Pharmacotherapy considerations in Palliative Care – A Review

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ABSTRACT

Noncommunicable diseases (NCDs), such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes, are the leading cause of mortality in the world. According to world health organization , In India The probability of dying between ages 30 and 70 years from the 4 main Non-Communicable Diseases(Cancers ,Diabetes, Cardiovascular Diseases ,Chronic Respiratory Diseases)is 26 % in the year 2014 [1] .

The WHO defined palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual [2].It has been considered both a general approach to patient care and a practice specialty. A palliative care approach can be applied at any point during the course of illness and should not be confused with hospice care, which incorporates the philosophies of palliative care, but is typically provided to patients with life expectancies of 6 months or less. The purpose of this review article is to focus on pharmacotherapy decisions of chronically ill patients during the later part of life and pharmacists responsibilities in hospice and palliative care.

Keywords: Pharmacotherapy, Palliative Care, Polypharmacy

ORIGIN

The practice of palliative care evolved from the hospice movement originally created in the United Kingdom. The first hospice was founded by dame cicely Saunders in 1967. The hospice movement in the United States has grown considerably from a volunteer based program to become a significant part of health care system. Starting in 2006 in the United States, palliative medicine is now a board certified sub-specialty of internal medicine with specialized fellowships for physicians who are interested in the field. Palliative care utilizes a multidisciplinary approach to patient care, relying on input from pharmacists, nurses, chaplains, social workers, psychologists and other allied health professionals in formulating a plan of care to relieve suffering in all areas of a patient's life. This multidisciplinary approach allows the palliative care team to address physical, emotional, spiritual and social concerns that arise with advanced illness.

DEVELOPMENT IN INDIA

In India, the earliest facilities to deliver palliative care within cancer centers were established in some places like Ahmadabad, Bangalore, Mumbai, Trivandrum, and Delhi in the late 1980s and the early 1990s. Palliative Care was initiated in Gujarat in 1980s with the opening of a pain clinic and palliative care service under the department of Anesthesiology at Gujarat Cancer and Research Institute (GCandRI) a Regional Cancer Centre in Western India. One of the important steps in the history of palliative care development in India was also began from here; forming of Indian Association of Palliative Care (IAPC). The IAPC was registered as Public Trust and Society in March 1994 in Ahmadabad. [3]

CONSIDERATION FOR DRUG DISCONTINUATION

Despite a relative lack of disease –specific guidelines or recommendations on how to approach discontinuation of drug therapy, some strategies have been proposed. One strategy suggests considerations of various dimensions of a patient's status simultaneously, such as life expectancy, drug related issues, goals of care, and realistic treatment targets or end points.

POLYPHARMACY

The average patients presenting to a palliative care service has five symptoms requiring treatment, this

increases to nine symptoms by the end of life. During course of illness there is a trend toward a gradual increase in the number of drugs for symptom management and a relative decline in the use of drugs for management of comorbid conditions. While the number of drugs used to treat symptoms increase, the potential for drug interactions and adverse events increases. There is a clear need to reduce polypharmacy. However the challenge lies in determining the appropriate time to discontinue the drug for chronic, comorbid conditions[4].

DRUG RELATED CONSIDERATIONS

First dimension to explore involves the properties of drug being considered for discontinuation. This includes considering the time necessary to observe a benefit from a particular drug. The pharmacologic activity of the drug should also be considered, especially because data are constantly emerging and certain drugs may have action and benefits. For example pleiotropic effects of atorvastatin such as enhancement effect of nitric oxide in the vasculature by increasing endothelial nitric oxide synthetase[5]. And decreasing the c-reactive protein values. Rapid course of some of these benefits supports the theory of pleiotropic effects. In general they can be continued for patients with a life expectancy greater than few months for those with recent cardiac events or symptoms (angina), or for the patient or family who views the drug as part of a maintenance and discontinuation would cause psychological distress. In attempting to lessen cardiac symptom burden, we must balance the benefit with risk of myopathy or rhabdomyolysis. Risk for statin related myopathy (eg; advanced age, female sex, hepatic or renal insufficiency, hypoalbuminemia, hypothyroidism, polypharmacy) are all commonly seen in palliative care settings.

POTENTIAL FOR ADVERSE OUTCOMES

The potential for ADR and drug-drug interactions should be considered with the specific population in mind. The drugs most commonly associated with ADRs were diuretics, antihypertensives (eg; calcium channel blockers, angiotensin –converting enzyme inhibitors) digoxin, antiplatlet agents, and nonsteroidal anti-inflammatory drugs. Many of these agents are under consideration for discontinuation when patient presents to a palliative care service. More than 75 % of ADR's leading to hospitalization are classified as type A meaning that they are caused by some pharmacologic property of the drug. [6] It had been noticed that many ADRs could be prevented in the palliative care setting. The number of inappropriate drugs is also an indicator for ADR-related admissions. The most common ADRs was acute gastritis from non steroidal anti inflammatory drug use, hypoglycemia from insulin, hypokalemia from diuretics was also noted.

DRUG RELATED INTERACTIONS

Attempts should be made to minimize adverse clinical outcomes caused by CYP drug -drug interactions. Although regimens differ among patients, patterns of drug use tend to occur in the palliative care population such that anticipating interactions is possible. The average regimen contained six standing drugs, and one in five patients had a regimen containing drugs that could cause clinically important drug -drug interactions involving CYP enzymes . The enzyme most commonly involved was 3A4 and the two most clinically important interactions noted were between omeprazole and diazepam (causing increased diazepam concentrations). An extensive review of literature in the Medline data base focusing to drug interactions in palliative care identified oxycodone, haloperidol, corticosteroids, tricyclic antidepressants, rifampin as the drugs most commonly implicated in drug-drug interactions for palliative populations. Haloperidol can be particularly problematic because it inhibits CYP2D6 which is necessary for the conversion of codeine, oxycodone and tramadol to analgesic metabolites. If haloperidol were added to a regimen containing one of these agents, increasing dose of haloperidol would further inhibit the conversion to active metabolites and clinician would likely increase the opioid dose [7]. This could result in overestimation of the proper analgesic dose and potentially cause toxic reactions when converting to an analgesic dose of another opioid.

DRUG METABOLISM

Acute febrile and viral illness as well as endocrine abnormalities can impair drug metabolism. Physiologic signs of inflammation (fever-reactive protein) have been associated with decreases in CYP

reactions. Impairment to oxidative pathways has been most consistently noted [8] .

CLINICAL CONDITIONS

Absorption from the gastrointestinal tract can be reduced because of nasogastric suction, altered peristalsis. Clinical conditions such as ileus, pancreatitis or gastrointestinal surgery limit use of oral route. Patients who have had more than 100 cm of ileum removed, often have severe malabsorption issues and limit the absorption of the drug. Some of the examples of criteria for drug discontinuation and definition are given in Table no 1.

SAFE DISCONTINUATION OF SELECTED DRUGS

The final issue is to determine whether it is safe to discontinue a particular drug. Few studies have evaluated this, and much of the data used to make such decisions come from extrapolating information from studies of drugs used to treat a given condition.

Statins: Although the prevalence of Hyperlipidemia increases with age, low-density lipoprotein cholesterol and total cholesterol values decrease in elderly and seriously ill patients. Hypercholesterolemia has been associated with conditions such as pneumonia, chronic obstructive pulmonary disease, cirrhosis. Withdrawal of statins during hospitalization for myocardial infarction and ischemic stroke is associated with increased morbidity and mortality compared with continued therapy at 90-day end points. Discontinuation after ischemic stroke is also a risk factor for all cause 1 year mortality. However, short term discontinuation in patients with stable cardiac conditions may not increase the risk of acute coronary syndromes.

Anticoagulation and antiplatlet agents

Often patients presenting to a palliative care service are taking either an antiplatlet or anticoagulant agent and a decision must be made regarding continuation of the agent. Issues with warfarin use in palliative care should be expected because patients with cancer are at increased risk of thromboembolic complications .the use of warfarin must be carefully noted. The risk of bleeding is increased in this population because of factors such as tumor site or metastases, drugs or chemotherapy and liver diseases. This population may have vitamin K deficiency from chronic malnutrition or prolonged antibiotic therapy. Safe warfarin use requires monitoring of patients international normalized ratio (inr). For a patient receiving palliative care any bleeding is distressing. A study of patients receiving warfarin who were admitted to a hospice program found that more frequent inr monitoring (i.e. from once every 6 days to once every 2.4 days) was required to adjust the warfarin dosing appropriately. The use of antiplatlets like aspirin and clopidogrel can be discontinued safely by physician's opinion.

THE PHARMACIST'S RESPONSIBILITIES [9]

The Pharmacist's Responsibilities High-quality hospice and palliative care requires both traditional and expanded pharmacist activities, including a variety of clinical, educational, administrative, and support responsibilities:

1. Assessing the appropriateness of medication orders and ensuring the timely provision of effective medications for symptom control. Pharmacists maintain patient medication profiles and monitor all prescription and nonprescription medication use for safety and effectiveness. Pharmacists provide patients with essential medications within a time frame that ensures continuous symptom control (especially pain relief) and avoids the need for emergency medical services.
2. Counseling and educating the hospice team about medication therapy. Pharmacists attend hospice team meetings to advise other team members about medication therapy, including dosage forms, routes of administration, costs, and availability of various drug products. This is done through regularly scheduled educational sessions. Pharmacists advise members of the hospice team about the potential for toxicity from and interactions with dietary supplements and alternative and complementary therapies.
3. Ensuring that patients and caregivers understand and follow the directions provided with medications. Pharmacists ensure that all medication labeling is complete and understandable by patients and their caregivers. Hospice pharmacists communicate with patients, either through the team or in person, about the importance of adhering to the prescribed drug regimen. Pharmacists explain the differences among addiction, dependence, and tolerance and dispel patient and caregiver misconceptions about

addiction to opiate agonists. Pharmacists ensure the availability of devices and equipment to permit accurate measurement of liquid dosage forms by patients and their caregivers. Pharmacists counsel patients about the role and potential toxicity of alternative and complementary therapies. When needed, hospice pharmacists visit patients' homes to communicate directly with patients and their caregivers and to make necessary assessments.

4. Providing efficient mechanisms for extemporaneous compounding of nonstandard dosage forms. Hospice pharmacists communicate with pharmaceutical manufacturers to determine the availability of nonstandard dosage forms. Medication-compounding needs in hospice care include the preparation of dosage forms to ease administration (e.g., concentrated sublingual solutions, topical medications), flavoring medications to promote compliance, eliminating or adjusting ingredients that patients cannot tolerate, and preparing or changing drug concentrations.

5. Establishing and maintaining effective communication with regulatory and licensing agencies. Because hospice patients often require large quantities of controlled substances, open communication with both state and federal controlled-substance agencies is important.

CONCLUSION

Very few patients take long term drugs for primary prevention (ie, no disease present).rather ,most drugs are taken for secondary prevention defined as presence of disease but no symptoms .often it is the drugs used for secondary prevention that are discontinued in palliative care populations. However, drugs used for tertiary prevention are often continued even up to the time of death .these are drugs used to limit the effect of a disease that is causing symptoms. The use of such drugs must be reviewed as patient begins to demonstrate functional deterioration.

Table no 1; Examples of criteria for drug discontinuation and definition of failure

Drug/Drug class	Criteria for Discontinuation	Definition of Failure
Nitrates	No chest pain for 3 months	Return of symptoms or electrocardiographic changes.
Histamine$_2$-receptor blockers	No proven peptic ulcer, gastrointestinal bleeding, or dyspepsia for 1 year	Return of upper gastrointestinal symptoms.
Potassium Supplement	k+ concentration >4.0 mEq/L	k+ concentration >3.5 mEq/L
Iron supplement	Iron concentration>80 mcg/dL	Iron concentration>50 mcg/dL

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