Ranitidine – Literature Review

Secondary & Tertiary Literature

1. Meta-analysis: Tran T, Lowry AM, and El-serag HB. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. *Aliment Pharmacol Ther* 2006; 25:143-153.

Study objectives:

- To evaluate randomized trials that examined the efficacy of several over-the-counter (OTC) GERD therapies, including antacids, alginates and H2-Receptor Antagonists (H2RAs: ranitidine, famotidine, nizatidine, and cimetidine).

Scope:

- *Studies included***:** All randomized-controlled trials comparing antacid, alginate/antacid combination, or H2RA at OTC doses to a placebo, which aimed to achieve the outcomes of interest (as listed below). Studies that used prescription-strength or high-dose GERD agents, and those which lacked well-defined outcomes of interest were excluded. A total of 10 studies included in the meta-analysis focused on comparing H2RAs to placebo, and 5 of these compared ranitidine to placebo.
- *Interventions/ duration***:** In the 5 studies comparing ranitidine to placebo, patients either received a single dose of ranitidine 75 mg 30 to 60 minutes before a provocative meal (2 trials, total n = 293 and 287 for ranitidine and placebo, respectively), or they received ranitidine up to 3 to 4 times a day as needed over a period of approximately 2 weeks (3 trials, total n = 1511 and 1274 for ranitidine and placebo, respectively).
- *Outcomes of interest:* Complete and adequate relief of GERD symptoms, subjective global improvement, and the use of rescue antacids.

Methods:

- In order to identify studies for this meta-analysis, two investigators performed independent searches of the medical literature using the MEDLINE database. The search was limited to randomized-controlled trials from 1972 to 2005, which were conducted in adults over the age of 19 and that were published in English. All resultant citations were reviewed independently by two investigators. The search included bibliographic reviews and contacting the product manufacturers for unpublished data. The quality of the identified studies was measured using the Jadad coring system, which rates quality from 0 to 5. The data presented in the chosen studies was extracted, tabulated and analyzed according to a standardized protocol.
- For each meta-analysis, the combined absolute benefit increase, relative benefit increase, and number needed to treat (NNT) were calculated.
- 14 trials were included in the analysis; 10 of these were randomized, placebo-controlled, double-blinded, parallel group trials that compared H2RAs to placebo, of which 5 focused on comparing ranitidine to placebo. The mean Jadad score of the 10 H2RA trials was 3.5.

Main results:

- Based on the 10 RCTs comparing H2RAs to placebo, it was found that there were no significant differences between the four H2RA agents studied in the trials (ranitidine, famotidine, nizatidine, and cimetidine).
- The trials examining the prevention of heartburn after a meal through the administration of a single dose of H2RAs 30-60 minutes prior to it found that the combined absolute benefit and relative

benefit were significantly increased with H2RAs (including ranitidine), and the NNT with H2RAs was 9.

- The trials evaluating the efficacy of H2RAs taken over 2 to 4 weeks found that H2RAs significantly increased relief of heartburn within 1 hour of drug ingestion (as indicated by a significantly improved absolute benefit and relative benefit and subjective improvement rated by the patients).
- Patients that were taking H2RAs were also found to require rescue antacids significantly less often than those on placebo.
- The efficacy of antacids was found to be less well-established than that of H2RAs and alginates. H2RAs were found to have slightly increased efficacy in providing complete relief for symptomatic episodes (absolute benefit increase of 10-12% and relative benefit increase of 19-41%), but have a slower onset of action.

Conclusions (relevant to H2RAs/ ranitidine):

- H2RAs, including ranitidine, are significantly superior to placebo in both the complete prevention of postprandial GERD symptoms and in increasing symptomatic improvement when used as a single dose prior to a provocative meal. H2RAs are also superior to placebo in providing adequate or complete relief and breakthrough of GERD symptoms when used over a period of 2 to 4 weeks. Therefore, the authors concluded that H2RAs used at OTC doses are efficacious at preventing and treating GERD symptoms.

Comments/ critical appraisal:

- The meta-analysis clearly stated the research objectives and outcomes of interest, and described the methodology used to identify articles in a detailed manner. The methodology used was appropriate to address the objectives, and included an extensive search of both MEDLINE and cited bibliographies. Two investigators identified studies independently and then worked together to reach a consensus, which increases the accuracy and validity of the meta-analysis. The review only included high quality studies that were randomized, placebo-controlled, double-blinded, and parallel-group to ensure the homogeneity of trial designs. It also used a Jadad score to evaluate the quality of evidence presented in these studies, and the mean score was calculated to be about 3.5, indicating that only trials of relatively high quality were included in this meta-analysis. Additionally, heterogeneity tests were performed for all of the analyses, which ensured that there was no significant heterogeneity. The authors did disclose the fact that a small publication bias was identified that they could not correct for, which may affect the overall conclusion of the analysis. However, due to all of the aforementioned factors, the internal validity of this meta-analysis is still deemed to be high.
- The results of the meta-analysis are both relevant and important since they address a gap in the literature, which generally focuses on the use of agents at prescription rather than OTC doses. However, though the meta-analysis specified that only studies of agents used at OTC doses were included, the severity of the symptoms that the patients of the studies were experiencing when using the medications were not described anywhere in the paper. Additionally, the review had broad inclusion criteria and provided no specific information (ex. demographic, co-morbidities, etc.) on the patients that were included. Consequently, it may be difficult to accurately determine what types of patients the results of the meta-analysis can be extrapolate to. Additionally, the meta-analysis did not examine the safety of the medications or the effects of long-term treatment, which are both important factors to consider when making therapeutic decisions. As a result of all of the factors outlined above, the external validity of the meta-analysis is not very high.

- Overall, though the meta-analysis has some limitations, it serves as a valuable reference that addresses the place of H2RAs in the treatment of GERD and establishes that they can act as effective OTC agents for the prevention and treatment of mild symptoms. Additionally, it also establishes that the four H2RAs, including ranitidine, are equivalent in terms of efficacy, and suggests that H2RAs may be slightly more efficacious at providing complete relief symptomatic relief than alginates and antacids. As a result, this meta-analysis is helpful in determining the place of ranitidine in the treatment algorithm of GERD.

2. Clinical Practice Guidelines: DeVault KR and Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2005;100:190-200.

Study objectives:

- The objective of these guidelines is to provide all health-care providers who address gastroesophageal reflux disease (GERD) an update on the guidelines that were originally published by the American College of Gastroenterology and its Practice Parameters Committee in 1995 and again in 1999 regarding the preferred diagnostic methods and treatment of GERD.

Scope:

- The scope of these guidelines includes both diagnosis and preferred treatment of GERD. The review of diagnostic methods includes empiric therapy and the use of endoscopy, ambulatory reflux monitoring, and esophageal manometry. The therapeutic review addresses the role of lifestyle modifications, over-the-counter (OTC) therapy, acid suppression, promotility therapy, prescription medications and maintenance therapy, antireflux surgery, and endoscopic therapy used in the treatment of GERD. GERD is defined in the guidelines as "symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus". The information in the guidelines is applicable to adult patients with the symptoms, tissue damage, or both that result from the reflux of gastric content into the esophagus.

Methods:

- In order to compile these guidelines, the original guidelines, which were based on an extensive review of the world literature on GERD, were reviewed again using the National Library of Medicine database. Appropriate studies identified from the database were reviewed, and a bibliographic review of these papers' citations was conducted. The evidence was evaluated using a hierarchy, whereby randomized, controlled trials (RCTs) were considered to have the greatest weight. When there was a lack of scientific data, recommendations were based on expert consensus obtained from both the literature and the experience of the authors and the Committee. The strength of evidence of each guideline was evaluated and assigned a rating from I to IV, where by I represents the strongest evidence (ex. at least 1 published systematic review of RCTs) and IV is the weakest evidence (ex. reports of expert consensus committees).

Main results:

- Specifically with respect to patient directed OTC therapy, the guidelines found that all four of the OTC H2 Receptor Antagonists (H2RAs) have shown to decrease gastric acid, particularly after a meal, and may generally be used interchangeably. The H2RAs were found to be particularly useful when taken before an activity that may result in reflux symptoms, such as prior to having a heavy meal or exercising, or when patients feel that they will soon experience these symptoms. It was also found that while the peak potency of H2RAs and antacids are similar, the H2RAs have a much longer

duration of action that may last up to 10 hours. In terms of using prescription doses of H2RAs, it was found that proton pump inhibitors are more effective than H2RAs in providing rapid symptomatic relief and healing esophagitis, however H2RAs may be effective when given in divided doses in patients with less severe GERD (level of evidence I).

Conclusions (relevant to OTC H2RAs):

- The guidelines state that antacids and OTC acid suppressants (including H2RAs) are options for patient-directed therapy for heartburn and regurgitation (level of evidence IV). However, patients should have additional evaluation and treatment when their symptoms persist, continuous therapy is required or alarm symptoms or signs develop.

Comments/ critical appraisal:

- There are a few limitations in this review that impact its internal validity. The guidelines did not provide detailed information regarding how the included studies were identified and selected, and also did not disclose specifics as to what changes were made since the last update. While the guidelines did not provide a rating of each piece of literature that they included, they did rate each guideline based on the strength of evidence that was used to support it. Due to these factors, the internal validity of the guidelines is of moderate robustness.
- In terms of the external validity of the guidelines, a few factors need to be taken into consideration. First, the guidelines did not state specifically which types of patients may be candidates for OTC therapy. Though they did state that patients should be referred for further evaluation and treatment when they meet specific criteria, as outline above in the conclusions section, they did not provide detail regarding how long the symptoms must persist for and the duration of time that patients may use OTC H2RAs before they move on to prescription therapy. The guidelines also did not describe specific products or the doses that were used. Overall, although the guidelines are useful in evaluating the efficacy of OTC H2RAs with respect to other OTC products, when attempting to extrapolate the data to a real life scenario, additional information is required in order to determine the appropriate dose and duration of treatment. However, the data presented in the guidelines is still applicable to the treatment algorithm because it establishes that all four H2RAs are interchangeable and appropriate for use for patient directed OTC therapy of GERD. Additionally, the guidelines state that H2RAs have a longer duration of action than antacids, which is helpful in establishing their place in therapy.

3. Web-based Resource: Kahrilas PJ. Medical management of gastroesophageal reflux disease in adults. UpToDate. Sep 22, 2011. Accessed on March 09 2012 from: www.uptodate.com

Source description:

- UpToDate is an evidence-based, peer-reviewed resource that is designed to help clinicians make therapeutic decisions. All of the content in UpToDate is written and edited by a global community of 4,800 physicians who are considered world-renowned experts in their specialties. The editor team consists of 45 in-house physicians, who provide a rigorous editorial process for each entry and ensure that all of the information is based on the latest available evidence. Recommendations are provided and graded based on the level of evidence. All topics are updated as new evidence becomes available and after it passes through the peer review process.
- This particular article provides a brief overview of gastroesophageal reflux disease (GERD) and describes in detail the different types of medical management options available to treat it. This topic was last updated in September 2011 and its literature review is current through January 2012.

Summary:

- The most common and effective treatment of GERD involves the reduction of gastric acid secretion with either proton pump inhibitors (PPIs) or H2RAs. Though these medications do not prevent reflux, they reduce the acidity of the refluxate. The doses of these medications should be titrated based on the severity of the patient's symptoms. In terms of efficacy, H2RAs have been shown to improve the healing rate of esophagitis by 10 to 24% relative to placebo. However, this benefit is not dose dependent and so H2RAs are not effective for severe esophagitis. All of the H2RAs that are available have equivalent efficacy when their doses are adjusted for their different potencies. If patients continue to experience symptoms of heartburn after 6 weeks of treatment with standard doses of H2RAs, they are unlikely to gain more benefit from this treatment and should be switched to a different therapy. In comparison to H2RAs, PPIs were found to be more effective in healing esophagitis.
- Overall, mild symptomatic GERD can generally be managed sufficiently with lifestyle and dietary modifications and antacids or nonprescription H2 receptor antagonists (H2RAs). OTC antacids and/or H2RAs should be used as the primary therapeutic regimen for these patients, in addition to lifestyle changes, and initiated based on the patient's history and response to any previously attempted GERD therapy. A stepwise therapeutic approach should then be taken with the goal of identifying the least potent, but still effective, regimen for the specific patient. Therapeutic changes should be made at 2-4 week intervals. However, the optimal care for GERD patients beginning with a suspected diagnosis and proceeding to a long-term maintenance therapy is still not completely clear.

Comments/ critical appraisal:

- In terms of the internal validity, there are a few considerations. First, the article did not identify how literature pieces were selected for inclusion. However, this is understandable given that this is a tertiary web-based resource that is meant to provide concise summaries for clinical practitioners so that they can provide appropriate therapies on an immediate basis. This source in general is known to provide up to date information that is robust and peer reviewed, and the information it provides in this article is consistent with practice guidelines (which are mentioned as well) and other literature. As a result, the internal validity of this source is relatively robust.
- In terms of external validity, this resource is useful for clinicians and patients because it provides the reader with a treatment algorithm, and also rates the different recommendations based on the evidence that is used to support them. However, it does not provide any detailed information regarding the doses of H2RAs that should be used, or any instructions on how to use the products. It likewise does not provide a description of what "mild symptomatic GERD" means, and does not discuss their safety, including side effects. As a result, it may be a little difficult to extrapolate this data to a patient population using only the information provided here. Nevertheless, this reference is applicable to the GERD treatment algorithm, in particular because it provides up to date information and shows that H2RAs such as ranitidine are still considered to be effective in the management of mild symptomatic GERD. It also adds that while H2RAs are effective, concurrent lifestyle and dietary modifications are crucial in the management of GERD; this information constitutes an important part of the treatment algorithm.

<u>Primary Literature</u>

4. RCT: Galmiche JP et al. On-demand treatment of gastro-oesophageal reflux symptoms: a comparison of ranitidine 75 mg with cimetidine 200 mg or placebo. *Aliment Pharmacol Ther* 1998; 12:909-917.

Study objectives:

- The objective of the study was to compare the efficacy and safety of low-dose ranitidine (75 mg) with those of either cimetidine (200 mg) or placebo given when needed for relief of typical GERD symptoms (heartburn and acid regurgitation).

Methods:

- *Design:* International, multicenter, double-blind, double-dummy, parallel group randomized-controlled trial.
- *Allocation:* Patients were randomly assigned to 1 of 3 treatments. Randomization methodology is not described.
- *Blinding:* double blinded.
- *Follow-up period:* 15 +/1 1 days.
- *Setting:* 122 centers in France and 16 centers in Germany.
- *Participants:* 1336 patients over the age of 18 who had symptomatic episodes of GERD (heartburn with or without acid regurgitation or epigastric burning) for at least 3 months and at least 4 episodes of heartburn the week before they were included in the study.
    - Exclusion criteria included patients with a past history of or concurrent gastric or duodenal ulcer, moderate or severe esophagitis, recurrent gastrointestinal (GI) bleeding; alarming signs (dysphagia, GI bleeding, weight loss, anemia); need for immediate upper GI endoscopy; previous gastric or esophageal surgery; a malignant disorder of the upper GI tract; hypersensitivity to cimeditine or raniditine; pregnancy or breast-feeding; poor expected compliance with treatment or inability to follow the protocol or fill in questionnaires; or any other medical condition likely to interfere with the conduct of the study or constitute an high risk for the patient.
- *Intervention:* Ranitidine 75 mg + cimetidine placebo (n=504), cimetidine 200 mg + ranitidine placebo (n=515), or ranitidine placebo + cimetidine placebo (n=270). Treatment was taken PRN up to 3 times per day (with at least 2 hours between drug doses) depending on the occurrence or persistence of heartburn.
- *Outcomes:* Primary endpoint was the proportion of patients who had relief of at least 75% of heartburn episodes during the trial period (within 2 hours of study drug ingestion and lasting for at least 5 hours). Secondary efficacy points included: discomfort due to GERD symptoms before and after treatment (based on a four-point scale); changes in GERD symptoms; outcome of heartburn intensity and frequency between day 0 and 15 based on a visual analog scale (VAS); total number of heartburn episodes and number of study drug doses taken; for each episode, the relief (yes/no), time to onset and duration of relief; at day 15, a global assessment of study treatment efficacy (based on a four-point scale); number of antacid doses taken. Safety was assessed based on the reporting of adverse events.
- *Patient follow-up:* Out of a total of 1336 patients recruited for the study, 1289 patients were included in the intention-to-treat population, 1090 were include in the per-protocol population, and 1316 were included in the safety population.

Main results:

- Primary end-point: The proportion of patients who had relief of at least 75% of heartburn episodes was significantly higher in the ranitidine group than the placebo group (41% vs. 28% for the intention-to-treat population, $P<0.001$; 44% vs. 31% for the per-protocol population, $P=0.002$;

respectively). No significant difference was found between the ranitidine and cimetidine groups (38% and 42%, respectively).

- Secondary end-points: There was a significantly lower grade of discomfort due to reflux symptoms at day 15 (P=0.004) and significantly more patients who considered the treatment to be effective (P<0.001) in the ranitidine than the placebo group. No statistically significant differences were found in either measure between the cimetidine and ranitidine groups (P=0.97 and 0.34, respectively), though a greater reduction in heartburn frequency was found in the ranitidine group at the end of the study period (P<0.05). A significantly higher number of patients in the placebo group took antacids, and a lower mean number of study drug doses was taken in the ranitidine compared to the placebo group.
- Safety: All 3 treatments were tolerated equally well, with a low overall incidence of adverse events and no significant differences between the groups. The majority of adverse events reported were gastrointestinal disorders, and the incidence was similar in all 3 groups. Withdrawal from the study due to an adverse event possibly related to the study treatment was equally low (<1%) in all 3 groups.
- Logistic multivariate analysis found that the likelihood of symptom relief, regardless of treatment, was greater in patients with mild discomfort, no previous use of proton pump inhibitors, and low heartburn frequency.

Conclusions:

- Ranitidine 75 mg or cimetidine 200 mg that are given on-demand are both effective and safe for the provision of adequate relief of heartburn in patients with no alarming signs or erosive esophagitis. Though ranitidine seems to have a greater efficacy, no statistically significant differences were found in this study.

Comments/ critical appraisal:

- In terms of internal validity, there are a number of factors that need to be taken into consideration. The trial has fairly high internal validity since it is a randomized, double-blinded, controlled trial. The study used both an intention-to-treat and per-protocol analyses, which reduce the likelihood that a bias was introduced when the results were analyzed. The authors also ensured to take into consideration the baseline characteristics of the patients in the different intervention groups and stated that these characteristics were similar in all groups. This matching of baseline characteristics eliminates potential confounding factor and makes it easier to establish a definitive causal association between the interventions used and the outcomes of the study. However, a limitation of this analysis is that while the authors state that there are no significant differences in the baseline characteristics, they fail to provide P-values within the comparison tables that would allow the reader to evaluate this information on their own. An additional limitation is that the authors do not provide information regarding how the randomization and blinding processes were carried out.
- In terms of the external analysis, there are a few considerations. First, the trial excludes patients below the age of 18, which do not allow for an extrapolation of data to this population group. However, they did include a population with a wide range of characteristics, and they did describe the demographic and clinical characteristics of the patients, which makes the results easy to extrapolate to specific patients in the clinical practice setting. A strength of this trial is that it included both efficacy and safety measures, which are both very important factors to consider when making therapeutic decisions. The duration of treatment was 15 days, which is similar to the 14 day period that is recommended for treatment with OTC H2RAs (after which the patient should be referred to a physician). Finally, the trial provides information regarding a comparison between

ranitidine and cimetidine, and provides some evidence that the use of ranitidine may be more efficacious. All of this information is helpful in determining the place of therapy of ranitidine in the treatment algorithm of GERD.

5. RCT: Ciociola AA, Pappa KA, and Sirgo MA. Nonprescription doses of ranitidine are effective in the relief of episodic heartburn. *American Journal of Therapeutics* 2001; 8:399-408.

Study objectives:

- The objective of the study was to compare the safety and efficacy of lower-than-prescription dose regimens of ranitidine 75 mg and 25 mg with placebo for the relief of episodic or intermittent heartburn.

Methods:

- *Design:* multicenter, double-blind, parallel group randomized-controlled trial.
- *Allocation:* Patients were randomly assigned to 1 of 3 groups. Randomization methodology is not described.
- *Blinding:* double blinded.
- *Follow-up period:* 1 week open-label antacid (Maalox) phase used to document the frequency of heartburn episodes and response to antacids, followed by randomization and a 2 week study phase.
- *Setting:* 36 sites in the United States.
- *Participants:* Inclusion criteria: adults 18 years of age or older with at least a 3-month history of heartburn, who have experienced episodes on at least 2 days per week during the 2-week period before study initiation, and who have attained adequate relief of symptoms with antacids in at least half of their episodes. Subjects also had to have treated heartburn for at least 2 days during the antacid open-label phase of the study.
    - Exclusion criteria: Clinically significant disease, history of ulcer or significant gastrointestinal (GI) hemorrhage, on a prescription of H2 receptor antagonists (H2RAs), metoclopramide, sucralfate, misoprostol, or proton pump inhibitors.
- *Intervention:* Ranitidine 75 mg (n=537), ranitidine 25 mg (n=539), or placebo (n=544). Treatment was taken as needed for the relief of heartburn up to 4 times daily (at least 3 hours following consumption of the last dose).
    - Subjects were allowed to use rescue antacids if adequate symptom relief had not been attained 2 hours after study drug administration and to treat heartburn if they had more than 4 episodes per day. They were also not permitted to consume any food or beverage during the 3 hours following the onset of heartburn episodes.
- *Outcomes:* Outcomes were measured using heartburn diaries and 3-hour electronic timers to record time of heartburn onset, time study drug was taken, heartburn severity, onset and adequacy of relief, antacid consumption, and whether any food or beverage was taken during the 3 hours following the onset of heartburn.
    - Primary efficacy endpoint: percentage of subjects with self-described adequate (defined as no longer bothersome symptoms) relief of heartburn within 60 minutes of ingestion of study drug that was sustained throughout the 3-hour diary record.
    - Secondary efficacy endpoints: percentage of subjects with onset of treatment success, duration of treatment success for first episodes, use of rescue antacids, successful treatment of nocturnal episodes, treatment success stratified by heartburn severity and by age, gender and race.

    - Onset and duration of treatment success were evaluated for the first and last reported heartburn episodes, as well as across all episodes combined. Endpoints were evaluated for both statistical significance and clinically significance, which was defined as ranitidine having to provide a therapeutic gain of at least 10% over placebo.
    - Safety was assessed by monitoring adverse events.
- *Patient follow-up:* Out of the 1835 patients initially enrolled, 215 were not follow-up on due to various factors such as withdrawal of consent, too little heartburn in the initial phase, antacid or diary noncompliance, adverse events and protocol violation. 1620 patients were randomly assigned to treatment, and of these 1546 comprised the intention-to-treat population, while 30 patients did not compete the study.

Main results:

- Primary efficacy endpoint: there was a statistically significant higher proportion of patients experiencing treatment success in the ranitidine 75 mg and 25 mg groups compared to placebo in the first and last reported heartburn episodes, as well as across all episodes combined. Only ranitidine provided clinically important improvement >10% (as previously defined).
- Secondary efficacy endpoints: Patients experienced statistically significant improvement in heartburn relief within 45 and 60 minutes of dosing for up to 12 hours with both ranitidine 25 mg and 75 mg than placebo. Successful treatment of nocturnal episodes was significantly higher in the ranitidine 75 mg compared to placebo, but not in the 25 mg group. Patients in both the 75 mg and 25 mg ranitidine groups consumed statistically significantly less antacids compared with those in the placebo group. Additionally, ranitidine 75 mg was both statistically and clinically superior to placebo in providing relief regardless of heartburn severity, the time of day, age (elderly vs. nonelderly), and gender. Finally, on most days when heartburn was experienced by patients, only 1 or 2 tablets of ranitidine were used.
- Safety: Incidence of all adverse events were similar in all 3 groups. Of note, in patients over the age of 65, GI events occurred more frequently in the ranitidine than the placebo groups ($P<0.024$).

Conclusions:

- Ranitidine 75 mg is both safe and effective in providing relief of episodic heartburn when taken up to twice daily for 14 days in subjects who do not require prescription medications,

Comments/ critical appraisal:

- The trial has fairly robust internal validity since it is double-blinded and randomized. However, both the randomization and blinding processes are not described. The study was funded by the manufacturer of ranitidine but a potential conflict of interests, or lack thereof, was not addressed anywhere in the paper; this element may have introduced bias into the trial findings. The trial uses an intention-to-treat analysis, which is appropriate for this type of trial and enables for a more accurate evaluation of the safety profile of ranitidine. It had pre-defined endpoints that were clinically significant, and it achieved the power that it out to achieve (80%) in order to detect a 10% difference between ranitidine and placebo groups in heartburn relief (defined as clinically significant) due to is relatively large sample size.
- In terms of external validity, a few factors need to be considered. First, the result of this study can be extrapolated to the patient population that would generally be using OTC heartburn medications, as it was able to recruit patients that were likely representative of this group and had a wide variability in demographic and clinical characteristics. The patient baseline characteristics are all accounted for and mentioned by the authors in the paper, which makes it easy for clinicians to

ensure that it is appropriate to extrapolate the results of the study to their patients. The analysis also shows that the results of the study can be extrapolated to the general population regardless of age (if over the age of 18) and gender, and that ranitidine 75 mg can be effective for both mild and more severe symptoms. Second, the authors did not only look at statistically significant improvements in treatment with ranitidine, but also discussed the clinical significance of their endpoints, which adds an important element to their analysis, given that statistically significant benefit does not always correlate with clinical significance in the practice setting. This finding makes the results of this study more applicable in helping determine ranitidine's place of therapy in the treatment algorithm. Finally, the results of the study show that most patients did not require more than 1 or 2 ranitidine 75 mg tablets to treat their symptoms on days of usage, which validates the general recommendation of not exceeding 150 mg of ranitidine in a day. It also provides valuable information to help determine the OTC dose of ranitidine to be used in the treatment algorithm, since it shows that 75 mg was needed to provide clinically significant results in many of the endpoints, while this was not always achieved with a 25 mg dose. More importantly, it shows that 75 mg provided statistically significant improvement in nocturnal symptoms compared to 25 mg, which is clinically relevant when deciding on an appropriate administration dose as many patients have been shown to experience their heartburn symptoms at night.

References:

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