

MANAGING CHEMOTHERAPY SIDE EFFECTS

REVIEWING PREVENTION AND TREATMENT STRATEGIES OF THREE
COMMON ISSUES

MICHELLE GARDINER, PHARMD, BCOP, CPP

AUGUST 12, 2020

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OBJECTIVES

- Identify tactics for preventing and treating acute infusion reactions
- Describe non-pharmacological and pharmacological ways to prevent or manage chemotherapy induced peripheral neuropathy
- Demonstrate an understanding of cancer-related fatigue and treatable contributing factors

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MEDICATIONS COMMONLY ASSOCIATED WITH ACUTE INFUSION REACTIONS

- TAXANES
 - PACLITAXEL (TAXOL®)
 - DOCETAXEL (TAXOTERE)
- PLATINUM-BASED
 - CISPLATIN (PLATINOL®)
 - CARBOPLATIN (PARAPLATIN®)
 - OXALIPLATIN (ELOXATIN®)
- CETUXIMAB (ERIBITUX®)
- RITUXIMAB (RITUXAN®)

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COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 5.0

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
<p>Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.</p> <p style="font-size: small; text-align: center;">Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Publish Date: November 27, 2017</p>					

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EXAMPLE OF EMERGENCY ORDER SET

NURSING OXYGEN ORDERS / INSTRUCTIONS- OXYGEN DEVICE: NASAL CANNULA LITERS PER / MINUTE: 2 KEEP SPO2 > OR = TO: 92 FOR GRADE 2 - MODERATE SYMPTOMS AND GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS

SODIUM CHLORIDE (NS) 0.9 % INFUSION 20 ML/HR, INTRAVENOUS- FOR GRADE 1 - MILD SYMPTOMS OR GRADE 2 - MODERATE SYMPTOMS

SODIUM CHLORIDE 0.9% (NS BOLUS) BOLUS 1,000 ML- FOR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS.

DIPHENHYDRAMINE (BENADRYL) INJECTION 25 MG 25 MG, INTRAVENOUS, ONCE AS NEEDED, FOR GRADE 1 - MILD SYMPTOMS, GRADE 2 - MODERATE SYMPTOMS, OR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS.,

FAMOTIDINE IV 20 MG- FOR GRADE 2 - MODERATE SYMPTOMS OR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS.

MEPERIDINE (DEMEROL) INJECTION 25 MG- ONCE AS NEEDED, RIGORS, STARTING WHEN RELEASED, FOR 1 DOSE FOR GRADE 1 - MILD SYMPTOMS OR GRADE 2 - MODERATE SYMPTOMS

METHYLPREDNISOLONE SODIUM SUCCINATE INJECTION 125 MG- 125 MG, INTRAVENOUS, ONCE AS NEEDED, FOR GRADE 2 - MODERATE SYMPTOMS OR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS.

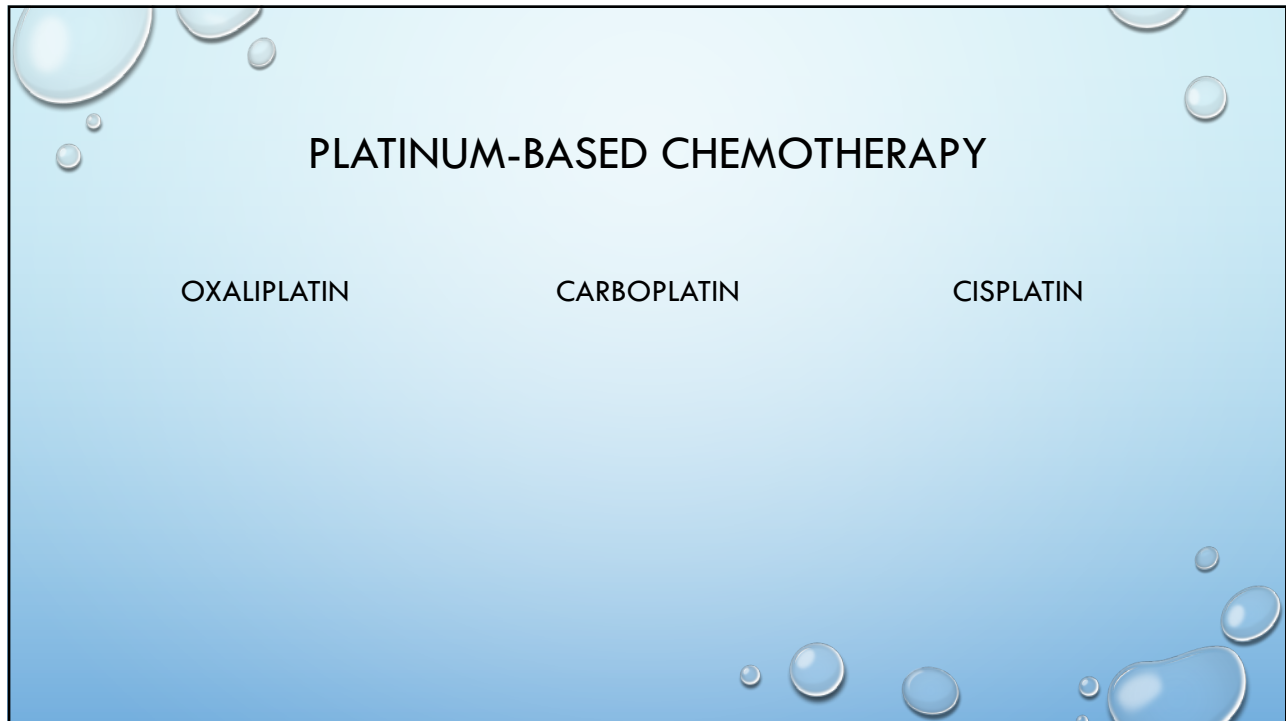
EPINEPHRINE IM 0.3 MG- 0.3 MG, INTRAMUSCULAR, ONCE AS NEEDED, FOR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS

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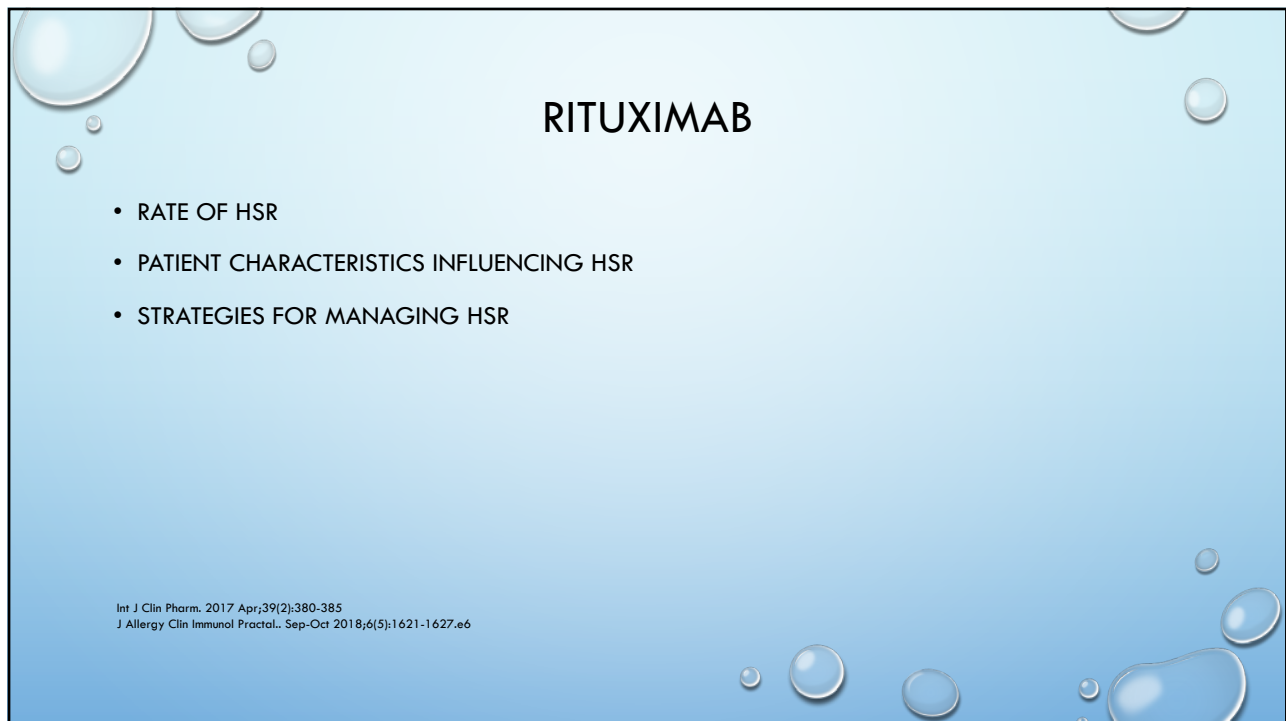
TAXANES

<p>PACLITAXEL</p> <p>SOLVENT: CREMOPHOR EL</p> <p>RATE OF HSR:</p> <p>CROSS REACTIVITY: ??</p>	<p>NAB-PACLITAXEL (ABRAXANE)</p> <p>SOLVENT: N/A</p> <p>RATE OF HSR:</p> <p>CROSS REACTIVITY: ??</p>	<p>DOCETAXEL</p> <p>SOLVENT: POLYSORBATE 80 (TWEEN)</p> <p>RATE OF HSR:</p> <p>CROSS REACTIVITY: ??</p>
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RAPID DRUG DESENSITIZATION

- SCENARIOS AND STRATEGIES
- PLATINS
- TAXANES
- CETUXIMAB

Clinic Rev Allerg Immunol (2018) 54:375-385
J Allergy Clin Immunol Pract. 2018 Jul-Aug;6(4):1356-1362

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CETUXIMAB (ERBITUX®)

EGFR receptor antagonist used in head neck cancer and metastatic colorectal cancers

Initial FDA approval had grade $\frac{3}{4}$ infusion reaction in < 5% of patients

Southwestern United States (including North Carolina and Tennessee) saw grade $\frac{3}{4}$ reactions of >20%

Preformed immunoglobulin E antibodies against galactose- α -1,3-galactose in serum

Cancer. 2016 Jun 1;122(11):1697-701. doi: 10.1002/ncr.29978. Epub 2016 Mar 15
<https://uspl.lilly.com/erbitux/erbitux.html#s18>.

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CETUXIMAB

<p>Alpha-gal assay for IgE antibodies</p> <ul style="list-style-type: none"> • Negative = < 0.10 kU/L • Included levels up to <0.35ku/l 	<p>Alpha-gal testing not mandated in pi</p> <ul style="list-style-type: none"> • Evaluate for history of tick bites • history of red meat allergy
<p>61.7% (37/60) patients negative</p> <ul style="list-style-type: none"> • Values: <0.10-0.23 kU/L • No anaphylaxis 	<p>Send out test</p> <ul style="list-style-type: none"> • 7 days for results
<p>38.3% (23/60) patients positive</p> <ul style="list-style-type: none"> • Values: <1.0-44.2 • Excluded from cetuximab arm 	<p>Premedicate</p> <ul style="list-style-type: none"> • Antihistamines • corticosteroids

Cancer. 2016 Jun 1;122(11):1697-701.
<https://uspl.lilly.com/erbitux/erbitux.html#s18>.

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CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY (CIPN)

RECOMMENDATIONS FOR PREVENTION AND TREATMENT

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CHEMOTHERAPY AGENTS ASSOCIATED WITH PERIPHERAL NEUROPATHY

- TAXANES
- PLATINUMS
- VINCA ALKALOIDS
- ERIBULIN
- BORTEZOMIB/CARFILZOMIB

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PREVENTION AND MANAGEMENT OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY IN SURVIVORS OF ADULT CANCERS: AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) GUIDELINE UPDATE

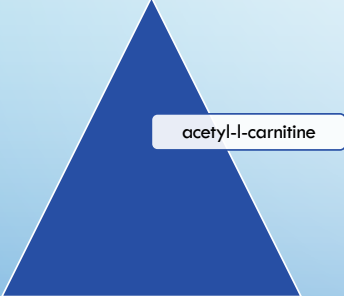
- PACLITAXEL MYALGIAS AND ARTHRALGIAS RECLASSIFIED AS ACUTE NEUROPATHY
- TOTAL CHEMOTHERAPY EXPOSURE ONLY RECOMMENDED PREVENTION STRATEGY



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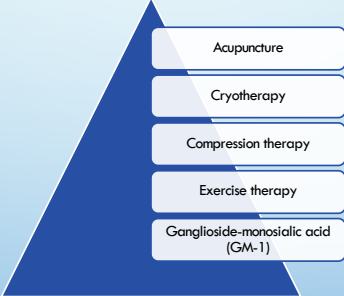
ASCO CIPN UPDATE: PREVENTION

**NOT RECOMMENDED:
POTENTIALLY HARMFUL**



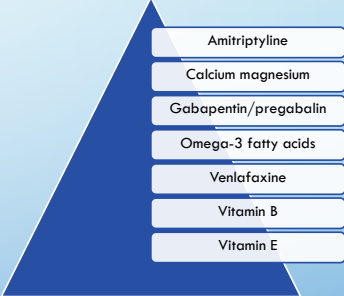
acetyl-L-carnitine

**RECOMMENDED IN
CLINICAL TRIAL:
REQUIRES MORE DATA**



- Acupuncture
- Cryotherapy
- Compression therapy
- Exercise therapy
- Ganglioside-monosialic acid (GM-1)

**NOT RECOMMENDED:
NO BENEFIT FOUND**



- Amitriptyline
- Calcium magnesium
- Gabapentin/pregabalin
- Omega-3 fatty acids
- Venlafaxine
- Vitamin B
- Vitamin E

ASCO Guideline Update. DOI: 10.1200/JCO.20.01399

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CRYOTHERAPY

KEEPING HANDS AND FEET COLD DURING
CHEMOTHERAPY ADMINISTRATION



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CRYOTHERAPY: POTENTIAL BENEFIT

HANAI, A ET AL. 2018

- FROZEN GLOVES AND SOCKS
- PATIENTS WERE OWN CONTROLS

RUDDY, KJ ET AL. 2019

- IMPROVEMENT SHOWN WITH POOLED CONTROL GROUPS FROM OTHER STUDIES

Breast 48:89-97, 2019
J Natl Cancer Inst 110:141-148, 2018

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ASCO TREATMENT RECOMMENDATIONS

For painful neuropathy

- Duloxetine

Not recommended outside of clinical trial

- Exercise therapy
- Acupuncture
- Scrambler therapy
- Gabapentin/pregabalin
- Topical gel treatment containing baclofen, amitriptyline HCL, plus/minus ketamine
- Tricyclic antidepressants
- Oral cannabinoids

ASCO Guideline Update. DOI: 10.1200/JCO.20.01399

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TRICYCLIC ANTIDEPRESSANTS

Amitriptyline, nortriptyline, desipramine and imipramine

Moved from: "reasonable to try" to "not recommended"

Lack of evidence for efficacy in treating CIPN

No new clinical trials since last update

Unfavorable side effects: drowsiness, irregular heart rate, confusion in older patients

ASCO Guideline Update. DOI: 10.1200/JCO.20.01399

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GABAPENTINOIDS GABAPENTIN AND PREGABALIN

Evidence for treating established CIPN is inconclusive

More clinical trials required before routine use endorsed by ASCO

Some insurance companies require failed trial of gabapentinoid before duloxetine

ASCO Guideline Update. DOI: 10.1200/JCO.20.01399

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PREGABALIN VERSUS DULOXETINE

BREAST CANCER PATIENTS TREATED WITH PACLITAXEL OR DOCETAXEL

Pregabalin

- 75 mg once daily x 1 week
- 150 mg twice daily x 5 weeks
- N=40
- Visual analog scale (VAS) scores improved in 37/40 (92.5%)

Duloxetine

- 30 mg once daily x 1 week
- 30 mg twice daily x 5 weeks
- N=42
- Visual analog scale (VAS) scores improved in 16/42 (38.1%)

Salehifar E et al. Clin Drug Investig. 2020 Mar;40(3):249-257. doi: 10.1007/s40261-019-00882-6.
Avan R et al. J Res Med Sci. 2018;23:52. doi: 10.1016/j.jrmp.2017.11.013

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DULOXETINE FOR PAINFUL CIPN

PATIENTS WHO COMPLETED CHEMOTHERAPY WITH PACLITAXEL OR OXALIPLATIN

231 patients randomized

↓

Randomized, double-blind, placebo-controlled crossover

↓

≥ grade 1 CIPN and ≥ 4/10 neuropathy-related pain

↓

Symptoms persisting for at least 3 months since chemotherapy completion

↓

Duloxetine 30 mg once daily then 60 mg once daily for 4 weeks

↓

2 week washout then cross over

JAMA. 2013;309(13):1359-1367

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CANCER – RELATED FATIGUE

CANCER-RELATED FATIGUE IS A DISTRESSING, PERSISTENT, SUBJECTIVE SENSE OF PHYSICAL, EMOTIONAL, AND/OR COGNITIVE TIREDNESS OR EXHAUSTION RELATED TO CANCER OR CANCER TREATMENT THAT IS NOT PROPORTIONAL TO RECENT ACTIVITY AND INTERFERES WITH USUAL FUNCTIONING.

NCCN Guidelines. Cancer-Related Fatigue. Version 2.2020. May 4, 2020.

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EVALUATING AND ASSESSING FATIGUE

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest; limiting self care ADL	----	----
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.					

Common Terminology Criteria for Adverse Events (CTCAE) v5.0

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EVALUATING AND ASSESSING FATIGUE

- SCALE OF 1-10
 - 0= NO FATIGUE AND 10= WORST FATIGUE YOU CAN IMAGINE
 - 0-3= NONE TO MILD
 - 4-6= MODERATE
 - 7-10= SEVERE
- DESCRIPTION
 - NONE
 - MILD
 - MODERATE
 - SEVERE

. NCCN Guidelines. Cancer-Related Fatigue. Version 2.2020. May 4, 2020.

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IDENTIFY AND TREAT UNDERLYING CAUSES

Fatigue

- Pain
- Emotional distress
- Inadequate nutrition
- Anemia
- Endocrine dysfunction

NCCN Guidelines. Cancer-Related Fatigue. Version 2.2020. May 4, 2020.

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INADEQUATE NUTRITION

NUTRITION CONSULT
PHARMACY
NURSING SUPPORT

- Nausea or vomiting
- Dysgeusia
- Loss of appetite
- Constipation
- Diarrhea
- Mucositis
- Gerd

NCCN Guidelines. Cancer-Related Fatigue. Version 2.2020. May 4, 2020.

This infographic features a light blue background with a bubble pattern. On the left, the text 'INADEQUATE NUTRITION' is at the top, followed by 'NUTRITION CONSULT', 'PHARMACY', and 'NURSING SUPPORT' stacked vertically. On the right, seven dark blue rounded rectangular boxes list symptoms: 'Nausea or vomiting', 'Dysgeusia', 'Loss of appetite', 'Constipation', 'Diarrhea', 'Mucositis', and 'Gerd'. A small copyright notice is at the bottom left.

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PAIN AND EMOTIONAL DISTRESS

- Insomnia
- Sleep interruptions
- Side effects of medication
- Reduced activity

NCCN Guidelines. Cancer-Related Fatigue. Version 2.2020. May 4, 2020.

This infographic features a light blue background with a bubble pattern. The title 'PAIN AND EMOTIONAL DISTRESS' is centered at the top. Below it, four dark blue rounded rectangular boxes are arranged in a 2x2 grid, containing the text: 'Insomnia' (top-left), 'Sleep interruptions' (top-right), 'Side effects of medication' (bottom-left), and 'Reduced activity' (bottom-right). A small copyright notice is at the bottom left.

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ANEMIA AND ENDOCRINE DISTURBANCES

- ANEMIA
 - IRON REPLACEMENT
 - TRANSFUSION
- HYPOTHYROIDISM
 - REPLACEMENT
- ADRENAL INSUFFICIENCY
- HYPOGONADISM
- HOT FLASHES

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NON-PHARMACOLOGICAL INTERVENTIONS

Sleep Hygiene

Avoid caffeine/nicotine in late afternoon	Consistent schedule	Avoid bright light in evenings	Turn off electronics 30 minutes before	Eat light at night
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NON-PHARMACOLOGICAL INTERVENTIONS

Physical activity	Yoga	patient specific considerations
<ul style="list-style-type: none"> Walk 30 minutes most days of the week Cardiovascular endurance Resistance training 	<ul style="list-style-type: none"> Twice weekly 	<ul style="list-style-type: none"> Bone metastasis Thrombocytopenia/anemia Recent surgery Safety issues (e.g. falling)

NCCN Guidelines. Cancer-Related Fatigue. Version 2.2020. May 4, 2020.

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PHARMACOLOGICAL INTERVENTIONS

Methylphenidate	<ul style="list-style-type: none"> Active treatment Advanced cancer End of life
Corticosteroids	<ul style="list-style-type: none"> Short term use Advanced cancer
Nutritional supplements	<ul style="list-style-type: none"> inconclusive
Modafinil	<ul style="list-style-type: none"> Not recommended
Antidepressants	<ul style="list-style-type: none"> Not recommended

NCCN Guidelines. Cancer-Related Fatigue. Version 2.2020. May 4, 2020.

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METHYLPHENIDATE

- USE WITH CAUTION
- FIRST RULE OUT AND TREAT UNDERLYING CAUSES
- SHOWS IMPROVEMENT IN FATIGUE COMPARED TO PLACEBO
- OPTIMAL DOSING IN CANCER PATIENTS AND OLDER ADULTS NOT ESTABLISHED
 - METHYLPHENIDATE 5 MG TO 36 MG DAILY IN TRIALS
 - METHYLPHENIDATE 5 MG ONCE DAILY STARTING DOSE
- SIDE EFFECTS
 - HEADACHE
 - NAUSEA

Cancer Care (Engl). 2016;25(6):970-979
 NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020
 J Clin Oncol. 2010 Aug 10;28(23):3673-9

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- CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHIC PAIN AND QUALITY OF LIFE AMONG CANCER PATIENTS. CANCER NURS 10.1097/NCC.0000000000000693 [EPUB AHEAD OF PRINT ON MARCH 18, 2019]
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