A Historical and Statistical Overview of NK_1 Receptor Antagonists in the Treatment of Chemotherapy-Induced Nausea and Vomiting

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Abstract

Chemotherapy-induced nausea and vomiting is one of the most common symptoms recorded by patients undergoing chemotherapy, particularly when taking highly emetogenic treatments such as cisplatin. The 2000s saw the breakout approval of neurokinin-1 receptor antagonists, which were able to reduce these symptoms at a higher rate than traditional antiemetics. As neurokinin-1 receptor antagonists gained popularity, newer drugs of this class were developed, both to improve efficacy or to resolve pharmacokinetic limitations of the previous drugs. A summary of the studies investigating the use of neurokinin-1 receptor antagonists over the past two decades provides key insight to some of the most promising antiemetics in contemporary medicine, as well as the statistical methods used to support such a statement.

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1. Introduction

Neurokinin-1 (NK_1) receptor antagonists have been a source of interest in clinical research since the early 1990s, when they emerged as a novel treatment to combat nausea and emesis in patients undergoing chemotherapy. This has proven to be an important topic in oncology research, as it is estimated that up to 80% of cancer patients receiving chemotherapy experience nausea and vomiting to some extent. The consequences of these side effects range from distressing to life-threatening. [11].

The discovery of NK_1 antagonists led to a subsequent push for several companies to develop pharmaceutical solutions in a variety of therapeutic areas. Although major depressive disorder and other psychological disorders were a heavy focus of preliminary clinical trials, the first FDA approved NK_1 antagonist was arepitant in 2003 for combating chemotherapy-induced nausea and vomiting (CINV).

Since then, a variety of different of NK_1 antagonists have undergone development, challenging the successful efficacy of arepitant for CINV and other causes of nausea, continuing the search for significance combating major depressive disorder, and even finding new uses for SP antagonists treating conditions such as itch sensitivity and opioid withdrawals.

The studies that have investigated and progressed the use of these NK_1 antagonists relied on many conventional and well-backed statistical methods in clinical research. However, as study complexity grows along with this family of drugs, innovative statistical approaches offer potential to maximize the usable knowledge obtained from previous studies and reduce redundancy and resource use in new studies.

2. Pharmacology of NK_1 Receptor Antagonists

The causes of CINV are complex and are still a subject of research, but the main mechanism by which CINV is induced occurs an area of the brainstem known as the area postrema. Here there is a chemoreceptor trigger zone (CTZ), in which neurotransmitters such as Substance P (SP) play a role in stimulating nausea and vomiting in response to the chemicals used in many chemotherapeutic treatments [11]. As a key response to noxious or stressful stimuli, SP is released in the presence of stressors that may pose a serious threat to the biological well-being of an organism. The receptor for SP, TACR1 (a tachykinin peptide), is found thoughout the human body, particularly along the central nervous system, where they aid in response functions such as pain and vomiting reflexes. By suppressing binding at these sites, NK_1 antagonists can also suppress symptoms of CINV.

3. Clinical History

3.1. Aprepitant Superiority Trials Leading to FDA Approval

As the first FDA approved treatment involving NK_1 antagonists, arepitant has become a popular antimetic for patients suffering from CINV. Approved in 2003, one of the many studies that lead to the eventual widespread adoption of arepitant for chemotherapy was that of Paul J. Hesketh et al.(2003) [1].

As a phase III superiority trial, the goal of this study was to prove that areptiant is able to reduce CINV to a greater degree than existing conventional treatments do. Instead of only using a placebo as control, this means the control to make statistical comparisons will be a well-established treatment for CINV with proven efficacy. A common way to perform these superiority studies is the 'add-in' study - that is, add an additional experimental medication to an already proven treatment, and compare the different outcomes. In Paul J. Hesketh et al., patients in the control group were administered a two-medication treatment of ondansetron and dexamethasone, while the other group recieved the same two drugs, but with an additional 125mg dose of aprepitant.

In their simplest forms, the null and alternate hypotheses of a superiority study are formulated as the following:

Null Hypothesis (H_0): There is no difference in efficacy between the new treatment and the control, or the new treatment is worse than the control.

$$H_0 : \mu_{\text{new}} \leq \mu_{\text{control}} \tag{1}$$

Alternative Hypothesis (H_1): The new treatment is superior to the control.

$$H_1 : \mu_{\text{new}} > \mu_{\text{control}} \tag{2}$$

In an experiment with no confounding factors, these μ would simply represent the mean of each group's incidence of emesis. However, in practice there are factors besides the controlled explanatory variables that influence the response variable. In order to account for the influence of all factors, including those which cannot not easily be manipulated for the experiment, a linear model is used to approximate the response variable as a sum of each explanatory factor and their respective model coefficient. In the case of the study performed by Paul J. Hesketh et al., this linear model took the form:

$$y_{ijkl} = \mu + \alpha_i + \beta_j + \gamma_k + \delta_l + \epsilon_{ijkl}$$

Where μ represents the mean rate of some metric being considered, α_i is the treatment used, β_j is the patient sex, γ_k is the the use of concomitant therapy, and δ_l is the region the patient is from (two

levels: United States, or other). ϵ_{ijkl} a the normally distributed error, or changes in the response variable for any individual that cannot be explained by any of the other variables. The values of each model component are estimated via maximum likelihood. In this experiment, the response variables in these models were defined as a simple true false for a variety of symptoms of CINV. Because this boolean value has a strict domain of [0,1], the linear model is generalized with a logit link function to perform logistic regression, ensuring that y_{ijkl} stays within this domain.

$$logit(p_{ijkl}) = log(\frac{p_{ijkl}}{1 - p_{ijkl}}) = \mu + \alpha_i + \beta_j + \gamma_k + \delta_l + \epsilon_{ijkl}$$

p_{ijkl} can be the probability of any true/false outcome for a patient with i treatment, j sex, k chemotherapy, and l country of origin. For this study, several symptoms associated with CINV were recorded to be modeled by this p_{ijkl}, including emesis, nausea, and whether or not a rescue therapy was needed. A metric, 'complete protection', was also created to indicate the absence of emesis, rescue treatment, or significant nausea. The overall rates of these symptoms were reported in both the aprepitant and control groups for comparison.

Although not specified in Hesketh et al., there are a few ways to evaluate the significance of a model component α_i. Some options include a likelihood ratio test or a score test, but for focusing on just one single component of a logistic regression model, a viable option is the Wald test:

$$W = \frac{\hat{\alpha}_1^2}{\text{var}(\hat{\alpha}_1)}$$

This tests the null hypothesis that $\alpha = 0$, or simply put, if whether or not aprepitant is added into the treatment has any effect at all. Because W is assumed to follow a χ^2 distribution, the significance of treatment in the model can be calculated from this distribution, returning a p-value that is easily interpretable. In the case of logistic regression models designed to test three different outcomes (no emesis, no rescue, and complete protection), the treatment type α_i was considered statistically significant below 0.1. This means that there is a < 0.1 chance of committing a type I error, or incorrectly rejecting the null hypothesis of $\alpha = 0$.

Table 1. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Treatment Group for Overall Study Phase (nominal P values reported). Hesketh et al.(2003) [1]

Treatment Group	Aprepitant Regimen (n = 260)	Standard Therapy (n = 260)
No emesis	77.7†	55.0
No rescue	80.8†	70.8
Complete protection	63.4†	49.2
Total control	45.5	40.0
No nausea	47.5	44.2
No significant nausea	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm. †$p < .01$ versus standard therapy (significance based on logistic regression model).

As shown in Table 1, there were other outcomes that were not considered statistically significant: total control, no nausea, and no significant nausea. Although not considered significant by the logistic regression model, it is certainly possible that these symptoms are also reduced due to the add-in treatment, but significance was not recognized due to insufficient power by the model. It was expressed that the study was designed to detect a 15-point difference in complete response at 0.05 significance with 90% power, given a sample size of n=470. Because 521 subjects were ultimately included in the study, the statistical power was higher than planned. But with only a 3.5% difference in nausea between groups, it still cannot be guaranteed that the power will be large enough to detect superiority given a difference of this size.

Along with a detailed assessment of tolerability confirming the safety of use, this phase III trial demonstrated clear statistical evidence of the efficacy of aprepitant in the treatment of CINV. Later that year, aprepitant was FDA approved and marketed to the general public, leading to subsequent phase IV trials to monitor its long-term effects.

3.2. Administration Alternatives to Aprepitant and the Development of a Prodrug

Despite the success of aprepitant in the treatment of CINV, there were some problems with its route of administration. Aprepitant was designed as a capsule to be taken orally, and given that it is a treatment for nausea and vomiting, some patients are not able to fully absorb its contents without emesis. For this reason there was great interest in developing a similar treatment administrable by IV. In 2008, a prodrug of aprepitant, fosaprepitant, was approved for medical use in the United States and Europe.

When comparing a proposed bioequivalent treatment such as fosaprepitant for aprepitant, there are important measures that are considered to prove that both drugs are absorbed and metabolized similarly. In bioequivalence studies, a few of these key pharmacokinetic metrics include:

- Area Under the Curve (AUC): The definite integral of the concentration in blood plasma over time
- C_{max} The maximum concentration reached after dosage
- T_{max} The time after dosage at which maximum concentration occurs

AUC is the most important of these metrics, as it directly correlates to the total amount of dosage absorbed in the bloodstream. However, C_{max} and T_{max} are sometimes used as well. The conventional requirement for these metrics, as set by the FDA, is to take the geometric mean of all observations, and then construct a 90% confidence interval for this geometric mean. With upper and lower bounds for each treatment determined, the ratio between the geometric means is required to be within the rage [0.80, 1.25].

In 2007, a study was conducted by Lasseter et al. [3] to determine which dose of fosaprepitant was bioequivalent to the approved aprepitant dose of 125 mg. Because the comparison of aprepitant and fosaprepitant is a comparison berween an oral administration and an IV, it's highly unlikely, and not worth expecting, that the C_{max} and T_{max} would be similar. Fosaprepitant injected intravenously has an instant sharp peak in blood concentration, while ingested aprepitant has a lower peak that occurs later as it is metabolized. Therefore, Lasseter et al. only set out to prove the bioequivalence using the AUC of the two drugs, with the following hypotheses:

Null Hypothesis (H_0): Some dose x mg Fosaprepitant is not bioequivalent to 125 mg aprepitant:

$$\text{Geometric Mean Ratio 90\% CI} \notin [0.80, 1.25] \quad (3)$$

Alternative Hypothesis (H_1): Some dose x mg Fosaprepitant is bioequivalent to 125 mg aprepitant:

$$\text{Geometric Mean Ratio 90\% CI} \in [0.80, 1.25] \quad (4)$$

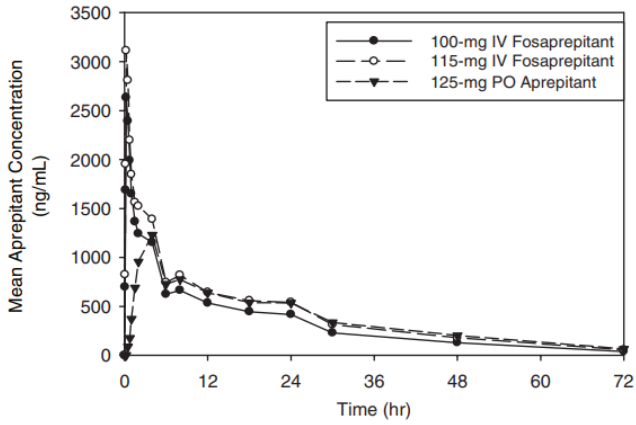

Figure 1. Average Blood Concentration of 125 mg Oral aprepitant vs 100 mg and 115 mg IV fosaprepitant. Note the high inital peak of fosaprepitant and the lower delayed peak of aprepitant. Figure from Lasseter et al. (2007)[3].

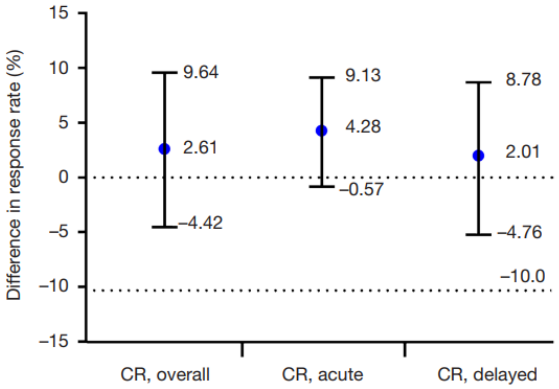

Figure 2. Differences in Complete Response Between Aprepitant and Fosaprepitant Groups During Acute (0-24 hrs) and Delayed (25-72) Periods. Non-inferiority Margin Denoted by Dashed Line at y=-10. Figure from Zhang et al. (2020)[9]

After calculating the AUC for a 115 mg IV dosage of fosaprepitant, it was calculated that the 90% confidence interval of the geometric mean ratio was [1.06, 1.20], with the aprepitant mean being 27.759 and the fosaprepitant mean being larger, at 29.611. Although being on the upper end of the specified limit, the geometric means comply with FDA regulations, rejecting the null hypothesis that the 115 mg IV dose of fosaprepitant and 125 mg dose of aprepitant are not bioequivalent, and accepting the alternative hypothesis that they are.

Even after bioequivalence is proven, it still is a good idea to verify that a novel bioequivalent treatment also yields similar results to the original treatment. Zhang et al. (2020)[9] performed a study in which they compared the efficacy of fosaprepitant and aprepitant in the treatment of CINV. Note that this study was performed over a decade after fosaprepitant FDA approval, and in that time, 150 mg IV became a standard dose size, and that dose was compared with 125 mg dose of aprepitant administered orally. The primary endpoint of the study was to measure complete response (no vomiting or rescue therapy). Because the goal of the study is to prove that the two drugs' performances are interchangeable, the null and alternative hypotheses are set up to reflect a non-inferiority test. This requires some margin δ which is used as distance below the original treatment that the 90% confidence interval of the new treatment cannot cross. In this experiment, it was decided that an acceptable margin of non-inferiority would be 10 points of complete response.

Null Hypothesis (H_0): Complete response of fosaprepitant is inferior to that of aprepitant.

$$H_0 : \mu_{\text{new}} \leq \mu_{\text{control}} - \delta \tag{5}$$

Alternative Hypothesis (H_1): Complete response of fosaprepitant is equal to or greater than that of aprepitant.

$$H_1 : \mu_{\text{new}} > \mu_{\text{control}} - \delta \tag{6}$$

Unlike Paul J. Hesketh et al, this study did not account for confounding factors impacting complete recovery by creating a logistic regression model. Instead, potential confounding factors were recognized and used to stratify treatment groups. The proportions of these factors, gender, first administration of chemotherapy, and the emetogenic potential of anticancer agent, were then tested with a chi-squared or Fisher's exact test to make sure that the two treatment groups had similar composition.

With a total of 644 patients evaluated for efficacy, 95% confidence intervals were constructed for the difference in CR acute(0-24 hrs), delayed (25-72)hrs, and total(0-72hrs) periods after highly-emetic chemotherapy. Given that each of these confidence intervals falls completely above the margin of non-inferiority, the null hypothesis is rejected and the alternative hypothesis that fosaprepitant is equal to or more effective than aprepitant is accepted.

3.3. Comparison of Subsequently Developed NK_1 Antagonists through Meta-Analysis

With the approval of aprepitant in 2003 and the approval of fosaprepitant in 2008, NK_1 antagonists were seeing rapid adoption as a remedy for CINV. This widespread adoption also brought attention to the observed limitations of their use, such as short half life, low bioavailability, and poor synergetic interactions with other drugs. As a result, drugs such as casopitant, netupitant, and rolapitant saw development in the late 2000s and early 2010s with the goal of resolving these downsides.

With five major NK_1 antagonists now offering viable treatment to CINV, comparing their efficacy became substantially more complicated. Designing an experiment which includes each of the five possible treatments is both challenging and costly, as the total number of enrolled patients now has to be significantly higher in order to maintain statistical power. Fortunately, modern meta-analysis techniques offer ways to pool together the results of multiple studies in order to aggregate their findings. Lu & Ades (2004) [2] proposed a methodology to design meta-analyses using hierarchical linear models in a Bayesian framework, and this method was applied by Rahman (2016)[6] to compare all five NK_1 antagonists mentioned in this paper.

In this Bayesian comparison of NK_1 antagonists, 19 different studies were utlimately included in the meta-analysis. Most of these studies compared the rates CR of between a control group given a placebo and a group given some NK_1 antagonist treatment, although some studies did compare NK_1 antagonists with eachother.

Because the primary endpoint of the meta-analysis is CR, a binary outcome, a binomial distribution can be used to model its occurence. Lu & Ades formulate these equations as the following for a comparison between K treatments:

$$r_{ik} \sim \text{bin}(p_{ik}, n_{ik})$$

$$\text{logit}(p_{i1}) = \mu_i - \frac{\delta_{i2}}{K} - \frac{\delta_{i3}}{K} - \cdots - \frac{\delta_{iK}}{K}$$

$$\text{logit}(p_{i2}) = \mu_i + (K-1)\frac{\delta_{i2}}{K} - \frac{\delta_{i3}}{K} - \cdots - \frac{\delta_{iK}}{K}$$

$$\vdots$$

$$\text{logit}(p_{ik}) = \mu_i - \frac{\delta_{i2}}{K} - \frac{\delta_{i3}}{K} + \cdots + (K-1)\frac{\delta_{iK}}{K}$$

$$(\delta_{i2}, \ldots, \delta_{iK})^T \sim \mathcal{N}(\delta, \Sigma)$$

$$\mu_i = \sum_k \frac{\text{logit}(p_{ik})}{K}$$

$$\delta_{ik} = \text{logit}(p_{ik}) - \text{logit}(p_{i1}), \quad k = 2, \ldots, K$$

With r_{ik} representing the total success of CR in trial i using treatment k, the effects, and their probabilities modelled by a logistic regression $\text{logit}(p_{ik})$. δ_{fik} represents the additional effect that a treatment k has on this probability p_{ik}) in trial i. The benefits of using a Bayesian methodology become clear here, as estimating the full posterior distributions of each of these parameters allows for the comparison of treatments that otherwise might not have necessarily been directly compared in a physical pairwise study

Once the posteriors distributions for these parameters are fully sampled using Monte Carlo sampling, these parameters representing each treatment k can be transformed in a variety of ways to compare the CR for that treatment. In the case of Rahman, he chose to use odds ratio to create pairwise comparisons for a select choice of treatment combinations. Odds ratio is a robust metric to use when extracting data from frequentist-oriented papers into a Bayesian meta-analysis, as it is designed with binary outcomes in mind and translates well into the computation of posteriors, given that the raw proportions and their sample sizes are also available.

$$\text{Odds Ratio} = \frac{\text{Odds of CR in Treatment Group}}{\text{Odds of CR in Control Group}}$$

$$= \frac{\text{Total with CR in Treatment/ Total without CR in Treatment}}{\text{Total with CR in Control/ Total without CR in Control}}$$

The five NK_1 antagonists mentioned so far, aprepitant, fosaprepitant, casopitant, netupitant, and rolapitant were all used in at least one pairwise comparison, but a variety of controls that were used throughout the 19 aggregated studies were also included, often as the denominator of the odds ratio. Some of these control drugs included dexamethasone, granisetron, and other non-NK_1 antagonist antiemetics.

For each odds ratio, a 95% credible interval was calculated. The interpreation of this credible interval in this case is similar to that of a frequentist confidence interval: if the interval includes 1, then it cannot be stated with high certainty that there is a difference between the two treatments. Rahman also performs the standard sensitivity analysis of fitting both a random and fixed effects model, or in other words, one model assuming there is a non-zero bias in each study, and model assuming the only differences come form the difference in treatments. Ideally the credible interval from both of these models would be in agreement in order to confidently back any conclusion about that odds ratio.

The two largest odds ratios comptued by the meta-analysis are those comparing NEPA (a combined dose of combination of netupitant and palonosetron) to control treatments that do not contain NK_1 antagonists. Among the higher credible intervals spanning entirely above zero there are also a few odds ratios of aprepitant against similar controls.

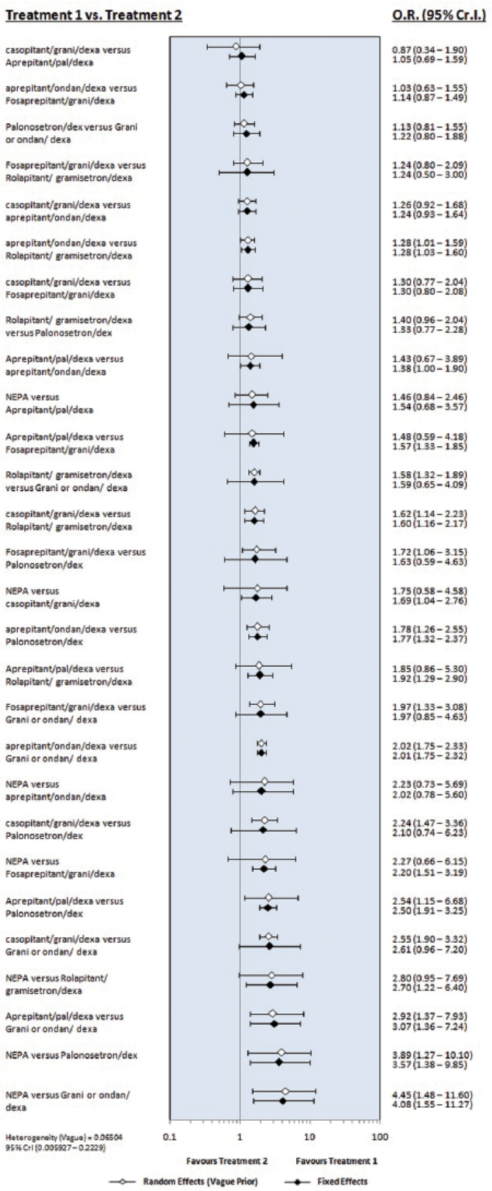

Figure 3. Forest plots of odds ratio (OR) of complete response (CR) associated with different NK_1 receptor antagonist based regimen. CI, credible interval; dexa, dexamethasone; grani, granisetron; ondan, ondansetron; NEPA, netupitant/palonosetron; palono, palonosetron. Figure from Rahman. (2016)[6]

Rahman concludes that his meta-analysis demonstrates the superiority of including NK_1 antagonists in the treatment of CINV, as all the odds ratios with a credible interval completely greater than one are cases of NK_1 antagonists vs controls. He also notes that casopitant appears to more effective in the treatment of CINV than rolapitant. Interestingly enough, the success of NEPA (the treatment containing netupitant) was absent from Rahman's conclusion, despite the two highest odds ratios against controls belonging to NEPA. NEPA was also compared to the next apparent strongest antiemetic, and in four different models had the following odds ratios means against aprepitant: 2.23, 2.02, 1.46, and 1.54. Although these odds ratios are impressive, their respective credible intervals all included 1, and therefore could not be used as conclusive evidence of NEPA's superiority. Given the consistency of these odds ratios in NEPA's favor, it may have been worth noting the relationship as a subject to investigate either directly in future studies or in a modified meta-analysis model. Later studies would in fact go on to compare NEPA and aprepitant in a pairwise trial, such as Zelek et al. (2023), which concluded that a single dose of NEPA was more effective at reducing CINV from than a three-day aprepitant regimen.

4. Discussion

In the early stages of NK_1 receptor antagonist development, the complexity of trials had a relatively low ceilig, as the majority of studies were simply following phase II and III protocol to advance the approval aprepitant. With the advent of fosaprepitant and eventually yet more drugs of the same class, studies grew in complexity as pharmacokinetic properties like bioavailablity and half-life became a point of investigation alongside efficacy.

Throughout the course of these studies, there were several statistical methods that stayed consistent in their utility evaluating the prophylactic efficacy for CINV. Many of these statistical methods reappeared, with slight variation, due to their usefulness in describing binomial data. The symptoms of CINV are various, with some of them such as nausea being more difficult to clearly reduce into a binary state. For this reason, the general trend in these studies was to use complete response (CR) metric as the primary endpoint which takes a binary value. This binary is recorded true when no vomiting or rescue treatment is needed, and false otherwise.

One of the most popular methods to model the binomial behavior of CR in these reviewed studies is the logistic regression model, which allows for the incorporation of confounding factors and their possible interaction effects. This method was used in the superiority study conducted Hesketh et al. (2003), formulating a logistic regression model and then testing for the significance of a treatment coeffecient. However, this method of targeting component significance becomes difficult when dealing with somewhat arbitrary margins in which the confidence intervals need to be contained. One standard approach, as performed by Zhang et al. (2020), is not to create a logistic regression model to account for confounding factors, but to compensate for these additional sources of variation by using them as a basis of treatment group stratification. Although this method is less robust to possible interaction effects, some statistical integrity is still maintained by performing a χ^2 or exact test to verify acceptable proportions.

Complementing the use of of logistic regression models, several of the reviewed studies also incorporated odds ratios, as odds ratios can easily be estimated by exponentiation components of these logistic models. The choice to use odds ratio or risk ratio is sometimes a difficult one, as FDA guidelines such as *Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry* [4] often contain more references to risk ratio. This decision is understandable given the superior interpretability of risk ratio, as a differences in risk ratio directly directly translate into the differencing probabilities of occurrence. This allows for a more intuitive understanding that may be better recieved by stakeholders or clinical practitioners that may not have as thorough of a statistical background. That said, the statistical advantages of odds ratio coupled with logistic regression have been clearly demonstrated throughout the selected NK_1 antagonist studies.

Many of these statistical tools that had proven utility in simpler pairwise trials, such as logistic regression and odds ratio, were naturally carried over into the Bayesian meta analysis of antiemetics conducted by Rahman (2016). While incorporation of Bayesian methods into clinical trials has become more feasible in recent years due to the advance of MCMC computing, large credible intervals can still hinder the certainty of conclusions. Further development of Bayesian meta-analysis models, possibly including Bayesian model averaging, may be a potential exploration to combat the mixed-versus-random-effects problem that often occurs in these models. Recent studies and software packages support the potential application of these Bayesian model averaging methods in meta-analysis studies (Gronau, 2021 [10]).

As of January 2024, novel NK_1 antagonists are still being developed. Drugs such as tradipitant are being studied in the treatment of other causes of nausea such as motion sickness (Polymeropoulos et al, 2020 [8]), and NK_1 antagonists previously discredited for the treatment of CINV are continuing to be studied in other therapeutical areas such as mental health (Ratti, Emiliangelo, 2012 [5]).

5. Conclusion

With the continuation of NK_1 antagonist development, both in CINV and other fields, the necessity for advanced multiple comparisons and meta-analysis techniques is further demonstrated. Traditional biostatistical conventions such as odds ratio and logistic regression have been further solidified in the study of binomial endpoints, but updated meta-analytic methods involving Bayesian statistics should continue to be a point of investigation as new packages and computational technology is developed.

To the current extent of knowledge obtained from clinical research, NK_1 antagonists are still one of the strongest prophylactic medications for CINV. Aprepitant and its IV prodrug fosaprepitant consistently yield strong protection for CR, whereas drugs such as rolapitant may be inferior in preventing vomiting, but have compensating advantages in bioavailabilty (Rashad & Rahman, 2017) [7]. Finally, netupitant has shown potential in recent studies to be the new strongest NK_1 antagonist in preventing CINV, but further investigation and more trials will be necessary before it can replace aprepitant as the industry-wide standard.

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