Complementary Therapy – What's the Evidence?

By Dr. Ernie Mak, BSc, MD, CCFP
Palliative Care Physician
and Rachel Whitty, BScPhm, RPh, ACPR
Pharmacy Clinical Site Leader
Princess Margaret Cancer Centre
University Health Network

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Objectives

- To develop a framework of examining the evidence on the efficacy and safety of complementary therapies
- To gain confidence in giving recommendations based on the framework

Complementary Therapy

- Definition
  - **Complementary** therapies are used **together with** conventional treatments. They may help people cope with cancer, its treatment or side effects rather than treat cancer itself.
  - **Alternative** therapies are used **instead of** conventional treatments.

Complementary therapy

- Examples
  - Acupuncture
  - Aromatherapy
  - Ayurvedic medicine (traditional Indian medicine)
  - Energy therapies (eg Reiki, healing touch)
  - First Nations healing
  - Massage
  - Mind-body medicine (eg biofeedback, yoga, meditation)
  - Naturopathic medicine
  - Traditional Chinese medicine

Quickfire Challenge!

- 26F with recurrent Ewing's sarcoma, started chemo (irinotecan & temozolamide)
  - Wants to go on high dose Vitamin C because it will help fight her cancer
  - Decides to change her diet to a "raw diet" to "live for her body"
  - Would you recommend that?
  - What information do you need to know to give your recommendations?

Why should we be concerned?

- Health Claims

Could MUSHROOMS prevent cervical cancer? Fungi extract kills virus and slows tumour growth

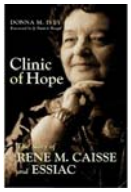
- **An extract in Japanese shiitake mushrooms kills the HPV virus**
- **The extract can also reduce the rate of cervical tumour growth**

By EMMA INNES

PUBLISHED: 10:46 GMT, 24 March 2014 | **UPDATED:** 09:06 GMT, 25 March 2014

"Fighting cancer is a battleground with many fronts."

- *"People seeking a successful treatment against the marauding force of cancer turn to anything and everything. Ever more possibilities keep opening up even as previously attempted ones prove futile. Always more believers appear by serendipity wanting to share their zealous convictions and remedies. Patients and their distraught families go through this quest in a twilight bubble with chequebooks open and pens in hand, a reality that … explains the motivation of people in authority who seek to navigate between possible cures and probable charlatans.* ***Fighting cancer is a battleground with many fronts."***



p. 13, forward by J. Patrick Boyer from Ivey, D.M. (2004). *Clinic of Hope The Story of Rene M. Caisse and Essiac*. Toronto, ON: Dundurn Press

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Complementary therapy

- Prevalence
  - Recent Italian study n=803 across primary tumour sites and phases of disease/care process showed **37.9%** of patients were using one or more types of complementary therapies
    - Most were diets/dietary supplements (27.5%), herbs (10.8%), homeopathy (6.4%), and mind-body therapies (5.5%)
    - 66% informed their MDs
  - Canadian study from 2002 n=871 with colorectal cancer showed **49%** used CAM
    - Most were psychological and spiritual therapies (65%), vitamins and minerals (46%), and herbs (42%)
    - 68% informed their MDs

Bonacchi, A, Fazzi, L, Toccafondi, A, et al. (2014). Use and Perceived Benefits of Complementary Therapies by Cancer Patients Receiving Conventional Treatment in Italy. Journal of Pain and Symptom Management. 47(1): 26-34

Tough, SC, Johnston, DW, Verhoef MJ, et al. (2002). Complementary and alternative medicine use among colorectal cancer patients in Alberta, Canada. Altern Ther Health Med. 8(2): 54-6, 58-60, 62-4

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Complementary Therapies in Palliative Oncology – Your Recipe for Success

Ingredients:

- Information
- Interactions
- Informed Consent

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Information

- Access to drug information from trusted sources
  - Purported Uses
  - Efficacy
  - Safety
  - Dosing
  - Formulation*

EVIDENCE


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Interactions

- Complete drug interaction assessment – especially interactions with cancer treatment
  - The Drug Interaction Toolbox

EVIDENCE

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Informed Consent

- Ensure your patient knows and understands the potential risks and potential benefits of treatment
  - Risks may be to:
    - Health (adverse effects, interactions)
    - Well being (pill/medication burden)
    - Financial

EVIDENCE

  - Does the potential benefit outweigh these? From your perspective? From your patient's?

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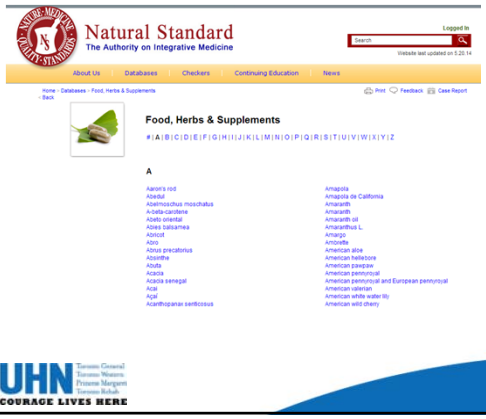
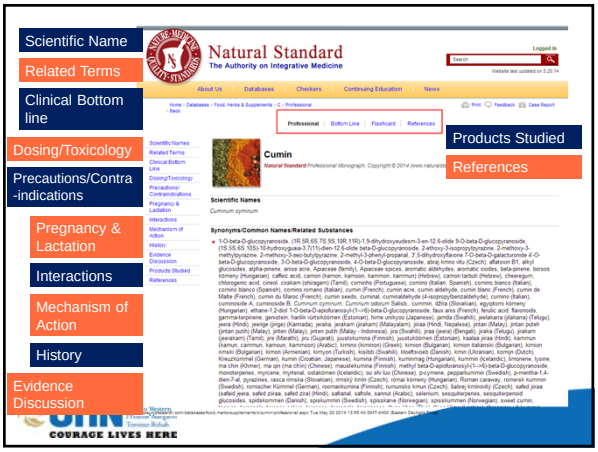
Pharmacy images courtesy of Canadian Society of Hospital Pharmacists, British Columbia Branch

INFORMATION



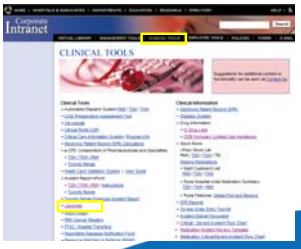


Levels of Evidence

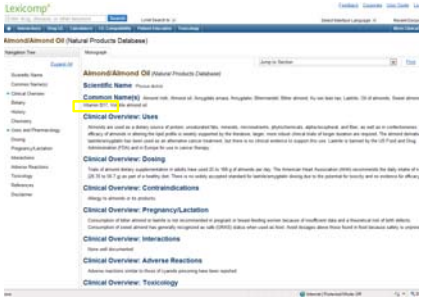
A	Strong Scientific Evidence
B	Good Scientific Evidence
C	Unclear or conflicting scientific evidence
D	Fair Negative Scientific Evidence
F	Strong Negative Scientific Evidence
Lack of Evidence	Unable to evaluate efficacy due to lack of adequate available human data.

Lexi-Comp – Drug Information and Drug Interaction Database

- Available on UHN Intranet
  - Go to Clinical Tools
  - Link under “Clinical Tools”



- Example: typed in “vitamin B17”

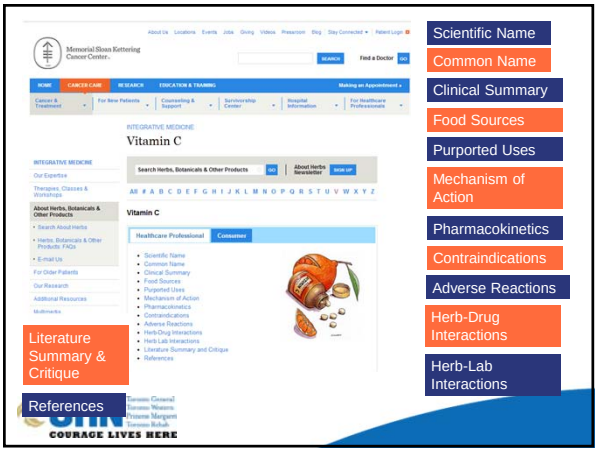


- No hits for “Essiac” or any of the four herbs, no hits for “shark cartilage”

Lexicomp®

Sample drug interaction database result

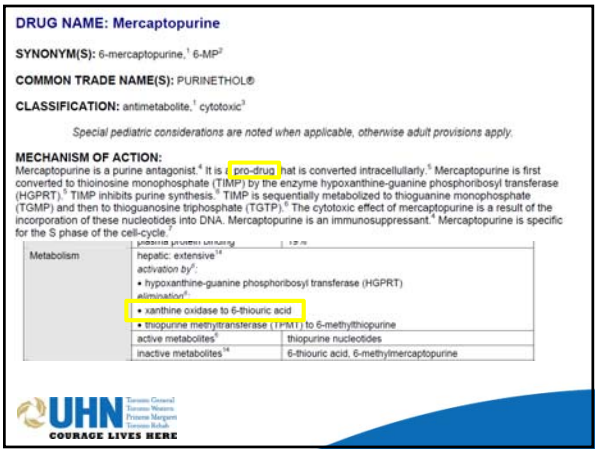
Lexicomp®



- Scientific Name
- Common Name
- Clinical Summary
- Food Sources
- Purported Uses
- Mechanism of Action
- Pharmacokinetics
- Contraindications
- Adverse Reactions
- Herb-Drug Interactions
- Herb-Lab Interactions
- Literature Summary & Critique
- References

Other Drug Information for Cancer Treatment

- Cancer Care Ontario www.cancercare.on.ca
  - “CCO Toolbox” > “Drug Formulary”
- British Columbia Cancer Agency www.bccancer.ca
  - Under “Health Professionals Info”, “Cancer Drug Manual”
- Both contain drug information for health care professionals and for patients



DRUG NAME: Mercaptopurine

SYNONYM(S): 6-mercaptopurine,[1] 6-MP[2]

COMMON TRADE NAME(S): PURINETHOL®

CLASSIFICATION: antimetabolite,[1] cytotoxic[3]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:
Mercaptopurine is a purine antagonist.[4] It is a pro-drug that is converted intracellularly.[5] Mercaptopurine is first converted to thioinosine monophosphate (TIMP) by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT).[5] TIMP inhibits purine synthesis.[5] TIMP is sequentially metabolized to thioguanine monophosphate (TGMP) and then to thioguanosine triphosphate (TGTP).[5] The cytotoxic effect of mercaptopurine is a result of the incorporation of these nucleotides into DNA. Mercaptopurine is an immunosuppressant.[4] Mercaptopurine is specific for the S phase of the cell-cycle.[7]

Metabolism	hepatic: extensive[14] *activation by*[5]: • hypoxanthine-guanine phosphoribosyl transferase (HGPRT) *elimination*[5]: • xanthine oxidase to 6-thiouric acid • thiopurine methyltransferase (TPMT) to 6-methylthiopurine
active metabolites[5]	thiopurine nucleotides
inactive metabolites[14]	6-thiouric acid, 6-methylmercaptopurine

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
allopurinol[16,21]	delayed, major, established; increased mercaptopurine toxic effect	inhibition of xanthine oxidase by allopurinol reduces the rate of mercaptopurine elimination	mercaptopurine dose reduction to 25% of standard dose when given concomitantly[3,6,14]
*cow's milk[8]	decreased bioavailability	mercaptopurine inactivated by high concentration of xanthine oxidase in cow's milk	required avoid concurrent intake
methotrexate[21]	delayed, moderate	moderate inhibition of	primarily a concern with

* Xanthine oxidase is present in various concentrations in other milk including human and goat's milk, therefore concurrent use may decrease levels/effects of mercaptopurine.[25-28]

8. Rivard GE, Lin KT, Leclerec JM, et al. Milk could decrease the bioavailability of 6-mercaptopurine. Am J Pediatr Hematol Oncol 1989;11(4).

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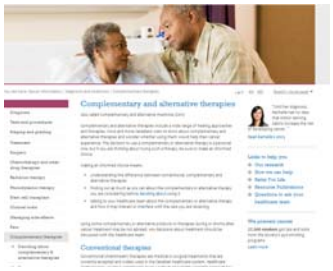
Canadian Cancer Society



Complementary therapies
- Deciding about complementary & alternative therapies
- Acupuncture
- Aromatherapy
- Art therapy
- Ayurvedic medicine
- Chiropractic care
- Energy therapies
- First Nations healing
- Massage
- Medical marijuana use
- Mind-body medicine
- Naturopathic medicine
- Traditional Chinese medicine

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INTERACTIONS

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Drug Interactions can result in…

- **decreased effectiveness** of a medication
- **increased toxicity** of a medication
- and/or an **adverse drug reaction**

Cipolle, RJ, Strand, LM & Morley, PC. Pharmaceutical Care Practice – The Patient Centered Approach to Medication Management Services, Third Edition. New York (USA); McGraw- Hill Companies Inc; 2012.

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Mechanisms of Drug Interactions – why do we care?

- "Knowledge of the mechanism by which a given drug interaction occurs is often **clinically useful**, as the mechanism could **influence** both the **time course** and the **methods** of **circumventing** the interaction or, in rare cases, **taking advantage of it**."

Scripture CD, Figg WD. (2006). Drug interactions in cancer therapy. Nature Reviews Cancer. 6: 546-558

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Pharmacodynamic Interaction

- two or more drugs have mechanisms of action that influence the same physiological process
- broad classification:
  - **Synergistic**: effect of two drugs greater than sum of individual effects
  - **Antagonistic**: effect of two drugs less than sum of individual effects
  - **Additive**: effect of two drugs merely the sum of individual effects
  - **Sequence-dependent**: order in which two drugs given governs effects

*may be used intentionally in oncology

Blower P, de Wit R, Goodin S, Aapro M. (2005). Drug-drug interactions in oncology: Why are they important and can they be minimized? Critical Reviews in Oncology/Hematology. 55: 117-142

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Pharmacokinetic Interaction

- one drug influences the **absorption, distribution, metabolism** and/or **excretion** of another drug

ABSORPTION
- drugs that influence GI motility may have a major effect on bioavailability of other drugs
- activities of drug-metabolizing enzymes and membrane transporter proteins in the intestinal epithelium may be inhibited or induced by other drugs – affects absorption

DISTRIBUTION
- competition for plasma or tissue protein binding
- effect of displacement difficult to predict → increase of the free fraction not only makes the drug more available for its target, but also increases the amount of drug available for metabolic and renal elimination

Blower P, de Wit R, Goodin S, Aapro M. (2005). Drug-drug interactions in oncology: Why are they important and can they be minimized? Critical Reviews in Oncology/Hematology. 55: 117-142

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Pharmacokinetic Interaction

- one drug influences the **absorption, distribution, metabolism** and/or **excretion** of another drug

METABOLISM
- Many drugs undergo two phases of metabolism: Phase I (functionalization reactions) and Phase II (conjugation reactions)
- Phase I: oxidation, hydroxylation, dealkylation, reduction (example: conversion of inactive prodrug to active metabolite, includes CYP P450 system)
- Phase II: glucuronidation, sulfation, acetylation, methylation

EXCRETION
- Drugs that alter renal or hepatic function can interfere with excretion of other drugs and their metabolites
- Secondary PK effects such as hepatotoxicity or nephrotoxicity of drugs can affect metabolism or excretion of other drugs

Blower P, de Wit R, Goodin S, Aapro M. (2005). Drug-drug interactions in oncology: Why are they important and can they be minimized? Critical Reviews in Oncology/Hematology. 55: 117-142

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Cytochrome P450 System

- >50 enzymes responsible for Phase I metabolism of many drugs, nutrients, endogenous substances, environmental toxins
- CYP3A4 → 3 = family, A = sub-family, 4 = specific isoform
- Estimated that >90% of drug oxidation in humans attributed to 6 main enzymes:
  - CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4
  - 85% of total hepatic metabolism attributed to: **CYP1A2, CYP2D6, CYP3A4**
  - some drugs metabolized by one isoform, others by multiple resulting in multiple metabolites
  - enantiomers may be metabolized by different isoforms (S-warfarin by CYP2C9, less active R-warfarin by CYP1A2, 2C19, 3A4)
  - Mostly in the liver though some in intestinal epithelium – CYP3A4 in small intestine has important role in first-pass metabolism, accounts for approx 70% of CYP activity in the intestine

Blower P, de Wit R, Goodin S, Aapro M. (2005). Drug-drug interactions in oncology: Why are they important and can they be minimized? Critical Reviews in Oncology/Hematology. 55: 117-142
Scripture CD, Figg WD. (2006). Drug interactions in cancer therapy. Nature Reviews Cancer. 6: 546-558

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Pharmacokinetics Review

- **First-pass effects**: The decrease in the bioavailability of an orally administered drug caused by enteric metabolism, hepatic metabolism or elimination before the drug reaches the systemic circulation
- **AUC**: The area under the curve in a graph of plasma concentration versus time. It is a measure of drug exposure.
- **Inhibitor**: inactivates specific CYP enzymes in an irreversible way. Metabolism will return to normal once the inhibitor has been removed and new enzymes have been produced.
- **Inducer:** increases the production of enzymes and therefore accelerates metabolism.
- **Cmax**: The highest concentration that a drug reaches in the serum/plasma

Scripture CD, Figg WD. (2006). Drug interactions in cancer therapy. Nature Reviews Cancer. 6: 546-558

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Drug-Food Interactions

- Food can affect the PK profile of some orally administered medications in various ways:
  - Delays gastric emptying
  - Raises intestinal pH
  - Increases hepatic blood flow
  - Slows GI transit

Table 2 | **Effect of food on the pharmacokinetics of orally administered anticancer agents**

Anticancer agents	Effect of food	Pharmacokinetic parameters affected
Busulfan[144], fluorouracil[145], methotrexate[146] and topotecan[147]	Delayed absorption (effect on rate)	Change in C_{max} and T_{max}
Altretamine[148], capecitabine[149], chlorambucil[150], estramustine[151], gefitinib[152], melphalan[153] and thioguanine[154]	Decreased absorption (effect on extent)	Change in AUC and C_{max}
Erlotinib[155] and tretinoin[156]	Increased absorption (effect on extent and/or rate)	Increase in AUC and usually C_{max} and/or T_{max}
Etoposide[157], imatinib[158], mercaptopurine[159] and temozolomide[160]	Unaffected absorption (no effect on rate or extent)	No significant change in AUC and C_{max}

AUC, area under the concentration–time curve; C_{max}, change in maximum plasma drug concentration; T_{max}, time to reach C_{max}. *Conclusion when 90% confidence interval for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, fall within the equivalence limits of 80–125% for AUC and C_{max}.

Scripture CD, Figg WD. (2006). Drug interactions in cancer therapy. Nature Reviews Cancer. 6: 546-558

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Drug-Food Interactions

- Foods can also alter enzyme activity
- Example: grapefruit juice = potent inhibitor of intestinal CYP3A4, increases bioavailability of various drugs (ex. cyclosporine, nifedipine)
  - Mechanism seems to be multifactorial, changes in PK which could result in toxic drug exposure are difficult to predict → clinical trials typically prohibit grapefruit juice → limited data re: interaction between grapefruit juice and anticancer agents

Scripture CD, Figg WD. (2006). Drug interactions in cancer therapy. Nature Reviews Cancer. 6: 546-558

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Patients with cancer are at increased risk of drug-drug interactions because they…

- typically receive a **large number of medications** as part of their cancer care (includes multi-drug chemotherapy regimens, hormonal agents, supportive care with antiemetics, analgesics, anti-infectives, among others)
- may self-administer **complementary/alternative medications** with a high potential for drug-drug interactions
- many patients with cancer are **aged 65 or older** and are more likely to
  - have **co-morbid conditions** which require additional medications
  - be affected by age-related **changes in hepatic and renal function** that render them more susceptible to drug-drug interactions

Blower P, de Wit R, Goodin S, Aapro M. (2005). Drug-drug interactions in oncology: Why are they important and can they be minimized? Critical Reviews in Oncology/Hematology. 55: 117-142

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Clinical Significance of Drug Interactions

- when a drug interaction changes the **relative** concentrations of a parent drug and its metabolite(s), which are approximately **equipotent** in terms of efficacy and safety considerations, inhibition and induction could be of little therapeutic consequence
- Consider whether substrate is metabolized by a single enzyme, or multiple enzymes
  - Example: cyclophosphamide = prodrug, active metabolite produced mainly by CYP2B6 and CYP3A4 in liver
  - as many as 6 enzymes (CYP2A6, CYP2B6, CYP3A4, CYP2C8, CYP2C9 and CYP2C19) have been implicated in cyclophosphamidemetabolism
  - therefore, PK less likely to be influenced by drug–drug interactions caused by the inhibition of an individual CYP

Scripture CD, Figg WD. (2006). Drug interactions in cancer therapy. Nature Reviews Cancer. 6: 546-558

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Predicting Clinical Significance of Drug Interactions

Box 2 | Conditions under which drug interactions are likely to be clinically significant

- Drug elimination occurs primarily through a single metabolic pathway.
- A drug is a potent inhibitor or inducer of a drug-metabolizing enzyme.
- One or both of the interacting drugs has a steep dose-response curve.
- One or both of the interacting drugs has a narrow therapeutic range.
- Inhibition of the primary metabolic enzyme or the induction of a secondary metabolic enzyme results in diversion of the drug into an alternative pathway, which generates a metabolite that has toxic or modified pharmacodynamic activity.
- A drug has nonlinear pharmacokinetics, or the interaction results in a conversion from linear to nonlinear pharmacokinetics.
- The drug is metabolized through, or inhibits, a polymorphic drug-metabolizing enzyme.

Based on material in REFS 1,51.

Scripture CD, Figg WD. (2006). Drug interactions in cancer therapy. Nature Reviews Cancer. 6: 546-558

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Table 3.2
Guide to drug interactions for a patient receiving methadone for analgesic purposes

Five principles of drug interactions
Reminder: Methadone is metabolized by CYP 450 3A4–2B6 > 2D6 >> 2C9, 2C19, 1A2

Effects of enzyme inducers and enzyme inhibitors

1. Inhibitor added to methadone: Generally results in an increase in serum levels of methadone.
2. Inducer added to methadone: Generally results in a decrease in serum levels of methadone (with corresponding decrease in effectiveness) **after 7 to 10 days**, unless the methadone dose is increased in anticipation of this interaction (not recommended in practice).
3. Methadone added to an inducer: Can lead to ineffectiveness of methadone (dose too low), except if the initial methadone dose is increased in anticipation of this interaction (not recommended in practice).
4. Discontinuation of an inhibitor: Methadone and an inhibitor are given together for a certain period (equilibrium is attained), and then the inhibitor is abruptly discontinued. Anticipated result (which can occur rapidly, after a few hours to a few days): decrease in serum levels of methadone (and probably a decrease in efficacy), increase in formation of metabolites.
5. Discontinuation of an inducer: Methadone and an inducer are given together for a certain period (equilibrium is attained), and then the inducer is abruptly discontinued. Result, after **2 to 3 weeks**: increase in serum levels of methadone (and probably an increase in its efficacy and toxic effects), decrease in formation of metabolites.

For every suspected drug interaction, contact a pharmacist to discuss the best course of action.

Hospital Pharmacists' Special Interest Group in Palliative Care. (2009). Care Beyond Cure: Management of Pain and Other Symptoms. Montreal, QC: Association des pharmaciens des établissements de santé du Québec.

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Created by Annie Thiboutot and Andrée Nitron, pharmacists. Revised April 2007.

Hospital Pharmacists' Special Interest Group in Palliative Care. (2009). Care Beyond Cure: Management of Pain and Other Symptoms. Montreal, QC: Association des pharmaciens des établissements de santé du Québec.

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How can I consistently discover and manage drug interactions in my practice?

In palliative oncology?

Involving complementary therapies?

The Drug Interaction Toolbox

Drug Interaction Database / Drug Information Resources

Best Possible Medication History (BPMH) and Completed Medication Reconciliation

Literature on Interaction

Patient Information

Professional Judgment

Clinical Guidelines/ Evidence/ Best Practice

Drug Interaction Database / Drug Information Resources

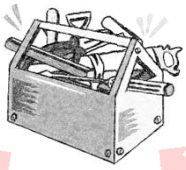
- UHN: LexiComp
- Does NOT include all complementary therapies!
- May need to infer interactions from available information

Best Possible Medication History (BPMH) and Completed Medication Reconciliation

- Need to know ALL medications your patient is taking, including complementary therapies, in order to assess drug interactions

Literature on Interaction

- Depending on severity of interaction and proposed management, may need to consult literature to see if there are any PD/PK studies and/or case reports of interaction that can be applied to your patient



Patient Information

- Indications for medications involved, adherence, patient status, lab parameters, goals of therapy, treatment plan, patient wishes

Professional Judgment

- Your specialized body of knowledge and training, clinical experience, and critical thinking skills are essential in determining how to manage drug interactions

Clinical Guidelines/ Evidence/ Best Practice

- Understand appropriateness of dosing of all therapies involved in interaction, other alternatives to generate options to manage interaction

INFORMED CONSENT

How should we act?

- Non-judgemental
- Non-paternalistic
- Patient-centred
- Be current with our knowledge

Complementary Therapies Commonly Encountered in Palliative Oncology

- High-Dose Vitamin C
- Essiac
- Mushrooms
- Shark Cartilage
- Curcumin
- Vitamin B17

High dose Vitamin C

- Ascorbic acid, water soluble
- Commonly in vegetables & citrus fruits
- Used orally or intravenously

- Claims: Antioxidant supplement, cold/flu prevention, wound healing, cardiovascular health, cancer prevention

High dose Vitamin C

- Cancer prevention
  - Purported mechanism of action: Vitamin C promotes collagen formation which resists malignant infiltration
  - PO Vit C has limited plasma concentration
  - IV Vit C higher conc; generates free radicals against tumor cells

High dose Vitamin C

- Efficacy
  - Improves QoL of terminal cancer patients
  - Reduce chemo toxicity for ovarian ca pts
  - Dietary intake foods high in vitamin C has been associated with a reduced risk of cancers of the mouth, esophagus, stomach, colon, or lung cancer in population studies (role of Vit C unclear)

High dose Vitamin C

BUT…

- Cancer cells preferential uptake Vit C
- Antioxidants may interfere with action of chemo/XRT relying on reactive oxygen species (vincristine, doxorubicin, methotrexate, cisplatin, bortezomib and imatinib)

High dose Vitamin C

- In clinical research, evidence of the protective effects of vitamin C supplements in lung and gastrointestinal cancers is lacking
- Evidence lacking in improved survival when used as chemo adjunct

High dose Vitamin C

- Efficacy

Indications	Grade of evidence
Scurvy	A
Common cold prevention (extreme environments)	B
Iron absorption enhancement	B
Urinary tract infection	B
Cancer prevention	C
Cancer treatment	C

High dose Vitamin C

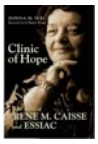
- Safety
  - Well-tolerated
  - Common side effects: GI upset, kidney stones, hemolytic anemia in G6PD deficiency
  - No standardization of dose/preparation
  - FDA approved as preservative, dietary supplement, nutrient (ie NOT approved as a therapeutic agent)

High dose Vitamin C

- Safety
  - Interaction: iron, some chemo, beta blockers
- Conclusion:
  - For cancer prevention/adjunct, inconclusive data to support its use. While likely safe to use, careful medication review is needed due to herb-drug interaction

Essiac

- Developed in 1920s by Rene Caisse, a nurse from Bracebridge, ON
- Based on a traditional Ojibwa remedy
- Herbal tea mixtures Essiac and Flor Essence – differences in formulations, both have been studied
- Other formulations exist, marketed as Essiac

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Essiac

- Essiac contains four herbs:
  - Sheep sorrel *(Rumex acetosella)*
  - Slippery elm *(Ulmus fulva)*
  - Burdock *(Arctium lappa)*
  - Rhubarb *(Rheum palmatum)*
- Flor Essence contains an additional four "potentiating" herbs:
  - Watercress (*Nasturtium officinale*)
  - Blessed thistle (*Cnicus benedictus*)
  - Red clover (*Trifolium pratense*)
  - Kelp (*Laminaria digitata*)

Essiac - Information

- What's the evidence? – EFFICACY
- Purported Uses
  - Cancer treatment (Grade C – Natural Standard)
  - Other: "Health maintenance", HIV/AIDS, Immunostimulation
- Mechanisms of Action
  - Rhubarb and sheep sorrel contain anthraquinones → stimulate secretion of mucosa and water, **stimulate peristalsis**
  - Anthraquinones isolated from rhubarb → **stimulation of IL-1, IL-6, and TNF** in vitro and **tumour necrosis** against sarcoma 37, breast cancer, and Ehrlich cell lines in mice
  - Burdock root → induce **hypoglycemia** in animal models
  - Other extracts may **induce macrophage** response, may **inhibit platelet activating factor** in vitro

Essiac - Information

- What's the evidence? – EFFICACY
- In vitro data
  - Antioxidant and cytotoxic properties in three in vitro studies
  - Stimulated growth of breast cancer cells via ER-dependent and ER-independent pathways in one in vitro study
  - Conflicting data regarding prostate cancer cell antiproliferative effects in two in vitro studies
- Case reports
  - Remission of hormone-refractory prostate cancer reported in a patient
- Clinical studies
  - Retrospective study of breast cancer patients found no improvement in quality of life or mood

Essiac - Information

- What's the evidence? – SAFETY
- Contraindications
  - Renal and hepatic insufficiency (theoretically)
- Adverse Reactions
  - Anorexia, nausea, myalgia, fatigue, generalized abdominal pain post-Essiac tea for 6 months – one case report, 59 year old woman – symptoms resolved after stopping tea
  - Increased bowel movements, frequent urination, swollen glands, skin blemishes, flu-like symptoms, slight headaches – manufacturer of Flor Essence

Essiac - Interactions

- What's the evidence?
- In vitro data
  - Shown to **inhibit cytochrome P450** enzymes in one in vitro study
    - most notably CYP1A2 (37%) and CYP2C19 (24%)*
- Case reports
  - Decreased clearance of an experimental chemotherapy drug reported in a patient taking Essiac – meeting abstract from 1999 *Proc Annu Meet Am Soc Clin Oncol*

**Seely D, Kenney DA, Myers SP, et al. In vitro analysis of the herbal compound Essiac. Anticancer Res 2007;27(6B):3875-82.*

Essiac – Informed Consent

- Financial impact
  - "The Original Essiac Company" is selling 1 unit of Essiac powder to make 2 litres of tea for $42 USD
    - Dosing??
  - Flor Essence –
    - Dosing – 1-2 oz of tea, 1-3 times daily (depending on indication) diluted with equal amount of purified hot water
    - $46.00 for 32 oz, $30 for 17oz
- What information would you discuss with a patient who asks you about Essiac?

Mushroom extracts

- Reishi/ling zhi
- Yun zhi/PSK (Polysaccharide-K)

Mushroom extracts

- Used in traditional Chinese medicine or similar medicine systems
- Taken as raw fungus, boiled in water, capsules or extracts
- Claims:
  - Reishi – immunomodulant, renoprotection, hepatoprotection
  - PSK – immunostimulant, anti-cancer

Mushroom extracts

- Cancer
  - Purported mechanisms of action:
  - Reishi - immunostimulation, increase cytotoxicity against cancer cell lines, inhibition of cell proliferation & growth
  - PSK - increased cytokine production, T-cell proliferation

Mushroom extracts

- Efficacy
  - Reishi:
    - In a systematic review and meta-analysis, reishi lacked effects on tumor response in some studies; however, immunological effects occurred
    - Improved QoL (authors affliated with product manufacturer) and may be useful as anti-emetic
  - PSK:
    - One study showed improved survival rates in gastric & colorectal cancer pts
    - mixed results in breast cancer, hepatocellular carcinoma, leukemia

Mushroom extracts

- Efficacy

Reishi

Indications	Grade of evidence
Cancer	C
Chronic hepatitis B	C
Inflammation	C
Liver protection	C
Weight loss	C

Mushroom extracts

- Efficacy

PSK

Indications	Grade of evidence
Colorectal cancer (adjuvant)	C
Leukemia	C
Liver cancer (adjuvant)	C
Lung cancer (adjuvant)	C
Breast cancer (adjuvant)	D

Mushroom extracts

- Safety
- Reishi
  - inhibit CYP2E1, CYP1A2, and CYP3A4
  - Increased risk of bleeding
- PSK
  - Rare adverse reactions

Mushroom extracts

- Conclusion
- Reishi
  - There is some evidence on immunostimulation but the role in anti-cancer therapy is unclear. Author affliation with product manufacturer also decreases credibility of results.
  - Given extensive intereaction with cytochrome P450, careful medical review is needed

Mushroom extracts

- Conclusion
- PSK
  - Results vary depending on cancer types and true effect is uncertain from current available data.
  - No major safety concerns

Shark Cartilage

- Obtained from spiny dogfish shark and hammerhead shark
- Capsules, powder, liquid, enema, injection

Shark Cartilage

- "The promotion of crude shark cartilage extracts as a cure for cancer has contributed to at least two significant negative outcomes: a **dramatic decline in shark populations** and a **diversion of patients from effective cancer treatments**. An alleged lack of cancer in sharks constitutes a key justification for its use. Herein, both malignant and benign neoplasms of sharks and their relatives are described… Additional justifications for using shark cartilage are illogical extensions of the finding of antiangiogenic and anti-invasive substances in cartilage. Scientific evidence to date supports neither the efficacy of crude cartilage extracts nor the ability of effective components to reach and eradicate cancer cells. The fact that people think shark cartilage consumption can cure cancer illustrates the **serious potential impacts of pseudoscience**… **Increased use of logical, collaborative discussion will be necessary to ensure a sustainable future for man and the biosphere**."
- *Ostrander, GK, Cheng, KC, Wolf, JC, Wolfe, MJ. (2004). Shark cartilage, cancer and the growing threat of pseudoscience. Cancer Res. 64(23):8485-91.*

Shark Cartilage - Information

- What's the evidence? – EFFICACY
- Purported Uses
  - Cancer prevention, cancer treatment - Grade D
  - Others: arthritis, colitis, diabetic retinopathy, glaucoma, hemorrhoids, immunostimulation, inflammation, Kaposi sarcoma, macular degeneration, osteoarthritis, osteoporosis, psoriasis, wound healing
- Mechanisms of Action – in vitro and animal model studies
  - Antiandrogenic activity and antitumour activity in 2 in vitro studies and in 4 animal model studies
- Pharmacokinetics
  - ?bioavailability – large macromolecules not usually absorbed by GI tract, may be digested by proteolytic enzymes in the gut
  - No bioavailability studies with shark cartilage published - ?which active component to look for in the blood
  - Some support for bioavailability from one human study

Shark Cartilage - Information

- What's the evidence? – EFFICACY
- Clinical studies
  - Controversial – lack of bioavailability data, unsatisfactory outcomes in clinical trials
  - two arm, randomized, placebo-controlled, double blind clinical trial in 2005 in patients with incurable breast or colorectal carcinoma (n = 83) showed no difference in OS, no improvement in QoL *
  - Phase II study in metastatic renal cell carcinoma (suggested benefit) and phase I/II study in advanced cancer (various diagnoses, no benefit)
  - Randomized, double-blinded, placebo-controlled phase III clinical trial in unresectable stage III NSCLC (n=188), no statistically significant difference in OS, time to progression, progression-free survival, tumour response rates**

**Loprinzi CL, Levitt R, Barton DL, et al. Evaluation of shark cartilage in patients with advanced cancer: a North Central Cancer Treatment Group trial. Cancer. Jul 1 2005;104(1):176-182.*

***Lu C, Lee JJ, Komaki R, et al. Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. J Natl Cancer Inst. Jun 16 2010;102(12):859-865.*

Shark Cartilage - Information

- What's the evidence? – SAFETY
- Contraindications
  - Liver disease
- Adverse Reactions
  - Most report low toxicity
  - From phase II study in renal cell carcinoma (n=22): **Infrequent:** Nausea, vomiting, dyspepsia, constipation, diarrhea, anorexia, hypoglycemia in a type II diabetic patient
  - 57-year old man experienced reversible hepatic dysfunction – case report – 10 weeks of treatment, experienced nausea, vomiting, diarrhea, anorexia, jaundice, low-grade fever, scleral icterus, and elevated liver function tests

Shark Cartilage – Informed Consent

- Financial impact
  - Prices vary, can be quite expensive – example approx $32 for box of 100 capsules, dosing varies between **3-12 capsules three times a day**
- Warnings
  - "Commercially available supplements contain varying amounts of shark cartilage. Some are composed primarily of fillers and **may not have any biological activity**."
- What information would you discuss with a patient who asks you about shark cartilage?

UHN COURAGE LIVES HERE

Curcumin

- Tumeric, Indian saffron, jiang huang
- Common spice in Asian cuisine
- Taken orally in various forms – tea, powder
- Claims: Alzheimer's Disease, cancer, inflammation, infection, cardiovascular

UHN COURAGE LIVES HERE

Curcumin

- Cancer
  - Purported mechanism of action: Induce apoptosis, modulate cell signalling, inhibit post-radiation proliferation of colonic cancer cells

Curcumin

- Efficacy
  - Most studies were in vitro or animal research exploring possible mechanisms of action in cancer cell lines
  - One human study on colon cancer pt but focusing on cellular mechanism, clinical significance unclear

Curcumin

- Efficacy

Indications	Grade of evidence
Alzheimer's disease	C
Cancer	C
Heart disease prevention	C
Inflammation	C
Liver protection	C
Weight loss	C

UHN COURAGE LIVES HERE

Curcumin

- Safety
  - Safe when used in amount found commonly in food
  - Interacts with drugs that are cytochrome P450 substrates
  - Anti-coagulating effect
  - Contraindicated in biliary obstruction, hyperacidity conditions, or gastric ulcers

Curcumin

- Conclusion
  - Although there has been extensive research in possible mechanisms of action, there is a paucity in human subject research. Hence clinical benefit of in vitro findings unknown.
  - Generally safe but has high risk of interaction with existing medications. Careful review is needed.

Vitamin B17

- aka Amygdalin aka Laetrile
- Naturally occuring cyanogenic glycoside derived from nuts, plants, pits of certain fruits (primarily apricots)
- Metabolized to glucose and cyanide
- Used as a cancer treatment in Russia in 1845, later in USA in 1920s, became more popular in 1970s → negative study results lead to decreased use, resurgence in early 2000
- Oral, injectable, IV forms
- Banned in the US, Canada, EU, available over the Internet

UHN COURAGE LIVES HERE

Vitamin B17 - Information

- What's the evidence? – EFFICACY
- Purported Uses
  - Cancer prevention, cancer treatment – Grade D
- Mechanisms of Action
  - Was based on theory, now disproven that cancer cells contained more of enzyme beta-glucosidase which metabolizes amygdalin to glucose and cyanide → believed to be cytotoxic
  - Purported by some promoters that amygdalin is a vitamin (B17) and that cancer develops due to deficiencies in B17 – NO DATA to substantiate this
- In vitro data
  - 2 studies suggest anti-cancer properties

UHN COURAGE LIVES HERE

Vitamin B17 - Information

- What's the evidence? – EFFICACY
- Clinical studies
  - 1982 clinical trial conducted by NCI failed to find effectiveness
- Systematic Reviews
  - Two conclude amygdalin is ineffective as a cancer treatment

UHN COURAGE LIVES HERE

Vitamin B17 - Information

- What's the evidence? – SAFETY
- Adverse Reactions
  - Several patients in 1982 clinical trial had symptoms of mild cyanide toxicity or significant levels of cyanide
  - Reported (oral): Dermatitis and **cyanide toxicity** consisting of nausea, vomiting, headache, dizziness, mental obtundation, cyanosis, hypotension, ptosis, neuropathies, coma, and **death**. (from clinical trial published in NEJM in 1982, a pharm/tox study from JAMA 1981, cases from JAMA 1978 and 1983)
  - Reported (oral): Severe cyanide poisoning following ingestion of 3 grams of amygdalin with **concurrent use of high doses of vitamin C**. (case report 2005 Annals of Pharmacotherapy)
- Other safety concerns
  - Evaluation of parenteral formulation showed **contamination with pyrogens and microbes**
  - Oral and parenteral formualtions **did not contain the labeled amount of amygdalin**

UHN COURAGE LIVES HERE

Vitamin B17 – Informed Consent

- Financial impact
  - Example $336 USD to start treatment with injections for 21 days, followed by $160 USD per month for tablets
  - Some websites encourage travel to clinics in Mexico or elsewhere, may cost thousands of dollars
- What information would you discuss with a patient who asks you about Vitamin B17?

UHN COURAGE LIVES HERE

Complementary Therapies in Palliative Oncology – Your Recipe for Success

Ingredients:

- Information
- Interactions
- Informed Consent

Quickfire Challenge!

- 26F with recurrent Ewing's sarcoma, started chemo (irinotecan & temozolamide)
  - Wants to go on high dose Vitamin C because it will help fight her cancer
  - Decides to change her diet to a "raw diet" to "live for her body"
  - Would you recommend that?
  - What information do you need to know to give your recommendations?

Summary

- Complementary therapy covers a broad range of treatments
- It will likely be used by a growing number of patients
- Extensive research is being conducted but the quality of evidence varies widely
- High quality, credible resources available

Summary

- Evaluation should be based on efficacy & safety including assessment of interactions
- Provide patient with information in a supportive, non-judgmental manner
- Utilize a multidisciplinary/ interprofessional team where available
- Ensure informed consent

Resources

- Natural Standard (access via BCCA link)
- Lexi-Comp (access via UHN Intranet)
- Memorial Sloan-Kettering
- Cancer Care Ontario Drug Formulary
- BC Cancer Agency Cancer Drug Manual
- Canadian Cancer Society Complementary and Alternative Therapies

Thank you! Questions?