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Antineoplastic therapy side effects and polypharmacy in older adults with cancer.

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Abstract

The geriatric oncology population requires special consideration in rehabilitation care planning due to drug side effects and potential drug interactions that occur with cancer treatment. Antineoplastic therapies incite side effects that are frequently managed with additional pharmacological interventions, often resulting in a cascade of drug side effects. Moreover, this population is disproportionately affected by multiple pre-existing co-morbidities that require the use of multiple medications. The aggregate impact of these pharmacological strategies increases the risk for adverse effects. This article will review the complexities of these drug interactions and will provide insight and awareness to guide rehabilitation interventions.

Keywords

Geriatric oncology; polypharmacy; function; cancer; morbidity; drug interaction

Introduction

Cancer disproportionately impacts older individuals in the United States with > 50% of all cancer diagnoses occurring after the age of 65.[1] At the point of a cancer diagnosis, these individuals are also likely to have several medical comorbidities[2] which require the use of multiple medications, both prescription and over the counter, to support condition

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Disclaimer: Brand names of drugs are identified in parenthesis accompanying the generic name in many instances throughout this manuscript, this is intended to familiarize the reader with commonly used drug agents and should not be considered as a preferred drug for any condition referenced.

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*https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf

†https://www.cancer.gov/

‡https://www.cancer.org/

§https://www.asco.org/

**www.nccn.org

management. Having multiple comorbidities increases the risk for potentially inappropriate medication (PIM) use and adverse drug interactions due to the multiple medications used to manage these conditions. Polypharmacy, or the use of multiple medications, is classified as either appropriate (based on presenting conditions) or problematic, when there is high risk for adverse drug interactions.[3]

Standard antineoplastic therapies including cytotoxic chemotherapy, biological immunotherapies, and hormonal agents tend to increase the risk of drug interaction and adverse events in the geriatric population.[4,5] Moreover, these cytotoxic agents are responsible for an array of side effects, many requiring pharmacological intervention. Managing the cascade of side effects from cancer treatments may require the use of drug therapies that are commonly recognized as potentially inappropriate medication outside of the oncology care continuum but are indicated under these unique circumstances. These drug interactions can have an adverse impact on function and contribute to an array of complications in the geriatric population.

In 2016 there were an estimated 15.5 million cancer survivors living in the United States, > 60% of whom were 65 years or older and this prevalence is projected to grow to > 73% of the survivorship population by 2040.[6] The majority of these individuals will experience high co-morbidity burden, often requiring complex pharmacological intervention. Rehabilitation providers should be aware of the impact of polypharmacy on older individuals with cancer and recognize how drug side effects and interactions can impact the onset and severity of functional impairments in this population. The purpose of this article is to provide a comprehensive review of common antineoplastic pharmaceutical agents, their side effects, and the potential drug interactions that may occur between these agents and those used to manage the comorbid conditions that commonly occur in older adults.

Geriatric Oncology

The specialized practice of geriatric oncology focuses on the needs of the older adult population of cancer survivors. For the purposes of this article, an individual is defined as a cancer survivor from the point of cancer diagnosis through the trajectory of their remaining lifespan.[7] The needs of the geriatric population warrant special consideration for two specific reasons. First, cancer is a disease of age and older adults are not only more likely to develop cancer, they are also more likely to have age-related co-morbidities that introduce more complexities and therefore require special consideration in developing cancer treatment care plans and follow up care.[8] Second, due to the rise in cancer survival rates over the last three decades, a large segment of the geriatric population has a history of past cancer treatments[4] and are likely to experience late effects of these treatments that impact function, such as persistent pain, neuropathies, balance deficits, cardiotoxicities, cognitive deficits, and other musculoskeletal impairments.[9] These persistent and late effects require both lifestyle and pharmacological interventions for optimal symptom and condition management.[8,9] Furthermore, individuals who have completed antineoplastic medical treatments with chemotherapy, surgery, radiotherapy, and immunotherapies may be on longer term medical treatment interventions including hormonal drug therapies,

corticosteroids, bisphosphonates and other pharmacological agents that mitigate their risk for disease recurrence or temporize persistent disease.

Due to these complexities, specific focus and attention is drawn to the physical and functional assessment and supportive care needs of the geriatric oncologic population.[10] Targeted approaches are recommended to improve assessment, intervention, and follow up care specific to the needs of this population.[11,12] A large part of the standard of care approaches for cancer disease management and cancer treatment side effect attenuation relies on pharmacological interventions.

Complexities of multiple medications in older adults

Older adults, in general, experience multiple comorbidities that require pharmacological management strategies. The American Geriatric Society recognizes the various issues derived from the use of polypharmacy in this population and has developed the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, a guideline for healthcare professionals that aims to improve recognition of inappropriate medication prescription and reduce the risk of adverse events related to PIMs.[13]

A challenge in geriatric oncology care however, is that many of the medications deemed as ‘potentially inappropriate’ by Beers Criteria are requisite in the treatment of cancer and in the management of cancer treatment-related side effects. This conundrum is addressed by the National Comprehensive Cancer Network, which offers a guideline specific to older adult oncology practice.[14] The NCCN guideline provides a comprehensive list of “medications that are of concern in older adults”. There is significant agreement between both the NCCN guideline and Beers Criteria on both medications of concern, and also on best practice for clinical approach to medication management in the oncologic population. Both entities recommend clinical consideration by the health care provider that recognizes the known benefits and needs of the oncologic patient and balances that with the medication risks. Close monitoring for adverse events, with greater frequency of follow up and greater attention to functional assessment are recommended.[15] Clinical providers should recognize that use of these drugs will be prevalent in the geriatric oncology population and should have a sound understanding of the commonly used antineoplastic agents, their side effects, common pharmacological management of the side effects, and their interplay with co-morbidity medication strategies.

Antineoplastic Agents

Antineoplastic pharmacological agents interfere with cell division, leading to cell kill (cytocidal effects) or failure to replicate (cytostatic effects).[16] These agents, however, are non-selective and their cytotoxic impact affects both healthy normal cells as well as malignant cells. Agents are delivered in a cyclic manner over a span of weeks to months or years in order to maximize the death of cancer cells and to allow for adequate recovery and survival of normal cells. In general, there is broad, multi-system impact from these agents. The general side effects of antineoplastic treatment are outlined in Table 1.

There are various classes of chemotherapeutic agents, immunotherapy and biological agents, and hormonal agents each with different impact on mechanisms of cell functions, such as

cellular division, metabolism, and cell growth.[17] These drugs are most effective when used in combination, as disruption to multiple cell functions over time accounts for greater success in eradicating cancer cells from the body. Many of the commonly used drug classes have distinct side effects that impact specific body structures and functions. Specific antineoplastic agents and their side effects are outlined in Table 2.

Due to the cyclic nature of antineoplastic treatments, the side effects are anticipated to occur most prevalently during the time period of drug delivery when systemic drug impact is greatest. Side effects however, can be cumulative over time with additional cycles of drug delivery and may become persistent, leading to chronic conditions. Outside of cancer care, managing cascading side effects of drugs with additional drugs is not often recommended, instead the primary inciting medication should be removed or altered. However, in oncology this may not be possible as the inciting drug is needed to kill cancer cells. Therefore, side effects such as nausea, swelling, neuropathies, constipation, and others, are routinely managed with additional medications.

An example of this cascade is seen with Taxane chemotherapy agents (Paclitaxel, Docetaxel). Taxanes are prevalent in cancer care as they are used to treat breast, ovarian, lung, bladder, prostate, melanoma, esophageal, and other solid tumors. Taxane agents are highly neurotoxic leading to peripheral neuropathies that can involve both sensory and motor impairment. While neuropathies are an anticipated side effect during drug administration, they can become more severe with progressive treatment cycles and may persist long after the completion of treatment.[18] For some individuals, peripheral neuropathies significantly impact daily life disrupting fine motor tasks, inhibiting activities of daily living (ADLs), and impairing mobility. To counteract this, medications such as Gabapentin, an anticonvulsant, are commonly prescribed for neuropathic symptom management.[19] Gabapentin has side effects, including some sedative effect. For patients undergoing or recovering from treatment for cancer, fatigue is already a commonly presenting symptom and the presence of drug-induced sedative effects can further compound symptoms and impairments. Additional treatment-related cascade examples include:

- Vinca Alkaloids (Vincristine, Vinblastine) used in treating acute leukemia, Hodgkin's and non-Hodgkin's lymphoma, and various types of sarcoma. These agents cause neurotoxicity that specifically affects the peristalsis of the bowel, resulting in constipation. Patients are often prescribed over the counter (OTC) and prescription-strength medications to relieve constipation. This cascade often results in diarrhea and can cause electrolyte imbalance putting the patient at further risk for dehydration and other metabolic deficiencies.
- Hormonal drug therapies are used in hormonally-driven breast, prostate, and ovarian cancer treatment and often cause symptoms of bone pain, especially in the back and long bones, as well as joint arthralgias. If these symptoms become intolerable, the patient can be switched to another medication within the class but most often medications such as nonsteroidal anti-inflammatory drugs (NSAID) are prescribed to mitigate the side effects. In an individual with a comorbid condition that requires anti-coagulation therapy, there is significant

risk for an adverse event as the NSAID may heighten anticoagulation and perpetuate a risk for bleeding.

In order for many patients to tolerate the antineoplastic therapies and effectively manage their cancer, polypharmacy is unavoidable. Although the few examples provided here speak to single agent side effects and management, it is clinically prudent to assume that in the presence of multi-drug cocktails there will be multiple side effects and therefore multiple drug interventions leveraged to manage these side effects. Drug interactions should be anticipated and monitored.

Pharmacological Management of Side Effects of Cancer Treatments

The use of drug interventions to manage side effects of antineoplastic drugs is critical to the success of oncology care. Maintaining chemotherapy dosing and cycle timing as close to regimen specificity is ideal. In many cases the only way to manage the rigors of the prescribed antineoplastic therapies is with careful pharmacological interventions that improve an individual's tolerance to cancer treatments and improve quality of life during cancer care. However, the use of additional drugs for managing the side effects of cancer treatment carries implications and risk for further drug interactions. Many of the medications used to manage the most common toxicities of antineoplastic therapies further alter body functions and can perpetuate a decline in functioning.

One of the most common side effects of many antineoplastic drugs therapies is nausea/vomiting (N/V). The key to treating N/V is prevention and there have been many therapeutic solutions that have come about in recent years. Unfortunately, current pharmacological options introduce side effects such as headache and constipation. In addition, they often are co-prescribed with corticosteroids for maximum benefit which can potentiate further adverse effects. At times medications used to treat side effects can be so effective that they cause an opposite reaction to occur. For example, a patient experiencing diarrhea may be prescribed multiple anti-diarrhea medications to prevent dehydration and electrolyte imbalance resulting in severe constipation.

Another example is the management of insomnia. Anxiety and insomnia are common symptoms experienced during treatment for cancer as patients are facing not only their mortality, but the stress of multiple medical appointments, struggling with side effect and their impact on daily function, and concerns regarding financial implications of their cancer medical care. Many patients are prescribed anti-depressants, specifically benzodiazepines and serotonin reuptake inhibitors (SSRIs). These drugs can have a sedative effect and impair cognition or exacerbate memory loss. Although these drugs are prescribed to help to improve an individual's quality of life, they may further complicate the common side effect referred to as "Chemo-Brain". The Mayo Clinic describes Chemo-Brain as, "a common term used by cancer survivors to describe thinking and memory problems that can occur after cancer treatment. Chemo brain can also be called chemo fog, chemotherapy-related cognitive impairment or cognitive dysfunction".[20] Individuals experiencing chemo-brain symptoms may also be taking medication for anxiety or insomnia which may worsen delays in thinking and judgement, and increase sedation, malaise, and depression which can negatively impact quality of life. Additionally, both benzodiazepines and hypnotics,

commonly used medications to manage insomnia, are identified as PIMs by the Beers criteria as they may present significant risk to older adults.[13]

Table 3 outlines many of the standard pharmacological strategies for side effect management and provides insight to their potential impact on function.[13,14,16] The NCCN *Medications of Concern* are designated in Table 3 and should serve as reminder to providers to assess for the presence of these drugs, recognize their indication in cancer care, and monitor for their functional impact.

Pharmacological Considerations with Pre-existing Co-morbidities

The majority of older individuals undergoing therapy cancer may also have pre-existing co-morbidities, most commonly; diabetes mellitus (DM), hypertension (HTN), hypercholesterolemia, arthritis, depression, anxiety disorders, incontinence, frailty, osteopenia/osteoporosis, and memory and cognitive impairments.[6] These conditions are commonly managed by a cadre of drug therapies and OTC medications.[21] Drug doses are prescribed and carefully monitored and adjusted over time to assure optimal condition management.

The introduction of antineoplastic therapies can cause physiological changes that necessitate drug dose alterations. For example, many antineoplastic agents result in thrombocytopenia which, at critical thresholds, increases the risk for bleeding. A patient who is closely managed with anticoagulant therapy, such as warfarin, will require oversight and intervention to assure safe platelet levels and to mitigate risk for an adverse bleeding event.

Antineoplastic therapies can also lead to drug interactions that introduce further complication or exacerbation of an existing condition such as with blood glucose, necessitating medication alteration. For example, the use of corticosteroids inhibits the effectiveness of many insulin management interventions and may lead to elevations in blood glucose even when individuals are taking their medications regularly. Glucose management can be exceedingly challenging for both type I and II diabetics through the duration of cancer treatment and warrants ongoing education and close oversight to alter dosages.

Best practice in identification and management of polypharmacy suggests that medication count is a predictor of risk for adverse events. While this is not inconsistent with risk stratification in the cancer population, rather than counting the sheer number of medications an individual is on; a prudent approach is to develop clinical understanding of the side effects of commonly used antineoplastic drugs and the drug agents leveraged to manage their side effects. Balancing this with knowledge of the number PIMs will enable an understanding of the risk vs benefit of the drug usage and will enable appropriate monitoring for early identification of adverse effects. Individuals with multiple comorbidities should be monitored with greater frequency and have close contact with the oncology providers overseeing care.

The combined use of numerous antineoplastic agents with various side effects, the requisite use of pharmacological interventions to manage the side effects of these agents, combined with existing drug interventions for co-morbidity management seems to lead to a near

infinite number of possible risks for serious adverse drug interactions in the older population of cancer survivors. Add to this the routine use of over-the-counter drugs and remedies such as herbal supplements and vitamins (which are beyond the scope of this paper), the risks increase exponentially.

Health care providers in rehabilitation medicine should be acutely aware of the antineoplastic agents used for medical cancer treatment, additional pharmacological agents prescribed for side effects management, and the pharmacological management of existing co-morbidities. Table 4 reviews common comorbidities and their pharmacological management strategies and describes the functional implications of how these interact with antineoplastic therapies.[22–31]

Drug interaction awareness in practice

Nearly one third of elderly cancer patients are exposed to severe drug interactions and potentially inappropriate medications.[32] The oncologic population is more likely to be exposed to PIMs as they may be indicated for optimal disease management. Rehabilitation providers should use prudent assessment methods to understand the pharmacological agents in use and their side effects and potential interactions. Although caution should be used in interpreting the Beer's Criteria, as drug indications during cancer care are different, medication review and reconciliation efforts should be considered a part of standard patient evaluation and intake. Further, the rehabilitation provider should leverage their understanding of cancer-related pharmacological strategies to assess whether emerging impairments and functional limitations are the result of a potential drug side effect or if there is elevated risk and need for monitoring and screening for impairment due to the risk of PIM adverse effects. There are several steps rehabilitation providers can take to optimize care and reduce risk.

First, providers should identify numerous resources that can provide them with up-to-date knowledge of commonly used antineoplastic agents and their known side effects. The internet provides obvious accessibility to resources; however, providers should seek out reputable websites for information such as; the National Cancer Institute (NCI), the American Cancer Society (ACS), the American Society of Clinical Oncology (ASCO), and the NCCN. These sites provide information on current standard practice in oncology care and evidence-based guidelines for pharmacological intervention. Additionally, NCI and ACS have excellent patient-focused resources which can be used for educational purposes. Scientific research in the field of antineoplastic therapies is rapidly evolving and new drugs are being used in clinical trials and in standard clinical practice with great frequency necessitating an ongoing awareness.

Second, providers should have intimate awareness of an individual's functional status and employ methods to routinely screen high risk individuals for treatment-related toxicities and late effects that negatively impact function. This approach enables early identification and awareness of pharmacologic-related adverse events, as the early manifestation of these events may present as changes in physical or cognitive functioning. In 2014, a consensus statement by the International Society of Geriatric Oncology (SIOG) recommended the use of a comprehensive Geriatric Assessment (GA) to detect functional impairments not

identified in routine history or physical examination related to cancer treatment toxicities.[12] They recommend the GA as a screening tool, as many components such as grip strength and gait speed are predictive of overall disability in this population.[30,33]

Prospective research using a GA tool in oncologic populations shows that it is more sensitive in identifying functional impairments than the current standard performance measures used in oncology practice.[34] Table 5 outlines the components of a GA, as studied by Jolly et al.[34] There are numerous clinical measurement tools and patient reported measures that are valid for use in this population. When choosing assessment tools, it is important to assure that each domain is assessed. Clinical feasibility of this assessment method is very good, and the measures included have a strong evidence base.[35,36] Since cancer care involves a protracted trajectory with an accumulated burden of morbidity throughout, an optimal framework for clinical assessment of function is one that starts at the point of diagnosis to obtain a baseline, and tracks an individual over the continuum of care to screen for changes in status indicative of emerging impairment.[37] This approach in prospective surveillance is touted as an optimal rehabilitation model for identification of adverse events and enabling tailored interventions and that may improve function and prevent cancer treatment-related disabilities.[38,39]

Lastly, it is imperative that health care providers work comprehensively as an integrated team with the patient. Leveraging survivorship care plans and enabling optimal communication among interdisciplinary care teams promotes high quality cancer care.[40] Team members should have an understanding of the medical therapies prescribed, their anticipated side effects, and should share changes in the plan of care so that all team members are aware and able to monitor for adverse effects. Providers should be aware of the mechanisms for managing functional decline and should have resources in place to assure optimal referral for appropriate interventions.[41]

Rehabilitation providers should have clear communication mechanisms with the cancer care team during the phases of cancer treatment to convey identified changes in functional status that may be associated with medication interactions. Once an individual completes active, medically directed cancer treatment follow up care typically moves out of the sphere of oncology and into primary care. Over the course of survivorship, providers should continue to monitor for potential late effects of cancer treatments as well as the emergence of additional age-related comorbidities both of which may necessitate pharmacological management. Functional screening and assessment should continue proactively.

Summary

The complexities of cancer pharmacological therapies introduce the potential for significant drug interactions that impact an individual’s function. Older adults have unique needs and risks for drug interactions due to common age-related, co-morbid conditions. Rehabilitation providers should familiarize themselves with the current standards for managing polypharmacy in the oncologic population. A prospective approach to surveillance and monitoring of drug therapies and functional status is an ideal model for optimizing outcomes.

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Table 1.

General Side Effects of Antineoplastic Therapies

- Immunosuppression
- Nausea and/or vomiting
- Anemia
- Alopecia
- Chemo-brain (cognitive memory loss)
- Dehydration
- Loss of appetite
- Constipation
- Mouth and mucous membrane sores
- Fatigue
- Skin and nail changes
- Fertility problems
- Neuropathies

Table 2.

Specific Antineoplastic Agents and Side Effects

Antineoplastic Agents	Side effects
Alkylating Agents • Cyclophosphamide (Cytoxan) • Ifosfamide (Ifex) • Melphalan (Evomela) • Busulfan (Busulfex) • Thiotepa (Tepadina) • Carmustine (Bicnu) • Dacarbazine • Temozolomide (Temodar)	• Cardiotoxicities ◦ Congestive heart failure ◦ Pericardial effusion ◦ Shortness of breath ◦ Dyspnea on exertion • Pulmonary fibrosis • Dizziness • Confusion and agitation • Joint pain • Anemia • Renal failure • Bladder toxicity
Anthracyclines • Daunorubicin (Daunomycin) • Doxorubicin (Adriamycin) • Epirubicin (Ellence) • Idarubicin (Idamycin)	• Cardiotoxicity ◦ Left ventricular dysfunction ◦ Congestive heart failure ◦ Cardiomyopathy • Pulmonary fibrosis
Anti-Androgens • Flutamide (Eulexin) • Nilutamide (Niladron)	• Muscle wasting • Osteoporosis • Erectile dysfunction
Antimetabolites • 5-flurouracil (Efudex) • Capecitabine (Xeloda) • Gemcitabine (Gemzar) • Fludarabine • Methotrexate (Trexall)	• Anemia • Shortness of breath • Skin rash/dermatitis • Peripheral numbness
Aromatase Inhibitors • Letrozole (Femara) • Anastrozole (Arimidex) • Exemestane (Aromasin)	• Joint arthralgia • Osteopenia/Osteoporosis • Hot flashes • Weight gain • Mood fluctuations
Taxanes • Paclitaxel (Taxol, Abraxane) • Docetaxel (Taxotere)	• Peripheral neuropathy • Cytopenia • Acute myocardial infarction • Diarrhea
Gonadotropin-releasing hormone agonist • GnRH-A (Cetrorelix)	• Osteoporosis • Weight gain • Heart failure • Heart disease
Luteinizing hormone agonist • Goserelin (Zoladex) • Leuprolide (Lupron) • Triptorelin (Trelstar)	• Bone pain • Sexual dysfunction • Anemia • Cognitive dysfunction
Kinase Inhibitors • Erlotinib (Tarceva) • Lapatinib (Tykerb) • Imantinib (Gleevac) • Gefinitib (Iressa)	• Hypertension • Acute myocardial infarction • Stroke • VTE • Interstitial lung disease • Bradycardia
Monoclonal Antibodies • Trastuzumab (Herceptin) • Alemtuzumab (Campath) • Bevacizumab (Avastin)	• Cytopenia • Pulmonary inflammation • Cardiotoxicity ◦ Congestive heart failure ◦ Hypertension • Reduced wound healing • Skin rash • Renal insufficiency
Platinum-based agents • Carboplatin (Paraplatin) • Cisplatin (Platinol)	• Neurotoxicity ◦ Neuropathy • Ototoxicity

Antineoplastic Agents	**Side effects**
• Oxaliplatin (Eloxatin)	• Rhabdomyolysis
Retiniods • Tretinoin (Refissa) • Alitretinion (Panretin)	• Increased intracranial pressure • VTE
Selective Estrogen Receptor Modifiers • Tamoxifen (Nolvadex) • Raloxifene (Evista)	• Hot flashes • Weight gain • Cognitive and memory dysfunction • VTE • Stroke
Topiosomerase Inhibitors • Irinotecan (Camptosar) • Topotecan (Hycamtin)	• Cytopenia • Severe diarrhea and dehydration
Vinca Alkaloids • Vincristine (Oncovin) • Vinblastine (Velban)	• Peripheral neuropathy • Dyspnea • Hypertension • Angina • Constipation • Acute myocardial infarction

Abbreviations: VTE-Venous Thrombotic Events

Table 3.

Antineoplastic treatment side effects, their pharmacological management and clinical considerations

Cancer Treatment-Related Symptoms	Commonly Prescribed Medication	Medication Side Effects	Interaction Considerations
Nausea/Vomiting	Serotonin Receptor Antagonists • Ondansetron (Zofran) • Granisetron (Kytril)	Blurred vision GI dysfunction Bradycardia Respiratory depression with risk of distress Sedation	Contraindicated with apomorphine, a dopamine agonist used in the treatment of Parkinson's disease. Risk of prolonged QT interval and reduced heart rate, may exacerbate CHF.
	Corticosteroids λ • Dexamethasone • Methylprednisolone (Medrol)	Tachycardia Fluid retention Mood disturbances Osteoporosis Muscle weakness Risk for bleeding Electrolyte imbalance Immune suppression	May interfere with HTN medications leading to elevation in blood pressure. May interfere with DM blood glucose management leading to high levels of blood glucose and difficulty controlling glucose levels. Risk of bleeds is elevated with the use of anticoagulant therapies. May worsen delirium in older adults.
	Neurokinin-1 (NK-1) Receptor Antagonist (substance p) • Aprepitant (Emend)	Infertility Dizziness Liver dysfunction Diarrhea	May reduce the effectiveness of antipsychotic drugs. May disrupt liver function and interfere with liver metabolism of other medications.
	NK1 Receptor Antagonist/ Serotonin-3 Receptor Antagonist • Netupitant (Akynzeo)	Dizziness Diarrhea Disruption of liver function with prolonged use Headache	Contraindicated with apomorphine, a dopamine agonist used in the treatment of Parkinson's disease, due to excessive lowering of blood pressure.
	Dopamine Receptor Antagonists • Metoclopramide λ^* (Reglan) • Domperidone (Motilium)	Depression Irritability Sexual dysfunction Sedation	Contraindicated with the use of antipsychotics. Contraindicated in people with suspected bowel obstruction. May exacerbate symptoms in individuals with Parkinson's disease. Corticosteroid use could enhance effect.
	Benzodiazepines λ^* • Clonazepam (Klonopin) • Alprazolam (Xanax) • Diazepam (Valium) • Lorazepam (Ativan)	Sedation Difficulty concentrating Blurred vision Loss of coordination Altered liver function with prolonged use	Opioid use can dangerously increase sedation and risk is high for suppressed respiration. Addiction risk. Increases the risk for elevated eye pressure in individuals with glaucoma. May cause cognitive impairment and increase fall risk in older adults.
	Cannabinoids • Nabilone (Cesamet) • Dronabinol (Marinol)	Euphoria Anxiety Drowsiness Fatigue	Avoid driving or operating heavy machinery. May cause unpredictable changes in blood pressure and heart rate in individuals with existing heart disease. May exacerbate existing psychiatric disorders.

Cancer Treatment-Related Symptoms	Commonly Prescribed Medication	Medication Side Effects	Interaction Considerations
			May increase the risk for seizures in individuals with epilepsy.
Pain	NSAIDS [*] • Ibuprofen (Advil) • Naproxen (Aleve)	Gastric irritation Risk for bleeding Decreased appetite Dizziness Drowsiness Edema	May increase the risk of gastric bleeding in individuals on anticoagulant therapy. May reduce the effectiveness of diuretics. May reduce kidney function and decrease the elimination of drug compounds, keeping their concentration high in the blood. This is concerning for lithium, and methotrexate. May counteract the action of anti-hypertension drugs, leading to an increase in blood pressure.
	Acetaminophen (Tylenol)	Anemia Thrombocytopenia Headache Nausea	Metabolism may be disrupted by the liver's need to metabolize other medications, such as Tegretol and Rifidin, reducing the effectiveness of Acetaminophen. Reduced effectiveness with the use of cholestyramine. May increase risk of bleeding with anticoagulant therapy.
	Narcotic Opioid Analgesics [λ*] • Oxycodone (Oxycontin) • Hydrocodone (Vicodin) • Morphine • Fentanyl	Itching Constipation Sedation Hallucinations Vomiting Abdominal pain Dry mouth	Significant risk of respiratory depression and sedation with Serotonin Receptor Antagonists. MAO Inhibitors are contraindicated. Significant risk of CNS depression, respiratory depression, low blood pressure, and sedation with benzodiazepines.
	Antidepressant SSRI [λ*] • Citalopram (Celexa)	Risk for bleeds Sedation Loss of appetite Blurred vision Nausea	MAO Inhibitors are contraindicated. May increase the risk for sedation with antihistamines, opioids, or benzodiazepines. May increase risk for bleeding with NSAIDS and anticoagulant therapies. May interfere with medical or laboratory tests possibly causing false results.
	Corticosteroids [λ] • Dexamethasone • Methylprednisolone (Medrol)	Tachycardia Fluid retention Mood disturbances Osteoporosis Muscle weakness Risk for bleeding Electrolyte imbalance Immune suppression	May interfere with HTN medications leading to elevation in blood pressure. May interfere with DM blood glucose management leading to high levels of blood glucose and difficulty controlling glucose levels. Risk of bleeds is elevated with the use of anticoagulant therapies.
	Anticonvulsants • Gabapentin (Neurotin)	Hallucinations Sedation Dizziness Loss of coordination Tremor	When used with antihistamines, antidepressants, muscle relaxants, and narcotics may cause marked drowsiness and increased sedation.

Cancer Treatment-Related Symptoms	Commonly Prescribed Medication	Medication Side Effects	Interaction Considerations
	Bisphosphonates • Zoledronic acid (Zometa) • Ibandronic acid (Boniva) • Letrozole (Femara)	Dizziness Headache Flu-like symptoms	Risk for osteonecrosis of the jaw with long term use. Risk for renal dysfunction with certain classes of antibiotics. Oral bisphosphonates may cause esophageal irritation and increase the risk for bleeds in individuals on NSAIDS or anticoagulant therapies. Diuretics may decrease effectiveness.
	Cannabinoids • Nabilone (Cesamet) • Dronabinol (Marinol)	Euphoria Anxiety Drowsiness Fatigue	Avoid driving or operating heavy machinery. May cause unpredictable changes in blood pressure and heart rate in individuals with existing heart disease. May exacerbate existing psychiatric disorders. May increase the risk for seizures in individuals with epilepsy.
Constipation	Stool Softeners • Docusate (Colace)	Stomach cramping Diarrhea Intestinal obstruction	No significant drug interactions are reported; however, caution is needed to avoid diarrhea which may magnify the risk of dehydration in chemotherapeutically altered individuals.
Bone Fragility	Bisphosphonates • Zoledronic acid (Zometa) • Ibandronic acid (Boniva) • Letrozole (Femara)	Dizziness Headache Flu-like symptoms	Risk for osteonecrosis of the jaw with long term use. Risk for renal dysfunction with certain classes of antibiotics. Oral bisphosphonates may cause esophageal irritation and increase the risk for bleeds in individuals on NSAIDS or anticoagulant therapies. Diuretics may decrease effectiveness.
	Calcitonin (Miacalcin)	Nausea/Vomiting Hot flashes Bone pain Headaches Nose bleeds (with nasal spray)	May reduce lithium concentrations and decrease its effectiveness.
Anemia	Iron Supplements	Nausea Constipation	Oral bisphosphonates and Calcium supplements may inhibit uptake.
	Hematopoietics • Epoetin Alpha (Epogen/Procrit)	Body aches Malaise Fatigue	May increase blood pressure necessitating adjustments to HTN medications.
Neutropenia	Benzodiazepines λ * • Clonazepam (Klonopin) • Alprazolam (Xanax) • Diazepam (Valium) • Lorazepam (Ativan)	Sedation Difficulty concentrating Blurred vision Loss of coordination Altered liver function with prolonged use.	Use with opioids can dangerously increase sedation and risk is high for suppressed respiration. Addiction risk. Risk for increase in eye pressure in individuals with glaucoma.

Cancer Treatment-Related Symptoms	Commonly Prescribed Medication	Medication Side Effects	Interaction Considerations
			May cause cognitive impairment and increase fall risk in older adults.
	Hematopoietics • Filgrastim (Neupogen) • Pegfilgrastim (Neulasta)	Joint pain Bone pain Malaise Fatigue	Closely monitor individuals with sickle cell and maintain hydration.
Insomnia	Hypnotics * • Eszopiclone (Lunesta) • Zolpidem (Ambien)	Dizziness Grogginess	Use with opioids could dangerously enhance sedative effect. Risk for worsening depression.
	Melatonin δ	Nausea/Vomiting Dizziness Angioedema Fatigue	Contraindicated in individuals with sleep apnea. May increase levels of sedation with SSRI's May increase the risk of bleeding with anticoagulant therapies.
	Progestin δ • Megestrol acetate (Megace)	Nausea/Vomiting Weight gain Mood changes Hot flashes	May increase the risk for blood clots. Not indicated with aromatase inhibitors, or other estrogen modifying agents.
Anorexia/Cachexia	Cannabinoids • Nabilone (Cesamet) • Dronabinol (Marinol)	Euphoria Anxiety Drowsiness Fatigue	Avoid driving or operating heavy machinery. May cause unpredictable changes in blood pressure and heart rate in individuals with existing heart disease. May exacerbate existing psychiatric disorders. May increase the risk for seizures in individuals with epilepsy.
	Testosterone δ (Androgel, Depo-testosterone, Testim)	Fatigue Insomnia Aggression Increased PSA (in men) Hypogonadism	May interact with anticoagulation therapies causing an elevated risk for bleeding. May decrease blood glucose, in individuals with DM. Insulin requirements may become variable.
	Progestin δ* • Megestrol acetate (Megace)	Nausea/Vomiting Weight gain Mood changes Hot flashes	May increase the risk for blood clots. Not indicated with aromatase inhibitors, or other estrogen modifying agents.
	Benzodiazepines λ* • Clonazepam (Klonopin) • Alprazolam (Xanax) • Diazepam (Valium) • Lorazepam (Ativan)	Sedation Difficulty concentrating Blurred vision Loss of coordination Altered liver function with prolonged use.	Use with opioids can dangerously increase sedation and risk is high for suppressed respiration. Addiction risk. Risk for increase in eye pressure in individuals with glaucoma. May cause cognitive impairment and increase fall risk in older adults.
	Antidepressant • Mirtazapine (Remeron)	Dizziness Drowsiness Lightheadedness Increased appetite Constipation	Contraindicated with MAO inhibitors. May increase the risk of serotonin syndrome if taken with other drugs that increase serotonin (SSRIs).

Cancer Treatment-Related Symptoms	Commonly Prescribed Medication	Medication Side Effects	Interaction Considerations
			May lead to marked drowsiness when taken with other sedative medications or narcotic medications.
Anxiety/Depression	Tricyclic Antidepressant • Amitriptyline (Elavil) • Desipramine (Norpramin)	Weight gain Constipation Drowsiness Fatigue	When used with opioid pain medication magnifies effects. Contraindicated in individuals on MAO Inhibitors and those on anticholinergics.
	Aminoketone Antidepressant • Bupropion (Wellbutrin)	Weight loss Sweating Tinnitus Dizziness Muscle pain Tachycardia Insomnia Constipation	May counteract anti-convulsants and increase the risk for seizures. May increase risk for seizures with benzodiazepines. Contraindicated with MAO inhibitors due to risk of severe reactions including uncontrolled HTN, hallucinations and paranoid feelings. Use with protease inhibitors, such as Ritonavir for HIV-related infection, may significantly reduce the effectiveness of Wellbutrin.
	MAO Inhibitors • Rasagiline (Azilect) • Phenelzine (Nardil) • Isocarboxazid (Marplan)	Orthostasis Weakness Dizziness Drowsiness Fatigue Agitation Changes in mood or behavior Weight gain Sexual dysfunction	Contraindicated for use with other antidepressants, opioids, and other serotonin antagonists as there is high risk for confusion, high blood pressure, hyperactivity, coma and death. May interact with anti-convulsants. May cause acute hypertension when used with antihistamines.
	Serotonin-norepinephrine reuptake inhibitor (SNRI) • Duloxetine (Cymbalta)	Nausea Dry mouth Insomnia Fatigue Constipation Increased blood pressure	Contraindicated with use of MAO Inhibitors and Tricyclic Antidepressants as it may lead to fatal reactions including high body temperature, muscle rigidity, rapid fluctuations of heart rate and blood pressure. Use with an SSRI may reduce liver metabolism of SNRI, increasing blood levels and risking adverse effects. May increase risk for bleeding with NSAIDs and anticoagulant therapies. May cause stomach and GI irritation reactions with Prilosec due to early dissolution. DM may increase the risk of stomach irritation due to slow gastric emptying.
	Selective Serotonin Reuptake Inhibitors (SSRI) $\lambda*$ • Citalopram (Celexa) • Fluoxetine (Prozac) • Praoxetine (Paxil)	Dry mouth Vision changes Depression Bleeding risk Prolonged QT interval Seizures	MAO Inhibitors are contraindicated. May have severe side effects with antipsychotics. NSAIDS may increase the risk for bleeding with anticoagulant therapies.

Cancer Treatment-Related Symptoms	Commonly Prescribed Medication	Medication Side Effects	Interaction Considerations
Dyspnea	Supplemental Oxygen	Dizziness Lightheadedness	Risk for falls
Sensory Neuropathy (Diabetic and CIPN)	Anticonvulsants • Gabapentin (Neurontin) • Carbamazepine* (Tegretol)	Hallucinations Sedation Dizziness Loss of coordination Tremor	Use with antihistamines, antidepressants, muscle relaxants, and narcotics may cause marked drowsiness and increased sedation. May contribute to extremity swelling when used with diuretics.
	Serotonin-norepinephrine reuptake inhibitor (SNRI) • Duloxetine (Cymbalta)	Nausea Dry mouth Insomnia Fatigue Constipation Increased blood pressure	Contraindicated with use of MAO Inhibitors and Tricyclic Antidepressants as it may lead to fatal reactions including high body temperature, muscle rigidity, rapid fluctuations of heart rate and blood pressure. Use with an SSRI may reduce liver metabolism of SNRI, increasing blood levels and risking adverse effects. May increase risk for bleeding with NSAIDs and anticoagulant therapies. May cause stomach and GI irritation reactions with Prilosec due to early dissolution. DM may increase the risk of stomach irritation due to slow gastric emptying.
Diarrhea	Octreotide (Sandostatin)	Stomach pain Nausea/Vomiting Gas Abnormal stool Constipation Fluctuating blood glucose Headache Gallbladder and pancreas problems	Interferes with nutrient absorption and may decrease absorption of oral medications. May reduce the effectiveness of oral diabetic medications, beta blockers, calcium channel blockers, and may disrupt fluid and electrolyte balance.
	Opium Tincture	Sedation Constipation Nausea/vomiting Itching	Opium tincture contains morphine and is contraindicated with MAO inhibitors as it may cause high blood pressure, hyperactivity, and death.

Abbreviations: GI – Gastrointestinal, QT – on EKG, the interval of time between start of the Q wave and end of the T wave associated with arrhythmias, CHF – Congestive Heart Failure, HTN – Hypertension, DM – Diabetes Mellitus, MAO – Monoamine Oxidase, CNS – Central Nervous System, NSAIDS – Non-steroidal Anti-inflammatory Drugs, SSRI – Selective Serotonin Reuptake Inhibitor, PSA – prostate specific antigen

*Classified as Potentially Inappropriate Medication by Beer's Criteria

λIdentified by NCNN as a *Medication of Concern for Older Adults*

δHormonal

Table 4.

Common comorbid conditions and their pharmacological management strategies as they impact physical function.

Condition	Commonly Used Medication Classes	Functional Implications from Interactions with Antineoplastic Therapies	Rehabilitation Clinical Considerations
Cardiovascular Disease[22]	Beta blockers Diuretics ACE inhibitors Statins	Risk for renal insufficiency with beta-blockers, compounded when combined with NSAIDS and diuretics. Diuretic use should be monitored and adjusted as it may further increase the risk for dehydration when nausea and vomiting from chemotherapy is prevalent. Diuretics magnify the effects of chemotherapy and may alter serum potassium and calcium levels resulting in changes in mental status. Hypokalemia in individuals with prior cardiac conditions increases risk of cardiac events. Hyperkalemia increases risk for renal complications.	Closely monitor vital signs for cardiac compromise with exercise prescription. Monitor cognitive status.Assess and monitor systemic swelling.Clinical presentation precautions: – Progressive dyspnea on exertion. – Altered mental status, inappropriate affect, hallucinations.
Arthritis	NSAIDS Glucocorticoids	Use of NSAIDS may reduce the effectiveness of antidepressants used for pain management or anxiety. Antineoplastic hormonal therapies, specifically aromatase inhibitors, can escalate arthritic pain. Risk for bleeding may be increased with chemotherapy-induced thrombocytopenia.	Monitor and assess joint range of motion and joint mobility. Encourage mobility and flexibility. Monitor for bleeding: gums and nosebleeds, and easy bruising. Assess falls risk and monitor for prevention.
Stroke[23]	Anticoagulants	Risk for bleeds may be magnified due to thrombocytopenia associated with many antineoplastic therapies.	Closely monitor for signs of bleeding. Reduce resistance exercise and limit activity as per thrombocytopenia guidelines.[24]
Diabetes (Type I and II)[25]	Insulin Metformin	Glucocorticoids, commonly used to manage cancer treatment side effects, may exacerbate diabetes or may convert pre-diabetics due to significant elevations in plasma glucose. Drug administration is cyclic during cancer medical treatment and glucose monitoring should be more frequent during treatment. Greater flexibility is warranted in glucose management. Prescribed standard daily administration of glucose may need to be withheld or adjusted. There is some evidence that metformin offers a protective effect in that it	Routine monitoring of vital signs. Nutritional assessment and education for intake. Monitor body weight. Prescribe exercise as per current guidelines.[27]

Condition	Commonly Used Medication Classes	Functional Implications from Interactions with Antineoplastic Therapies	Rehabilitation Clinical Considerations
		inhibits cancer development and cell growth.[26] Nutritional status and oral intake should be considered. Nausea and vomiting may preclude the individual from adequate intake. Parenteral nutrition will also alter blood glucose levels requiring monitoring and proactive management.	
Depression	Antidepressants	Combination of many antidepressant medications with opioids to manage cancer pain may result in dangerous levels of sedation.	Monitor mood state and sedation. Assess fall risk and monitor for prevention.
Dementia[28] and Cognitive function[29]	Central Acetylcholinesterase inhibitors (Aricept)	Respiratory function may be depressed when used with other sedating drugs including benzodiazepines, antihistamines, muscle relaxants and opioids. Sedation may be marked. NSAIDS and other anticoagulant therapy may increase the risk for bleeds.	Monitor vital signs. Assess and monitor mental status and cognitive function. Monitor for sedation. Assess fall risk and monitor for prevention. Monitor for bleeding: gums, nosebleeds, and easy bruising.
Osteoporosis	Bisphosphonates Calcium Vitamin D	Antineoplastic hormonal therapies will negatively impact bone density, causing further decline in DEXA scores. Risk for bone fragility and fracture is heightened and fall risk is increased. NSAIDS prescribed for cancer pain management may perpetuate gastric and GI issues.	Assess for frailty and fall risk.[30] Prescribe weight bearing exercise as per guidelines.
Erectile dysfunction and Benign Prostatic Hypertrophy	Vasodilators	May be contraindicated during cancer treatment as it may negatively impact blood pressure. May preserve erectile function when used protectively during radiation therapy.	Monitor vital signs. Monitor urinary habits: •Difficulty initiating the urine stream. •Increased frequency of urination. Assess for changes in sexual function.
Glaucoma	Prostaglandin analogs Beta blockers Alpha agonists	Benzodiazepines introduce risk for increased eye pressure.	Monitor for visual disturbance, complaints of headaches, eye pressure or pain.
Lung disease[31]	Antihistamine bronchodilators	Beta-adrenergics are contraindicated for use with tricyclic antidepressants and MAO inhibitors due to potential severe and fatal effects on blood pressure and heart rate. Beta-adrenergics used with other stimulant medications may increase heart rate, blood pressure and increase the risk of underlying coronary heart disease complications.	Monitor vital signs. Assess heart rate response with activity. Monitor oxygen saturation and assess need for supplemental oxygen.

Table 5.

Components of the Geriatric Assessment as described by Jolly et al

Domain	Clinical Measures	Patient Reported Measures
Function	• Timed up and go • Karnofsky Performance Status • Grip Strength	• VAS Physical Function Scale (0–20) 20 = not limited at all • VAS Instrumental Activities of Daily Living Scale (0–14) 14 = can do without help • Number of falls in the past 6 months
Cognition	• Blessed Orientation-Memory Concentration test	
Body Composition	• Body mass index	
Comorbidity		• Number of medications • Number of comorbidities
Psychological		• Five-Item Mental Health Index
Social (MOS)		• MOS social Activity Limitation • MOS Social Support Survey
Nutrition		• Unintentional weight loss in past 6 months

Abbreviations: VAS, Visual Analog Scale; MOS, Medical Outcomes Survey