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Antiemetic medications: Agents, current research, and future directions

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Abstract
Antiemetics are drugs used against nausea and vomiting that is elicited by a wide array of provocative stimuli. The principal objective of this review paper was to describe the agents that are used, current research in new mechanisms and future directions. There are seven main categories of antiemetics available in the clinics and each category has different mechanisms of action, clinical indications and adverse effects. Although emesis occurs after chemotherapy, radiotherapy, postoperatively and as a side effect of many drugs such as antidepressants, yet, there are no ideal and universal antiemetics available in the clinics because the existing antiemetics target only one or a few stimuli that trigger the reflex. Currently, researchers are trying to find methods to diminish the unwanted adverse effects of existing antiemetics and to discover new antiemetics that may be targeted at different receptors. They are also trying to explore new strategies to improve the efficacy of existing antiemetics, to develop drugs that do not cross the blood brain barrier and to discover new antiemetics for the prophylaxis and treatment of nausea.

Keywords: antiemetics, nausea, vomiting, motion sickness, chemotherapy-induced nausea and vomiting, postoperative nausea and vomiting, current work, future strategies

1. Introduction
Nausea is a sensation of discomfort in the stomach with an involuntary urge to vomit [1]. Emesis, or vomiting, is a physiological response to the presence of irritating and harmful substances in the gut or bloodstream. It sometimes occurs because of provocative vestibular stimulation (motion sickness) or psychological stimuli such as odors, fear, and dread [2]. Nausea often, but not always, precedes vomiting, i.e. a person can suffer nausea without vomiting [2]. Emesis is a complex process that requires central neurologic coordination while nausea does not require activation of the vomiting reflex [2]. Nausea and vomiting occur due to several reasons [1], including: i) Medication/treatment-induced emesis such as antidepressants, opiates, cancer chemotherapy, antibiotics, ipecac syrup, and radiotherapy, ii) Labyrinth disorders such as motion sickness and Meniere's disease, iii) Endocrine causes such as pregnancy, iv) Increased intracranial pressure such as hemorrhage and meningitis, v) Central nervous system (CNS) causes such as anticipatory migraine and bulimia nervosa, vi) Postoperative causes such as general anesthetics and analgesics procedural, and, vii) Infectious/ inflammatory causes such as gastroenteritis and pancreatitis.

1.1 Pathophysiology of Emesis
Emesis occurs when the vomiting center is stimulated (Figure 1). Once the vomiting center is stimulated, the vomiting reflex occurs, which is divided into three phases (Figure 2): i) Pre-ejection phase, which is characterized by a sensation of nausea with gastric relaxation and retro peristalsis, ii) Retching phase, which is characterized by a labored movement of abdominal and respiratory muscles before vomiting, and, iii) Ejection phase, which is characterized by an intense contraction of abdominal muscles and relaxation of upper esophageal sphincter, resulting in expulsion of gastric contents [3].

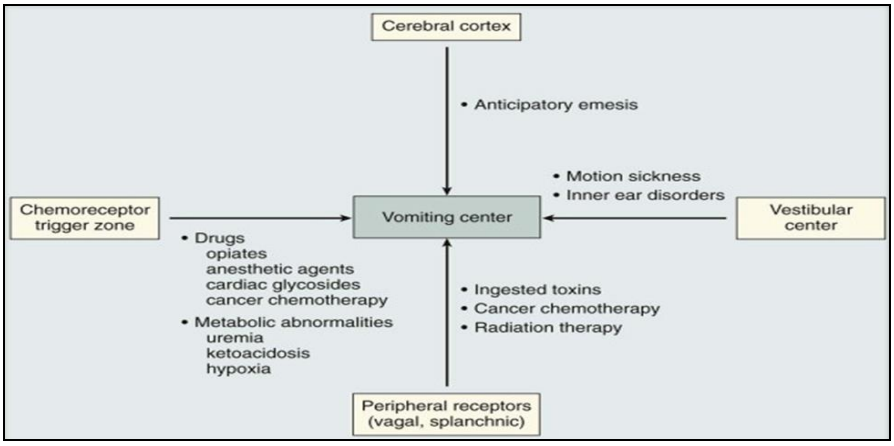

Fig 1: Pathophysiology of emesis [1].

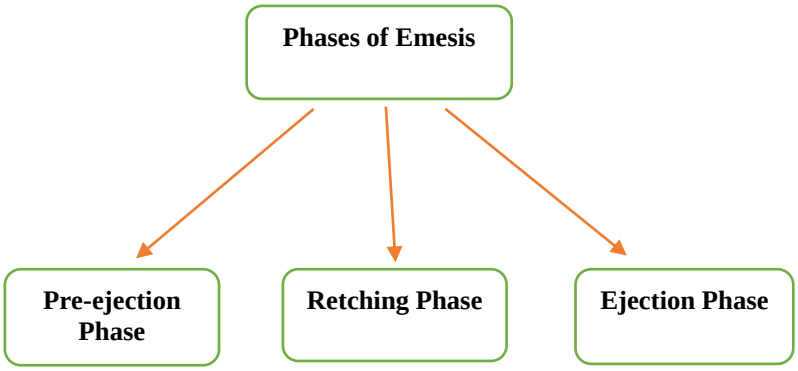

Fig 2: Phases of emesis.

The following areas can stimulate the vomiting center (Table 1) [1]:

1. **Chemoreceptor Trigger Zone (CTZ)**: This zone is close to the area postrema (AP) on the floor of the 4th ventricle of the brain and is located outside the blood brain barrier (BBB) [1]. This area contains dopamine D2, serotonin 5-HT3, opioid, histamine H1, acetylcholine (ACh), and substance P/ neurokinin1 (NK1) neuroreceptors engaged in the control of nausea and vomiting [1]. When the CTZ activated, it does not initiate emesis itself but relays stimuli to the vomiting center, which produces the actual act of emesis [1].
2. **Vestibular Apparatus**: Vestibular apparatus is located in the inner ear and is responsible for the balance in most mammals. This apparatus activates the emesis center when stimulated by diseases such as motion sickness, Meniere's disease, and labyrinthitis (inner ear disorder) [1], or when sensitized by medications. This system has a rich supply of muscarinic and H1 receptors [1].
3. **Gastrointestinal Tract (GIT):** GIT can activate emesis center by stimulation of vagal afferents (cranial nerves IX and X) or by release of serotonin from the gut enterochromaffin cells, which in turn stimulates 5-HT3 receptors on vagal afferents [1]. The GIT can be irritated by cancer chemotherapy, radiotherapy, infections, and certain drugs [1].
4. **Cerebral Cortex:** When the higher cortical centers such as cerebrum are affected by conditioned stimuli or certain psychiatric conditions, this can also result in emesis [1].

Table 1: Areas, types of receptors and stimuli involved in emesis.

Areas	Types of Receptors	Stimuli
1. Chemoreceptor Trigger Zone (CTZ)	D2, 5-HT3, opioid, H1, ACh and Substance P/NK1	Cancer chemotherapy, opiates, cardiac glycosides, uremia, ketoacidosis and hypoxia.
2. Vestibular Apparatus	Muscarinic and histamine H1	Motion sickness, Meniere's disease and labyrinthitis.
3. Gastrointestinal Tract (GIT)	5-HT3	Cancer chemotherapy, radiotherapy and gastroenteritis.
4. Cerebral Cortex	–	Smell, sight, thought and anticipatory emesis.

1.2 Types and Severity of Emesis

There are main different types of emesis, including: i) Acute emesis, which happens within the first 24 hours after administration of cancer chemotherapy [4], ii) Delayed emesis, which begins after the first 24 hours of chemotherapy and may last for 6-7 days [4]. This type of emesis is quite difficult to treat with standard antiemetics and may require a combination therapy, iii) Anticipatory emesis, which happens before the next chemotherapy treatment is given [4], iv) Cyclic emesis, which is characterized by paroxysmal, recurrent and uncontrollable episodes of vomiting and occurs mostly every 2-3 months [4]. This kind of emesis is mostly seen in migraine [4], and, v) Projectile emesis, is a type of severe vomiting in which the stomach contents are forcefully ejected to a large distance without feeling of nausea [4]. This type of vomiting is commonly seen in congenital pyloric obstruction [4].

1.3 Complications of Emesis

Vomiting may lead to several sequelae, especially if it is recurring over a period of hours or days. Some of the complications associated with repeated vomiting include: i) Dehydration (hypovolemia) due to water and electrolytes loss [5], ii) Electrolyte imbalances mainly hypokalemia [5], iii) Aspiration pneumonia due to entering of the vomitus (gastric contents) into the airway passages and lungs [5], iv) Hyperemesis gravidarum during pregnancy, v) Enamel erosion [5], vi) Mallory-Weiss Syndrome (partial tear of gastroesophageal mucosa) due to severe and repetitive vomiting [5], and, vii) Boerhaave's Syndrome (full rupture of gastroesophageal mucosa) due to extreme, prolonged and repetitive bouts of vomiting [5].

Nausea and vomiting are major concerns for patients undergoing cancer chemotherapy, radiotherapy and surgical procedures [1]. They are also commonly associated with pregnancy [1]. Antiemetics are agents that are used to treat nausea and vomiting associated with morning sickness during pregnancy, motion sickness, cancer chemotherapy, radiotherapy, general anesthetics, and other drugs. This paper will review the classes of antiemetics by mechanisms, uses, and side effects, describe their current work, and discuss future directions on advancing the field.

2. Classifications, Mechanisms of Action, Medical Indications and Adverse Effects of Antiemetic Drugs

Antiemetics are classified into seven main categories based

on their mechanisms of action (Figure 3). Each category of antiemetics has different mechanisms of action, medical uses, and side effects.

2.1 Type 3 Serotonin (5-HT3) Receptor Antagonists

The 5-HT3 receptors are found in several sites involved in emesis, including nucleus tractus solitarius (NTS), the vagal afferents, and the AP [6]. Ondansetron (Zofran) and Palonosetron (Aloxi) are 5-HT3 receptor blockers, which prevent nausea and vomiting by inhibiting the serotonin from binding to the 5-HT3 receptors [6]. Ondansetron was the first-generation 5-HT3 receptor blocker used for the prevention and treatment of postoperative nausea and vomiting (PONV) [7, 8] and acute nausea and vomiting associated with cancer chemotherapy [8, 9]. Presently, Palonosetron is a second-generation 5-HT3 receptor blocker and is more efficacious and safer than other 5-HT3 receptor antagonists in the prophylaxis and treatment of both acute and delayed chemotherapy-induced nausea and vomiting (CINV) [8, 10] and PONV in patients undergoing laparoscopic surgery [11]. However, 5-HT3 receptor blockers have no role in the prophylaxis and treatment of nausea and vomiting due to motion sickness. The most common adverse effects of 5-HT3 receptor blockers are dry mouth (xerostomia), constipation or diarrhea, light-headedness, abdominal pain, renal insufficiency, sensations of warmth, hiccups, thrombocytopenia, and electrocardiographic changes [6]. 5-HT3 receptor blockers should be used with caution in patients with hepatic failure, renal impairment, bowel obstruction, and impaired cardiac function [6].

2.2 Dopamine D2 Receptor Antagonists

Dopamine D2 receptor blockers such as phenothiazines, butyrophenones, and olanzapine are drugs that block dopamine D2 receptors in the CTZ [2]. Phenothiazines such as prochlorperazine (Compro) are antipsychotic drugs and commonly used for treatment of nausea and vomiting associated with motion sickness, migraine, radiotherapy, chemotherapy, postoperative, viral gastroenteritis, and severe morning sickness during pregnancy [6]. Butyrophenones such as droperidol (Inapsine) are antipsychotic drugs used to treat many psychiatric disorders such as schizophrenia as well as act as powerful antiemetic agents by their inhibition of D2 dopaminergic receptors in the CTZ [6]. Droperidol is very effective in small dose (0.625-1.25 mg/kg IV) for the prevention and treatment of PONV [7 2, 8]. Olanzapine (Zyprexa) is an atypical antipsychotic drug and a D2 dopaminergic receptor blocker. It has also a high affinity for α1-adrenergic, serotonergic (5-HT2A, 5-HT2C, 5-HT3, 5-HT6), histaminic H1, and five muscarinic (M1, M2, M3, M4, M5) receptors [6]. Olanzapine is mainly used for treatment of schizophrenia, but it has been reported to be effective against nausea and vomiting associated with cancer chemotherapy and PONV associated with opioids [7, 6]. The most common adverse effects of D2 receptor blockers are sedation, dry mouth, visual disturbances, perceptual disturbances, bradycardia (abnormal slow heart rate), hypotension, somnolence (sleepiness), QTc prolongation, depression, urinary retention (inability to urinate), neuroleptic malignant syndrome, and extrapyramidal symptoms (EPS) such as akathisia (inability to sit) and dystonia (a movement disorder that causes the muscles to contract involuntarily) [6].

2.3 Histamine H1 Receptor Antagonists

Histamine H1 receptor blockers such as promethazine (Phenergan) and dimenhydramine (Dramamine) are first-generation antihistamines and have antiemetic properties stemming from their blockade of H1 receptors in the vestibular nuclei [8]. Promethazine has a strong sedative effect and is a drug of first choice for treatment of nausea and vomiting related to motion sickness, increased intracranial pressure, and severe morning sickness during pregnancy [6]. Dimenhydramine uses for treatment of nausea and vomiting due to motion sickness, and it is safe and efficacious as an antiemetic during early pregnancy [2], but should be avoided during the third trimester because it stimulates the uterine contractions [6]. Promethazine has a strong anticholinergic activity whereas dimenhydramine has a weak anticholinergic effect [8]. H1 receptor antagonists may cause sedation, drowsiness, dry mouth, blurred vision, impaired thinking, urinary retention, hallucinations, nightmares, confusion, insomnia, headache, and extrapyramidal symptoms such as dystonia [6]. H1 receptor blockers should be used carefully in patients with hypertension, heart failure, myocardial infarction, hepatic failure, and epilepsy [6].

2.4 Muscarinic Acetylcholine Receptor Antagonists

L-hyoscine (Scopolamine) is a tropane alkaloid drug that blocks the muscarinic acetylcholine emetic receptors in the vestibular apparatus. It acts as an antispasmodic and is used as a transdermal patch for the prophylaxis of motion sickness. It is also very effective in small dose (1mg/24h IV) for the prophylaxis and treatment of PONV related to opioids [8]. In general, scopolamine has no role in the treatment of CINV. Long-term use of scopolamine may cause numerous unwanted side effects such as sedation, dry mouth, dyshidrosis (inability to sweat), bradycardia, urinary retention, dyspnea (difficulty in breathing), seizures, hypotension, mydriasis (dilation of the pupil), blurred vision, and somnolence [6]. Scopolamine should be used with great caution in patients with glaucoma, seizures, and renal failure [6].

2.5 Synthetic Cannabinoids

The plant Cannabis sativa (Marijuana) contains more than 80 different sorts of cannabinoids, but the most popular component is Δ^9-tetrahydrocannabinol (Δ^9-THC). Dronabinol (Marinol) and nabilone (Cesamet) are synthetic Δ^9-THC that block emesis via agonism of CB1/CB2 cannabinoid receptors in the NTS, AP, and dorsal motor nucleus in the brainstem [6]. Marinol and Cesamet are food and drug administration (FDA) approved for the treatment of nausea and vomiting associated with chemotherapy and radiotherapy in patients who have failed to respond to the other antiemetic medications [12]. Marinol can also stimulate the appetite and has been used in patients with acquired immune-deficiency syndrome (AIDS) and anorexia [13]. Cesamet can also stimulate appetite, particularly in patients with cachexia [13]. A number of adverse effects have been noticed after intake of cannabinoids such as dry mouth, palpitation (rapid and irregular heartbeat), tachycardia (abnormal rapid heart rate), postural hypotension (low blood pressure occurring when standing up), euphoria, somnolence, depression, hallucinations, visual disturbances, and panic (sudden fear) [6]. Dronabinol should be prescribed with a great caution to persons with a history of abuse, heart

failure, pregnant and breastfeeding women, the elderly, and those younger than 18 years [6].

2.6 Corticosteroids

Corticosteroids such as dexamethasone (Maxidex) are used to control nausea and emesis associated with cancer chemotherapeutics [14] and to treat intractable hyperemesis gravidarum of pregnancy [6]. Basically, Laiq *et al*. conclude that dexamethasone is very effective in the treatment of PONV in women undergoing gynecological laparoscopic surgery [15]. The dose required for this effect is very low (4-8 mg I.V.) given early during the anesthetic [8]. According to Fero *et al*., "although its mechanism of action has not been completely described, experiments in animal models suggest that dexamethasone acts centrally through inhibition of the nucleus tractus solitarius" [8]. Chronic and long-term use of corticosteroids may cause several side effects such as diabetes mellitus, depression, insomnia, anxiety, euphoria (feeling of happiness), osteoporosis, muscle weakness, peptic ulcer, sodium and water retention, hypertension, edema, and cataracts [6]. Corticosteroids should be used with caution in patients with diabetes mellitus, heart failure, peptic ulcer, and osteoporosis [6].

2.7 Substance P/ Neurokinin1 (NK1) Receptor Antagonists

Aprepitant (Emend) is a novel antiemetic drug that belongs to class of drugs called NK1 receptor blockers. It crosses the BBB and mediates its effect by blocking the NK1 receptors in the CNS [6]. Aprepitant is useful for the prevention and treatment of PONV and both acute and delayed CINV (in combination with 5-HT3 receptor blocker/dexamethasone) [16]. The first-generation 5-HT3 receptor antagonists and dexamethasone are very effective against acute emesis (first 24h after chemotherapy) [17], while NK1 receptor antagonists have antiemetic effects against delayed emesis (24-72h after chemotherapy) [18]. Chronic use of aprepitant may cause dizziness, confusion, light-headedness, loss of appetite, dry mouth, urinary retention, dyspnea, tachycardia, dyspepsia (indigestion), anorexia, weight loss, constipation or diarrhea, and sunken eyes [6]. Table. 2 below summaries the types of antiemetic drugs and their respectful uses.

Table 2: Common antiemetic classes and their clinical uses.

Antiemetic Drugs	Clinical Uses
5-HT3 Antagonists	Ondansetron (Zofran) and Palonosetron (Aloxi) prevent and treat both acute and delayed CINV and PONV by inhibiting the serotonin from binding to the 5-HT3 receptors.
D2 Antagonists	Phenothiazines such as prochlorperazine (Compro) are commonly used for treatment of nausea and vomiting associated with motion sickness, migraine, radiotherapy, chemotherapy, postoperative, viral gastroenteritis, and severe morning sickness during pregnancy. Butyrophenones such as droperidol (Inapsine) are used to treat psychiatric disorders such as schizophrenia and also act as antiemetic agents by their inhibition of D2 dopaminergic receptors in the CTZ. Olanzapine is used for treatment of schizophrenia, but it has been reported to be effective against nausea and vomiting associated with cancer chemotherapy and PONV associated with opioids.
H1 Antagonists	Promethazine (Phenergan) is used for treatment of nausea and vomiting related to motion sickness, increased intracranial pressure, and severe morning sickness during pregnancy. Dimenhydramine (Dramamine) is used for the treatment of nausea and vomiting due to motion sickness, and it is safe and efficacious as an antiemetic during early pregnancy.
ACh (M) Antagonists	L-hyoscine (Scopolamine) is used as a transdermal patch for the prophylaxis of motion sickness.
Synthetic Cannabinoids	Dronabinol (Marinol) and nabilone (Cesamet) are FDA approved for the treatment of nausea and vomiting associated with chemotherapy and radiotherapy in patients who have failed to respond to the other antiemetic medications.
Corticosteroids	Dexamethasone (Maxidex) is used to control nausea and emesis associated with cancer chemotherapeutics and to treat intractable hyperemesis gravidarum of pregnancy.
Substance P/NK1 Receptor Antagonists	Aprepitant (Emend) is used to prevent and treat PONV and both acute and delayed CINV (in combination with 5-HT3 receptor blocker/dexamethasone).

Fig 3: Mechanisms of action of antiemetic drugs.

3. Current Research

The efficacy of any antiemetic therapy is dependent upon the time at which the drug is administered relative to the emetic stimulus onset. In clinical trials, treatment with first-generation 5-HT3 receptor blockers such as ondansetron combined with corticosteroids such as dexamethasone during the first chemotherapy treatment (first 24h) reduced the incidence of acute emesis by nearly 70% [17, 19]. However, the first-generation 5-HT3 receptor blockers are less effective in inhibiting acute nausea than in inhibiting acute vomiting, and they are ineffective against delayed nausea and emesis and anticipatory nausea and vomiting (ANV) [9]. More recently, NK1 receptor blockers such as aprepitant have been developed to reduce delayed emesis induced by cisplatin [18]. Unlike D2 receptor blockers and H1 antihistamines, aprepitant is non-sedative and, unlike droperidol and 5-HT3 receptor blockers, has not been associated with QTc prolongation [8]. However, NK1 receptor antagonists alone or in combination with 5-HT3 receptor blocker/corticosteroid are also less effective against nausea [17, 9]. In 2008, the FDA approved fosaprepitant, an intravenous form of aprepitant. Rolapitant and casopitant are new NK1 receptor antagonists currently under investigation and not yet approved by the FDA [8].

In 2003, the FDA approved palonosetron for the prevention and treatment of both acute and delayed CINV [10], while in 2008, the FDA approved palonosetron for the treatment of PONV [8]. Palonosetron is a novel and a second-generation 5-HT3 receptor blocker, which differs from other agents in its class by higher receptor-binding affinity, longer half-life (40h) [20], and lack of QTc prolongation [8]. Palonosetron is more effective and safer than other 5-HT3 receptor blockers. Recent studies have shown that the higher efficacy of palonosetron results from allosteric modulation of the 5-HT3 receptor leading to persistent inhibition of receptor function, 5-HT3 receptor internalization, and inhibition of signaling crosstalk between 5-HT3 and NK1 receptors [10]. According to Fero *et al*., "more recently, a lower dose of 0.075 mg palonosetron has been shown to reduce the incidence of PONV over a 72-h period" [8]. Future research should discuss the advantages of including palonosetron as a first-line treatment.

Buspirone, a partial 5-HT1A agonist, produces its antiemetic/antinausea effects by acting on the final common pathway regardless of the trigger stimulus [21]. Buspirone has shown antiemetic efficacy when given in some animal models [22] such as cats, dogs, Suncus murinus, and pigeons. However, its efficacy for prevention and treatment of CINV

[22] and PONV in surgical patients [23] failed in the clinical trials, probably because the doses were too low (1mg/kg).

Olanzapine is a thienobenzodiazepine, which acts on multiple receptors such as histamine, serotonin, dopamine, adrenergic, and muscarinic receptors. A recent phase II trial showed that olanzapine, when combined with dexamethasone and palonosetron, was very efficacious in controlling acute and delayed CINV in patients receiving both highly and moderately emetogenic chemotherapy [24]. In addition, the latest phase III trial by Navari *et al*. demonstrated that addition of olanzapine to the dexamethasone and azasetron (5-HT3 receptor blocker) improved delayed CINV in patients receiving highly or moderately emetogenic chemotherapy [24]. Olanzapine is also more effective against PONV especially for the late postoperative periods. However, olanzapine is just being investigated for delayed post-chemotherapy nausea [25].

Another system that may be an effective target for the prevention and treatment of anticipatory nausea and vomiting (ANV), delayed nausea and vomiting, and CINV is the endocannabinoid system [26]. The endocannabinoid system in the brain helps the body to control nausea and vomiting, as well as pain, mood, and appetite [27]. According to Pertwee, "dronabinol is a synthetic Δ^9-THC that entered the clinic in 1985 as antiemetic and in 1992 as an appetite stimulant" [12]. In the recent studies, several clinical trials compared the efficacy of dronabinol in the treatment of CINV with other antiemetic drugs. One clinical trial has compared the effectiveness of ondansetron, dronabinol, or the combination for the treatment of delayed CINV [28, 29]. Meiri *et al*. indicated that the efficacy of ondansetron or dronabinol alone was similarly effective for the treatment of delayed CINV, but the combined therapy (dronabinol/ondansetron) was not more effective than either drug alone [29]. Another synthetic Δ^9-THC, levonantradol, has been investigated in the phase I clinical trials, but severe side effects limited its indication. Recently, in 2005, cannabidiol (CBD), or Sativex, was made and available as a buccal spray for the treatment of pain in adult patients with multiple sclerosis and in cancer patients with advanced pain [30]. CBD has a very low affinity for the CB1and CB2 receptors [27]. As has been reported by others, CBD has no effect in reducing motion sickness-induced vomiting in the Suncus murinus [31], and the effectiveness of this drug in reducing nausea and emesis has not been investigated yet. Some studies reported that the CBD is non-toxic and does not affect the physiological parameters (body temperature, heart rate, and blood pressure) [32]. Conversely, other studies reported that this cannabinoid can induce some adverse effects such as inhibition of hepatic metabolism, decreased fertilization, and decreased activities of p-glycoproteins [32]. Further research are required to emphasize these reported safety and adverse effects.

In general, cannabinoids have two main limitations. These are potent side effects and narrow therapeutic window. Consequently, Pertwee concludes that there are many challenges to use cannabinoid receptor agonists as medicines +. One challenge is to find methods to minimize the unwanted side effects of CB1/CB2 receptor agonists [12]. The second challenge is to identify additional therapeutic targets for cannabinoid CB1/CB2 receptor agonists [12]. The third challenge is to discover new strategies for improving the efficacy of the cannabinoid receptor agonists in the clinics [12]. Among these are: i) Targeting pain with phytocannabinoids such as Δ^9-tetrahydrocannabivarin (Δ^9-THCV), CBD, and cannabigerol (CBG). ii) Targeting CB1 receptors located outside the BBB. iii) Selectively targeting CB2 receptors. iv) Targeting cannabinoid receptors expressed by a particular tissue. v) Multi-targeting. vi) Targeting up-regulated cannabinoid receptors. And/or, vii) Using low-dose of a CB1 or CB2 ligand plus a second drug [12]. In addition, some future directions continue to explore: i) The Pharmacological action of THCV, CBD and CBG. ii) The therapeutic targets for THCV, CBD and CBG. iii) The therapeutic strategies for THCV, CBD and CBG. And, iv) The pharmacological actions and therapeutic targets of other phytocannabinoids.

4. Conclusion

The seven main classes of antiemetics were described in terms of their mechanism of action, medical uses, and adverse effects. Current work demonstrates that palonosetron and aprepitant are more efficacious and safer than other antiemetics in the prevention and treatment of both acute and delayed CINV and PONV but failed to show efficacy in the prevention and treatment of motion sickness and nausea. In addition, the current clinical trials failed to show the efficiency of buspirone in the prophylaxis and treatment of CINV and PONV because the doses were too low. Furthermore, even though olanzapine acts on multiple receptors and is more effective against acute and delayed vomiting, its efficacy in reducing nausea is still under investigation. Moreover, current research demonstrates that the cannabidiol, or Sativex, has no role in reducing motion sickness-induced nausea and vomiting, and the effectiveness of this medication in controlling nausea and vomiting has not been investigated yet. Finally, scientists are trying to find approaches to reduce the unwanted side effects of cannabinoids and to explore new strategies to improve the effectiveness of cannabinoid receptor agonists in the clinics for the treatment of nausea.

5. Future Directions

Even though vomiting is fully controlled in nearly 90% of the patients by the existing antiemetics, nausea (acute and delayed) continues to be a challenge and still remains a significant issue in cancer chemotherapy treatment and as a side effect of many drugs such as antidepressants [25]. Nausea is not as well controlled as emesis, so there is a particular interest in the trials to investigate medications with potential anti-nausea effects.

Palonosetron, unlike other 5-HT3 receptor blockers, exhibits long lasting allosteric modulation of the 5-HT3 and NK1 receptors [10]. Work continues to develop further insight into its unique efficacy.

Previously tested 5-HT1A agonists were broad-spectrum antiemetics acting on the final common pathway [21]. However, the full agonists tested clinically induced anxiety/panic attacks, making them unsuitable for therapeutic use [21]. The results of a phase I clinical trial with 5-HT1A/1D agonists such as ETI-385 are pending [33]. If successful, the optimum ratio of 1A to 1D agonism needs to be determined.

6. Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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