Expert Opinion

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Tachykinin NK_1 receptor antagonists for the control of chemotherapy-induced nausea and vomiting

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The treatment of neoplastic disease with chemotherapeutic cytotoxic drugs has long been associated with profound nausea and vomiting (emesis). This became the most feared side effect of this type of treatment and was so severe that some patients would withdraw from further treatment, thus jeopardising their clinical outcome and possibly life expectancy. The introduction of the 5-HT_3 receptor antagonists had a significant impact in this area, offering substantial reductions in emesis, largely through prophylactic treatment. Unfortunately, some forms of emesis were resistant to treatment with these drugs, so the search has continued to identify new chemical entities with a higher level of efficacy and a broader spectrum of activity. Data generated in animals has identified tachykinin NK_1 receptors as highly important in the emetic reflex and experimental evidence strongly supports NK_1 receptor antagonists as highly efficacious anti-emetic agents, with unparalleled broad spectrum activity. Several novel antagonists have recently entered clinical development and data are emerging to support their anti-emetic activity. This area continues to attract substantial medicinal chemical research effort. Most major pharmaceutical companies are seeking new matter through structural refinement of early leads or discovery of novel compounds from library screening. The scope of chemical lead matter has advanced from early piperidine and quinuclidines to a spectrum of templates that improve expectations for a well-tolerated therapeutic agent. Recent success in combining 5-HT_3 and NK_1 antagonists in emesis treatment is expected to greatly advance clinical outcomes with newer and safer agents.

Keywords: emesis, nausea, NK_1, substance P, tachykinin, tachykinin receptor antagonist, vomiting

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1. Introduction

The introduction of the 5-HT_3 receptor antagonists revolutionised the treatment of emesis associated with cancer treatment with cytotoxic chemotherapeutic agents. Until this date, intractable nausea and vomiting had become a common feature associated with many chemotherapy regimens, particularly those that included highly-emetogenic platinum-containing compounds, such as cisplatin. Prior to the launch of the prototypical 5-HT_3 receptor antagonist ondansetron, treatment of these troublesome adverse events was based on high doses of metoclopramide, antipsychotic agents such as chlorpromazine and haloperidol and iv. benzodiazepines, agents whose use was fraught with problematic side effects, including profound sedation and dyskinesias.

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Whilst the introduction of this class of agents was undoubtedly a significant step forward, a number of features of the emetic response to chemotherapy regimens proved resistant to treatment. Specifically, whilst the degree of control of vomiting on day one of the first cycle of chemotherapy was impressive, the maximum efficacy of the 5-HT_3 antagonists was found to diminish upon subsequent cycles of treatment. Delayed emesis, primarily seen 2 days following treatment and lasting for 3 or more days, was also difficult to control with this class of agent [1]. The efficacy of the 5-HT_3 receptor antagonists in controlling nausea has been less impressive than their control of vomiting, with complete control of nausea being commonly achieved in only 50% of patients. In spite of recent attempts to arrive at consensus regarding optimal doses, dosing schedules and routes of administration for these agents [2], this remains the most troublesome side effect currently reported by patients undergoing chemotherapy.

Although of less direct relevance to this review, the 5-HT_3 antagonists are also used for the treatment or prophylaxis of post-operative nausea and vomiting. Whilst these agents have some, albeit modest, efficacy in this indication [3], there are few data that demonstrate clear superiority over older agents, including the dopamine receptor antagonists [4]. The 5-HT_3 antagonists are also poorly effective at treating emesis associated with treatment with opioid analgesics [5] or emesis associated with perturbations of the vestibular system, including motion sickness [6]. Clearly, the sub-optimal anti-emetic profile of the 5-HT_3 receptor antagonists creates an opportunity to identify and develop superior agents with greater efficacy and a broader spectrum of activity.

The precise locus for the anti-emetic activity of the 5-HT_3 receptor antagonists remains unclear. There is still debate over whether the most important site of receptor blockade lies within the central or the peripheral nervous system, or indeed whether receptor blockade at both sites is important. What is clear, however, is that many chemotherapeutic agents evoke a significant release of 5-HT from enterochromaffin cells within the wall of the small intestine. 5-HT thus released stimulates 5-HT_3 receptors located on afferent nerve fibres of the vagus nerve that project into dorsomedial medullary structures in the brainstem. These sensory fibres also appear to have 5-HT_3 receptors on their central terminals, which modulate the release of neurotransmitters in this region and may represent a further site of drug activity. Considering these sites of drug action, one option for producing agents with greater efficacy and potentially a broader spectrum of activity would be to identify a drug target sitting at a more central site in the emetic reflex, ideally at a site of convergence for the processing of sensory information.

2. Tachykinins, tachykinin receptors and the emetic reflex

The tachykinins are a family of peptide neurotransmitters that includes substance P, neurokinin A and neurokinin B. These peptides interact specifically with a family of membrane-associated G-protein coupled receptors termed NK_1, NK_2 and NK_3. A fourth member of this receptor family has been found, NK_4 [7,8], but the precise nature of this receptor has yet to be elucidated. Substance P has the highest affinity for NK_1 receptors, neurokinin A the highest affinity for NK_2 receptors and neurokinin B the highest affinity for NK_3 receptors. However, this selectivity is not absolute and the potential exists for these ligands to interact with any member of the receptor family.

2.1 Anatomy

Neuroanatomical studies have demonstrated substance P immunoreactivity in numerous structures within the human brainstem, including the dorsal motor nucleus of the vagus nerve, the reticular formation and the nucleus of the solitary tract [9-11]. These nuclei are of major significance in the physiology of the emetic reflex. Complementary to these data, autoradiographic analysis has localised tachykinin NK_1 receptors to many of the same regions [12]. To date, no studies of human brainstem have investigated the distribution of either neurokinin A or neurokinin B in any of the regions and nuclei of the implicated in the emetic reflex. Similarly, the localisation of tachykinin NK_2 and NK_3 receptors in the nuclei of the human brainstem has not yet been studied.

2.2 Pharmacology

It has been known for many years from work in animals that substance P can evoke neuronal excitation in the area postrema of the dorsal brainstem [13]. This region lies at the base of the fourth cerebral ventricle and is in close apposition to the nucleus of the solitary tract. These regions receive dense afferent projection from the proximal GI tract and are fundamentally important in the emetic reflex. It might be expected that any agent which excites neurones in these regions could evoke emesis and this has been shown to be the case in dogs, where iv. administration of substance P evokes vomiting [14]. Data generated in ferrets also supports a role for tachykinin receptors in eliciting the emetic reflex, with the selective NK_1 receptor agonist, GR73632 evoking a profound emetic response following intracerebroventricular administration [15]. These data raise the possibility that the tachykinin NK_1 receptor is involved in the emetic reflex and moreover, if the site of action is within the CNS, that it represents a convergent target for diverse emetogenic inputs.

The value of this hypothesis relies on being able to demonstrate that selective tachykinin receptor antagonists can modulate the emetic response to clinically relevant emetogens. A number of studies, primarily by scientists from Pfizer, Glaxo Wellcome (now GlaxoSmithKline) and Merck have demonstrated this in animals unequivocally. In the ferret, the prototypical NK_1 receptor antagonist, CP-99,994, dose-dependently inhibited the emetic response to cisplatin. This effect could be mimicked by administration of the compound at lower doses directly to the brain, suggesting a central site of

action, as implicated by earlier work with the agonist, GR73632 and the peptide antagonist GR82334 [15,16]. Importantly, CP-100,263, the inactive enantiomer of CP-99,994, was inactive against cisplatin-induced emesis in the ferret, confirming the NK_1 receptor-mediated nature of the emetic response [17]. The central site of action has been confirmed with data obtained using agents that very poorly penetrate the blood-brain barrier [18]. The highly potent NK_1 receptor antagonist L-743,310 is inactive against an emetic challenge with cisplatin, unless it is given centrally when it completely blocks the emetic response. More recently, direct microinjection of the highly potent NK_1 antagonist GR205171 into discrete nuclei of the brainstem has confirmed that, at least in dogs, NK_1 receptors in an area adjacent dorsally to the nucleus ambiguus represent a likely site of action [19].

Subsequent to these seminal studies, the NK_1 receptor antagonists have been shown to have an unprecedented broad spectrum of anti-emetic activity in a very wide range of animal species, including the dog, ferret, cat, pig and shrew. Specifically, NK_1 receptor antagonists prevent emetic responses to chemotherapeutic agents (both acute and delayed emetic responses), radiation, volatile and gaseous anaesthetic agents, ipecacuanha, morphine, ethanol, copper sulfate and motion. These data are particularly exciting because they include agents and stimuli that have been refractory to anti-emetic treatment with 5-HT_3 antagonists in both animals and, more importantly, man. In particular, in two animal models of delayed emesis, the NK_1 receptor antagonists L-754,030 (and its prodrug, L-758,298), GR205171, PD 154075 and CP-99,994 have all been demonstrated to inhibit the delayed emetic response to cisplatin in ferrets and piglet [20-23].

2.3 Clinical data

A number of NK_1 receptor antagonists have progressed to clinical trial for determination of their anti-emetic efficacy in a clinical setting. In a study of cisplatin-induced emesis, addition of the Pfizer NK_1 receptor antagonist, CJ-11,974 (Ezlopitant), to an anti-emetic regime comprising the 5-HT_3 antagonist granisetron and dexamethasone was superior to use of the 5-HT_3 antagonist and steroid alone [24]. In this study, both acute (day 1) and delayed (days 2 to 5) emesis were significantly better controlled than when a regime of standard care was employed. Significantly, nausea was also better controlled in the patient group treated with CJ-11,974. Similar data has also been generated from a study with the Merck NK_1 antagonist, L-754,030 [25]. The anti-emetic efficacy of the NK_1 antagonists has been confirmed in subsequent studies, demonstrating the efficacy of NK_1 antagonists, especially in the delayed phase of emesis [26,27]. These studies have confirmed that the triple combination of NK_1 antagonist, 5-HT_3 antagonist and dexamethasone seems to represent the best treatment option.

In general, the NK_1 receptor antagonists have been well-tolerated. Adverse events occurring in > 10% of patients have included dizziness, perversion of taste, headache, anorexia, abdominal pain, constipation, diarrhoea and asthenia. Most of these events have occurred at similar rates in patients treated with NK_1 antagonists and in those receiving the standard care of 5-HT_3 antagonists plus dexamethasone. Diarrhoea appears more prevalent in the patient group treated with NK_1 antagonists, although diarrhoea is a common side effect in patients treated with cisplatin. The overall benefit of the NK_1 antagonists in terms of improvements in patients' quality of life is still to be determined.

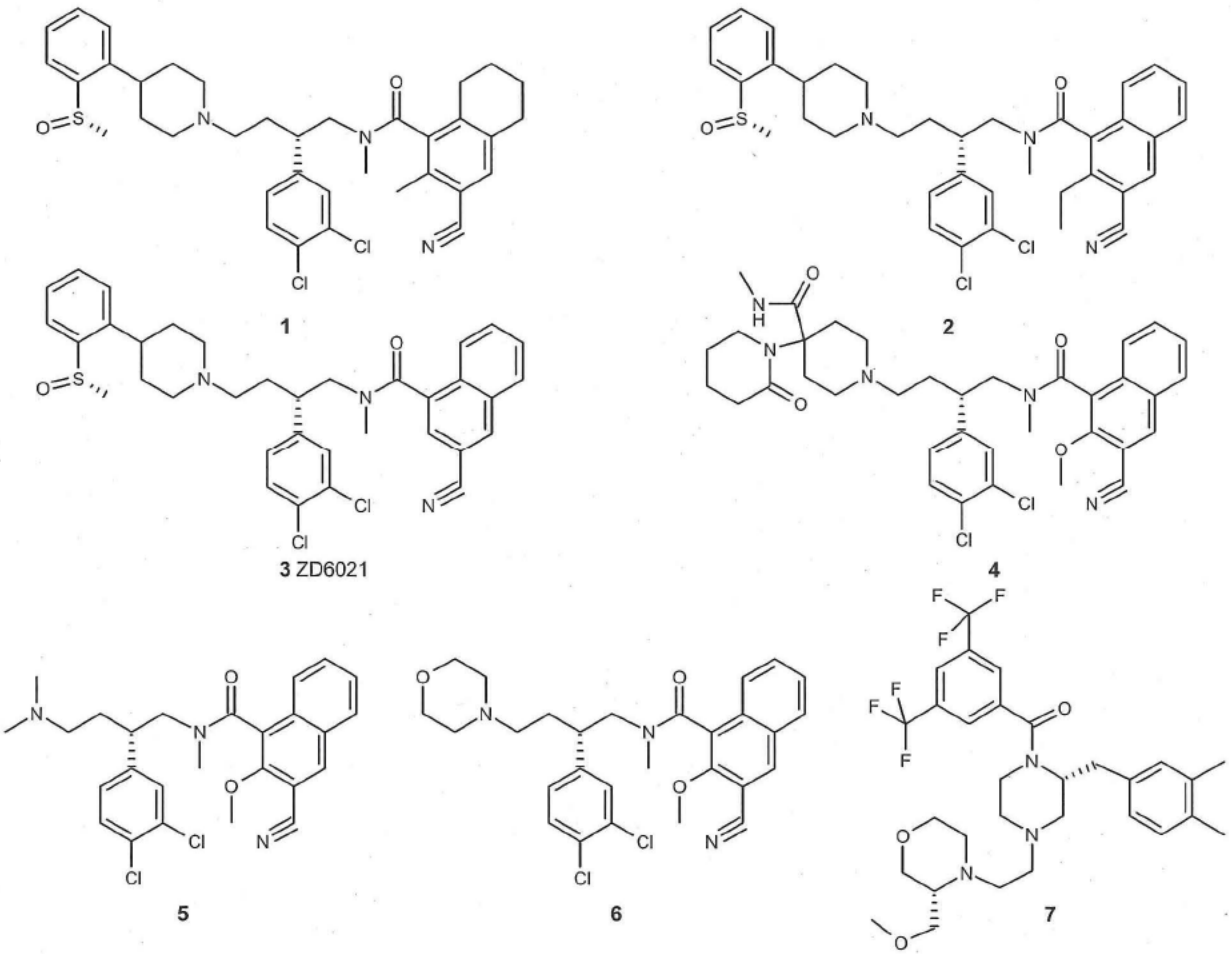
Two Phase II studies have also examined the efficacy of NK_1 receptor antagonists in post-operative nausea and vomiting (PONV). In a small study aimed at treatment of established PONV following major gynaecological surgery, the Glaxo NK_1 antagonist, GR205171 (vofopitant), was superior to placebo at controlling symptoms over a 24 h period following iv. administration [28]. In a larger study looking at prophylaxis of PONV following abdominal hysterectomy, oral dosing with the Pfizer NK_1 antagonist, CP-122,721, was superior to iv. treatment with a 5-HT_3 antagonist [29]. In this study, combination of the NK_1 antagonist with a 5-HT_3 antagonist appears to prolong the emesis-free period and thus be the most superior treatment option.

The only other form of emesis that has been studied clinically with the NK_1 receptor antagonists is that evoked by motion. In this small study in volunteers, GR205171, at a dose shown to be efficacious in the treatment of PONV, failed to control motion-induced nausea either alone or in combination with a 5-HT_3 receptor antagonist [30]. These data are in stark contrast to those obtained in motion-induced emesis in animals, where NK_1 antagonists were highly efficacious anti-emetic agents and raise the possibility that the broad spectrum anti-emetic profile demonstrated in animals with this class of agent may not be mirrored in humans.

3. Tachykinin NK_1 receptor antagonists

Most major pharmaceutical companies are working towards advancing improved new compounds to the clinic, as evidenced by the large number of patent applications published in recent years. For example, Astra Zeneca has expanded on a previous claim with five new patent applications claiming novel naphthalenecarboxamides, such as compounds **1** - **6** [101]. The phenylsulphinyl naphthalenecarboxamides **1** - **3** are relatively nonselective, binding to each of the tachykinin receptors, although with more affinity for NK_1 and NK_2 over NK_3 [102-104]. The pharmacological properties of compound **3**, also known as ZD6021, have been studied extensively [31].

Piperidinylbutyl naphthalene carboxamide derivatives such as the specifically claimed compound **4**, reportedly provide greater selectivity for NK_1 and NK_2 over NK_3 [105]. The substitution pattern about the naphthalene and piperidine rings may also be altered to give compounds with enhanced selectivity for either NK_1 or NK_2. However, the greatest NK_1 selectivity is realised *via* the aminobutyl- and the morpholinylbutyl-substituted naphthamides (i.e., **5** and **6**, respectively) [106]. The 3,4-



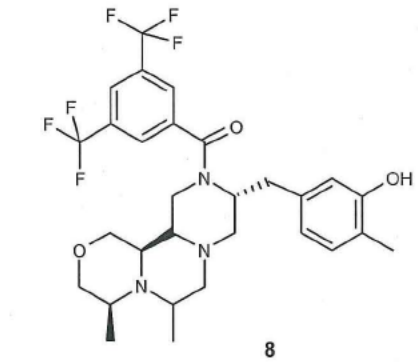
dichloro substitution about the phenyl ring and the 3-cyano functionality of the naphthalene ring system appears to be particularly important features in each of these series. Altogether these patents list over 120 synthesised examples and eight specifically claimed compounds. Several examples are reported to be orally-active in guinea-pig models of extravasation and bronchoconstriction but no emesis data are reported.

A 1998 report from Fujisawa [107] discusses structural modifications of their previously patented [108,109] aroylpiperazine compounds. Several compounds were shown to be brain-penetrant and active at 1 mg/kg iv. in a copper sulfate-induced ferret emesis assay. This degree of potency is an improvement over the earlier patented compounds. The two patents list 196 examples, 16 of which are specifically claimed and two of which (7 and 8) are shown.

Glaxo has reported a series of novel piperizine derivatives that feature an unusual urea central link between an aryl substituted piperazine and Merck's bistrifluoromethyl phenethyl amine [110]. Derivative 9 displays excellent oral activity in the CNS model of agonist-induced gerbil foot tapping (ED_{50} = 0.04 mg/kg). The compound is formulated as the acetate salt and is suitable for ip. and sc. administration.

The anti-emetic efficacy of NK_1 receptor antagonists against chemotherapy-induced emesis is enhanced when combined with a 5-HT_3 receptor antagonist. For this reason, the efficacy of a combination of NK_1 antagonist (GR205171 10) and the 5-HT_3 antagonist, ondansetron, was assessed in motion-induced nausea [30]. Administration of GR205171 with and without ondansetron was compared to placebo in a model of moderate motion-induced nausea. However, there were no significant differences between either GR205171 alone or GR205171 plus ondansetron with placebo.

Hoffmann-La Roche has reported recently four new sets of claims on carboxamide structures. including one each on pyridines [111] and biphenyl derivatives [112] and two on pyrimidines [113,114]. Together these patents list 245 synthetic examples and 88 specifically claimed compounds. The bulk of the claimed chemical matter lies in the pyrimidine series (compounds 11 and 12) and these compounds also appear to provide slightly greater *in vitro* NK_1 binding potencies. The pyrimidines each exhibit K_i values of ~ 0.6 nM in CHO cells transfected with the human recombinant NK_1 receptor, while the pyridyl (13) and biphenyl (14) compounds exhibited potencies of 2.8 and 1.4 nM, respectively. *In vivo* biological data were not provided. The Roche compounds are similar in structure to a series appearing in a Japanese patent issued to Yamanouchi. 15 Compounds are reported, including 15 and 16, but biological data are not supplied.



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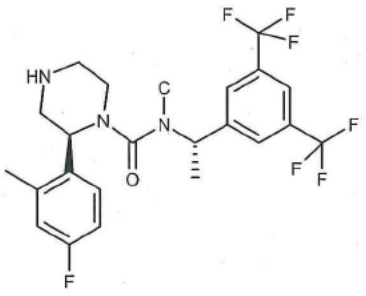

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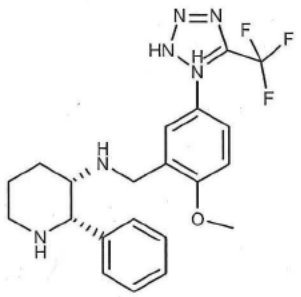

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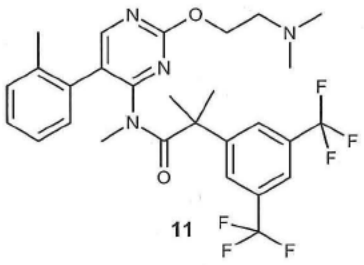

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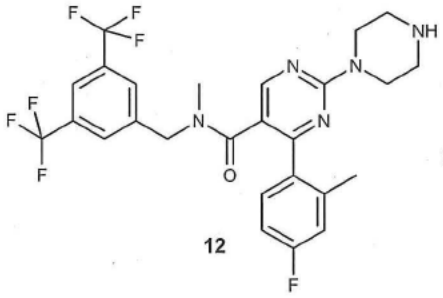

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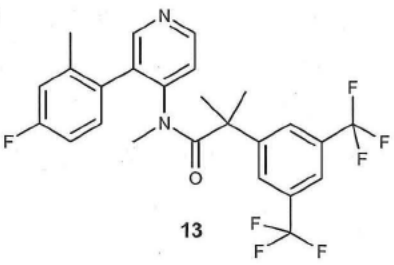

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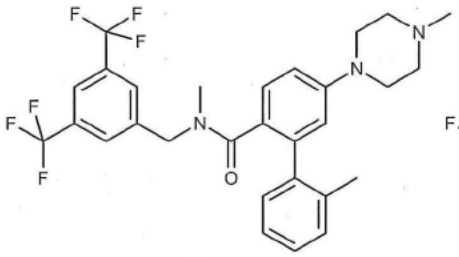

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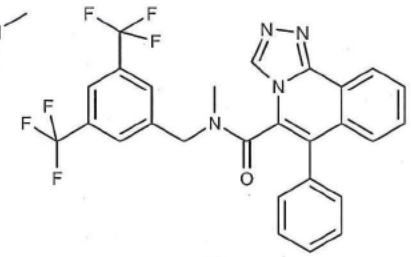

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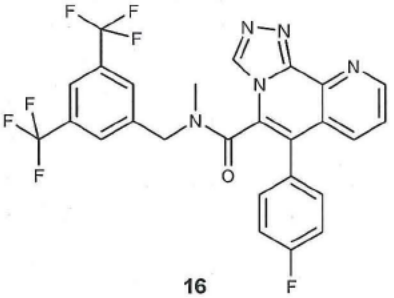

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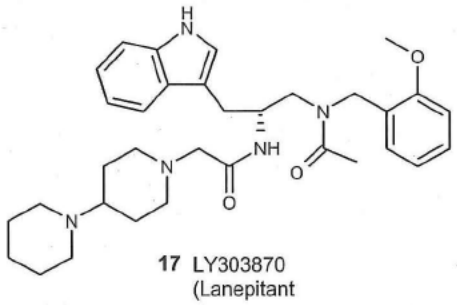
Lilly has been issued a patent claiming bisindoles as tachykinin receptor antagonists and 5-HT receptor agonists [115]. Although related somewhat to Lilly's lanepitant, these structures differ most notably in the presence of an additional indole group, and thus giving it greater mass (i.e., compound **18**). 60 Compound examples are named in the patent but none are specifically claimed and experimental data are not reported.

Merck has recently incorporated dialkylamine-substituted azo-heterocycles on their previously reported morpholine template *via* a methylene bridge to the ring nitrogen. These compounds offer increased aqueous solubility and long duration of action. This obviates the need for a prodrug as in the case of MK-869 (**19**). A specific crystalline polymorph of compound **20** that is thermodynamically stable and which is suitable for inclusion in a pharmaceutical formulation has been claimed [116] and two chemical process patents to this compound have also been granted [117,118]. A specific thermodynamically stable polymorph of MK-869 (L-754,030) was also claimed as suitable for inclusion in pharmaceutical formulations [119]. A further report describing the anti-emetic profile of MK-869 and its water soluble prodrug L-758,298 demonstrated efficacy against acute and delayed cisplatin-induced emesis in ferret [23,120].

Several specific therapeutic patent applications have been filed for morpholine **21** [121-124] in addition to the claims of the original report [125]. The hydroxymethyl benzyl substituent improves physical chemical properties such as solubility in the same manner as azo-heterocycles compared with MK-869. Compound **21** displays the following preclinical profile: NK_1 IC_{50} = 0.12 nM; antagonism of substance P-induced gerbil foot tapping: IC_{50} = 0.38 mg/kg (5 min), 2.2 mg/kg (24 h); inhibition of substance P-induced emesis in the ferret: ID_{90} 1mg/kg po; inhibition of substance P-induced guinea-pig vocalization: ID_{50} 0.91mg/kg p.o. A variety of non-basic substituted pyran NK_1 antagonists have also been reported with binding affinity (IC_{50}) reported ≤ 100 nM [120]. The pyran substituents range from the aminomethyltriazole of **22** to hydroxymethyl, carboxy and vinyl.

A series of spiro-piperidine derivatives with and without direct phenylpiperidine substitution has been reported (compounds **23** and **24**, respectively) [127,128]. The trifluoromethyltetrazole originally favoured by Glaxo has been incor-



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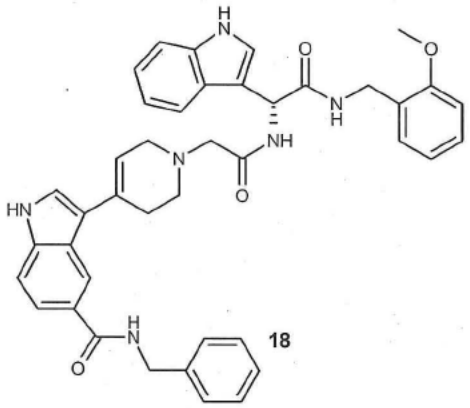

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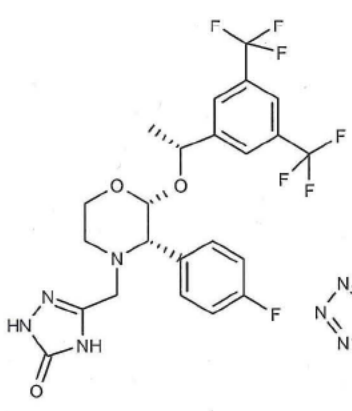

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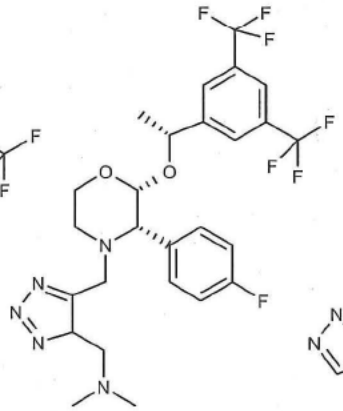

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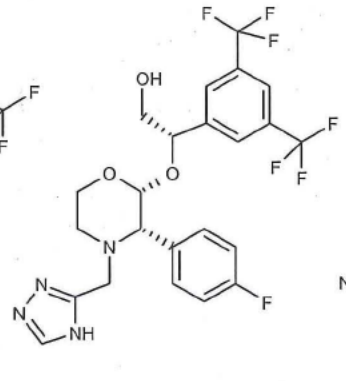

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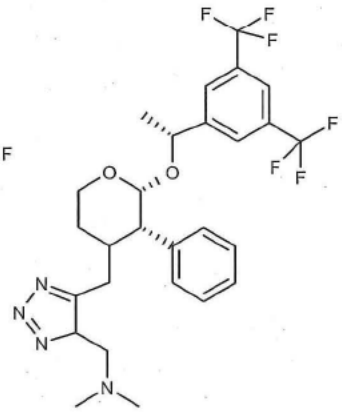

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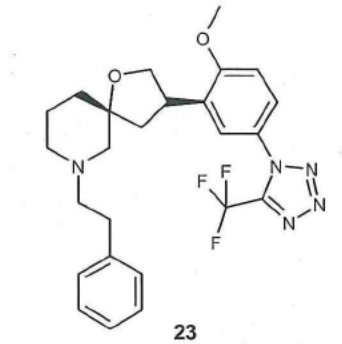
porated into each system. Both series reportedly display NK_1 binding affinity < 1 μM and attenuate substance P-induced retching in ferret. It should be noted that the aromatic ring appended to the furan ring may be a heterocycle [129] or may be substituted by imidazole or fluoromethoxy to reduce metabolic degradation [130]. Replacement of the furan ring with a pentanone affords a third series of spirocyclic piperidine antagonists, represented by **25**, with and without substitution of the piperidine nitrogen [131]. The 23 compounds specified have binding affinity < 100 nM. Merck has also revealed non-basic spiro-ethercycloalkane structures **26** as NK_1 antagonists, although the scope of the claims also includes basic compounds [132,133]. The reported binding affinities span a range from 0.5 nM to 10 μM.

Merck has reported a 2-arylindole lead **27** from a combinatorial library [134] and biological data has been published [32,33]. These reports describe the SAR information designed to improve pharmacodynamics, which lead to **28** as one of several potent antagonists in the substance P-induced gerbil foot tapping assay. The authors indicate that high first pass metabolism limited bioavailability of these compounds. The structurally-related 4,4-disubstituted piperidine **29** was claimed as a combined SSRI/NK_1 antagonist [135]. This class of compounds reportedly exhibit NK_1 binding affinity < 10nM and attenuate substance P-induced retching in ferret.

Novartis has continued their work in the area of proline dipeptides exemplified by the earlier lead compound **30**. The present series includes the quinazoline **31**, which is designated the preferred agent [136]. These compounds span a range of K_i values from 0.01 - 10 nM at the NK_1 receptor as measured by [^{3}H]-substance P displacement from Cos-7 cells transfected with the human recombinant NK_1 receptor. The current application also covers compounds wherein a quinazoline nitrogen atom is replaced with oxygen or sulfur. Seven synthetic examples are provided but no specific biological data are given.

Pfizer has continued to discuss novel antagonists within their amino-piperidine domain. The most recent report [137] stems from incorporation of a fused tricyclic ring containing an embedded tetrazole (compound **32**). These structures extend the scope of previous reports from Pfizer [138] and from GlaxoWellcome [139-141]. The agents display antagonism of substance P-induced gerbil foot tapping and capsaicin-induced plasma extravasation. These compounds have been profiled against verapamil Ca^{2+} binding In rat heart and metabolic half-life in human liver microsomes. In a related discussion, a claim from Hisamitsu has appeared for compounds of general Type **33** [142]. Compounds from this series exhibit NK_1 binding in the range of 1 nM and are 90% efficacious at 0.3 mg/kg in an *in vivo* model of cisplatin-induced emesis.



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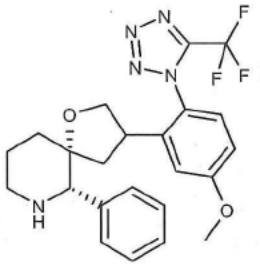

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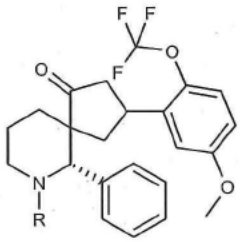

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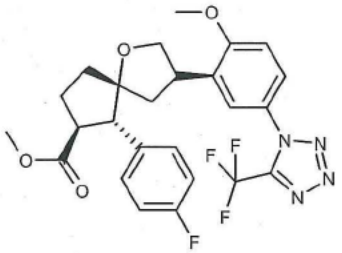

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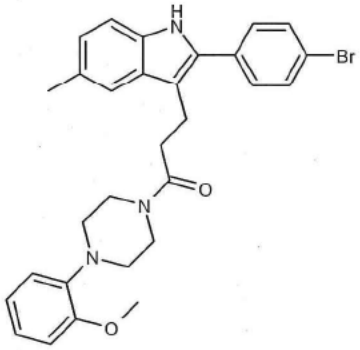

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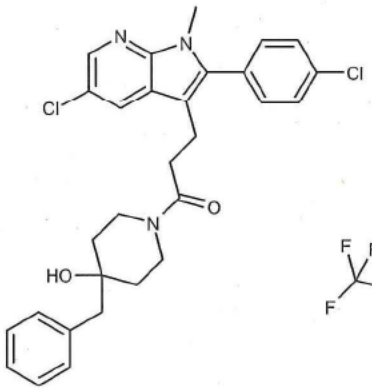

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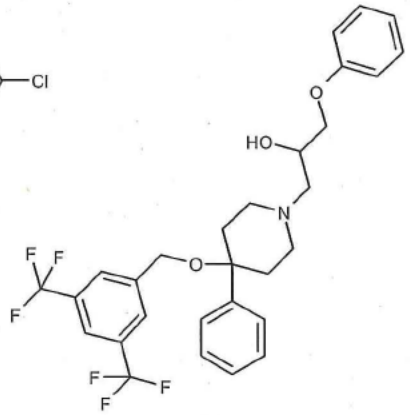

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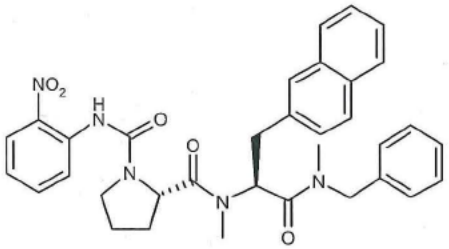

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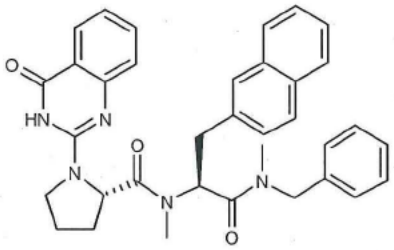

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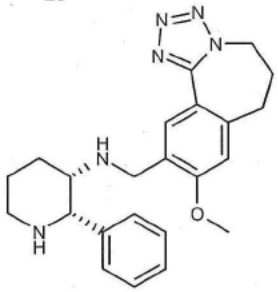

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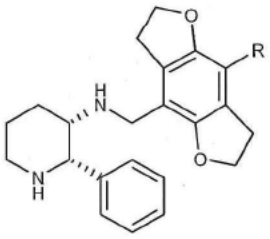

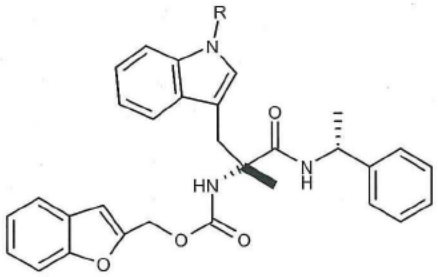

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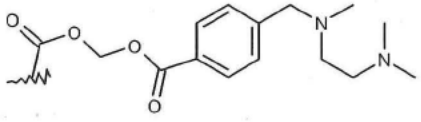

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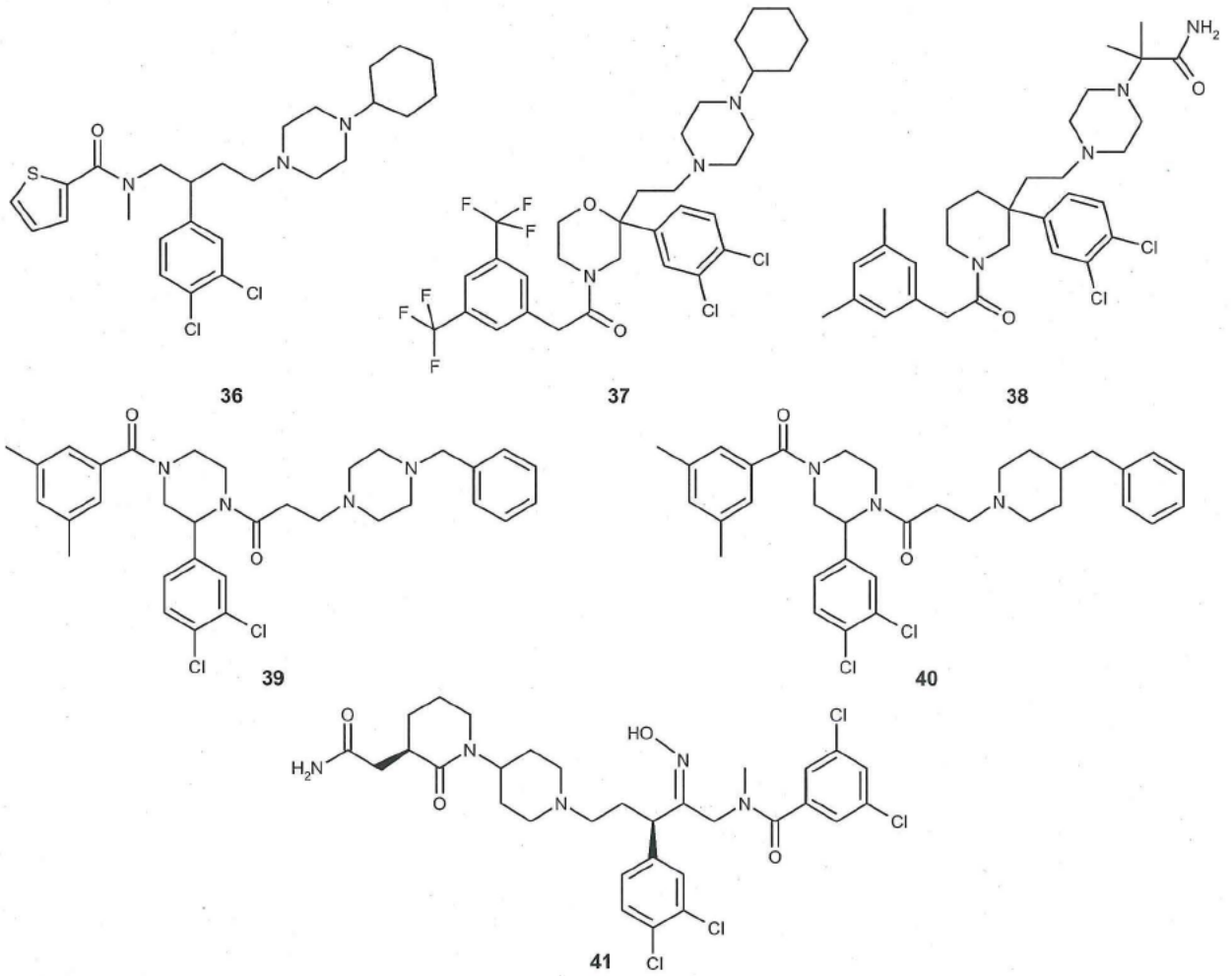
Warner-Lambert (now Pfizer Global R&D) had previously discussed a tryptophan-based NK_1 antagonist found to be efficacious in the ferret emesis model (34) [143]. They have now extended the scope of this class of compound to include water-soluble prodrugs such as the compound 35 [144]. Intravenous dosing of cannulated rats with 36 demonstrated 100% reconversion to the parent antagonist as demonstrated by HPLC analysis of plasma samples. This prodrug also achieved 46% bioavailability upon p.o. administration.

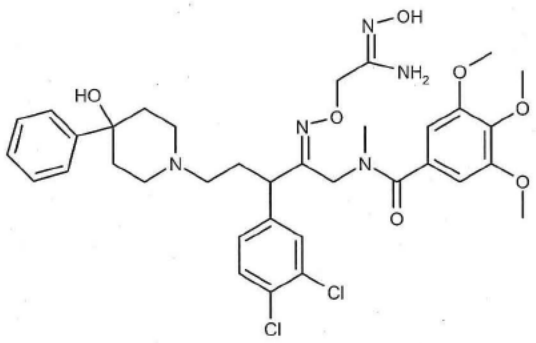
Sanofi has expanded on their previous claims by incorporating piperidine or morpholine rings into the earlier structures to yield 36 - 38 [145-147]. The resultant rigidification of the structures appears to have imparted greater selectivity for the NK_1 receptor. The compounds reportedly exhibit NK_1 receptor binding affinities of ~ 0.01 nM whereas the NK_2 and NK_3 affinities are ~ 10 and 100 nM, respectively. However, no specific data are provided.



Schering has claimed the use of piperazine derivatives as selective antagonists of either NK_1, NK_2, or NK_3, as well as for use as NK_1/NK_2 dual receptor antagonists [148]. 52 Compound examples are described, with 38 being specifically claimed. The piperazine **39** appears to be the highest affinity NK_1 antagonist with a K_i value of 3 nM. The compound also has affinity for the NK_2 receptor (K_i = 25 nM). Interestingly, replacement of one of the piperazine rings of this compound with a piperidine ring reverses the selectivity, providing a compound that is more selective for the NK_2 receptor over the NK_1 receptor (compound **40**, 7.5 and 71 nM, respectively).

A 1997 Schering patent claims substituted oximes, hydrazones and olefins as tachykinin receptor antagonists [149]. The oxime series was subsequently found to be more potent than the hydrazones and olefins, prompting publication of additional patent documents covering these structures (e.g., **41** - **43**) [150,151]. Together, these documents report 187 synthesised examples, including 162 specifically claimed compounds. The compounds were essentially non-selective, displaying comparable affinity for NK_1 and NK_2 receptors (~ 0.2 - 6 nM). Some of the compounds are also high affinity NK_3 antagonists (K_i ~ 0.05 - 50 nM) although these structures are not specifically identified. The binding assays were performed on CHO cells transfected with human recombinant receptors and provided K_i values of ~ 0.2 - 6 nM. The dual NK_1/NK_2 activities make the compounds attractive as potential asthma treatments (NK_1 and NK_2 receptors are associated with vascular leakage and with muscle contraction, respectively) and this appears to be the main focus of the patents. Emesis is claimed as an additional potential therapeutic indication, but no data are included to support this.

Recent reports from Takeda describe napthiridine derivatives such as **44** - **46** that includes the clinical candidate TAK-637 [34,35,152]. The 8-membered azacyclic ring was originally installed to simplify synthetic and developmental issues arising from atropisomerism of the earlier straight chain amide series. The chiral 9-methyl group was likewise installed for synthetic reasons, enabling a stereoselective synthesis of the desired atropisomer. It was subsequently found that that the newer series, although less potent *in vitro*, exhibited higher *in vivo* potencies and were orally-active in a guinea-pig model of capsaicin-induced plasma extravasation. Replacement of



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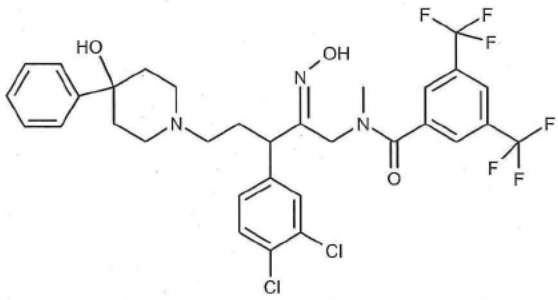

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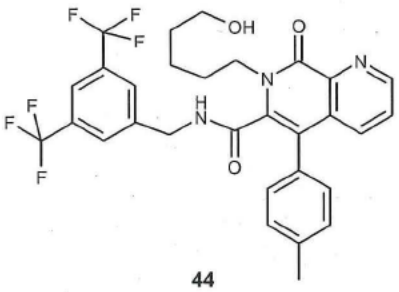

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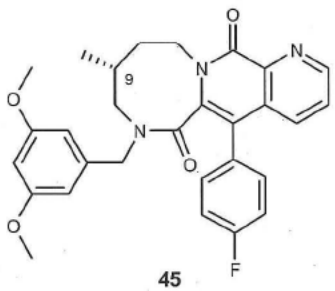

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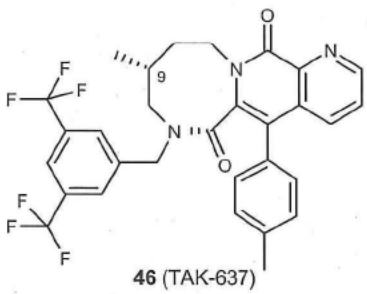

46 (TAK-637)

the preferred 8-membered ring with 6-, 7- and 9-membered rings also provides active compounds. The NK_1 binding affinities for compounds related in structure to **44** and **45**, determined *via* measurement of inhibition of radiolabelled substance P binding to IM-9 cells, span a range of IC_{50} = 0.05 - 1.6 nM. Among the most potent compounds appears to be the hydroxypentyl compound **44** (IC_{50} = 0.05 nM) although this compound is not specifically claimed. All these documents describe over 220 synthesised examples and 8 specifically claimed compounds. Some of the examples described in these manuscripts are also potent inhibitors of the NK_2 receptor but selectivity details are not provided. The compounds were assayed to measure their ability to inhibit capsaicin-induced plasma extravasation in the guinea-pig trachea *in vivo* and emesis data are not provided.

4. Expert opinion

Even in the era of 5-HT_3 receptor antagonists, the control of certain aspects of the nausea and vomiting associated with cancer chemotherapy remains problematic. Delayed emesis and the emesis that occurs following multiple cycles of chemotherapy are difficult to treat with existing agents. In addition, currently used agents have much reduced effectiveness in controlling nausea and this is a major concern for patients. Therefore, the medical need for anti-emetic agents with greater levels of efficacy and broader spectra of anti-emetic activity is clear.

The potential value of anti-emetic targets situated at points of convergence of sensory emetic stimuli has been postulated. Largely though, the utilisation of prototypical agonists and antagonists, the tachykinin NK_1 receptor has been identified as one such target and the profound anti-emetic activity of antagonists at this receptor has been demonstrated. Extensive experimentation in animals defined the breadth of anti-emetic activity, but recent studies using elegant micro-injection techniques appear to have pinpointed the locus of activity of these agents. Our developing knowledge of the anatomy and physiology of the neurocircuitry of the emetic reflexes in the brainstem and the increasing use of human tissue for such studies will generate further targets for investigation. Continued structural refinement and SAR of early NK_1 antagonist leads has expanded to include properties such as enhanced CNS penetration, reduced interaction with calcium channels and improvement in metabolic profile with elimination of drug-drug interactions. The scope of chemical lead matter combined with early results and feedback from clinical studies improves chances for a well-tolerated therapeutic agent in the future.

Clinical studies for the treatment of emesis have commenced with a small number of these agents. Early data are encouraging and suggests useful levels of activity against delayed emesis and nausea. Efficacy appears be maximised by the use of a NK_1 antagonists within a combination of drugs including 5-HT_3 receptor antagonists and the steroid, dexamethasone, however, optimal treatment regimes will need to be defined in larger multi-centre trials. It is also likely that, over the next few years, a number of 5-HT_3 receptor antagonists will become available in generic form, thus making the option of combination therapy more financially attractive. As a result of emerging clinical data and changes to the marketplace, the place of these agents in the control of chemotherapy-induced nausea and vomiting will be defined.

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