four weeks), the dose will be increased to the maximum allowed dose, provided it is reasonably tolerated by the patient. If there is still no improvement, then one of the following two approaches should be considered:

- If the patient reports no improvement on the highest possible dose of the antidepressant, that particular antidepressant should be stopped. The physician should switch to a completely different antidepressant and repeat the whole process.
- If the patient reports some modest improvement on the highest recommended dose of the antidepressant, the physician will keep that antidepressant and augment it (or combine it) with another antidepressant or with a mood stabilizer, such as lithium or olanzapine, which is also considered a mood stabilizer in addition to being an atypical antipsychotic.

Answered by:
Hany Bissada, MD, FRCPC
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Memorable Quote

“ To be able to enjoy one’s past life is to live twice. ”

Marial

3. Pregnancy and *Candida*-positive urine cultures



I have frequently come across urine cultures positive for *Candida albicans* in pregnant women. Complaints are of dyspnea. Is treatment warranted? If so, which drug should be used?

Submitted by:
M. Vijh, MD, BS, MB, CCFP
Toronto, Ontario

The presence of *Candida* in the urine is common and usually does not indicate renal tract infection. Simple contamination of specimens at the time of procurement accounts for most cases, therefore, the crucial first step is to obtain a repeat fresh urine sample to evaluate for persistent candiduria. Even when *Candida* is persistently present, asymptomatic bladder colonization is most likely and these patients generally do not require treatment. Persistent symptoms of cystitis or pyelonephritis and the presence of increased urinary leukocytes, however, suggest a true urinary infection. These patients should be considered for treatment. Usual treatments include fluconazole, flucytosine and amphotericin B (systemic or bladder irrigation). Although options are more limited during pregnancy, recent evidence suggests fluconazole, 200 mg, orally, once daily, for seven to 14 days, may be given safely during pregnancy. Patients with persistent candiduria should be evaluated for diabetes mellitus, renal insufficiency or genitourinary tract abnormalities.

Resources available—contact *The Canadian Journal of Diagnosis* at diagnosis@sta.ca.

Answered by:
Paul S. Gibson, MD
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Calgary, Alberta

4. LBD & PDD co-existence



Can the diagnosis of Lewy Body dementia co-exist with a Parkinson's disease/dementia diagnosis and what is the current suggested treatment for Lewy Body dementia?

Submitted by:
Y.H. Nashed, MD
 Kingston, Ontario

Resources

1. McKeith I, Del Ser T, Spano P, et al: Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. *Lancet* 2000; 356(9247):2031-6.
2. Wesnes KA, McKeith Ig, Ferrara R, et al: Effects of rivastigmine on cognitive function in dementia with Lewy bodies: A randomised placebo-controlled international study using the cognitive drug research computerised assessment system. *Dement Geriatr Cogn Disord* 2002; 13(3):183-92.

Answered by:
Peter McCracken, MD, FRCPC
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 University of Alberta
 Staff
 Glenrose Rehabilitation Hospital
 Edmonton, Alberta

Although Parkinson's disease (PD) can evolve into Lewy Body dementia (LBD), it must do so within one year. Dementia appears before motor symptoms in LBD, while in Parkinson's disease with dementia (PDD), the motor symptoms exist more than a year before the dementia symptoms. The pathologic findings in these two entities are virtually indistinguishable.

Diagnosing PDD:

- 1) Diagnosis of PD first
- 2) Diagnosis of dementia (after more than one year of motor symptoms)

Diagnosing LBD:

- 1) Identify core features (Table 1)
- 2) Look for supporting clinical evidence (Table 2)

Both conditions show deficits in attention, behaviour and executive function but differ in the spatial and temporal evolution of the disease. The best treatment for LBD is a cholinesterase inhibitor. The best trial featured the use of rivastigmine, or rivastigmine tartrate and enrolled in a multi-centred study of 120 patients with LBD. Improvements were seen in the group treated for attention, mood and behaviour. Some effects were shown to persist for 96 weeks.

Table 1

Core features

- Fluctuating cognition with pronounced variation in attention and alertness
- Recurrent and detailed visual hallucinations
- Spontaneous motor features of Parkinson's disease

One core feature indicates the possibility of Lewy Body dementia (LBD) and two core features indicate probable LBD.

Table 2

Supporting clinical features

- Repeated falls, syncope, transient loss of consciousness
- Systematized delusions and hallucinations
- Neuroleptic sensitivity

5. Metformin vs. TZD

? Between metformin and the thiazolidinediones (TZDs), what is the best initial treatment for Type 2 diabetes?

Submitted by:
Noel Rosen, MD
Toronto, Ontario

Both agents can be used as the initial treatment for Type 2 diabetes and each will have pros and cons. Your choice must be individualized for each patient.

The recent Canadian Diabetes Association 2003 Clinical Practice Guidelines has a useful algorithm:

- For patients with mild to moderate hypoglycemia with a hemoglobin A1c of < 9% and a body mass index (BMI) ≤ 25, metformin is the medication suggested first. Patients

Your treatment choice must be individualized for each patient.

with a BMI < 25 can be started with metformin, a thiazolidinedione, insulin secretagogue, insulin or acarbose. Patients with marked hyperglycemia with a hemoglobin A1c > 9.0% can be started with two oral agents from different classes or insulin would be indicated.

Answered by:
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Staff Teacher
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Staff
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6. Prophylactic bisphosphonate and long-term steroid therapy

? Is there a role for prophylactic bisphosphonate use in patients on long-term steroid therapy?

Submitted by:
M.I. Ravalia, MD
 Twillingate, Newfoundland

Yes. Any of the currently available bisphosphonate medications can be used. With steroid therapy (prednisone or dexamethasone) and no proven fracture, the product normally used is etidronate disodium calcium carbonate. Alendronate and risedronate can also be prescribed. Concurrent steroid therapy of 7.5 mg or more (prednisone or its equivalent of dexamethasone) or more definitely places the patient at an increased risk of osteoporosis. Doses of 2.5 mg or less of prednisone are less hazardous, although regular bone densitometry should be considered to gauge bone status, and additional bisphosphonate therapy may not be advantageous. A steroid prescription of four weeks or more would be regarded as long-term therapy and age and gender should be taken into account with prophylaxis.

Two studies in particular support the use of prophylactic bisphosphonates:

- Adachi *et al.*, found it was reasonable to conclude that etidronate therapy had a protective effect with respect to the fracture rate in corticosteroid-treated, postmenopausal women.¹
- Cohen *et al.*, in a later study showed that bone loss in patients beginning long-term corticosteroid treatment can be significantly reduced, and possibly prevented, with concomitant risedronate therapy.²

References

1. Adachi JD, Bensen WG, Brown J, et al: Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997; 337(6):382-7.
2. Cohen S, Levy RM, Keller M, et al: Risedronate therapy prevents corticosteroid-induced bone loss: A twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 1999; 42(11):2309-18.

Answered by:
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 Calgary, Alberta

7. Can men be tested for HPV?



Is there human papillomavirus (HPV) testing available for men?

Submitted by:
Kinga Koprowicz, MD, CCFP
 Kirkfield, Ontario

The answer is yes, but no.

Three types of viral tests exist:

1. Digene's Hybrid Capture® 2 is not accredited for use in men, but is frequently used in research. There are nononcogenic and oncogenic cocktails. Outside of evaluative or prevention research, Digene's Hybrid Capture 2 has no place in the clinical field.
2. Roche has a polymerase chain reaction (PCR) for single genotype testing and for a cocktail of genotypes. Again, it is used in men in research settings, but has not been evaluated for clinical use in men.
3. There are the consensus PCR probes or home-brew PCR. This is a genotype by genotype assay that is very useful in research, but not in the clinic. It is very time-consuming since it is not done by machine.

Human papillomavirus (HPV) testing should be used for triage in women with atypical squamous cells of undetermined significance. Its place in primary screening is being debated, as more trials are underway; results of the Canadian cervical cancer screening trial are expected in the coming year. Testing men for HPV has no role at this moment in a regular clinical setting since it has not been validated. A false positive may yield more problems than no test at all.

Answered by:
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8 • What's the biochemical basis of free/total PSA?

? What is the biochemical basis of free/total PSA?

Submitted by:
M. deRoode, MD
 Burks Falls, Ontario

Small amounts of enzymatically active, prostate-specific antigen (PSA) leaks into the serum (more so when cancer is present). Upon reaching the serum, its proteolytic activity is neutralized by alpha-1-antichymotrypsin (ACT) or a-2-macroglobulin. We are only able to measure the PSA that is bound to ACT using anti-PSA antibodies. This complexed component is the major portion of PSA in serum, while a small amount is in a non-complexed form (free or fPSA).

Free to total serum PSA ratio (%fPSA) is higher in men with benign prostatic hyperplasia (BPH) than in men with prostate cancer. The molecular basis for the differences in PSA binding to ACT between BPH and cancer is unclear. By using a %fPSA cutoff of 25%, the specificity of PSA screening improves. In the PSA range of 4 µg/L to 10 µg/L, approximately 20% of biopsies can be avoided, while keeping the sensitivity to detect cancer at 95%. In younger men, this may be important, since PSA cutoffs are being lowered to 2.5 µg/L in many centres and lead to better detection of cancer, but also more unnecessary biopsies.

Personally, I use %fPSA to help decide if a repeat biopsy is warranted. Patients in whom %fPSA levels are worrisome (below 15%) should be re-biopsied or at least followed closely when biopsies are negative, since they are at higher risk of having cancer on repeat biopsy. Several other PSA variation markers are being investigated, including complexed PSA, human glandular kallikrein, Pro-PSA and baseline PSA. The bottom line is to find ways to improve on the specificity of PSA, which remains an excellent tool in prostate cancer detection. This will allow us to reduce the rate of unnecessary biopsies while allowing us to focus on patients at higher risk.

Answered by:
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 Director of Urologic Oncology
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9. Testing and treating WNV

? What testing do you recommend for mildly symptomatic patients (e.g., with a mild headache, fatigue and no fever) concerned that they may have contracted West Nile virus? Is there any specific treatment available?

Submitted by:
Bill Taylor
 Moncton, New Brunswick

Further testing to confirm the suspected diagnosis of West Nile virus (WNV) infection would include clinical signs of meningeal inflammation, which this individual does not demonstrate. The clinical signs include: nuchal rigidity, Kernig's or Brudzinski's sign, photophobia or phonophobia.

Other evidence of acute infection include one or more of the following: fever $> 38\text{ C}$ or $< 35\text{ C}$, cerebrospinal fluid pleocytosis 5×10^6 leukocytes per l and a white blood cell count $> 10 \times 10^9/L$.

Serologic testing should include serum or cerebrospinal fluid for immunoglobulin M antibody to WNV. The polymerase chain reaction is also being utilized.

In terms of treatment, some antiviral therapies have potential but, to date, ribavirin has not shown any reduction in disease or viremia.

Neutralizing antibodies in animal models has shown some benefit and studies utilizing immunoglobulin therapy are being conducted.

Answered by:
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10. Cholesterol-lowering agents and children

The Canadian Journal of Diagnosis and Dr. Dean would like to include additional information to the answer provided in the August 2005 issue. Please see shaded text below.

? What is the youngest age at which cholesterol-lowering agents can be safely used?

Submitted by:
A.S. Guron, MD, BS
 Stephenville, Newfoundland


Bile acid resins have been used for many years in children older than age 10 with familial hypercholesterolemia. It is difficult for children to use the granules and there is a risk of choking on the large cholestyramine tablets. Colestipol tablets are more palatable for this age group. The effect is a reduction in low-density lipoprotein (LDL) of 10% to 20%.

There have been five published clinical trials of statin therapy since 1996 (simvastatin, pravastatin, lovastatin and atorvastatin) in children older than age 10, but none are approved yet for use in this age group in Canada. Lowering cholesterol levels in childhood has not been shown to reduce coronary artery disease (CAD) in adult life. In fact, many children with hypercholesterolemia do not meet the criteria for treatment in adulthood.

It is important to be aware of the guidelines for screening only selected children at risk using non-fasting total cholesterol levels and to measure fasting lipids when the total cholesterol is > 5.2 mmol/L. It is imperative to work with a nutritional expert when working with children to maximize lifestyle intervention when LDL > 3.4 mmol/L. The guidelines for drug therapy when LDL > 4.9 mmol/L are based on a family history of hypercholesterolemia or LDL > 4.1 mmol/L with a family history of CAD before age 55. These levels are very different than the levels recommended for adults with risk factors, such as diabetes. See www.aap.org for guidelines.

Recommended reading

1. Belay B, Belamarich P, Racine AD: Pediatric Precursors of Adult Atherosclerosis. *Pediatr Rev* 2004; 25(1):4-14.
2. McCrindle B: Lipid abnormalities in Children with Metabolic Syndrome. *Can J Diabetes* 2004; 28(3):226-37.
3. American Academy of Pediatrics. Committee on Nutrition. Cholesterol in Childhood. *Pediatrics* 1998; 101:141-7.
4. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Type 2 diabetes in Children and Adolescents. *Can J Diabetes* 2003; 27:S91-93.

Atorvastatin is the only statin drug approved by Health Canada for use in males and postmenarchal females aged 10 to 17 years with heterozygous familial hypercholesterolemia. 

Answered by:
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