

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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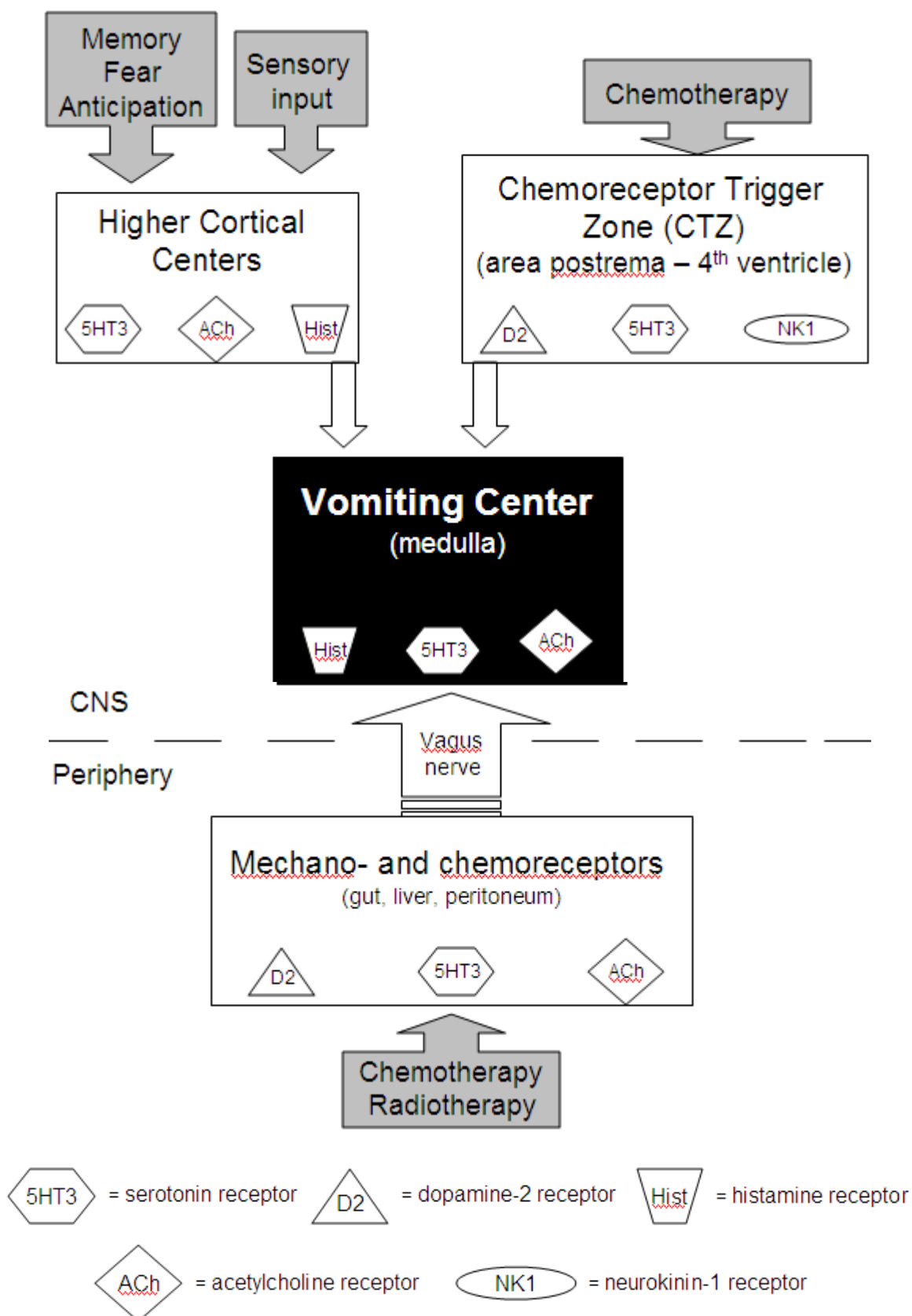
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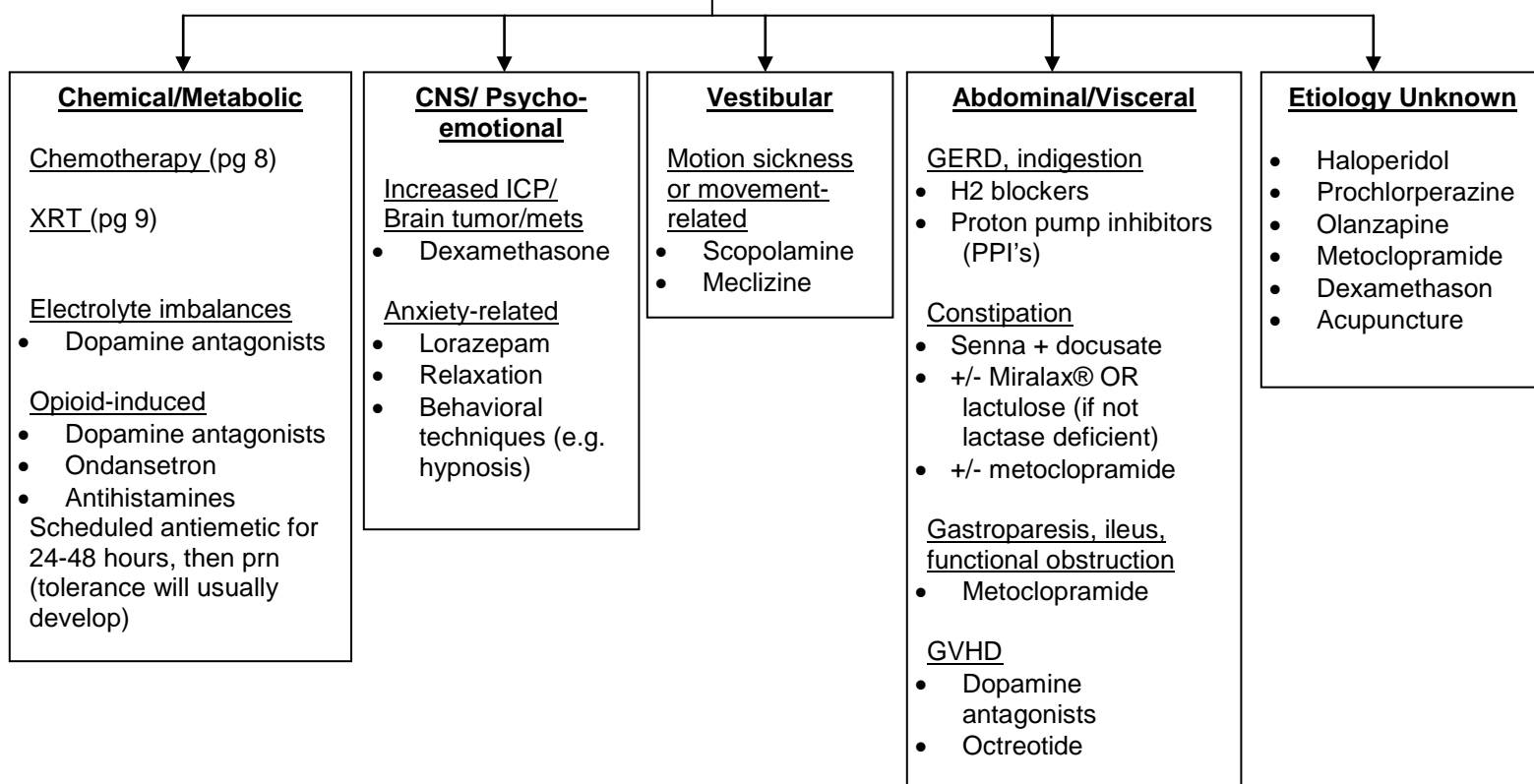
Table of Contents

Pathophysiology of Nausea/Vomiting	3
Possible Etiologies of Nausea/Vomiting	4
Assessment of the Patient with Nausea/Vomiting	4
Chemotherapy-Induced Nausea/Vomiting (CINV)	
Risk factors/protective factors	5
Definitions	5
Emetogenicity of Oral Antineoplastic Agents	5
Emetogenicity of Intravenous Antineoplastic Agents	6
Management of CINV	
General Concepts	7
Combination Chemotherapy Regimens	7
Consecutive-day Chemotherapy Regimens	7
Prophylactic Antiemetic Therapy	
Highly Emetogenic Chemotherapy	8
Moderately Emetogenic Chemotherapy	8
Low-Minimally Emetogenic Chemotherapy	8
Radiation-Induced Nausea/Vomiting	9
Refractory Nausea/Vomiting	9
Classes of Commonly Used Antiemetics	10
Extrapyramidal Symptoms (EPS)	11
Movement Disorder Screening	12

Pathophysiology of Nausea and Vomiting



Possible Etiologies and Suggested Treatment



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)

Quality 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

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

Emetogenicity is based on the percentage of patients who experience emesis in the absence of effective antiemetic prophylaxis.

Emetogenic potential of oral chemotherapy agents

Moderate-high emetic risk	<ul style="list-style-type: none"> ▪ Altretamine ▪ Busulfan ≥ 4 mg/day ▪ Crizotinib ▪ Cyclophosphamide ≥ 100 mg/m²/day ▪ Estramustine ▪ Etoposide 	<ul style="list-style-type: none"> ▪ Lomustine (single day) ▪ Mitotane ▪ Procarbazine ▪ Temozolomide > 75 mg/m²/day ▪ Vismodegib
Minimal-low emetic risk	<ul style="list-style-type: none"> ▪ Axitinib ▪ Bexarotene ▪ Bosutinib ▪ Busulfan < 4 mg/day ▪ Cabozantinib ▪ Capecitabine ▪ Chlorambucil ▪ Cyclophosphamide < 100 mg/m²/day ▪ Dasatinib ▪ Dabrafenib ▪ Erlotinib ▪ Everolimus ▪ Fludarabine ▪ Gefitinib ▪ Hydroxyurea ▪ Imatinib ▪ Lapatinib ▪ Lenalidomide 	<ul style="list-style-type: none"> ▪ Melphalan ▪ Mercaptopurine ▪ Methotrexate ▪ Nilotinib ▪ Pazopanib ▪ Pomalidomide ▪ Ponatinib ▪ Regorafenib ▪ Ruxolitinib ▪ Sorafenib ▪ Sunitinib ▪ Temozolomide ≤ 75 mg/m²/day ▪ Thalidomide ▪ Thioguanine ▪ Topotecan ▪ Tretinoin ▪ Vandetanib ▪ Vemurafenib ▪ Vorinostat

Adapted from NCCN Clinical Practice Guidelines in Oncology. V.1.2014. Antiemesis.

Emetogenic potential of intravenous chemotherapy agents

High emetic risk (> 90% frequency of emesis)	<ul style="list-style-type: none"> ▪ AC combination (either doxorubicin or epirubicin w/ cyclophosphamide) ▪ Carmustine > 250 mg/m² ▪ Cisplatin ▪ Cyclophosphamide > 1,500 mg/m² 	<ul style="list-style-type: none"> ▪ Dacarbazine ▪ Doxorubicin ≥ 60 mg/m² ▪ Epirubicin > 90 mg/m² ▪ Ifosfamide ≥ 2,000 mg/m² per dose ▪ Mechlorethamine ▪ Streptozocin
Moderate emetic risk (30-90% frequency of emesis)	<ul style="list-style-type: none"> ▪ Aldesleukin > 12-15 million international units/m² ▪ Amifostine > 300 mg/m² ▪ Arsenic trioxide ▪ Azacitadine ▪ Bendamustine ▪ Busulfan ▪ Carboplatin ▪ Carmustine ≤ 250 mg/m² ▪ Clofarabine ▪ Cyclophosphamide ≤ 1,500 mg/m² ▪ Cytarabine > 200 mg/m² 	<ul style="list-style-type: none"> ▪ Dactinomycin ▪ Daunorubicin ▪ Doxorubicin < 60 mg/m² ▪ Epirubicin ≤ 90 mg/m² ▪ Idarubicin ▪ Ifosfamide < 2,000 mg/m² per dose ▪ Interferon alfa ≥ 10 million international units/m² ▪ Irinotecan ▪ Melphalan ▪ Methotrexate ≥ 250 mg/m² ▪ Oxaliplatin ▪ Temozolomide
Low emetic risk (10-30% frequency of emesis)	<ul style="list-style-type: none"> ▪ Ado-trastuzumab emtansine ▪ Aldesleukin ≤ 12 million international units/m² ▪ Amifostine ≤ 300 mg/m² ▪ Brentuximab vedotin ▪ Cabazitaxel ▪ Carfilzomib ▪ Cytarabine 100-200 mg/m² ▪ Docetaxel ▪ Doxorubicin liposomal ▪ Eribulin ▪ Etoposide ▪ 5-fluorouracil ▪ Floxuridine ▪ Gemcitabine ▪ Interferon alfa >5 <10 million international units/m² 	<ul style="list-style-type: none"> ▪ Ixabepilone ▪ Methotrexate > 50 <250 mg/m² ▪ Mitomycin ▪ Mitoxantrone ▪ Omacetaxine ▪ Paclitaxel ▪ Paclitaxel, albumin bound ▪ Pemetrexed ▪ Pentostatin ▪ Pralatrexate ▪ Romidepsin ▪ Thiotepa ▪ Topotecan ▪ Ziv-aflibercept
Minimal emetic risk (< 10% frequency of emesis)	<ul style="list-style-type: none"> ▪ Alemtuzumab ▪ Asparaginase ▪ Bevacizumab ▪ Bleomycin ▪ Bortezomib ▪ Cetuximab ▪ Cladribine ▪ Cytarabine < 100 mg/m² ▪ Decitabine ▪ Denileukin difitox ▪ Dexrazoxane ▪ Fludarabine ▪ Interferon alfa ≤ 5 million international units/m² 	<ul style="list-style-type: none"> ▪ Ipilimumab ▪ Methotrexate ≤ 50 mg/m² ▪ Nelarabine ▪ Ofatumumab ▪ Panitumumab ▪ Pegaspargase ▪ Peginterferon ▪ Rituximab ▪ Temsirolimus ▪ Trastuzumab ▪ Valrubicin ▪ Vinblastine ▪ Vincristine ▪ Vincristine liposomal ▪ Vinorelbine

General concepts in the management of CINV

Goal: Prevention of nausea/vomiting is the goal for patients receiving chemotherapy.

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

Route of administration: Oral and intravenous 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 and agents that target the NK-1 receptor for 2-4 days after completion of chemotherapy or, on day 1, with intravenous agents shown to have efficacy for this period of time (e.g. palonosetron, fosaprepitant). Carboplatin, cisplatin, cyclophosphamide, and adriamycin are frequently associated with delayed nausea and vomiting.

Other etiologies: Other possible etiologies of nausea/vomiting should be addressed and properly managed (e.g. provide an H2 blocker or proton pump inhibitor to prevent dyspepsia, which may mimic nausea).

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).

Combination chemotherapy regimens

- Give agents that are effective for the highest emetogenicity level of any single agent in the regimen (e.g. cisplatin and etoposide: use agents recommended for cisplatin).

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 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 ¹ 16 mg PO or IV	Dexamethasone 4 mg PO BID
Dexamethasone 12 mg PO or IV	OR 8 mg PO daily
Fosaprepitant ² 150 mg IV	

¹In selected highly 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 the dose is administered.

²If the highly emetogenic agent is not given each week (e.g. cisplatin/gemcitabine or cisplatin/naelbine), fosaprepitant should ONLY be provided on the same day as the highly emetogenic agent (e.g. cisplatin).

Suggested Antiemetics for Selected Moderately Emetogenic Chemotherapy Regimens

Regimen 1: Palonosetron containing regimen preferred for combination chemotherapy including oxaliplatin, carboplatin and irinotecan

Day 1 (30 minutes prior to chemotherapy)	Days 2-3
Palonosetron 0.25 mg IV	Dexamethasone 4 mg PO BID
Dexamethasone 12 mg PO or IV	OR 8 mg PO daily

Regimen 2:

Day 1 (30 minutes prior to chemotherapy)	Days 2-3
Ondansetron ¹ 16 mg PO or IV	Dexamethasone 4 mg PO BID
Dexamethasone 12 mg PO or IV	OR 8 mg PO daily

Aprepitant should only 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).

For patients who have aprepitant added, the 5HT₃ receptor antagonist of choice is oral ondansetron.

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

Suggested Antiemetics for Low-Minimally Emetogenic Chemotherapy

- Prophylaxis may consist of any ONE of the following:
 - Dexamethasone 4-8 mg PO or IV
 - Metoclopramide 10 mg PO or IV
 - Prochlorperazine 10 mg PO or IV
- Routine prophylaxis is not necessary for minimally emetogenic chemotherapy (e.g. bevacizumab).

Suggested Antiemetics for Radiation-Induced Emesis

<u>Emetic risk</u>	<u>Radiation field</u>	<u>Recommended prophylaxis</u>
High	Total-body irradiation	Ondansetron 8-24mg/day +/- corticosteroid prior to each fraction
Moderate-low	Upper abdomen, abdominal-pelvic, mantle, lower thorax craniospinal irradiation, cranial radiosurgery	Ondansetron 8mg/day prior to each fraction
Minimal	Breast, head and neck, cranium, extremities	No routine prophylaxis recommended.

Refractory 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)
 - Fosaprepitant/aprepitant (only if patient receiving a corticosteroid and 5HT₃ receptor antagonist).
 - 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)
 - Administer palonosetron and discontinue ondansetron for 48 hours
5. If the above strategies are ineffective consider:
 - Cannabinoid (dronabinol, nabilone)
 - Continuous infusion metoclopramide (1-5 mg/hour)

***See chart on page 10 for dosing and drug classification.

Classes of Commonly Used Antiemetics		
	<u>Dose/Routes</u>	<u>Side effects/Management</u>
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	Somnolence/fatigue; ↑ dexamethasone levels (reduced dose = 12 mg) ↓ warfarin levels (monitor INR closely)
Fosaprepitant (Emend IV)	150 mg IV on day 1	
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	
Antihistamines		
Diphenhydramine (Benadryl®)	25-50 mg IV/PO q 4-6 hours	Sedation, confusion (especially in patients > 65 years)
Dimenhydrinate (Dramamine®)	50-100 mg PO/IV q 4-6 hours	
Meclizine (Antivert®)	25-50 mg PO daily	
Promethazine (Phenergan®)	12.5-25 mg PO/PR/IV 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
Cannabinoids		
Dronabinol (Marinol®)	2.5-10 mg BID-TID	Confusion, ataxia
Nabilone (Cesamet®)	1-2 mg BID	
Anxiolytics		
Lorazepam (Ativan®)	0.5-2 mg PO/IV q 4-6 hours	Confusion, sedation
Atypical Antipsychotics		
¥Olanzapine (Zyprexa®)	2.5-10 mg daily	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, bradykinesia, 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 with 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.psychiatrytimes.com/clinical-scales/movement_disorders.

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