Experts on Call

Answers to your questions from our medical experts

1. COX-2 agents and arthritis options

Regarding COX-2 agents, what arthritis options exist?

Submitted by: Glynis M. Koponen, MD, Brampton, Ontario

COX-2 selective inhibitors, as opposed to NSAIDs, were initially developed to avoid the undesirable GI side-effects of NSAIDs. However, controversies surrounding the cardiovascular (CV) side-effects of these agents led to the withdrawal of rofecoxib from the market a couple of years ago and valdecoxib was removed due to serious skin reactions. Until recently, celecoxib has remained on the market as the only agent in this class. In fact, all NSAIDs are now thought to possibly increase CV toxicity and therefore, should be used at the lowest possible doses and avoided in high-risk cardiac patients. Current recommendations suggest using COX-2 agents only for those at significant risk of GI toxicity from NSAIDs.

Regarding the specific question of other options in this class, lumiracoxib was recently approved in Canada at a dose of 100 mg q.d. for osteoarthritis. This was based on the results of the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET). This large study showed a significant decrease in upper GI complications vs. comparator NSAIDs ibuprofen and naproxen, with no increase in serious CV events. Etoricoxib is another agent currently under review but not yet approved in Canada.

For resources, please contact diagnosis@sta.ca

Answered by: Dr. Michael Starr

2. Obesity-causing malignancy

Apart from endometrial carcinoma, is there any other malignancy which is directly associated with obesity?

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

Obesity has been associated with an increased risk of several cancers including:

- Endometrial
- Colorectal
- Breast
- Esophageal

Women with a BMI > 40 have a 60% higher risk of dying from all cancers than women of normal weight. While biologically plausible, epidemiologic data alone is unable to establish a causative relationship between obesity and cancer. However, the association does seem robust given the findings from multiple observational studies. In the US, it is suggested that obesity may account for 14% of cancer deaths in men and 20% of cancer deaths in women.

Reference

1. Calle EE, Rodriguez C, Walker-Thurmond K, et al: Overweight, obesity and mortality from cancer in a prospectively studies cohort of US adults. N Engl J Med 2003; 348(17):1625-38.

Answered by: Dr. Sharlene Gill

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3. Dealing with GAD

What are the best strategies for dealing with a patient who has GAD?

Submitted by: Dominic Eustace, MD, Saskatoon, Saskatchewan

Generalized anxiety disorder (GAD) is a chronic anxiety disorder characterized by persistent, excessive and difficult to control free-floating anxiety, usually associated with psychic and somatic symptoms that may include:

- irritability,
- fatigue,
- poor concentration,
- muscle tension and
- sleep disturbances.

Cognitive behavioural therapy (CBT) is the first-line of treatment for GAD and produces good results, comparable to therapy with antidepressant medications. Either individual or group CBT is effective; however, this psychological therapy is expensive and not always available, particularly in small towns and in under-serviced communities.

In terms of pharmacological treatment, there is good evidence in the literature to support the use of selective-serotonin reuptake inhibitors (SSRIs) as first-line agents, including the following at their respective recommended doses:

- escitalopram,
- sertraline and
- paroxetine.

There is also strong evidence to support the use of a selective-norepinephrine reuptake inhibitor (SNRI), such as venlafaxine extended release, as a first-line agent in GAD.

If the above first-line agents fail to produce relief after a sufficient trial (with an adequate dosage for an adequate time, up to six weeks), then a switch to a second-line agent may be recommended. Buspirone, bupropion and finally imipramine are worth trying as second-line agents for GAD.

Benzodiazepines are recommended only for short-term use in GAD because of their side-effects, including:

- sedation and
- potential for dependence and
- withdrawal issues.

After an initial rapid relief of anxiety, the anti-anxiety effect of the benzodiazepine will progressively diminish over time and can become comparable to placebo after four to six weeks of continuous treatment.

CBT is the first-line of treatment for GAD and produces good results comparable to therapy with antidepressant medications.

Finally, if all of the above fail, atypical antipsychotics, such as olanzapine and risperidone may be added as adjunctive third-line agents for patients who are refractory to adequate trials with first-line and second-line agents. Atypical antipsychotics cause weight gain and other metabolic side-effects.

Answered by: Dr. Hany Bissada

4. *H. pylori* and halitosis

Does *H. pylori* play a role in a patient who has halitosis?

Submitted by: Adam Kayumi, MD, Mississauga, Ontario

Halitosis is common, with 10% to 50% of the population having persistent symptoms. There are a wide variety of causes for halitosis. Poor oral hygiene is the most common. The role of *Helicobacter pylori* (*H. pylori*) in halitosis is unclear. However, there are several small studies which have shown that *H. pylori* is associated with halitosis. One small study has shown that the eradication of *H. pylori* was associated with improvement of halitosis.

Resource
1. Ierardi E, Amoruso A, La Notte T, et al: Halitosis and *Helicobacter pylori*: A possible relationship. Dig Dis Sci 1998; 43(12):2733-7.

Answered by: Dr. Robert Bailey; and Dr. Justin Cheung

5. Risk of prostate cancer with testosterone therapy

Regarding testosterone replacement therapy in men, what is the risk of prostate cancer?

Submitted by: Sameh Hassan, MD, Toronto, Ontario

It has been found that prostate volume and PSA levels increase with testosterone treatment. With testosterone therapy, some older men may experience an exacerbation of benign prostatic hyperplasia (BPH) presenting as urinary outflow abnormalities.

Prostate cancer is related to testosterone levels. Theoretically, a higher dose of testosterone, when given pharmacologically, will increase the risk compared to a lower testosterone level. However, there are no long-term studies looking at the incidence of prostate cancer with testosterone therapy. Therefore, it is recommended to screen men for prostate cancer before and during treatment with testosterone.

A digital rectal examination and measurement of serum PSA should be performed three months after the start of treatment and then yearly. The patient should be referred for a prostate biopsy if any nodules or other abnormalities are detected (*i.e.*, an elevation in the PSA). The testosterone therapy should be discontinued and re-evaluated once the abnormalities have been resolved.

Answered by: Dr. Vincent Woo

6. Mango allergy

Please discuss mango allergy

Submitted by: Michael Keating, MD, Saint John, New Brunswick

Mango is the second most frequently cultivated tropical fruit worldwide. Mango, together with pistachio and cashew, belongs to the *Anacardiaceae* family. All three foods may cause severe anaphylactic reactions. However, immediate oral symptoms are most frequently seen after the ingestion of mango fruits (known as the Oral Allergy syndrome). The incidence of mango fruit allergy is apparently high in subjects with "celery-mugwort-spice syndrome," as well as in those with a latex allergy. Two major mango allergens with 30 kDa and 40 kDa and a 46 kDa-allergen (putative chitinase) have been identified. Cross-relativities have been described between mango fruit allergens and mugwort pollen (a weed), birch pollen, celery, carrot and apple. Latex and avocado allergens also cross-react with mango allergens.

Mango allergens can be quite stable during technical processing, resulting in preservation of allergenicity and thus, increasing the potential for systemic reactions in allergic individuals.

On a side note, the observation that acute allergic contact dermatitis can arise on first exposure to mango in patients who have been sensitized beforehand by contact with poison ivy and other urushiol-containing plants has also been documented, suggesting a cross-reactivity between these allergens.

Answered by: Dr. Tom Gerstner

7. Role of CA125 in ovarian cancer screening

What is the role of CA125 in ovarian cancer screening?

Submitted by: K. Narang, MD, Calgary, Alberta

Single measurements of cancer antigen-125 (CA125) lack sufficient sensitivity and specificity to be recommended as a screening test for ovarian cancer. The positive predictive value of annual CA125 testing is estimated to be < 3%. Therefore, unless new evidence emerges supporting its use, CA125 is not recommended for ovarian cancer screening at the present time.

Answered by: Dr. Sharlene Gill

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8. Testing for an allergy to antibiotics

What is the best way to test for an allergy to antibiotics? How reliable is it?

Submitted by: Gregory Hammond, MD, Winnipeg, Manitoba

The most important aspect of an assessment for antibiotic allergy is the history. A detailed history of all the symptoms and their time course is most helpful in identifying the likelihood of an IgE-mediated allergy, or a delayed immune mechanism. Beyond that, intradermal skin testing is available for penicillins and other β-lactams, although they are only standardized to the major and minor components (*i.e.*, relevant allergenic metabolites) of penicillin.

These tests are predictive only for an IgE-mediated reaction to the penicillins and not other immune mechanisms (*e.g.*, immune complex, T-cell mediated) which may occur in the setting of Stevens Johnson Syndrome, urticarial vasculitis, or serum sickness, for example. In the setting of any prior reaction, the predictive value of intradermal skin testing to penicillins for an IgE-dependent reaction is between 50% and 80%. Negative test results indicate a reduced risk of subsequent reactions to < 2%.

Answered by: Dr. Tom Gerstner

9. Dealing with intermittent episodes of bronchospasm

A middle-aged person suffers from intermittent episodes of bronchospasm triggered by exercise, colds and exposure to potential aeroallergens. These episodes resolve promptly with inhaled bronchodilators and occasionally inhaled corticosteroids. Should this patient receive regular medication?

Submitted by: David Grunbaum, MD, Montreal, Quebec

It is possible that the patient described will benefit from regular medication. However, there is a need to establish a clinical diagnosis first. Although the symptoms are suggestive of asthma, other possibilities exist including:

- chronic obstructive pulmonary disease,
- recurrent bronchitis and even
- congestive heart failure.

A thorough history and physical examination, focusing on the cardiac and respiratory systems, followed by specific objective tests to help confirm any clinical suspicions that arise, should be undertaken. Only then can appropriate therapies be determined for this individual.

Answered by: Dr. Paul Hernandez

10. Abdominal pain in a West African immigrant

Please provide a clear plan for an immigrant from West Africa who has unremittent abdominal pain.

Submitted by: Albert Prossin, MD, Verdun, Quebec

Unremittent or chronic abdominal pain can be a challenging problem encountered by primary care physicians, gastroenterologists and surgeons. Many varied disorders can produce chronic abdominal pain. The workup requires, as always, a complete and careful clinical history and physical examination in addition to diagnostic testing.

Common structural or organic diseases include:

- peptic ulcer disease,
- gallstones,
- chronic pancreatitis,
- abdominal neoplasms,
- inflammatory bowel diseases,
- mesenteric ischemia,
- pelvic inflammatory diseases,
- endometriosis,
- abdominal adhesions and
- intestinal obstruction.

It is important to note that functional abdominal pain syndromes are also common causes of chronic abdominal pain in Africa. These include:

- irritable bowel syndrome,
- functional (non-ulcer) dyspepsia and
- functional abdominal pain syndrome.

Diseases that are more common in patients emigrating from Africa that may present with abdominal pain are:

- schistosomiasis,
- leishmaniasis,
- TB and
- HIV.

Investigations of the following are a good start to ruling out these conditions:

- bloodwork,
- abdominal ultrasound or CT scan and
- stool for culture ova and parasites.

If no cause for the chronic abdominal pain is found with these initial investigations, the possibility of functional abdominal pain needs to be considered. Refer the patient to a gastroenterologist, who may wish to further investigate with upper and lower endoscopy. As well, they also have experience in dealing with functional abdominal pain.

Resource

1. Feldman M: *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. Eighth Edition. W. B. Saunders, An Imprint of Elsevier, St. Louis, 2006.

Answered by:
Dr. Robert Bailey; and Dr. Matt Butler

If no cause for the chronic abdominal pain is found with initial investigations, the possibility of functional abdominal pain needs to be considered.

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11. Antifungals for schizophrenia?

Have you ever heard of using antifungals in the treatment of schizophrenia?

Submitted by: Cara Wilson-Haffenden, MD, North Vancouver, British Columbia

There is no place for antifungals in the treatment of schizophrenia.

Answered by: Dr. Hany Bissada

12. Total testosterone

Is there a specific cut off value for total testosterone? Is there a specific time of day for testing; should levels be checked during treatment and is there a level that we want to reach or just resolve the symptoms?

Submitted by: John E. Dawson, MD, Ottawa, Ontario

Gonadal function diminishes as part of normal aging. In men, this process is not universal and when it occurs it is usually subtle in its clinical manifestations. Clinical diagnosis of andropause is problematic because neither a low serum testosterone nor symptoms are truly diagnostic of the condition. However, the presence of symptoms is a *sine qua non* for diagnosis and should be coupled with a low or borderline-low objective biochemical measure of testosterone status.

Testosterone values decline while sex hormone-binding globulin (SHBG) levels increase with aging. In young men, about 60% of circulating testosterone is bound to SHBG, 38% is bound to albumin and 1% to 2% is free. The testosterone that is free and bound to albumin is considered to be capable of entering tissues and responsible for the actions of testosterone. SHBG-bound testosterone is inaccessible to tissues and not active. The active component (free plus albumin bound) is called bioavailable or bioeffective testosterone (BT). Epidemiologic studies suggest that BT correlates better with symptoms associated with testosterone deficiency than total testosterone. There is a substantial circadian rhythm with higher values being obtained in the morning (between 8 a.m and 11 a.m.) mainly in young men. In addition, in both young and old persons, there is substantial variability (> 20%) from week to week. Thus, two samples obtained a week or two apart, ideally in the morning, would seem to be a minimal criterion.

Testosterone replacement therapy should maintain physiological levels of serum testosterone and one should never aim to increase testosterone levels to supraphysiologic levels. Monitoring should include evaluating clinical response and measuring BT, complete blood count, liver function tests, lipid profile and PSA at three, six, 12 and 18 months and then each six months.

Answered by: Dr. Hugues Widmer; and Dr. François Bénard

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13. Efficacy of glucosamine in patients with osteoarthritis

What is the efficacy of glucosamine in patients presenting with osteoarthritis? Are there any contraindications or special monitoring to do for patients taking this medication?

Submitted by: Louise Frenette, MD, Sherbrooke, Quebec

Physicians are often at a loss as how to advise their patients on the use of neutriceuticals. The evidence is often anecdotal or biased and even if a product has shown promise in clinical trials, there is little quality control to assure that your patient is purchasing an equivalent product.

The use of glucosamine sulfate for the treatment of osteoarthritis (OA) falls into this category. In the 1990s, two small studies out of the Prague Institute demonstrated analgesic and disease-modifying (preservation of joint space) properties of glucosamine and chondroitin. The Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), a large randomized trial sponsored by the National Institutes of Health, was designed to address the analgesic properties of this product. This study involved 1,583 knee OA patients, randomized to one of four arms:

- 500 mg of glucosamine hydrochloride t.i.d.
- 400 mg of sodium chondroitin sulfate t.i.d.
- A combination of glucosamine hydrochloride and sodium chondroitin sulfate
- 200 mg of celecoxib q.d.

The primary endpoint was a 20% improvement in pain, measured on the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain scale, at week 24. In the overall results, celecoxib was statistically superior to placebo ($p = 0.008$), but the differences between the other groups and placebo did not reach statistical significance.

The authors concluded that there was no evidence of efficacy for glucosamine and/or chondroitin compared with placebo, although in the predetermined subgroup of patients with moderate-to-severe pain, there was a statistically significant effect of the combination of supplements vs. placebo (79.2% vs. 54.3% of patients, $p = 0.002$).

Many patients and their physicians are wary of using NSAIDs. Glucosamine and chondroitin have had a very positive side-effect profile in the aforementioned studies and no specific monitoring is required. However, patients taking coumadin should be warned of potential complications. One small study showed an increase in the international normalized ratio of patients combining glucosamine and coumadin.

In most patients, it would not be unreasonable to recommend a short term trial of glucosamine and chondroitin, but they should be informed of the limits of the current clinical data.

Answered by:
Dr. Michael Starr; and Dr. Elizabeth Hazel

14. Taking bisphosphonates

How long can a patient take a bisphosphonate?

Submitted by: Gayle Garber, MD, Conception Bay South, Newfoundland

Bisphosphonates have become the standard therapy for the prevention and treatment of osteoporosis, with excellent efficacy data for fracture prevention. Longer-term data of continuous use, over five to 10 years, is now available and efficacy appears to be sustained without evidence of significant long-term safety concerns. In fact, bone biopsy data in long-term users shows that there is maintenance of bone quality over time. Therefore, bisphosphonates appear to be safe and effective for long-term use.

The decision to stop therapy would need to be made on a patient-to-patient basis, taking into account the changes in bone mineral density scores and individual patient risk factors over time.

Answered by: Dr. Michael Starr

15. Difference between ACE inhibitors?

Is there a difference between angiotensin-converting enzyme (ACE) inhibitors?

Submitted by: Tim Brandys, MD, Ottawa, Ontario

With regards to difference in effect: not really! However, there are differences in relative tissue binding and pharmodynamic properties.

Although only one ACE inhibitor, enalapril, has been studied in mortality trials in chronic heart failure, multiple ACE inhibitors have been proven to be more or less equally effective when administered in oral form within a few days of an acute coronary syndrome in post-MI trials. ACE inhibitors have a proven track record in preventing heart failure in two settings:

- enalapril in asymptomatic left ventricular (LV) dysfunction and
- ramipril and perindopril in the cardiovascular at-risk patient without LV dysfunction.

These observations support the conclusion that the effects of ACE inhibition are class effects. It is important to note that doses should preferably be titrated to target doses (*e.g.*, target doses for ramipril, perindopril and enalapril are 10 mg q.d., 8 mg q.d. and 10 mg b.i.d., respectively).

Answered by: Dr. Igal A. Sebag

16. Testosterone therapy contraindications

Why is testosterone therapy contraindicated in a patient diagnosed with sleep apnea?

Submitted by: P. L. Tham, MD, London, Ontario

Exacerbation of sleep apnea may occur during testosterone supplementation therapy. Proper assessment and treatment of the sleep apnea are indicated during testosterone supplementation. Careful consideration should be given to the need for testosterone treatment if the sleep disturbances deteriorate.

Exacerbation of sleep apnea may occur during testosterone supplementation therapy.

Answered by:
Dr. Hugues Widmer

17. Prevalence of cancer

Is it true that the prevalence of cancer is higher overall in sedentary/overweight people, as compared to people who have active lifestyles or do regular aerobic exercise?

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

The association between obesity, physical activity and the incidence of cancer has been the subject of much epidemiologic study. This issue is particularly relevant given the current trends towards increasing obesity and sedentary lifestyle. Several mechanisms have been proposed to explain this possible association, including:

- hyperinsulinemia and insulin resistance,
- depressed immune function,
- altered prostaglandin levels and
- bile acid metabolism.

Several studies have demonstrated a decreased risk of cancer with increased physical activity, notably colon and breast cancer, with limited evidence favouring a benefit for prostate and endometrial cancer. While the optimal duration, intensity and frequency of physical activity is not well established, the evidence in colon cancer suggests that risk reduction is proportional to hours of activity per week and metabolic equivalent hours. In addition to smoking cessation and weight control, the American Cancer Society recommends 30 minutes of moderate-to-vigorous physical activity per day.

Answered by: Dr. Sharlene Gill

18. When not to use antidepressants in depression

When are antidepressants not indicated in depression?

Submitted by: **Paul Steinberg, MD,** Edmonton, Alberta

When the depressed mood is due to an adjustment disorder triggered by a psychosocial stressor, such as a job loss or a relationship break up, then psychological treatment, either individual or group therapy using cognitive-behavioural therapy (CBT) or interpersonal therapy (IT), may be the first-line of treatment, before prescribing an antidepressant.

When the depressed mood is due to an adjustment disorder triggered by a psychosocial stressor, then psychological treatment may be the first-line of treatment.

Also, in psychotic depression, antidepressants should be prescribed only in combination with an antipsychotic medication, to address both the depressed mood and the psychotic symptoms (*e.g.*, mood congruent delusions). Prescribing antidepressants alone may aggravate the psychotic symptoms.

In depressed patients who are imminently suicidal, antidepressants should be prescribed only after the patient is hospitalized, otherwise, antidepressants prescribed to an imminently suicidal outpatient could provide the patient with the required energy to commit suicide before improving his/her mood.

In pregnancy and during breastfeeding, antidepressants should be prescribed very cautiously and only when the severity of the depressive symptomatolgy and/or the risk of suicide warrant the risk of prescribing an antidepressant during pregnancy. Most antidepressants have not been formally evaluated in pregnant women (due to obvious ethical considerations) and the information available is mostly based on animal studies and case histories of individual patients who took an antidepressant during their pregnancy. To date, sertraline and fluoxetine are considered relatively safe during pregnancy and breastfeeding. Paroxetine is contraindicated during pregnancy due to its potential to cause teratogenic malformations to the fetus. No information is yet available on the following regarding their use in pregnancy and during breastfeeding:

- citalopram,
- escitalopram,
- venlafaxine and
- bupropion. Dx

Answered by: **Dr. Hany Bissada**