1. Long-term Isotretinoin

Can you take Isotretinoin on a long-term basis in low doses?

Submitted by: **David J. Mathies, MD,** Huntsville, Ontario

Use of Isotretinoin on a long-term basis, in low doses to treat acne vulgaris would be an off-label use, as it is not approved in this dosing regimen. However, anecdotally there are dermatologists who have used the drug off-label in patients who relapse quickly after traditional intermittent courses of Isotretinoin. Usually this is restricted to men.

There is a precedent for using Isotretinoin long term, as it has been used prophylactically to prevent skin cancer in immunosuppressed patients, such as solid organ transplant patients. It has also been used in hereditary diseases such as basal cell nevus syndrome, congenital ichthyoses, Darier's disease and in acquired disorders of keratinization such as pityriasis rubra pilaris. Again, these would all be off-label uses of this drug and should be used only by a dermatologist experienced with its use. Major concerns of long-term usage include teratogenicity (thus, Isotretinoin would not be considered for long-term use in women of child bearing potential), ocular toxicity (including decreased night vision) and skeletal abnormalities.

Answered by: **Dr. Richard Haber**

2. Isolated Low Ferritin

Please advise on the appropriate therapy of isolated low ferritin.

Submitted by: **K. Abel, MD,** Leduc, Alberta

Clinically, a patient with isolated low ferritin without anemia is said to have an iron depleted state, rather than iron deficiency anemia. This typically precedes the appearance of microcytosis and the eventual development of anemia. The management, or therapy in this situation is similar to iron deficiency anemia. Hence, it is still essential to determine the underlying cause of low iron stores, just as in iron deficiency anemia, and to replace these stores with iron supplementation. Oral iron supplementation is the preferred initial route. However, we would advise clinicians to be cautious with iron replacement in older patients with hemoglobin in the high to normal range, as replacement may unmask an underlying polycythemia rubra vera.

Answered by: **Dr. Cyrus Hsia and Dr. Leonard Minuk**

3. Management of Hypertensive Crisis

A patient of mine presents with BP 300/130 (*i.e.*, hypertensive crisis) in my office. What advice can you give on management? He was not on any medication before this.

Submitted by: John McSorley, MD, Airdrie, Alberta

This is a very high blood pressure. If the patient is asymptomatic, this constitutes a hypertensive urgency (*i.e.*, asymptomatic diastolic BP $\geq$ 130 mmHg). If the patient has hypertensive encephalopathy (cerebral edema), retinal hemorrhages/exudates or papilledema, acute coronary syndrome, heart failure, aortic dissection or acute renal failure, this is a hypertensive emergency and the patient needs to be transported to the emergency department for immediate evaluation and treatment with parenteral drugs (*i.e.*, nitroprusside, labetalol).

Assuming this is hypertensive urgency, I would recommend the following:

- Repeat BP after resting in a quiet, darkened room.
- Obtain ECG, electrolytes, creatinine and urinalysis.
- Start antihypertensive therapy with a long acting calcium channel blocker (*e.g.*, nifedipine XL 30 mg q.d. or amlodipine 5 mg q.d.)
- Have the patient monitor their BP at home and call you with the results in one to two days. They should be seen again within one week to assess response to therapy.
- With such a high BP, it is important to ask about precipitating factors such as excessive dietary salt intake, NSAID use or other drugs such as anabolic steroids, cocaine, amphetamines, sympathomimetics and decongestants or supplements such as ephedra and ma haung. Secondary causes of hypertension such as renal artery stenosis should be considered if there is a 30% or more increase in serum creatinine with ACE inhibitor or ARB therapy.

As a final caution, it is important not to lower the BP too quickly, to avoid precipitating myocardial or cerebral ischemia. The initial goal is a BP of less than 160/100 mmHg over several days of therapy.

Answered by: Dr. Bibiana Cujec

4. Migraines and Oral Contraceptives

Which migraneur can be safely kept on OCP?

Submitted by: Lynn Crosby, MD, Halifax, Nova Scotia

The use of combined oral contraceptives is contraindicated in migraines with aura, and combined oral contraceptives should be stopped in patients suffering from migraine without aura, if they develop the symptoms of aura. However, the newest combined oral contraceptives may be well tolerated by patients with migraine without aura; such patients generally do not have an exacerbation of headaches. The international classification of headache disorders clearly describes two types of headaches which are evidently related to the use of combined oral contraceptives; these are exogenous hormone-induced headache and estrogen-withdrawal headache.

Answered by: Dr. Abdul Qayyum Rana

5. Mandatory Referral to Dermatology

Do you think routine referral to dermatology should be mandatory for all patients older than 65 years-of-age?

Submitted by: E.G. Nurse, MD

This would not be a cost effective use of dermatology services and should not be mandatory. Referrals to a dermatologist should be guided by the nature of the dermatologic problem, and are appropriate if the primary care physician is uncertain about or unable to make a diagnosis, or is uncomfortable with or inexperienced in using specific drugs for treatment.

Routine full body skin examinations should be part of a full physical examination done by a primary care physician. Patients at high risk of skin malignancies, especially those with a family history of melanoma, multiple dysplastic nevi and previous melanoma or non-melanoma skin cancers are best followed by a dermatologist, but there is no specific age-related criteria for referring these patients.

Answered by: Dr. Richard Haber

6. Investigation of Endometriosis

What is the initial step to investigate endometriosis? When do you decide to treat it? Which type do you consider critical in young females?

Submitted by: H. Ayad, MD, Pinawa, Manitoba

The initial investigation to endometriosis is a good history and pelvic exam. The primary presentation is usually pelvic pain, though endometriosis may present as infertility or a pelvic mass. The patient usually complains of dysmenorrhea that lasts beyond 48 hours (primary dysmenorrhea) and dysparunia. During pelvic exam cervical motion tenderness, scarring and/or a pelvic mass may be noted. The primary goal in treatment of endometriosis is for control of symptoms, usually through dietary changes (*e.g.*, macrobiotic diet, restriction of dairy products) and medical therapy. The first-line treatment consists of non-steroidal anti-inflammatory drugs, combined hormonal contraceptives (cyclical or continuous), the progestin intrauterine system or depo-medroxyprogesterone acetate. Second line therapies are danazol, gonadotropin-releasing hormone agonists (with or without add-back) or aromatase inhibitors. Surgery is reserved for the management of a mass, obstruction (bowel or ureters), or infertility due to endometriosis. There are no "critical" forms of endometriosis for any age group, as the severity of the symptoms rarely relate to the extent of the disease. Symptom relief is the aim, and there are none that ensure amelioration of the pathology, especially once the therapy is discontinued.

Resource:
1. ACOG Committee Opinion. No. 310. Endometriosis in Adolescents. Obstet Gynecol 2005;105(4):921-7.

Answered by: Dr. Victoria Davis

7. Continuation of First-line Antibiotics

With regards to antibiotic resistance, should we immediately switch once newer and more potent antibiotics are available, or should we continue using first line antibiotics until they become useless?

Submitted by: Roland Fuca, MD, Ottawa, Ontario

The answer to this question is based upon local epidemiology. Clearly, if a first-line agent continues to be effective against the pathogens which are being encountered in a specific region, the prescriber should continue using these first-line agents. The level of antimicrobial resistance in the community for any given pathogen may not be known, and frequently specimens for culture may not be taken given the nature of the condition (*e.g.*, cellulitis, otitis media). The reality of clinical medicine is that therapy is often started empirically, prior to the availability of a culture report, and thus if therapeutic failures are being observed in one's practice, switching the type of antibiotic based upon local epidemiology is clearly warranted. It may be prudent to continue to use more established agents which continue to be effective, as they are often more economical than the newest therapies. Ultimately, the decision to switch to a newer or different antimicrobial agent should be based upon observed clinical response.

Answered by: Dr. John Embil

8. Von Hippel-Lindau Disease

What is the psychiatric condition to watch out for in von Hippel-Lindau disease?

Submitted by: Des Griffin, MD, Surrey, British Columbia

Von Hippel-Lindau disease (VHL) is a rare, genetic, multi-system disorder characterized by the abnormal growth of tumours in certain parts of the body (angiomatosis). The tumours of the central nervous system (CNS) are benign and are comprised of a nest of blood vessels called hemangioblastomas (or, angiomas in the eye). Hemangioblastomas may develop in the brain, the retina of the eyes, and other areas of the nervous system. Other types of tumours develop in the adrenal glands, the kidneys or the pancreas. Symptoms of VHL vary among patients and depend on the size and location of the tumours. Symptoms may include headaches, problems with balance and walking, dizziness, weakness of the limbs, vision problems and high blood pressure.

There is no psychiatric condition specific to VHL. Depending on the size and the location of the hemangioblastoma in the brain, any psychiatric presentation is possible; patients essentially present with physical symptoms such as headaches, vision problems, dizziness and problems with balance and walking.

Answered by: Dr. Hany Bissada

9. Gamma-globulin Levels

What level of gamma-globulin do we accept without treatment?

Submitted by: Claude Roberge, MD, Sherbrooke, Quebec

Quantitative immunoglobulin levels are helpful in various clinical settings. However, when levels are below (hypogammaglobulinemia) or above (hypergammaglobulinemia) reference ranges, further clinical assessments should be made. In hypogammaglobulinemia, the overall clinical setting, not the specific immunoglobulin level, typically determines the need for therapy. For example, patients with chronic lymphocytic leukemia (CLL), with severe recurrent bacterial infections associated with hypogammaglobulinemia require therapy with intravenous immunoglobulins (IVIG). Various types of congenital causes of hypogammaglobulinemia require their own therapies with IVIG. Further, judicious and early use of antibiotics is required in the appropriate clinical settings.

For hypergammaglobulinemia, it is essential to determine if the gammopathy is monoclonal or polyclonal. In monoclonal gammopathy, the differential includes monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, primary amyloidosis, Waldenstrom's macroglobulinemia and other lymphoproliferative disorders. The differential of polyclonal gammopathy also includes a heterogeneous group of disorders including liver disease, connective tissue disease, infections and both hematologic and solid malignancies. All of these have different management and therapeutic strategies.

Answered by: Dr. Cyrus Hsia and Dr. Leonard Minuk

10. Diagnosis of Clinical Hypothyroidism

How to diagnose clinical hypothyroidism?

Submitted by: Daniel Solonyna, MD, Pointe-Claire, Quebec

The diagnosis of hypothyroidism is made from a clinical history and examination consistent with hypothyroidism, as well as laboratory confirmation. Typical symptoms may include tiredness, weight gain, depression, constipation, dry skin and brittle nails, to name a few. Many patients may have only a few symptoms, or may be relatively asymptomatic. Additional exam findings include bradycardia or delayed reflexes. Upon palpation, the thyroid gland may be small, normal, diffusely enlarged or nodular. Laboratory screening for most individuals should consist of a TSH level; an elevated TSH level is consistent with hypothyroidism. Central hypothyroidism is less common, and other signs of pituitary or central CNS findings will likely be present. A free T4 and a free T3 may also be utilized with the TSH to help make the diagnosis.

Answered by: Dr. Vincent Woo

11. ASA and Warfarin

Is low dose acetylsalicylic acid (ASA) of value for patients taking warfarin?

Submitted by: Alan Payilanis, MD, Montreal, Quebec

Low-dose acetylsalicylic acid (ASA 81 mg daily), in combination with warfarin, is recommended in patients with mechanical valve prostheses, and patients with bioprostheses who are at higher risk of thromboembolic events, because of LV dysfunction, prior embolic events or atrial fibrillation. The combination of ASA and warfarin has added benefit in decreasing the risk of thromboembolic events in these high risk patients.

The most common indication for warfarin is non-valvular atrial fibrillation. Warfarin is beneficial in secondary prevention following myocardial infarction (WARIS II study),[1] and it is not necessary to combine ASA with warfarin in all patients with atrial fibrillation and coronary artery disease. There is a small added benefit of ASA when combined with warfarin in preventing vascular events in patients with coronary artery disease, however this comes at the cost of increased bleeding complications. If a patient has recently had acute coronary syndrome with stent deployment and also has had, or currently has atrial fibrillation, they need to be on ASA and clopidogrel to prevent stent thrombosis, as well as continuing on warfarin. ASA does not provide adequate protection against stroke in patients with atrial fibrillation who have a CHADS score of two or more (*i.e.*, patients with heart failure, diabetes, hypertension, prior systemic embolism or those aged 75 years or greater). Clopidogrel should be discontinued after one month in patients with bare metal stents, and after one year if a drug eluting stent was deployed. The risk of bleeding is significantly increased with dual antiplatelet and warfarin therapy, and clopidogrel should be discontinued as soon as possible.

Reference:
1. Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, Aspirin, or Both After Myocardial Infarction. N Engl J Med 2002;347(13):969-74.

Answered by: Dr. Bibiana Cujec

12. Inhaled Corticosteroids for Asthma

Which inhaled corticosteroids and their relative potencies are used to treat asthma?

Submitted by: K. Davis, MD, Ottawa, Ontario

Inhaled corticosteroids (ICS) are the cornerstone, anti-inflammatory, chronic maintenance asthma medications. They have been shown to improve asthma symptoms, health-related quality of life and lung function, and reduce airway inflammation and asthma exacerbations. Various forms of patient-actuated delivery systems of ICS are available in Canada, including pressurized metered dose inhalers (MDI) and dry-powder inhalers (DPI). Different ICS, trade names, dose equivalencies in adults and delivery systems are illustrated in the table below:[1]

Table 1:
Types of Inhaled Corticosteroids

ICS	Trade Name	Dose (mcg)	Device Type
Beclomethasone dipropionate HFA	QVAR	200	MDI
Budesonide	Pulmicort	400	DPI
Ciclesonide	Alvesco	200	MDI
Fluticasone propionate	Flovent	250	MDI, DPI

Reference:
1. Lougheed MD, Lemiere C, Dell SD, et al. Canadian Thoracic Society Asthma Management Continuum – 2010 Consensus Summary for Children Six Years of Age and Older, and Adults. Can Respir J 2010; 17(1):15-24.

Answered by: Dr. Paul Hernandez

13. Prophylactic Treatments for Alzheimer's

What are your suggestions regarding prophylactic treatments for Alzheimer's disease (*i.e.*, folic acid)?

Submitted by: Mark Goodbaum, MD, Thornhill, Ontario

Folic acid is not a prophylactic treatment for Alzheimer's disease, per se. However, if serum homocysteine level is higher than normal, then it should be treated with folic acid, as high homocysteine is a vascular risk factor. Folate levels are also checked, in addition to serum B12 level, as part of work up for dementia. Serum folate level can be increased or normal in B12 deficiency. Decreased serum folate is not evidence of tissue deficiency; RBC folate is for this reason checked. Decreased RBC folate is seen in both folate and B12 deficiency.

Answered by: Dr. Abdul Qayyum Rana

14. Subclinical Hyperthyroidism

What do we do if we have a patient with a TSH < 0.10 but normal Free T4 & Free T3, without symptoms or signs?

Submitted by: Catherine Jean, MD, Montreal, Quebec

This is referred to as subclinical hyperthyroidism. The etiologies are the same as overt hyperthyroidism. Epidemiological studies have shown that in high-risk patients (*e.g.*, the elderly, those with pre-existing cardiovascular disease and post-menopausal women), there is a higher risk of atrial fibrillation, osteoporosis and death with this condition. However, what we do not know is if we reduce the risk of developing these complications, if we treat this condition. Thus, treatment is controversial. Most would recommend treating subclinical hyperthyroidism condition if it is persistent, a definite etiology is found, TSH is undetectable, and the patients are high risk, as mentioned above. Treatment modalities are similar to overt hyperthyroidism.

Answered by: Dr. Ally Prebtani

15. Topical Acne Therapy

Could you comment on choices of topical acne therapy and why?

Submitted by: John Quinn, MD, Kingston, Ontario

Canadian Consensus Guidelines from 2000 on the treatment of acne vulgaris, suggested an algorithm assessing acne, based on whether scarring was present or absent. Presence of scarring was an indication for systemic therapy. In the absence of scarring, and with milder degrees of inflammatory (papules and pustules) and non-inflammatory (comedones) acne, topical therapy is an appropriate choice. The principal agents used to treat acne topically in Canada are retinoids (*e.g.*, tretinoin, adapalene, tazarotene), benzoyl peroxide and topical antibiotics. Topical retinoids should be used in all topical acne treatment regimens, because of their comedolytic effect (they treat the primary lesion of acne, the microcomedone), but in addition, they do have anti-inflammatory effects and therefore are useful for inflammatory acne as well. Frequently they are combined with a topical antibiotic such as clindamycin or erythromycin, or with benzoyl peroxide, agents which are most useful for inflammatory acne lesions.

Patients must be advised to apply the topical agents all over the face, not just to the "affected" areas, in order to have a prophylactic effect on the acne. Topical tretinoin should be applied at night as it is not photostable. However adapalene or tazarotene are photostable and can be used morning or night.

Topical antibiotics can be quite effective in controlling inflammatory acne, but the major concern with long term use is the development of *P. acnes* resistance. Using them in conjunction with benzoyl peroxide can prevent the development of this resistance. In Canada, there are combination products containing clindamycin or erythromycin and 5% benzoyl peroxide which are very useful topical agents.

The major side effects of benzoyl peroxide, when used in appropriate concentrations (usually 5% or more) are skin irritation and bleaching of coloured fabrics.

A common topical regimen would be use of topical tretinoin at night and a combination clindamycin/benzoyl peroxide agent in the morning. Patients must be informed that it can take six to eight weeks to see a good anti-inflammatory effect, and even longer (three months) to see a good comedolytic effect.

Answered by: Dr. Richard Haber

16. Drug Holiday from Bisphosphonates

If a drug holiday from bisphosphonates is chosen, how long should it be? Should this holiday happen after five years or 10?

Submitted by: David Hoayan, MD, Scarborough, Ontario

There is currently no consensus on how long to continue bisphosphonate (BP) therapy. However, for some women, stopping therapy after five years may be reasonable, as there appears to be a residual benefit on BMD and fractures for up to five years, as was illustrated in the Fracture Intervention Trial Long-term Extension (FLEX). This study included postmenopausal women who had previously received alendronate for five years in the Fracture Intervention Trial (FIT).

At the completion of FIT, women were randomly assigned to an additional five years of either alendronate or placebo. Women at highest risk for fracture were excluded from FLEX (those with FLEX baseline T-scores either below -3.5, or below their FIT baseline). In women who were switched to placebo after five years of alendronate, there was a gradual decline in BMD, but mean BMD remained at or higher than levels recorded 10 years earlier. There was also no significant difference in the rate of vertebral fracture compared to those who remained on alendronate throughout.

This data provides evidence that stopping bisphosphonate therapy after five years (with careful BMD and risk factor assessment follow-up) may be reasonable for some women, provided they are not in the highest risk category for fractures. If a drug holiday is chosen, then careful follow up for these women is necessary (*i.e.*, regular BMD and risk factor assessment). If the risk category increases, BP therapy should be reinstituted.

Resource:
1. Black DM, Schwartz AV, Ensrud KE, et al. Effects of Continuing or Stopping Alendronate After 5 Years of Treatment: the Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial. JAMA 2006;296(24):2927-38.

Answered by: Dr. Michael Starr

In women who were switched to placebo after five years of alendronate, there was a gradual decline in BMD, but mean BMD remained at or higher than levels recorded 10 years earlier.

17. CRP and the Prescription of Statins

Should C-reactive protein (CRP) play a routine role (in addition to Framingham criteria) in the prescription of statins for dyslipidemia?

Submitted by: F. C. McGrath, MD, Delta, British Columbia

Highly selective C-reactive protein (hsCRP) is an acute phase protein produced by hepatocytes that is an independent risk factor for coronary artery disease (CAD) and vascular events. Recently, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study showed that aggressive lowering of cholesterol (decrease of 50%) and CRP (decrease of 37%) with rosuvastatin 20 mg q.d., in men > 50-years-old and women > 60-years-old without diabetes or known CAD and with LDL < 3.4 mmol/L and hsCRP > 2.0 mg/L, resulted in about a 40% reduction in myocardial infarction, stroke and death over a two year period. The patients in this primary prevention study achieved the lowest levels of LDL cholesterol of any similar study and, for the first time, a survival benefit with statin therapy was seen in patients without known CAD.

Testing for highly selective CRP is not routinely available in Canadian laboratories. Cost varies from $15 to $60 per assay. CRP is more easily tested and used as a marker of infection, but is not sensitive enough at the lower range of values that still indicate cardiovascular risk (*i.e.*, < 3-5 mg/L). hsCRP testing should be performed similarly to a fasting lipid profile, under basal conditions at least one to two months after any type of illness or trauma. A value > 10mg/L should prompt a search for infection or inflammation. Highly selective CRP is most useful for defining cardiovascular risk in patients without known CAD or diabetes who are in the intermediate risk range (10 to 20% 10-year risk of a cardiac event) as calculated by the Framingham score. The Reynolds Risk score in women uses hsCRP and family history of CAD in those less than 60 years-of-age to better define the 10-year risk of vascular events in women who fall in the 10 to 20%, 10-year risk category. With the addition of these two risk factors, about 40% of women in the intermediate risk category can be re-classified into low risk or high risk. Obviously, patients with longstanding diabetes or known CAD should be treated to achieve an LDL cholesterol of < 2.0 mmol/L, regardless of the level of hsCRP.

Highly selective CRP should not be used as a target for therapy, but rather to further define risk and desirable LDL levels in patients without known CAD, who fall in the intermediate risk category. In other words, an LDL cholesterol of < 3.5 mmol/L, although a reasonable target in patients who are at intermediate risk of cardiac events, is too high if the hsCRP level is > 2.0 mg/L.

Resources

1. Ridker PM, Danielson E, Fonseca FAH et al for the JUPITER Study Group. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-reactive Protein. N Engl J Med 2008;359(21): 2195-2207.
2. Ridker PM, Buring JE, Rifai N, Cook NR. Development and Validation of Improved Algorithms for the Assessment of Global Cardiovascular Risk in Women: The Reynolds Risk Score. JAMA 2007;297(6):611-9.

Answered by: Dr. Bibiana Cujec

18. Antidepressant Use in the Elderly

What is the best choice of antidepressant medication in the elderly?

Submitted by: Ted Osman, MD, Mount Brydges, Ontario

Elderly patients benefit from the same psychopharmacological agents as younger patients. However, the clinician must be aware that aging and medical conditions associated with aging have an impact on pharmacokinetics, and increase the sensitivity to adverse effects even at low plasma concentrations of antidepressant drugs. Changes in hepatic metabolism prolong the clearance of most drugs in older people, increasing the likelihood that the parent drugs and their active metabolites will accumulate and cause toxicity. Older patients are more likely than younger patients to develop delirium, constipation, urinary retention, dry mouth and orthostatic hypotension. For this reason, the dosages of antidepressant medication should be increased at a slower pace in older patients than in younger adults.

The SSRIs have fewer cardiac adverse effects than tricyclic antidepressant agents and are often used as drugs of first choice, especially in patients with mild, nonmelancholic depression or in patients with cardiac disease. Drug interactions should be considered in elderly patients receiving SSRIs. Fluoxetine and paroxetine inhibit the cytochrome P450 (CYP) 2D6 liver cytochrome isoenzyme, while sertraline, citalopram and escitalopram are much weaker inhibitors of the 2D6 isoenzyme.

The serotonin and norepinephrine reuptake inhibitor venlafaxine XR (Effexor XR) was found effective in hospitalized depressed patients as well as in drug-resistant depressed patients. Venlafaxine XR has limited drug-drug interactions and may be selected in elderly patients taking drugs interacting with other antidepressant drugs, who require treatment. Daily dosages of 112.5 to 225 mg are adequate for the majority of elderly patients. Blood pressure should be monitored, especially in patients receiving dosages above 225 mg q.d., since venlafaxine XR can increase blood pressure. Dx

Answered by: Dr. Hany Bissada