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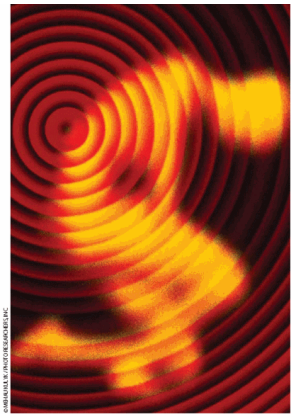
# Pain management in cancer patients



Most patients with advanced cancer, and up to 60% of patients with any stage of the disease, experience significant pain. The World Health Organization (WHO) estimates that 25% of all cancer patients die with unrelieved pain. Although pain can be relieved adequately in most cancer patients, it remains under-treated due to unfounded fears of opioid addiction, unavailability of analgesics from pharmacies, and cultural reasons; however, it is the responsibility of healthcare professionals to address these barriers. The management of cancer-related pain is an ethical responsibility of healthcare professionals to relieve unnecessary suffering, as part of the duty to care.

## Overview

The management of cancer- and treatment-related pain is not restricted to cancer patients with a poor prognosis. Significant pain adversely impacts function and affects all domains of quality of life. Tolerance to therapy is the most important determinant to the success of cancer therapy. Pain, which reduces the patient's performance status, reduces potential tolerance of cancer therapy and may cause patients to discontinue their cancer treatments. Recent studies have demonstrated that improved pain management results in improved survival. Based on this, clinical trials should account for pain levels in reporting survival outcomes.

The cause of cancer pain should be treated whenever possible. By doing so, rapid, lasting pain relief frequently can be achieved. Also, the need for pain medications may be diminished, thus reducing side effects and drug interactions.

The principles of cancer-related pain management are straightforward. Effective management of cancer-related pain can be accomplished by local healthcare providers, including oncologists and family physicians. More complex cancer pain syndromes may require the coordination of multidisciplinary professionals, including pain medicine specialists, palliative care and hospice care providers.

## Pathophysiology

Pathophysiologic classification of pain forms the basis for therapeutic choices. Cancer-related pain may be broadly divided into pain caused by ongoing tissue damage (nociceptive), or by nervous system dysfunction that is not associated with ongoing tissue damage (non-nociceptive or neuropathic). Often, cancer-related pain is the result of both nociceptive and neuropathic causes.

Damage to the nervous system may result in pain and loss of sensation and function. Such pain is typically described as burning or lancinating. Patients may report bizarre complaints, such as painful numbness, itching, or crawling sensations. The post amputation phenomenon of phantom pain (pain referred to the lost body part) may be disabling.

## Psychological Factors

Psychological factors, and comorbid psychiatric diagnoses such as depression, may be associated with, and even result from, chronic unrelieved pain. Depressed mood and anxiety often are a consequence of the physiological impact of pain, including lack of sleep and declining function and nutrition.

"Psychogenic pain" or somatoform pain disorder is extremely rare in cancer patients; psychogenic pain should be considered a diagnosis of exclusion. "Pseudo-addiction" is an iatrogenic *physiological* syndrome caused by the inadequate treatment of

## In this issue

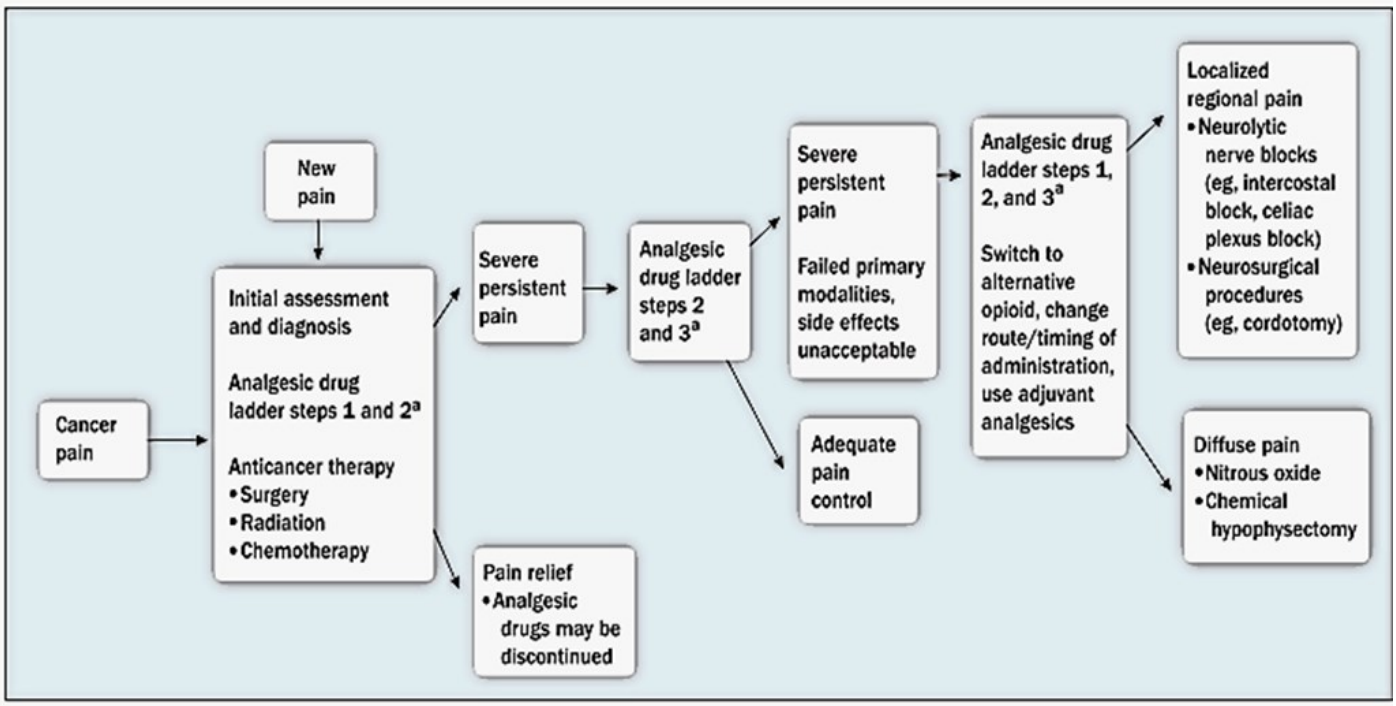



**FIGURE 1:** Algorithm for the integration of pharmacologic management approaches to cancer pain.
[a]Step 1 – Nonopioid ± adjuvant; Step 2 – Opioid + nonopioid ± adjuvant; Step 3 – Strong opioid ± nonopioid ± adjuvant
Adapted from Foley KM, Arbit E, in DeVita VT, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology, 3rd ed, vol 2, pp 2064–2087. Philadelphia, JB Lippincott, 1989.

pain resulting in behaviors similar to that of opioid *psychological* dependence (addiction). Pseudo-addiction immediately resolves with adequate treatment of pain.

## Pain syndromes

Cancer pain syndromes vary by tumor type and are related to patterns of tumor growth and metastasis. Pain may also be related to antineoplastic therapy. Many patients have pain caused by other comorbid nonmalignant conditions such as arthritis.

## Elements of management

Fig 1 shows an algorithm for integration of pharmacologic management approaches to cancer pain. First and foremost, elements of cancer pain management include adequate management of symptoms, to relieve suffering, while undertaking a diagnostic evaluation that determines the etiology of the pain. Once the cause of the pain is determined, specific interventions are selected to target the etiology to provide durable pain relief, and prevent potential cancer-related morbidity, like pathologic fracture and spinal cord compression.

Interventions to relieve cancer pain should be chosen according to (1), cause of pain (2), patient prognosis and performance status (3), prior therapies,and most importantly (4), patient preferences.

Ongoing care is needed to monitor the efficacy of the pain management plan relative to the evolution of other symptoms during treatment, or to later disease progression. Recurrent pain or new sites of pain often are the first indications of cancer progression.

The steps in medical decision-making are to:

• determine whether primary antineoplastic therapy (systemic therapy, radiotherapy, and surgery) is indicated.

• tailor pharmacologic analgesic therapy to individual needs (including analgesics, neural ablation and stimulation, neuraxial infusion).

• consider concurrent nonpharmacologic analgesic treatments such as physical therapy.

• monitor response and modify treatment accordingly (Figure 1).

The patient is the focus of care, although family members and others often participate in treatment decisions and require emotional support.

## Medical Evaluation

### Pain History

The medical evaluation should begin with a thor-

ough history including the location, severity, and characteristics of the patient's pain. Pain represents the most common presenting symptom in medicine, and may reflect an acute condition, for example, appendicitis or a chronic condition such as bone metastases. The physiologic signs of acute pain—elevated blood pressure and pulse rate—are unreliable in subacute or chronic pain. The chronic pain of cancer usually is progressive over several months. The patient diagnosed with cancer usually seeks medical attention when an acute exacerbation of pain occurs, or when chronic pain significantly impacts function or quality of life, such as interfering with sleep. Restriction in function and fatigue, therefore, represent different physiologic signs of chronic pain.

Most cancer patients report more than one site of pain. A detailed history of each type and site of pain should be elicited.

## Pain rating scales

Validated and reliable pain scales allow evaluation of response to analgesic therapy. There are standardized tools that can be used for patients who are unable to communicate, such as preverbal children and impaired adults. In non-communicative agitated patients, it is acceptable to treat pain presumptively.

## Physical examination

The assessment should evaluate the putative mechanisms that may underlie the pain. This includes careful neurologic testing, especially if neuropathic pain is suspected. A neuropathic process is likely when pain occurs in an area of reduced sensation, or when the patient is experiencing allodynia (i.e., when usually non-painful stimuli are reported as painful) or hyperpathia (summation of painful stimuli).

## Review of disease extent and current conditions

The extent of disease and current medical conditions must be understood. As with any sign or symptom of cancer, pain and neurologic debility must be carefully monitored.

## Diagnostic Tests

Diagnostics should be reviewed and supplemented as necessary. Any new site of pain or increase in pain severity should be diagnostically evaluated, as pain is often the most common sign of disease progression.

## Treatment and drug history

Cancer treatment and prior analgesic interventions, along with their outcomes, should be known. Psychological dependency on any drug, including alcohol, must be identified. However, psychological dependency on any drug should not impede adequate pain management; when necessary, pain management specialists should be consulted to assist in such cases.

## Psychosocial assessment

To establish trust, the clinician should explore with the patient the significance of the pain complaint in terms of function and quality of life. The impact of pain and other symptoms on functional status must be understood in order to establish treatment goals.

Suffering may also be attributable to many factors besides physical complaints of pain. The clinician should ask about such socioeconomic and personal factors as financial worries, loss of independence, family problems, social isolation, and fear of death. Often, cancer patients meet diagnostic criteria for the psychiatric diagnosis of adjustment disorder with anxiety and/or depressed mood.

## Subgrouping of patients

To help define therapeutic goals, the patient's performance status and prognosis may be considered. Pain in children is underreported and should be specifically elicited using age-appropriate assessment scales.

## Pharmacologic treatment

In the past, WHO devised a three-step analgesic ladder outlining the use of non-opioid analgesics, opioid analgesics, and adjuvant medications for progressively severe pain. According to this schema, a non-opioid analgesic, with or without an adjuvant agent, should be tried first (step 1). If pain persists or increases on this regimen, the patient should be switched to an opioid plus a non-opioid agent, with or without an adjuvant medication (step 2). If pain continues or intensifies despite this change in therapy, a more potent dose of opioid analgesic should be prescribed, with or without a non-opioid and/or an adjuvant agent (step 3). This WHO three-step analgesic ladder has been especially useful in breaking barriers that impeded the control of cancer-related pain worldwide.

However, it is now accepted practice that the level of pain should determine what level of analgesic

should be prescribed. It is now recognized that patients with severe cancer pain should initially receive opioid analgesics and not suffer through two inadequate analgesic courses before receiving relief with an appropriate type of administered analgesic. While concerns exist about opioid side effects, it is also important to recognize the significant potential side effects of nonsteroidal anti-inflammatory agents (NSAIDs).

## Non-opioid analgesics

Non-opioid analgesics, primarily NSAIDs, are associated with ceiling effects (maximum allowable dose), and exceeding the maximum dose ranges can result in severe organ toxicity. Potential side effects, such as hematologic, renal, and gastrointestinal reactions, may be of significant clinical concern in cancer patients (Table 1). Cyclooxygenase (COX)-2 inhibitors are many times more potent against COX-2 than COX-1. Clinicians are advised to watch the emerging literature regarding the safety of these agents. These concerns extend to non-opioid analgesics that are compounded with opioid analgesics; when possible, it is advisable to prescribe opioids alone without NSAIDs.

## Opioid analgesics

General guidelines for opioid therapy are outlined in Table 2.

***Dosage.*** Opioid agonists do not exhibit ceiling effects. Dosing is guided by efficacy. Most opioid side effects can be anticipated and controlled. Unlike opioids alone, the nonopioid component limits the dosages of tablets that combine an NSAID or acetaminophen and an opioid (Table 3).

***Routes of administration.*** The oral route should be used when possible, although some patients may express a preference for an alternative route. If the oral route is not feasible based on patient preference, physical difficulties, especially with swallowing, or side effects, alternative routes (e.g., transdermal, transmucosal, rectal, and spinal) are indicated. Such alternative routes of administration of certain opioid agonists may improve patients' quality of life and may be particularly useful for treating certain types of cancer pain.

***Side effects***. Side effects of opioids can usually be anticipated and prevented. In particular, with regular opioid dosing, laxatives should be prescribed for constipation.

**Table 1** Nonopioid analgesics and NSAIDs useful for treating cancer pain

| Generic name (usual dosage range) | Maximum dose/day | Adverse effects/ comments |
|---|---|---|
| Acetaminophen (325–975 mg q4–6h) | 4,000 mg | Hepatic and renal impairment |
| Acetylsalicylic acid (aspirin, ASA) (325–975 mg q4–6h) | 4,000 mg | Dyspepsia and GI ulceration, antiplatelet effect, bleeding |
| Celecoxib | 400 mg | See note[a] |
| Choline magnesium trisalicylate (500–1,500 mg q8–12h) | 4,500 mg | Dyspepsia, reduced antiplatelet effect, hypermagnesemia in renal failure |
| Choline salicylate (435–870 mg q3–4h) | 5,220 mg | Dyspepsia, reduced antiplatelet effect |
| Magnesium salicylate (300–600 mg q4h) | 4,800 mg | Same as choline salicylate |
| Salsalate (1,000–1,500 mg q8–2h) | 4,000 mg | Same as choline salicylate |
| Sodium salicylate (325–650 mg q3–4h) | 5,200 mg | Same as choline salicylate |
| Ibuprofen (200–800 mg q4–6h) | 2,400 mg | [b]Dermatitis + |
| Ketoprofen (25–75 mg q6–8h) | 300 mg | [b]Headache +++ |
| Ketorolac tromethamine (oral: 10 mg q4–6h; parenteral: 60 mg, then 15–30 mg q6h) | Oral: 40 mg Parenteral: 120 mg | [b]Limit duration of therapy; headache +++, GI bleeding [b]Limit therapy to 5 days; headache +++, GI bleeding |
| Meclofenamate sodium (50–100 mg q4–6h) | 400 mg | [b]Headache +, dermatitis + |
| Mefenamic acid (250 mg q6h) | 1,000 mg | [b]Limit therapy to 7 days |
| Naproxen sodium (220–550 mg q8–12h) | 1,375 mg | [b]Headache + |
| Naproxen (250–500 mg q8–12h) | 1,500 mg | [b]Headache + |

[a] Monitor emerging literature regarding safety concerns.

[b] Minor adverse reactions include dyspepsia, heartburn, nausea, vomiting, anorexia, diarrhea, constipation, flatulence, bloating, epigastric pain, abdominal pain, dizziness, and drowsiness. Major adverse reactions that may appear at any time include renal failure, hepatic dysfunction, bleeding, and gastric ulceration.

+ Each plus sign represents a 5% incidence of the reported adverse effect.

GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs

Adapted with permission from American Pain Society: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 5th ed. Skokie, Illinois, American Pain Society, 2003.

• *Physical dependence on and tolerance*-Physical dependence on and tolerance to some effects develop with chronic opioid use. Tolerance to respiratory depression, sedation, and nausea is likely. Nausea can occur with opioid-naive patients receiving initial analgesic doses, and it should be controlled with antiemetic therapy. Tolerance to analgesia is not a major clinical problem and can usually be managed by changing the dose or substituting another analgesic agent.

Most current definitions of addiction imply a behavioral syndrome. An important distinction is that addiction does not require physical dependence or tolerance. Tracked over several decades, aberrant drug-taking rarely occurs in patients without a history of substance abuse. Consistent with current guidelines, compliance should always be monitored when opioid analgesics are prescribed.

**Table 2 : Guidelines for the use of opioid analgesics**

| |
|---|
| Start with an analgesic with the potential to provide relief |
| Know the essential pharmacology of the analgesic: |
| Analgesic type |
| Pharmacokinetics |
| Influences of coadministered drugs, disease, or age on analgesic disposition and response |
| Equianalgesic starting dose for the drug and route to be used |
| Route of administration and a dosage form to fit the patient's needs |
| Individualize/titrate the dosage |
| Administer analgesics regularly after the initial dose titration |
| Provide for breakthrough pain |
| Use drug combinations that enhance analgesia |
| Recognize and treat side effects |
| Make conversions from one route to another or from one agent to another using known equianalgesic doses |
| Manage physical dependence (ie, prevent withdrawal) |

Adapted with permission from Inturrisi C: Cancer 63(suppl):2308-2320, 1989.

## Precautions during chronic therapy

During chronic opioid therapy, certain precautions should be observed:

• Meperidine is **contraindicated** in the treatment of cancer pain, as normeperidine, a toxic metabolite of meperidine, accumulates and can cause significant side effects like seizures.

• Propoxyphene is also **contraindicated** due to accumulation of norpropoxyphene (and this drug has come off of the market in the United States).

• Placebo use is **contraindicated** as the patient's report of pain should be accepted as would be any other medical symptom.

• Physical withdrawal symptoms can be avoided by tapering doses.

• A change in mental status **should not** be attributed to opioid therapy until medical and neurologic factors have been fully evaluated. Especially important is to exclude potential disease progression including brain metastases.

• The mixed agonist-antagonist and partial opioid agonist drugs are **not** recommended for cancer pain

• Methadone has unique pharmacokinetics and a pain medicine expert should be consulted before prescribing it.

## Adjuvant medications

Neuropathic pain may be less responsive to standard analgesics alone. Adjuvants, such as antidepressants, anticonvulsants, benzodiazepines, local anesthetics, neuroleptics, psychostimulants, antihistamines, corticosteroids, levodopa, calcitonin, and bisphosphonates, improve the effectiveness of standard analgesics and are useful for particular indications. These agents may be administered via oral and other routes. Administration of topical local anesthetics, NSAIDs and other preparations, and anesthetic and neurosurgical procedures (Tables 4,5) should also be considered. Referral to a pain specialist should be considered for refractory neuropathic pain.

**Table 3 Opioid-agonist analgesics for mild-to-moderate pain**

| Drug | Equianalgesic dose to 650 mg of aspirin[a] | Dose interval | Half-life (h) | Comments |
|---|---|---|---|---|
| Codeine | 32–65 mg | q4–6h | 2–3 | See notes[b, c] |
| Hydrocodone | — | q3–4h | 4 | See note[b] |
| Oxycodone | 2.5 mg | q3–6h | 2–3 | See note[b] |

[a] The equianalgesic dose should not be interpreted as the starting, standard, or maximum dose but rather as a guide for switching drugs or changing routes of administration.

[b] Doses of products containing aspirin, ibuprofen, or acetaminophen should be limited accordingly and monitored for safety.

[c] Doses above 65 mg provide diminished incremental analgesia with increasing doses, but side effects may worsen.

Adapted with permission from American Pain Society: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 3rd ed. Skokie, Illinois, American Pain Society, 1992.

## Bone metastases: paradigm for oncologic treatment of pain surgery for bone metastasis

Surgical intervention is warranted for bone metastases to stabilize a pathologic fracture or preempt an impending fracture. The objectives of surgery are to palliate pain, improve patient mobility and function, and control the disease in the bone to prevent further morbidity when nonsurgical therapies fail. In general, surgery involves excision of all gross tumor followed by stabiliza-

Table 4 : **Anesthetic/neurosurgical approaches for controlling cancer pain**

| Procedure | Usual indication(s) | Examples |
|---|---|---|
| Local anesthetic blocks with or without steroids | Diagnostic blocks<br>Prognostic blocks<br>Acute pain, muscle spasm<br>Premorbid chronic pain<br>Postsurgical syndromes<br>Herpes zoster | Trigger point injection<br>Intercostal block<br>Epidural steroids |
| Neurolytic/neuroablative blocks and ablative neurosurgery | Localized refractory pain that is expected to persist, usually in the presence of a short life expectancy; pain localized to a region that is associated with a low risk of neurologic complications | Alcohol celiac plexus block<br>Phenol intercostal block<br>Percutaneous cordotomy<br>Midline myelotomy |
| Spinal analgesics | Refractory pain, usually in the lower body but may be widespread or diffuse | Externalized epidural catheter<br>Intrathecal catheter with fully implanted pump |

tion of the bone before or after fracture by means of an internal fixation or prosthetic device. Restoring the anatomic integrity of the spinal cord by relieving bony compression (eg, due to vertebral collapse) is an absolute indication for surgery, with rare exception based on prognosis.

**Indications.** Clinical parameters, such as the patient's general medical condition, performance status, nature of the primary tumor, effectiveness of other therapies, extent of extra-skeletal disease, and degree of osseous involvement, as well as the patient's life expectancy, must be considered before surgery.

**Table 5** **Neurolytic procedures[a] that may be considered early in certain pain situations**

| Procedure | Indication |
|---|---|
| Celiac plexus neurolysis | Abdominal pain, back pain |
| Superior hypogastric plexus neurolysis | Pelvic pain |
| Phenol saddle block | Perineal pain with urinary diversion |
| Thoracic subarachnoid neurolysis | Focal chest wall pain |
| Intercostal neurolysis | Focal chest wall pain |
| Lumbar subarachnoid neurolysis | Unilateral leg pain |

[a] The risk-benefit ratio of these procedures in the specified settings is sufficiently favorable and well established to warrant early consideration.

• *Fracture and long bone pain*—In general, the presence of a pathologic fracture, an impending fracture, or a painful lesion in a long bone despite radiotherapy should be considered to be indications for surgery. A pathologic fracture can also result from structural insufficiency and can develop in the absence of a viable tumor following treatment with irradiation and/or systemic therapy. Current guidelines derived from retrospective clinical studies include lytic lesions > 2.5 cm in diameter, cortical destruction > 50%, and pain despite local irradiation. In the proximal femur, an avulsion fracture of the lesser trochanter places the hip at high risk for fracture.

• *Clinical criteria for surgery*—All surgical interventions should be performed with the intent to provide benefit that will outlast the patient's anticipated survival. All patients should be medically fit for anesthesia and the planned surgical procedure. The surgical goals should be achievable with reasonable certainty, and the potential benefits should outweigh the operative risks. The surgical goal of a stable, painless extremity allows optimal patient function and mobility.

• *Lesion site*—Major long bones (femur, tibia, and humerus), the vertebrae, and periacetabular regions demand specific attention. Osseous destruction sufficient to compromise the mechanical integrity of these bones should be addressed surgically. Lesions in the weight-bearing bones of the lower extremity (femur and tibia) are particularly vulnerable to fracture.

Lesions in the humerus should be treated surgically when the upper extremities serve a weight-bearing function (e.g., assisted ambulation using a walker, crutches, or cane). Early surgical intervention, aggressive rehabilitation, and vigilant postoperative surveillance may optimize patient outcome.

Surgical techniques are designed to correct anatomical disruption. Vertebral augmentation techniques, vertebroplasty and kyphoplasty, are minimally invasive techniques of percutaneous injection of bone cement (methyl methacrylate) directly into vertebral bodies. With a low complication rate, these procedures are being used more commonly in conjunction with other treatments and even as a first-line approach for management of painful malignant spine fractures. It has been reported that there is a correlation between

symptom duration and restoration of vertebral body height after kyphoplasty.

## Radiation therapy

Cancer pain can often be relieved by radiation therapy delivered by localized external-beam irradiation, wide-field external-beam irradiation (eg, hemibody irradiation), or systemic treatment with radioactive isotopes such as strontium-89 chloride [Metastron], samarium-153 lexidronam [Quadramet] and alpharadin). Other examples of cancer pain due to primary or metastatic cancer that are amenable to irradiation include headache from central nervous system (CNS) involvement, pain due to localized neural involvement (e.g., brachial plexus or sciatic nerve), visceral pain (e.g., adrenal or pelvic masses), and pain due to obstruction (e.g., urethral, esophageal).

## Systemic radiotherapy

Like bone scans, systemic radiotherapy localizes in all of the bone metastases, while delivering minimal radiation to uninvolved normal bone; no radiation is delivered to adjacent soft tissues. Based on this, systemic radiotherapy is highly indicated in patients with diffuse metastases localized to bone without a soft tissue component. Systemic radiotherapy is contraindicated in bone metastases with soft tissue extension, as no treatment will be administered to the soft tissue component by the systemic radiotherapy. Given the localization of radiation to the bone, the only known toxicity is mild myelosuppression. The risk of myelosuppression depends on the extent of prior therapies, like chemotherapy, that have previously compromised the bone marrow elements.

**Strontium-89**. Strontium-89 is a systemic radionuclide that has clinical efficacy in the palliation of pain from bone metastases, and its levels in bone are regulated much like calcium. The greatest published experience is with strontium-89 in prostate cancer.

**Samarium-153.** Samarium-153 is a β-emitting radioisotope that is bound to a phosphonate that preferentially localizes in active bone, specifically in sites of metastatic disease. Samarium-153 is associated with a lower incidence and severity of hematologic toxicity than is strontium-89.

**Alpharadin [radium-223 chloride].** Alpharadin is an alpha-pharmaceutical with a shorter half-life of 11.4 days, which allows repeated dosing to response.

## Systemic therapy

Systemic therapy is the most common cancer treatment for bone metastases. The type of systemic therapy depends on the tumor type, prior systemic therapies, hematologic status, and performance status.

## Physical treatments

Cancer patients may benefit from formal physical therapy and rehabilitation. Physical modalities, such as massage, hydrotherapy, transcutaneous electrical nerve stimulation, electroacupuncture, and trigger-point manipulation, are indicated for musculoskeletal pain. Also, any of these techniques may enhance exercise tolerance in a patient undergoing rehabilitation. Electrical stimulation may also be applied to the peripheral nerves, spinal cord, and deep brain structures to relieve pain.

## Management of psychological, sociocultural, and spiritual factors

A multimodal approach to pain management recognizes the complexity of the human being, especially one with a terminal illness. Psychological, sociocultural, and spiritual factors significantly affect the patient's quality of life.

Empathic care helps relieve existential suffering integrated throughout the course of illness.

## Psychiatric diagnoses

Psychiatric conditions, such as anxiety and depression, and psychological factors must be thoroughly addressed, as revealed by emerging evidence from the disciplines of psycho-oncology and psychoneuroimmunology. Techniques such as guided imagery, hypnosis, relaxation, and biofeedback also assist in pain management.

## Sociocultural influences

Sociocultural factors may affect the patient's experience and expression of pain. However, it is important to recognize that rating of pain severity on validated pain scales is not affected by sociocultural factors. Unrelieved pain, in addition to its negative physiologic effects, may represent the presence and progression of cancer, resulting in fear, anger, disappointment, and other negative emotions. Fear of unrelenting and unbearable suffering as cancer pro-

gresses becomes a particularly important emotion when pain is not adequately relieved. By relieving pain, healthcare providers reassure patients that they will not suffer throughout their course of cancer.

### Existential distress

Achieving relief of psychic suffering allows the patient and family to realize improved quality of life and find peace in the face of failing health and imminent death. Prayer, meditation, counseling, clergy visits, and support groups may all be beneficial. Palliative care of the family includes bereavement counseling in anticipation of the loss of a loved one, and after the patient's death.

## Conclusion

The goals of pain management must be frequently reviewed and integrated into the overall management plan. Communication among the professional staff, patient, and family is essential. A sensitive, frank discussion with the patient regarding his or her wishes should guide medical decision-making during all phases of the illness.

*Article reprinted with permission from Cancernetwork.com*

*http://www.cancernetwork.com/cancer-management/pain-management-article?GUID=409EAAC3-63BF-4023-8594-D0B5963CE5D3&rememberme=1&ts=22112013*

## TEST YOUR KNOWLEDGE

***1) Which of the following adjuvants can be used along with standard analgesics in cancer pain management?***

A. Antidepressants
B. Local anesthetics
C. Neuroleptics
D. Benzodiazepines
E. All of the above

2) *Which of the following is an opioid analgesic?*

A. Meclofenamate sodium
B. Ketorolac
C. Oxycodone
D. Choline magnesium trisalicylate
E. None of the above

3) *Which of the following is not true with regard to use of opioid analgesics?*

A. Individualize/titrate the dose
B. Provide for breakthrough pain
C. Do not use drug combinations that enhance analgesia
D. Recognize and treat side effect
E. Prevent withdrawal

## Is there a problem?

A 60 year old patient with diabetes active peptic ulcer and asthma was given the following prescription for primary prevention of cardiovascular disease. Is there any major error in the prescription?

**CGK HOSPITAL**

Patient Name: Mr. Ali Age: 60 years
Address: Street No.12

Rx

Aspirin tablet
81 mg once daily
Send one pack

Dr. BSP
Signature Date: 1/06/14

**Answer (Prescription Exercise)**

Aspirin is contraindicated in a person with active peptic ulcer.

*Source:*
*British National Formulary*

TOPICAL ISSUES AND CONTROVERSIES

# How safe is your medicine cabinet?

Vioxx was on the market for 5 years before manufacturer Merck voluntarily withdrew it in 2004 due to an increased risk of heart attacks and strokes. An estimated 88,000–139,000 Americans had heart attacks while taking Vioxx, and as many as 55,000 died. Soon after, other painkillers in the same class of medicines came under scrutiny, including Bextra, which Pfizer removed from the market in 2005 upon the recommendation of the US FDA.


Americans cried out for better oversight of approved drugs. Then, in 2007, a cardiologist in Cleveland showed that Avandia, a blockbuster anti-diabetic drug, increased the risk of heart attacks. An FDA advisory committee reviewed the evidence and found the claim to be true, but voted to keep Avandia on the market because of its efficacy, while mandating that the drug carry the FDA's strictest warning label. Today, the national system for monitoring approved drugs has not gotten any better, critics say - despite the 2007 FDA Amendments Act (FDAAA) that granted the agency more power to oversee drugs once they hit the market.

Post-market drug safety is a hot issue not only because of high-profile drug scares, but also because of accelerating efforts to get drugs to market sooner.

The number of adverse events reported to the FDA has dramatically increased over the last decade, from about 200,000 reports in 2001 to 900,000 in 2012. But adverse events themselves are not a failure of the drug-approval system. Clinical trials include only 500 to 3,000 patients, so the full range of a medication's side effects is not likely to be apparent until it is used by the general population, which includes people typically excluded from clinical trials, such as those with comorbidities, pregnant women, and senior citizens. FDA approval of a drug is therefore not a gold stamp of safety, but a point on a continuum when the FDA makes a judgment call that the benefits of a drug outweigh its risks.

The goal of post-market drug safety monitoring, therefore, is not to prevent adverse events from happening, but to detect them early and efficiently, making adjustments when required.

However, the current system depends on spontaneous, voluntary reporting- through a reporting system called MedWatch- and any voluntary system is prone to vast under-reporting. One way to more thoroughly detect a drug's side effects is through electronic medical records.

In 2011, in a study of 19,478 women aged 65y or older, a team tracked whether women with breast cancer had an increased risk of heart disease when undergoing chemotherapy that included anthracyclines. They found that this type of chemotherapy increased the risk of heart failure by 25%, but had no effect on other types of heart disease (*Cancer, 115:5296-308, 2009)*.

Indeed, the FDA's own project, a national electronic system called Sentinel, proved useful in investigating whether dabigatran (Pradaxa), shared the same risk of serious bleeding as the already available warfarin, or whether the new drug's risk was higher. Through MedWatch, the FDA received many reports of bleeding associated with Pradaxa, but was unable to conclude whether the number of reports was higher than expected. Using the Sentinel system, the FDA determined there was no higher rate of bleeding than warfarin, but did put out a safety announcement in December 2012 that Pradaxa should not be used by patients with mechanical heart valves, who were more likely to experience strokes, heart attacks, and blood clots on Pradaxa than on warfarin.

Launched in 2008, FDA's pilot version of Sentinel, Mini-Sentinel, now includes data from 110 million individuals collected from numerous healthcare sources and compiled by the Harvard Pilgrim Health Care Institute, a research arm of the not-for-profit insurance provider. But so far, Sentinel has only been used to track suspected adverse events,

not to identify new ones. Indeed, this seems to be a general limitation of such reporting systems. In 2010, a team at Brigham and Women's Hospital in Boston developed a system to send automated reports straight from a doctor's note entered into an electronic medical chart to the FDA.

After the 2004 withdrawal of the widely prescribed Vioxx, the FDA asked the Institute of Medicine of the National Academies (IOM) to evaluate the US post-market safety-monitoring system. The resulting IOM report called for increased FDA staff and organization on the post-approval side.

FDA hearings about a post-market clinical trial of Avandia spurred the agency to request a second assessment from the IOM, which subsequently produced a second set of recommendations in May 2012. This time, a key suggestion was that the FDA create a better system for tracking individual drugs. The IOM recommended that the FDA create a benefit-and-risk assessment and management plan, or BRAMP, for every approved drug: a single, publicly accessible document that would detail safety issues and post-marketing studies as a way to continually weigh the drug's benefits against its risks.

Another major recommendation from the 2012 IOM report was for the FDA to require more and earlier post-market studies. In 2007, the FDA ordered the TIDE trial, a randomized post-market clinical trial comparing Avandia with Actos, after the initial evidence of Avandia's potential dangers was published. The trial was halted in 2010 after additional studies confirmed Avandia's risks, which raised ethical concerns about knowingly giving patients a potentially dangerous drug.

The FDA could simply require that companies start gathering data on the outcomes of patients taking their new drugs right after approval, increasing the chances of catching adverse events early. These observational studies should at least be done for drugs of heightened concern, such as those with demonstrated risk factors during clinical trials or those likely to be widely used for common, chronic conditions.

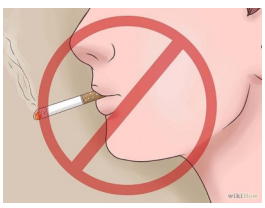
In addition, the FDA should require more long-term observations of drugs' effects. The current post-marketing system is geared toward detecting acute drug reactions, yet some adverse reactions don not show up until 5, 10, even 20 years later.

*Adapted from* *http://www.the-scientist.com//?articles.view/articleNo/35284/title/How-Safe-Is-Your-Medicine-Cabinet-/*

# Lifestyle changes could prevent 50% of common cancers

More than 50% of cancer could be prevented if people simply implemented what is already known about cancer prevention, according to a research at the Union for International Cancer Control (UICC) World Cancer Congress 2012.

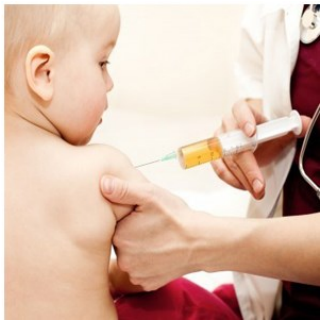
A number of interventions, largely involving lifestyle behaviors, but also involving higher-cost interventions in high-income countries, could prevent a large proportion of cancers in 15-20 years if widely applied.



Among lifestyle interventions is smoking cessation. A third of cancer in high-income countries is caused by smoking. If smoking rates could be reduced to about 11%, the USA could see a 75% reduction in smoking-related cancers in 10-20 years.

Similarly, it is estimated that being overweight or obese causes approximately 20% of cancer today. If people could maintain a healthy body mass index (BMI), the incidence of cancer could be reduced by approximately 50% in 2-20 years.

Estimates that poor diet and lack of exercise are each associated with about 5% of all cancers. Improvement in diet could reduce cancer incidence by 50% and increases in physical activity could reduce cancer incidence by as much as 85% in 5-20 years.



Eradicating the main viruses associated with cancer worldwide by implementing widespread infant and childhood immunization programs targeting 3 viruses- HPV and hepatitis B and C- could lead to a 100% reduction in viral-related cancer incidence in 20-40 years. Then there are the "higher tech" interventions that, at least in high-income countries, could prevent a significant proportion of cancer and cancer-related mortality, starting with breast cancer.

Tamoxifen was shown to reduce the rate of both invasive and noninvasive breast cancer by 50% or more, compared with placebo, at 5 years. Similarly, raloxifene has been shown to reduce the risk for invasive breast cancer by about 50% at 5 years, according to the Study of Tamoxifen and Raloxifene (STAR) in postmenopausal women at increased risk for breast cancer. Women in STAR who received raloxifene also had 36% less uterine cancers than control subjects.

The decrease in breast cancer incidence by 10% to 15% in the USA following the results of the Women's Health Initiative were clearly not due to changes in mammography, but rather to the removal of a late promoter of breast cancer which is the use of hormone replacement therapy.

And bilateral oophorectomy in women carrying the *BRCA1* or *BRCA2* gene, although rare, has been associated with a 50% reduction in breast cancer risk among high-risk women. It has also been estimated that weight loss after menopause (more than 9 kg) reduces breast cancer risk by 50% in 2-20 years.

In addition, it was noted that 20 years of follow-up has shown that aspirin is associated with a 40% reduction in mortality from colon cancer. Screening for colorectal cancer has a similar magnitude of mortality reduction (30-40%).

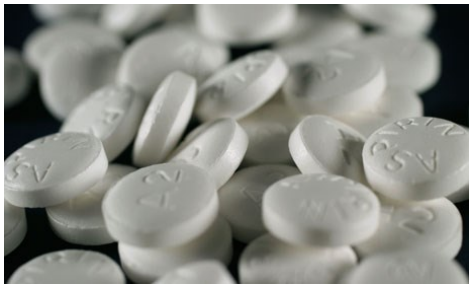
Indeed, a recent study showed that after a median follow-up of 11.9 years, there was a 21% relative risk reduction in the incidence of colorectal cancer and a 26% reduction in mortality in adults screened with flexible sigmoidoscopy, with a repeat screening at 3 or 5 years, compared with those treated with the usual care (*N Engl J Med. 2012;366:2345-2357*).

Since 30 years, epidemiologists were already showing that smoking, dietary intake, lack of physical activity, and obesity- accounted for more than half of all cancer.

Changes cannot be expected to occur overnight but the challenge is to develop a new form of cancer science called implementation science, aiming to take the benefits of discoveries to the people for population-wide health benefits.

***Adapted from: http://www.medscape.com/viewarticle/770357?src=nldne***

# *Aspirin use for cancer prevention and reduction of cancer mortality*

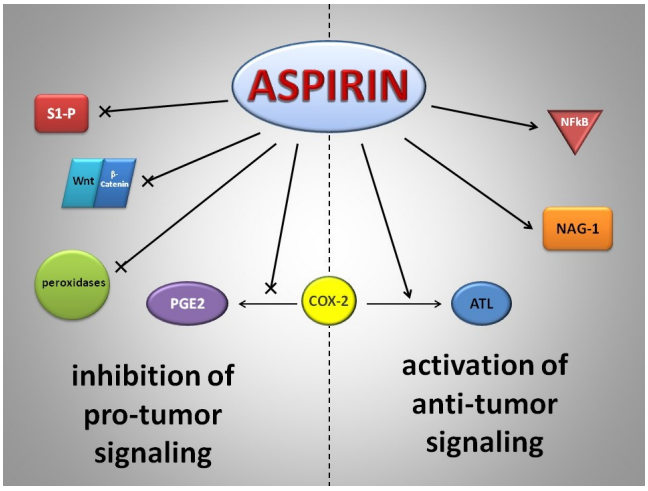


Evidence from 3 new studies demonstrates that aspirin can reduce the risk for cancer-related mortality. In the first study, comparing daily aspirin with no aspirin to prevent vascular events, aspirin use reduced the risk for non-vascular death in all 51 trials examined. When data from 34 trials were examined (n =69,224), there were fewer deaths from cancer in the aspirin than in the control group (562 vs 664 deaths). Although these results are compelling, they do have limitations. These analyses exclude the largest randomized trials in primary prevention. The Women's Health Study (WHS) of 39,876 women treated with alternate-day aspirin 100 mg over 10 years and the Physicians' Health Study (PHS) of 22,071 men treated with alternate-day aspirin 325 mg over 5 years were not included in the current study because of possible differences in the biologic effect between alternate-day and daily aspirin intake. However, in these 2 studies, aspirin was not associated with a lower risk for colorectal cancer or overall cancer incidence or mortality. Another limitation, is that the researchers only used 6 randomized trials to analyze low-dose aspirin in the primary prevention of cancer.

A third limitation is that because the included studies were designed to examine cardiovascular

end points, there was no information about cancer screening or surveillance. Despite the limitations, they show quite convincingly that aspirin seems to reduce cancer incidence and death across different subgroups and cancer sites, with an apparent delayed effect. These data might not be the final word on aspirin, as far as making a population-based recommendation, because the WHS and PHS remain significant counterbalancing trials that have not shown a cancer benefit with alternate -day aspirin up to 10-12 years.

Another factor to be considered is the adverse events from daily aspirin. Even though there is a convincing case that the vascular and anticancer benefits of aspirin outweigh the harms of major extra-cranial bleeding, less serious adverse effects on quality of life, such as less severe bleeding, are not accounted for in these analyses.




Nonetheless, until data from forthcoming trials and longer-term follow-up from the WHS and PHS become available, this impressive collection of data moves us another step closer to broadening recommendations for aspirin use.

In the second study data was from 5 large randomized trials of daily aspirin (75 mg or more daily) for the prevention of vascular events in the UK. The cohort consisted of 17,285 trial participants, 987 of whom had a new solid cancer diagnosed during a mean follow-up of 6.5 years. Aspirin use reduced the risk for cancer with distant metastasis. The risk for cancer with distant metastasis was reduced by 36%, and the risk for adenocarcioma was reduced by 46%. Among patients with adenocarcinoma who did not have metastasis at their initial diagnosis and who remained on trial treatment up to or after diagnosis, the use of aspirin reduced the risk for metastasis on subsequent follow-up by about 70%.

The third study looked at the effect of aspirin on metastases, but with a different approach. The authors compared the effect of aspirin on the 20 year risk for cancer-specific mortality between observational studies and randomized trials. Overall, results from observational studies were similar to those from randomized trials, and showed that regular aspirin use lowered the long-term risk for several cancers and for distant metastasis. The authors note that there is an urgent need for more data for effects on metastasis when aspirin is started after diagnosis of cancer.

**Cancer prevention**

Perhaps the most compelling evidence for the cancer prevention effects of aspirin comes from the examination of the national medical records of individuals enrolled in nine non-cancer clinical trials.

Taken together, these studies represent data from >23,000 patients who regularly took aspirin (at least ≥ 75 mg/day). While none of these studies intended cancer outcomes to be primary endpoints, the meta-analysis of these studies demonstrated nearly 20% decreased risk in overall cancer mortality after a 20 year follow-up period, with most of the benefit occurring after five years of aspirin use. In another recent meta-analysis, 51 trials (representing ~77,500 patients) of daily aspirin versus no aspirin were evaluated for cancer death and adverse effects. Aspirin reduced the risk of cancer death and colorectal cancer and lymphoma. The aspirin benefit occurred after 5 years of follow-up.

However, the results have been mixed, due to different study designs, uneven use of aspirin, as well as the long time periods and large patient numbers required to collect statistically significant results. Even among the studies presented herein, there is a potential contradiction in the outcomes from aspirin use and hematological malignancies among the long-term use and the short-term studies. However, clinical data are accumulating that support the use of aspirin, an inexpensive and widely available drug, to prevent two of the top mortal diseases, adenocarcinoma and myocardial infarction. Prospective cancer prevention trials would provide definitive evidence of aspirin's cancer prevention efficacy and determine if the risk of potential adverse effects, like bleeding, is genuinely mitigated with long-term use.

*References:*
*1) Aspirin Reduces Cancer Mortality and Risk for Distant Metastases. Medscape. Mar 20, 2012.*
*2) http://www.medscape.com/viewarticle/778845*

IN THE NEWS

# Obesity-fighting drug may improve metabolism

A hormone-mimicking drug known as LY has shown promise in treating a variety of metabolic problems associated with obesity. (*Cell Metabolism Sept 3, 2013*)

Many patients with type 2 diabetes also face a number of metabolic disorders- including hypertension, elevated LDL cholesterol levels, reduced HDL, and sugar intolerance- that are difficult to target and treat with just one drug.

Previous research has indicated that administering a hormone called FGF21 may improve overall metabolism in obese mice. The results of the present LY study- a randomized trial conducted by the drug's maker, Eli Lilly and Company- mark the first findings of similar effects in humans.

Over the course of a month, 46 obese patients with type 2 diabetes were injected with a dose of LY, a variant of the human form of FGF21. At the end of the trial, patients administered the drug showed reduced LDL and triglyceride levels, improved HDL levels, and a decrease in artery-clogging lipoproteins. The drug also appeared to cause modest weight loss, but did not have a statistically significant effect on glucose levels.

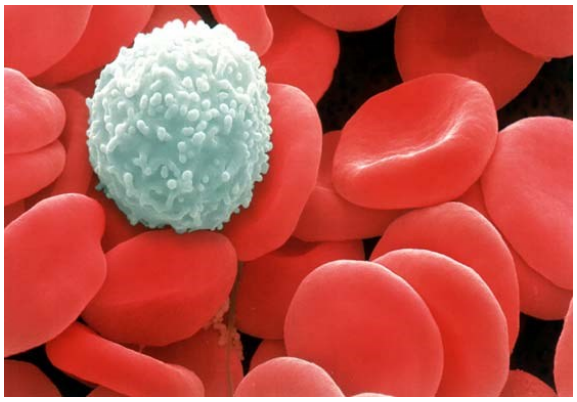
Longer and larger studies of LY are needed to evaluate the drug's safety and determine whether its benefits stand up over time.

*Adapted from* *http://www.the-scientist.com//?articles.view/articleNo/37342/title/Obesity-Fighting-Drug-May-Improve-Metabolism/*

# Blood test detects lung cancer

A blood test that detects a combination of proteins can distinguish between early lung cancer and noncancerous lung nodules, according to a study published in *Science Translational Medicine.*

The two types of nodules are currently difficult to distinguish using imaging. The test showed a 90% negative predictive value in a study of 104 patient samples from three clinical sites. Further validation on 37 samples from a single site showed a 94% negative predictive value. This molecular test may complement the current tools used by clinicians to diagnose early-stage lung cancer.



The early lung cancer detection test is being developed by Seattle-based molecular diagnostic company Integrated Diagnostics. The test detects the levels of 13 proteins in a patient's blood sample and could prevent unnecessary biopsies of lung nodules detected by CT scans. The researchers used a systems biology approach, screening 371 blood-based proteins on 143 patient samples with either benign or stage 1A lung cancer that were matched for nodule size, age, gender, and clinical site. Multiple reaction monitoring (MRM) mass spectrometry is used to analyze the relative concentrations of biomarkers. The technology allows simultaneous analysis of many protein levels.

Further analysis to understand the role of these biomarker proteins showed that all 13 are likely regulated by four transcription factors that bind to the regulatory elements of the 13 genes that encode the proteins. All four transcription factors have been associated with lung inflammation and lung cancer, as well as oxidative stress pathways.

The validation using 104 patient samples showed a test sensitivity of 71% and specificity of 44%. The study researchers assumed that the rate of cancer prevalence was 15%. At the same cancer prevalence rate, the sensitivity was 82% and the specificity was 66% in the discovery cohort of 143 samples. The protein levels were found to be independent of known risk factors for pulmonary nodules: the size of the nodule detected, history of smoking, and age. According to the authors, 20% of patients with detectable lung nodules who undergo biopsy or surgery actually have a malignant nodule. Therefore, a reliable test that can discriminate between a benign lung mass and a cancerous lung mass

is needed to prevent unnecessary invasive procedures and surgery.

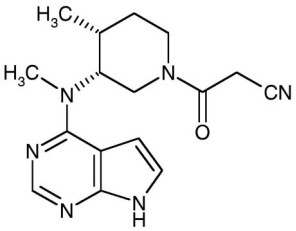
Still, the study cohorts used here are retrospective, and a prospective validation trial is needed to understand the full clinical potential of the blood test. Additionally, the authors note that the test results are not integrated with clinical risk factors, although they also note that pulmonologists vary broadly in the use of clinical risk factors, and so, it is actually preferable to have a molecular diagnostic test that produces a score independent of clinical risk factors. Interpreting the test results would likely depend on the calculated risk clinicians currently use to assess whether a nodule could be cancerous. Factors that go into the risk calculation include size of the nodule, its location, smoking history, age, emphysema, and family lung cancer history. In a low-risk patient with a 1-2% risk of lung cancer, the patient would still likely need a follow-up CT scan since the blood test could not definitely exclude malignancy. The test is seen as potentially being the most helpful in intermediate-risk patients with a calculated risk of malignancy between 10 and 20%. In this group, a negative test might obviate the need for additional workup, such as a PET scan or biopsy. This may make a clinician more comfortable opting for radiographic follow-up rather than an invasive procedure.

*Source: http://www.cancernetwork.com/news/blood-test-detects-lung-cancer?GUID= 409EAAC 3-63BF-4023-8594-D0B5963CE5D3&rememberme=1&ts=23102013*

# New pill might relieve severe rheumatoid arthritis

Rheumatoid arthritis (RA) affects about 1.3 million Americans, according to the Arthritis Foundation.

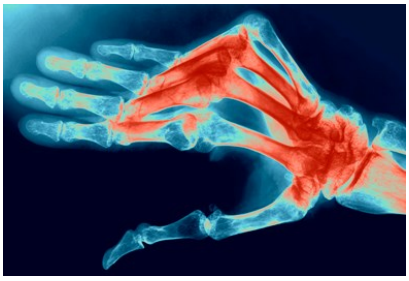
A new oral medication may be available soon for people with RA who have not gained relief from other medicines. Patients with severe forms of the disease often need drugs that must be injected, typically twice a month.




The new drug, tofacitinib, was approved by an advisory panel of the U.S. FDA in May 2012. However, the drug carries the risk of serious side effects, as do injectable treatments. The risks include blood and lymphatic system disorders, infections, and cancer.

The new drug, called a JAK inhibitor, blocks signals that activate inflammatory immune responses involved in RA. The hope is that JAK inhibitors will help improve the lives of those not getting enough relief from other medications.

In a research conducted by Fleischmann and his team, about 700 patients who had been taking methotrexate with inadequate relief were randomly assigned to take either 5 or 10 mg of tofacitinib twice daily, 40 mg of Humira (Adalimumab) every two weeks, or an inactive placebo. Patients in the placebo group who didn't see notable improvement in their joint pain were switched after 3 months to either 5 or 10 mg of tofacitinib. Participants were rated on a commonly used index of disability and checked for clinical signs of disease activity.



The 12-month study showed that tofacitinib was superior to placebo and similar to Humira in its effectiveness.

The second study involved about 610 patients who had had an inadequate response to methotrexate. Tofacitinib was found to be associated with reductions in symptoms of rheumatoid arthritis and improvement in physical functioning.

Experts not associated with the study think the new drug, if approved by the FDA, would be a positive treatment option.

Tofacitinib could be used as a first-line agent, before taking a patient to a biologic but the studies involved a relatively small number of patients and no long-term data. A better understanding of the drug's safety picture is needed to determine at what point patients might turn to tofacitinib.

The cost of the drugs is close to the price of the biologics. Fleischmann estimated that the current cost of those drugs to a consumer without insurance is about $25,000 a year.

Tofacitinib would be manufactured by Pfizer Inc., which funded both studies.

Source: *http://www.drugs.com/news/new-pill-might-relieve-severe-rheumatoid-arthritis-39726.html*

# STATE OF KUWAIT
## Pharmaceutical & Herbal Medicines Control and Registration Administration

### *New Pharmaceutical products approved from January to May 2014*

Airfast Tablets 10mg; Montelukast 10mg; Tabuk Pharma Mfg. Co. KSA.
Airtal Tablets 100mg; Aeclofenac 100mg; Almirall Prodesfarma S.A. Spain
Aldurazyme Conc. for Soln. for Infusion 500U; Laronidase 500U; Genzyme Europe B.V. Netherlands
Alzental Suspension; Albendazole 20mg; EIPICO Egypt
Alzental Tablets 200mg; Albendazole 200mg;EIPICO Egypt
Atorcor Tablets 10, 20, 40, 80mg; Atorvastatin 10, 20, 40, 80mg; Lab. Cinfa S.A. Spain
Avalon Avocaine Spray; 10%Lidocaine-100mg; Middle East Pharm. Ind. Co. Ltd. KSA
Avonex Soln. for Inj. In PFP; 30mcgInterferon Beta-1a 30mcg; Biogen Idec Ltd. U.K.
Azimac Tablets 500mg; Azithromycin-500mg; Riyadh Pharma K.S.A.
Bi Preterax Arginine Tabs; 10mg/2.5mgPerindopril Arginine 10mg, Indapamide 2.5mg; Les Lab Servier France
Brevibloc Premixed Soln. for Infn; 10mg/ml Esmolol Hydrochloride 10mg; Baxter Healthcare Ltd. U.K.
Cardex Tablets 2.5, 5, 10mg; Bisoprolol Fumarate-2.5, 5, 10mg; Tabuk Pharm. Mfg. Co. KSA
Cardoz Tablets 25mg; Carvedilol-25mg; IPCA Lab. Ltd. India
Cefovex Tablets 250mg; Cefuroxime-250mg; Oman Pharma Co. LLC(Zynova) Sultanate of Oman
Co-Tabuvan Tablets 160/12.5mg;Valsartan 160mg, Hydrochlorothiazide 12.5mg; Tabuk Pharma Mfg. Co. KSA.
Co-Tabuvan Tablets 160/25mg; Valsartan 320mg, Hydrochlorothiazide 25mg; Tabuk Pharma Mfg. Co. KSA.
Co-Tabuvan Tablets 320/12.5mg; Valsartan 320mg, Hydrochlorothiazide 12.5mg; Tabuk Pharma Mfg. Co.KSA.
Co-Tabuvan Tablets 320/25mg; Valsartan 320mg, Hydrochlorothiazide 25mg; Tabuk Pharma Mfg. Co. KSA.
Co-Tabuvan Tablets 80/12.5mg; Valsartan 80mg, Hydrochlorothiazide 12.5mg; Tabuk Pharma Mfg. Co. KSA.

Deriva Aqueous Gel 0.1%; Adapalene-1mg; Glenmark Pharm. Ltd.India
Eliquis Tablets 5mg; Apixaban-5mgBMS/Pfizer EEIG/U.K.
Eylea Soln. for Injection 40mg/mlAlfibercept; Bayer Pharma AG Germany
Fabrazyme Powd. For Conc. for Soln. for Infn. 5, 35mg; Agalsidase Beta 5, 35mg; Genzyme Europe B.V. Netherlands
Fampyra PR Tablets 10mg; Fampridine-10mg; Biogen Idec Ltd. U.K.
Fozanate Tablets 70mg; Alendronic Acid 70mg; Global Pharma Co. Ltd. U.A.E.
Gridokline Tabs 75mg; Clopidogrel 75mg; GSK Ireland
Hairgaine for Men Topical Solution 5%; Minoxidil 50mg; Medpharma Pharm. & Chemical Ind. U.A.E.
Hairgaine Gel 2%; Minoxidil 20mg; Medpharma Pharm. & Chemical Ind. U.A.E.
Herceptin Solution for Injection 600mg/5ml; Trastuzumab 600mg; F.H. La Roche Ltd Switzerland
Inlyta Tablets 1, 5mg; Axitinib1, 5mg;Pfizer Ltd. U.K.
Ipramax Tablets 25mg;Topiramate-25mg; Tabuk Pharm. Mfg. Co. KSA
Irinotel Conc. for Soln. for Infusn. 40mg/2ml and 100mg/5ml; Irinotecan Hydrochloride 40 and 100mg; Fresenius Kabi Oncology Ltd. India
Ivemend Powder for Solution for Infusion 150mg/vial; Fosaprepitant 150mg; MSD U.K.
Jakavi Tablets 5, 15, 20mg; Ruxolitinib 5, 15, 20mg; Novartis Pharma Schweiz AG Switzerland
Klarihist Syrup; Loratadine 5mg; The United Pharm. Mfg. Co. Ltd. Jordan
Klarihist Tablets;10mg Loratadine 10mg; The United Pharma Mfg. Co. Jordan
KO Act Tabs. 1g; Amoxicillin 875mg, Clavulanic Acid 125mg; Aurobindo Pharma Ltd. India

Levacin Tablets; Acino Pharma AG Switzerland
Levacin Tablets 100/25mg and 200/50mg; Carbidopa 25mgLevodopa, 100mg and Carbidopa-50mg Levo dopa-200mg; Acino Pharma AG Switzerland
Levoflox Tablets 500mg; Levofloxacin 500mg; National Pharm. Industries Co. Sultanate of Oman
Lukaline Chewable Tabs. 4, 5mg; Montelukast 4, 5mg; GSK Ireland
Lukaline Chewable Tabs. 5mgMontelukast 5mg; GSK Ireland
Meropenem Labatec IV 500 mg, 1g Pwd. For Inj/Infusion; Meropenem- 500mg, 1g; Labatec Pharma S.A. Switzerland
Montal Chewable Tabs. 4, 5, 10mg; Montelukast-4, 5, 10mg; Lab. Cinfa S.A. Spain
Orencia Soln. for subcutaneous Inj. PFS 125mg; Abatacept 125mg; BMS Co. USA.
Orvakline Tabs 10, 20, 40mg; Atorvastatin 10, 20, 40mg; GSK Ireland
Oxaliplatin Actavis Lyophilisate for Soln. for infn. 50, 100mg; Oxaliplatin 50, 100mg; Actavis Group PTC ehf Iceland
Oxatev Tablets 500mg; Levofloxacin, 500mg; Sandoz GmbH Austria
Panadol Cold & Flu Vapour Release Powder for Oral Soln; Paracetamol 500mg; GSK Export Ltd./U.K.
Pantonex DR Tablets 20, 40mg; Pantoprazole 20, 40mg; IPCA Lab. Ltd. India
Paracetamol B. Braun IV Infusion Soln.1g/100ml; Paracetamol 1000mg; B.Braun Melsungen Germany
Paracetamol B. Braun IV Infusion Soln. 500mg/50ml; Paracetamol, 500mg;B.Braun Melsungen Germany
Paraxone Capsules; Chlorzoxazone 250mg, Paracetamol 300mg; Jazeera Pharm. Ind. KSA
Paxitab Tablets 20mg; Paroxetine 20mg; Tabuk Pharma Mfg. Co. KSA.
Paxitab Tablets 40mg; Paroxetine 40mg; Tabuk Pharm. Mfg. Co. KSA.
Posicaine 200 Soln. for inj; Articaine HCl, 40mg Epinephrin, 0.005mg; Novocol Pharma of Canada Inc. Canada
Saflutan Eye Drops 15mcg/ml; Tafluprost 4.5mcg; MSD The Netherlands
Seebri Breezhaler Inhalation Powdr. Hard capsules, 50mcg; Glycopyronium 50mcg; Novartis Pharma Schweiz AG Switzerland
Siofor Tablets 1000mg; Metformin HCl 1000mg; Laboratori Guidotti SpA Italy
Stivarga Tabs 40mg; Regorafenib 40mg; Bayer Pharma AH Germany
Supirocin Oint. 2%; Mupirocin-20mg; Glenmark Pharma Ltd. India
Tabuvan Tablets 40mg; Valsartan 40mg; Tabuk Pharma Mfg. Co. K.S.A.
Tabuvan Tablets-80, 160, 320mgValsartan-80, 160, 320mg; Tabuk Pharm. Mfg. Co. KSA
Telfast D Extended Release Tabs. 60/120mg; Fexofendaine HCl-60mg Pseudoephedrine HCl-120mg; Sanofi-Aventis US LLC, U.S.A.
Ursofalk Tablets 500mg; Ursodeoxycholic acid,500mg; Dr. Falk Pharma GmbH- Germany
Vacodil Tablets 6.25mg; Carvedilol-6.25mg; Aurobindo Pharma Ltd. India
Xifaxan Tablets 200mg ; Rifaximin-200mg; Norgine B.V. Netherlands
Z Cil 1000 (Ampicillin for Inj. USP 1000mg); Ampicillin 1000mg; Aurobindo Pharm. Ltd. India

## Answers to: Test your knowledge

**Correct answers:**
**1-e; 2-c; 3-c**

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