Adult Guidelines for Assessment and Management of Nausea and Vomiting

To Prevent and Manage Nausea and Vomiting
Induced by Chemotherapy Or
Related to Other Oncologic Etiologies

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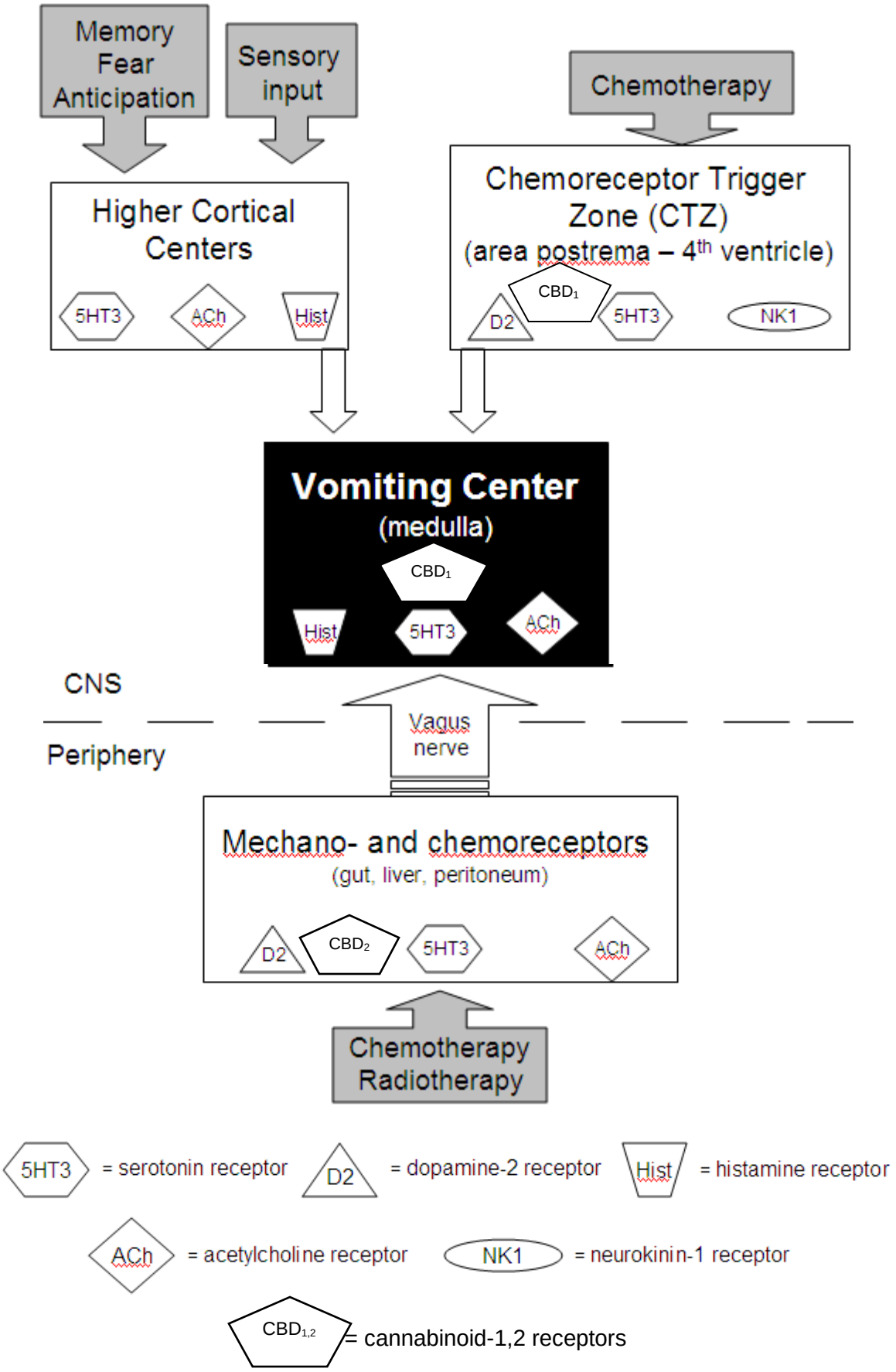
Pathophysiology of Nausea and Vomiting



Possible Etiologies and Suggested Treatment for Nausea and Vomiting

Chemical/Metabolic

Chemotherapy (pg 8)

XRT (pg 9)

Electrolyte imbalances
- Dopamine antagonists

Opioid-induced
- Dopamine antagonists
- Ondansetron

Scheduled antiemetic for 24-48 hours, then prn (tolerance will usually develop)

CNS/ Psycho-emotional

Increased ICP/ Brain tumor/mets
- Dexamethasone

Anxiety-related
- Lorazepam
- Relaxation
- Behavioral techniques (e.g. hypnosis)

Vestibular

Motion sickness or movement-related
- Scopolamine
- Meclizine

Abdominal/Visceral

GERD, indigestion
- H2 blockers
- Proton pump inhibitors (PPI's)

Constipation
- Senna
- +/- Miralax® OR lactulose (if not lactase deficient)
- +/- metoclopramide

Gastroparesis, ileus, functional obstruction
- Metoclopramide

Small Bowel Obstruction
- Dexamethasone
- Octreotide
- Metoclopramide
- H2 Blocker

GVHD
- Dopamine antagonists
- Ondansetron
- Octreotide

Etiology Unknown
- Haloperidol
- Prochlorperazine
- Olanzapine
- Metoclopramide
- Dexamethasone
- Acupuncture

Patient Assessment

History: past antiemetics use/effects

Nausea intensity (0-10), duration, description

Aggravating or activating factors (thought/smell of food, eating, drinking, not eating, medications, movement, time of day)

Q**U**ality of life disturbances resulting from nausea and vomiting

Symptoms associated with nausea/vomiting: Dizziness, fatigue, anxiety/depression, sweating, pain, constipation/diarrhea

Emetic episodes per 24 hours

Alleviating factors: Distraction, lying down, medication, food, vomiting, time

Chemotherapy-Induced Nausea and Vomiting (CINV)

Risk Factors: h/o GI conditions, younger than 50, female, past nausea/vomiting associated with chemotherapy, hyperemesis gravidarum, h/o motion sickness

Protective Factors: high alcohol consumption (greater than 5 alcoholic drinks per day)

Definitions

Acute chemotherapy induced nausea and vomiting usually begins within minutes to hours after chemotherapy and lasts up to 24 hours.

Delayed nausea and vomiting develops more than 24 hours after chemotherapy and may last several days.

Anticipatory nausea and vomiting begins before chemotherapy, and is often associated with poorly controlled acute and delayed nausea and vomiting.

Breakthrough nausea and vomiting occurs despite preventive therapy and is treated with an as needed regimen.

Refractory nausea and vomiting occurs when antiemetic prophylaxis and/or rescue have failed. See page 10 for therapy considerations.

Classification of chemotherapy agent emetogenicity
Emetogenecity is based on the percentage of patients who experience emesis in the absence of effective antiemetic prophylaxis.

Emetogenic potential of intravenous antineoplastic agents

High emetic risk (> 90% frequency of emesis)	▪ AC combination (any regimen w/ an anthracycline and cyclophosphamide) ▪ Carboplatin AUC $\geq$ 4 ▪ Carmustine > 250 mg/m^2 ▪ Cisplatin ▪ Cyclophopshamide > 1,500 mg/m^2	▪ Dacarbazine ▪ Doxorubicin $\geq$ 60 mg/m^2 ▪ Epirubicin > 90 mg/m^2 ▪ Ifosfamide $\geq$ 2,000 mg/m^2 per dose ▪ Mechlorethamine ▪ Streptozocin
Moderate emetic risk (30-90% frequency of emesis)	▪ Aldesleukin > 12-15 million international units/m^2 ▪ Amifostine > 300 mg/m^2 ▪ Arsenic trioxide ▪ Azacitadine ▪ Bendamustine ▪ Busulfan ▪ Carboplatin AUC < 4 ▪ Carmustine $\leq$ 250 mg/m^2 ▪ Clofarabine ▪ Cyclophopshamide $\leq$ 1,500 mg/m^2 ▪ Cytarabine > 200 mg/m^2 ▪ Dactinomycin	▪ Daunorubicin ▪ Dinutuximab ▪ Doxorubicin < 60 mg/m^2 ▪ Epirubicin $\leq$ 90 mg/m^2 ▪ Idarubicin ▪ Ifosfamide < 2,000 mg/m^2 per dose ▪ Interferon alfa $\geq$ 10 million international units/m^2 ▪ Irinotecan ▪ Melphalan ▪ Methotrexate $\geq$ 250 mg/m^2 ▪ Oxaliplatin ▪ Temozolomide ▪ Trabectedin
Low emetic risk (10-30% frequency of emesis)	▪ Ado-trastuzumab emtansine ▪ Aldesleukin $\leq$ 12 million international units/m^2 ▪ Amifostine $\leq$ 300 mg/m^2 ▪ Atezolizumab ▪ Belinostat ▪ Blinatumomab ▪ Brentuximab vedotin ▪ Cabazitaxel ▪ Carfilzomib ▪ Cytarabine 100-200 mg/m^2 ▪ Docetaxel ▪ Doxorubicin liposomal ▪ Eribulin ▪ Etoposide ▪ 5-fluorouracil ▪ Floxuridine ▪ Gemcitabine	▪ Interferon alfa >5 - <10 million international units/m^2 ▪ Irinotecan liposomal ▪ Ixabepilone ▪ Methotrexate > 50 - <250 mg/m^2 ▪ Mitomycin ▪ Mitoxantrone ▪ Necitumumab ▪ Omacetaxine ▪ Paclitaxel ▪ Paclitaxel, albumin bound ▪ Pemetrexed ▪ Pentostatin ▪ Pralatrexate ▪ Romidepsin ▪ Talimogene laherparepvec ▪ Thiotepa ▪ Topotecan ▪ Ziv-aflibercept
Minimal emetic risk (< 10% frequency of emesis)	▪ Alemtuzumab ▪ Asparaginase ▪ Bevacizumab ▪ Bleomycin ▪ Bortezomib ▪ Cetuximab ▪ Cladribine (2-chlorodeoxyadenosine) ▪ Cytarabine < 100 mg/m^2 ▪ Daratumumab ▪ Decitabine ▪ Denileukin difitox ▪ Dexrazoxane ▪ Elotuzumab ▪ Fludarabine ▪ Interferon alfa $\leq$ 5 million international units/m^2 ▪ Ipilimumab ▪ Methotrexate $\leq$ 50 mg/m^2 ▪ Nelarabine	▪ Nivolumab ▪ Obinutuzumab ▪ Ofatumumab ▪ Panitumumab ▪ Pegaspargase ▪ Peginterferon ▪ Pembrolizumab ▪ Pertuzumab ▪ Ramucirumab ▪ Rituximab ▪ Siltuximab ▪ Temsirolimus ▪ Trastuzumab ▪ Valrubicin ▪ Vinblastine ▪ Vincristine ▪ Vincristine (liposomal) ▪ Vinorelbine

Adapted from NCCN Clinical Practice Guidelines in Oncology. V.2.2017. Antiemesis.

Emetogenic potential of oral antineoplastic agents

Moderate-high emetic risk (≥30% frequency of emesis)	▪ Altretamine ▪ Busulfan ≥ 4 mg/day ▪ Ceritinib ▪ Crizotinib ▪ Cyclophosphamide ≥ 100 mg/m^2/day ▪ Estramustine ▪ Etoposide ▪ Lenvatinib	▪ Lomustine (single day) ▪ Mitotane ▪ Olaparib ▪ Panobinostat ▪ Procarbazine ▪ Rucaparib ▪ Temozolomide > 75 mg/m^2/day ▪ Trifluridine/tipiracil
Minimal-low emetic risk (<30% frequency of emesis)	▪ Afatinib ▪ Alectinib ▪ Axitinib ▪ Bexarotene ▪ Bosutinib ▪ Busulfan < 4 mg/day ▪ Cabozantinib ▪ Capecitabine ▪ Chlorambucil ▪ Cobimetinib ▪ Cyclophosphamide < 100 mg/m^2/day ▪ Dasatinib ▪ Dabrafenib ▪ Erlotinib ▪ Everolimus ▪ Fludarabine ▪ Gefitinib ▪ Hydroxyurea ▪ Ibrutinib ▪ Idelalisib ▪ Imatinib ▪ Ixazomib ▪ Lapatinib ▪ Lenalidomide	▪ Melphalan ▪ Mercaptopurine ▪ Methotrexate ▪ Nilotinib ▪ Osimertinib ▪ Palbociclib ▪ Pazopanib ▪ Pomalidomide ▪ Ponatinib ▪ Regorafenib ▪ Ruxolitinib ▪ Sonidegib ▪ Sorafenib ▪ Sunitinib ▪ Temozolomide ≤ 75 mg/m^2/day ▪ Thalidomide ▪ Thioguanine ▪ Topotecan ▪ Trametinib ▪ Tretinoin ▪ Vandetanib ▪ Vemurafenib ▪ Venetoclax ▪ Vismodegib ▪ Vorinostat

Adapted from NCCN Clinical Practice Guidelines in Oncology. V.2.2017. Antiemesis.

General concepts in the management of CINV

Goal: To prevent nausea/vomiting in patients receiving antineoplastic agents.

Antiemetic selection: Selection of an appropriate antiemetic regimen should be based on the emetic risk of antineoplastic agents, prior experience with antiemetics, and patient-specific risk factors (see page 5).

Route of administration: Oral and intravenous antiemetic formulations have equivalent efficacy when used at appropriate doses.

Anticipatory nausea and vomiting: May respond to prophylactic use of anti-anxiety agents (e.g. lorazepam) and behavioral interventions (meditation, relaxation) along with aggressive control of acute and delayed nausea/vomiting.

Delayed nausea: For regimens that are frequently associated with delayed nausea/vomiting, treat patient with **scheduled** oral antiemetics that include dexamethasone. Olanzapine may also be considered. Carboplatin, cisplatin, oxaliplatin, cyclophosphamide, and doxorubicin are frequently associated with delayed nausea and vomiting.

Other etiologies: Other possible etiologies of nausea/vomiting should be addressed and properly managed (e.g. use of H2 blockers or proton pump inhibitors* for management of dyspepsia which may mimic nausea).
*Caution: potential drug interactions with TKIs

Combination therapy has been shown to improve the efficacy of the primary antiemetic. However, **do not** use two agents from the same class of antiemetics in combination. (e.g. metoclopramide and prochlorperazine). This can significantly increase the side effects and does not increase efficacy (see page 10). Olanzapine should be used with caution in combination with other dopamine antagonists and other CNS depressants.

Combination chemotherapy regimens

- Give agents that are effective for the highest emetogenic risk level of any single agent in the regimen (e.g. cisplatin and etoposide: use agents recommended for cisplatin) with the exception of anthracycline and cyclophosphamide combinations which synergistically lead to high emetogenicity.

Consecutive-day chemotherapy regimens

- Risk of acute and delayed nausea/vomiting is based on the risk of each agent
- Antiemetic prophylaxis for a given day should be based on the agent with the highest emetogenicity administered on that day
- Prophylaxis for delayed nausea/vomiting should continue for 2-3 days after the last dose of high- to moderately emetogenic chemotherapy

Suggested Antiemetics for Highly Emetogenic Chemotherapy

Day 1 (30 minutes prior to chemotherapy)	Days 2-4
Ondansetron 16 mg PO or IV	Dexamethasone[2] 8 mg PO daily
Dexamethasone 12 mg PO or IV	
NK1 receptor antagonist[1] IV	
+/- Olanzapine[3] 5-10 mg PO daily	+/- Olanzapine 5-10 mg PO daily

[1]In highly-emetogenic treatment regimens where the highly-emetogenic agent is only given on day 1 and not days 8 or 15, the NK1 antagonist is only given on day 1. (e.g. cisplatin/gemcitabine or cisplatin/navelbine)

For highly-emetogenic treatment regimens given over consecutive days (e.g. 3-5 days of cisplatin), the NK-1 antagonist is given on day 1. For select NK1 receptor antagonists, a repeat dose may be necessary to cover the delayed CINV period (e.g. day 5 administration of fosaprepitant I a 5-day cisplatin regimen)

[2]According to the ASCO 2017 Antiemetic Guideline Update, dexamethasone may be omitted in the delayed setting for AC containing chemotherapy regimens.

[3]Olanzapine may be added to cisplatin and other highly emetogenic chemotherapy regimens especially where nausea is a concern. Use caution in high risk patients such as elderly, patients taking other CNS depressants or those at risk of orthostatic hypotension. Consider starting at 5 mg in these patients.

DFCI/BWH/MGH considers the FOLFIRINOX regimen to be highly emetogenic.

Suggested Antiemetics for Moderately Emetogenic Chemotherapy

Day 1 (30 minutes prior to chemotherapy)	Days 2-3
Ondansetron[4] 16 mg PO or IV	Dexamethasone[5] 8 mg PO daily
Dexamethasone 12 mg PO or IV	
+/- NK1 receptor antagonist[6]	

[4] Ondansetron is recommended for moderately emetogenic **ORAL** chemotherapy requiring daily CINV prophylaxis.

[5] Dexamethasone may be omitted in the delayed setting for regimens in which delayed CINV is not common.

[6] NK1 receptor antagonist may be added for prevention of nausea and vomiting from moderately emetogenic chemotherapy regimens in patients with refractory nausea and vomiting from previous regimens/cycles or other risk factors (page 5).

Suggested Antiemetics for Low Emetogenic Chemotherapy

Prophylaxis may consist of any ONE of the following:

-Dexamethasone 4-8 mg PO or IV
-Ondansetron 4-8 mg PO or IV
-Metoclopramide 10 mg PO or IV
-Prochlorperazine 10 mg PO or IV

Suggested Antiemetics for Minimally Emetogenic Chemotherapy

Routine prophylaxis is not necessary for minimally emetogenic chemotherapy

Suggested Antiemetics for Radiation-Induced Emesis

Emetic risk	Radiation field	Recommended prophylaxis
High (>90%)	Total-body irradiation	Ondansetron 8-24mg/day +/- corticosteroid prior to each fraction
Moderate (30-90%)	Upper abdomen, craniospinal irradiation	Ondansetron 8mg/day day +/- corticosteroid prior to each fraction
Low (10-30%)	Brain, head and neck, thorax, pelvis	No routine prophylaxis recommended.
Minimal (<10%)	Extremities, Breast	No routine prophylaxis recommended.

Refractory Chemotherapy-Induced Nausea and Vomiting

If initial therapy is ineffective:

1. Reevaluate for additional cause(s) (see page 4).
2. Increase dose of selected agent(s) (see page 10).
3. Ensure patient's antiemetic regimen includes both scheduled and as needed agents.
4. Consider adding an additional agent or rotating to a different drug in the same class.
    - Additional agents to consider adding include:
        - Corticosteroid
        - Ondansetron (If the patient has not received palonosetron within the last 48-72 hours)
        - NK1 receptor antagonist (only if patient receiving a corticosteroid and 5HT3 receptor antagonist).
            - NK1 receptor antagonists should not be used to treat ongoing nausea and vomiting rather used in the prophylactic setting on subsequent cycles of chemotherapy. Additional doses post-chemotherapy have not been shown to be efficacious.
        - Olanzapine (use caution in combination with dopamine antagonists due to similar MOA; consider discontinuation of prochlorperazine, metoclopramide or haloperidol)
    - Rotate to a different dopamine antagonist (e.g. haloperidol, metoclopramide)
    - In selected highly and moderately emetogenic regimens, ondansetron may be replaced with palonosetron 0.25 mg IV prior to chemotherapy. This requires the discontinuation of all other 5HT3 antagonists, including those taken at home, for 48 hours after palonosetron is administered.
    - Cannabinoids – dronabinol (Marinol, Syndros), nabilone (Cesamet)

***See chart on page 11 for dosing and drug classification.

Classes of Commonly Used Antiemetics		
	Dose/Routes	Side effects/Management
Serotonin Antagonists		
¥Ondansetron (Zofran®)	8-24 mg IV/PO/day max single dose is 16 mg	Constipation (provide prophylactic bowel management) QT prolongation
¥Palonosetron (Aloxi®)	0.25 mg IV x 1 (may repeat in 48-72 hours with multi-day chemo regimens)	
¥Granisetron (Kytril®)	10 mcg/kg IV /2mg PO daily	
¥Dolasetron (Anzemet®)	100 mg PO daily	
Substance P (NK1) Antagonists		
Aprepitant (Emend®)	125 mg PO day 1 80 mg PO days 2-3	Infusion site reactions; IV contains polysorbate 80 = risk of HSR ↑ dexamethasone levels ↓warfarin levels (monitor INR closely)
Fosaprepitant (Emend IV®)	150 mg IV on day 1	
Aprepitant injectable emulsion (Cinvanti®)	130 mg IV on day 1 (highly emetogenic) 110 mg IV on day 1 (moderately emetogenic)	Does not contain polysorbate 80 110 mg dose to be followed day aprepitant 80 mg on days 2, 3
Rolapitant (Varubi®)	180 mg PO day 1 OR 166.5 mg IV day 1	↑ Thioridazine and Pimozide- avoid combo Monitor digoxin and warfarin Monitor AEs of BCRP substrates (methotrexate, topotecan, irinotecan) May increase levels of antidepressants (due to CYP2D6 inhibition)
Dopamine Antagonists		
¥Prochlorperazine (Compazine®)	10 mg PO TID-QID (max 40 mg/day) 25 mg PR BID	EPS (see page 11 for definitions and management) QT prolongation
Perphenazine (Trilafon®)	2-8 mg PO q 4-6 hours (max 24 mg/day)	
¥Metoclopramide (Reglan®)	10-40 mg PO/IV TID-QID	
¥Haloperidol (Haldol®)	0.5-2 mg IV/PO q 4-8 hours	
¥Droperidol (Inapsine®)	2.5-5 mg IV q 3-4 hours	EKG monitoring required (Not available at BWH)
Corticosteroids		
Dexamethasone (Decadron®)	4-20 mg PO/IV daily-bid	Delirium, anxiety, insomnia (reduced dose if possible)
Methylprednisolone (Solu-medrol®)	50-100 mg IV daily	
Atypical Antipsychotics		
¥Olanzapine (Zyprexa®)	2.5-10 mg daily	Sedation, orthostatic hypotension
Antihistamines		
Dimenhydrinate (Dramamine®)	50-100 mg PO/IV q 4-6 hours	Sedation, confusion (especially in patients > 65 years) Avoid use of promethazine with dopamine antagonists due to similar MOA
Meclizine (Antivert®)	25-50 mg PO daily	
Promethazine (Phenergan®)	12.5-25 mg PO/PR q 4 hours	
Trimethobenzamide (Tigan®)	300 mg PO TID-QID 200mg PR TID-QID	
Anticholinergics		
Scopolamine (Transderm Scop®)	1.5-3 mg TD q 72 h	Dry mouth, blurred vision, delirium
Cannabinoids		
Dronabinol (Marinol®)	2.5-10 mg BID-TID	Confusion, ataxia
Nabilone (Cesamet®)	1-2 mg BID	
Dronabinol (Syndros®)	2.1 mg/m^2-4.2 mg/m^2 1-3 hours prior to chemo then every 2-4 hours post chemo	Oral Solution 5 mg/ml (2.1 mg = 2.5 mg capsules)
Anxiolytics		
Lorazepam (Ativan®)	0.5-2 mg PO/IV q 4-6 hours	Confusion, sedation

¥ These medications have been known to prolong the QTc interval and lead to Torsades de Pointes. EKG monitoring is recommended when using these medications with other QTc prolonging medications (e.g. methadone) or in patients with a previous prolonged QTc.

Extrapyramidal Symptoms (EPS)/Movement Disorders

Many antiemetics are related to the antipsychotic class of medications and therefore pose a risk of movement disorders including: akathisia, extrapyramidal side effects, Tardive Dyskinesia (TD), and Parkinsonism.

Akathisia

Motor restlessness manifesting as inability to keep still, rocking back and forth, purposeless shaking of foot/leg, or pacing.

- Reduce or stop the agent if possible
- Add beta blocker (propranolol preferred)
- **NOT** effective: anticholinergics (diphenhydramine, benztropine)

Dystonic reactions

Acute onset of muscle spasm, commonly involving neck muscles (torticollis). Can be very painful and poses the highest risk in young males, but can be seen in all age groups and can occur after a single dose.

- Reduce or stop the agent if possible
- Benztropine or diphenhydramine
- Benzodiazepine (lorazepam, clonazepam)

Parkinsonism

May be reported as a new tremor, sense of being slowed down or stiff movements; manifest as "pill rolling" tremor at rest, cogwheeling, bradykinsia, and even mask-like facies. Patients can seem more depressed, stooped and slowed.

- Reduce or stop the agent if possible
- Benztropine or diphenhydramine
- Amantadine

Tardive dyskinesia (TD)

Irregular stereotyped or choreoathetoid movements which are under temporary volitional control and are ameliorated by action and sleep and augmented by distraction and stress. Patients are often not aware or distressed despite visually obvious movements.

- Stop the agent if possible
- **May not resolve if treatment is continued**

Manifestations of TD

- Orofacial: (most common) lip smacking, chewing, tongue thrusting, lateral jaw movements, grimacing, eye blinking.
- Limb: fidgety movements of hands and feet, or writhing (athetoid) movements.
- Trunk: slow, writhing movements.
- Respiratory: asynchronous breathing, tachypnea, or grunting due to diaphragmatic involvement. May be misinterpreted as anxiety or COPD.
- Speech: impaired phonation and articulation due to tongue, laryngeal, and diaphragmatic involvement. Speech may be unintelligible.

Note: New onset EPS have been reported with all of the antipsychotic agents, although the reported incidence of EPS in association wit the newer antipsychotics (atypicals or second-generation) is lower than with conventional agents.

Movement Disorder Screening

For patients on neuroleptics*, metoclopramide, or prochlorperazine

Every visit watch for **PUR**

Postural abnormalities
- Pregnancy stance
- Pelvic thrust
- Altered gait

Unintentional movements
- Finger tap
- Mouth and leg movement

Restless
- Hands, arms, and legs

*chlorpromazine, thioridazine, haloperidol, clozapine, risperidone, olanzapine, quetiapine

If a patient is believed to be exhibiting signs of a movement disorder, the use of the Abnormal Involuntary Movement Scale (AIMS) is recommended. This scale can be found at: http://www.psychiatrictimes.com/clinical-scales/movement_disorders.

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