Multimodal Pain Protocol After Head and Neck Surgery in the Context of the Current Opioid Crisis

By

Eugenie Du, MD

A Master's Paper submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Public Health in the Public Health Leadership Program

Chapel Hill

2018

Sue Tolleson-Rinehart, PhD, Advisor and First Reader

June 29, 2018

Date

Mark C. Weissler, MD, FACS

Mark Weissler MD, Second Reader

July 2, 2018

Date

ABSTRACT

Background: The United States is in the midst of a public health crisis of prescription opioid addiction, abuse and overdose. Use of narcotic medication in the post-surgical setting may contribute to the problem. Multimodal analgesic plans have the potential to decrease narcotic requirements in patients after surgery; however, there is little prospective data to show efficacy in Head and Neck (H&N) surgery patients.

Methods: An IRB approved, quality improvement initiative was undertaken to implement a multimodal analgesic protocol for all H&N surgery patients at a tertiary referral center. The protocol was implemented November 2017 and post-protocol data from January 2018 to May 2018 were compared to pre-protocol data from May 2017 to October 2017. Data were abstracted from the electronic health records as well as through pre-operative and post-operative surveys. Average pain scores and opioid use in Morphine Milligram Equivalents (MME) before and after protocol implementation were compared.

Results: One-hundred-and-five post-protocol patients were compared to 167 pre-protocol patients. The adjusted median MME in the first 24 hours after surgery decreased significantly from 93.7mg to 58.6mg (p=0.026) with protocol implementation. When averaged over the length of stay (MME/HD), there was no significant change between the pre and post protocol cohort (57.9mg vs 46.8mg,

p=0.211) The average pain score immediately after surgery was 3.6 and on the day of discharge was 2.7; neither measure changed with protocol implementation.

Conclusion: Our multimodal analgesia plan reduced narcotic use immediately after surgery but not over the course of hospitalization. There was no difference in average reported pain scores. This study shows that implementation of a multimodal narcotic-sparing analgesia plan after H&N surgery is feasible. Future studies will need to further refine the optimal analgesia plan, optimize pain regimens for various patient characteristics and assess the long-term efficacy, safety and cost of such regimens.

ACKNOWLEDGEMENTS

First, I would like to acknowledge the Department of Otolaryngology – Head and Neck Surgery. In particular, this project would not have been possible without the guidance and support of the Division of Head and Neck. Furthermore, I would like to acknowledge Dr. Michelle Tanner, Dr. Zainab Farzal, Brien Pace, Katherine Adams and Elizabeth Stephenson for their help in data collection. I would also like to acknowledge Dr. Miriam Jowza from the Department of Anesthesia for guidance in developing an appropriate multimodal analgesia plan. I would like to acknowledge Emily Hoke and Kelly Felten from the Quality Improvement Office at UNC-Chapel Hill Hospital. Finally, I would like to acknowledge Dr. Sue Tolleson-Rinehart, Dr. Mark Weissler, Dr. Adam Zanation and Dr. Trevor Hackman for their mentorship and for being my sounding boards on this work. I would also like to thank the Translational and Clinical Science Institute grant support (1ULTR001111 from the Clinical and Translational Science Award program of the National Center for Advancing Translational Science, National Institutes of Health) for the use of REDCap for the database and survey collection infrastructure.

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

INTRODUCTION

Knowledge of opioids has been around for millennia and they have been used both as recreational drugs and for medicinal purposes. Morphine, the first synthetic opioid analgesic, was extracted from opioid in 1903 in Germany.[1] In the 19th and 20th centuries, use of opioids in medicine was restrained by recognition of its addictive properties. [1,2] Extensive scientific research has expanded our understanding of how opioid agents interact with the nervous system. However, no one has been able to synthesize a form that retains its analgesic properties without the potential side effects of respiratory depression, gastrointestinal upset and potential for dependence and addiction. [2] This began to change at the turn of the 20th century for several reasons. An influential communication to the editors at the *New England Journal of Medicine* by Dr. Porter of the Boston Collaborative Drug Surveillance Group reported that of "11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction." [3] This brief letter was subsequently cited more than 600 times and "grossly misrepresented" as conclusive evidence that addiction with opioids was rare. [4] In 1998, a small case series of 38 patients published in *Pain* suggested that opioid therapy could be a "safe, salutary and more humane alternative" to surgery or no treatment for intractable non-cancer pain.[5] This was followed by an influential article in the *Lancet* that argued that "politics, prejudice, [and] ignorance" have led to undertreatment of chronic, cancer, and acute pain. [6] Gradually, even though the

safety and efficacy of chronic opioid use in non-cancer pain was never established, clinicians began to prescribe opioid therapy for acute, episodic pain.

During this same period, there was a widespread push from various governmental, pharmaceutical, and health care agencies to assess and treat pain. [7,8]In an editorial in the *Annals of Internal Medicine*, Dr Max, the President of the American Pain Society, wrote that physicians had failed patients because they were not being held accountable for inadequate pain control. [9] Shortly after, The U.S. Veterans Health Administration rolled out a campaign to assess and document patient pain as "The Fifth Vital Sign." Similarly, the Joint Commission on Accreditation of Healthcare Organization (JACHO) announced that pain assessment needed to be standard of care. [10] As a response, physicians began to use prescription narcotics with more frequency. Even though most prescriptions were written for short-term, episodic use, pain experts began to notice a pattern of de facto long-term use in certain patients. In contrast to traditional long-term opioid therapy for chronic pain or addiction, de facto long-term use was patient selected, had considerable variability in medication type, dosage and frequency, and accounted for a disproportionately high amount of narcotics dispensed. [11] We now understand that this subset of patients had become addicted to prescription narcotics.

Currently, the United States is in the midst of a public health crisis involving abuse, addiction and overdose related to opioid medication. Analgesic medications are the most commonly prescribed class of medications in America. [12] Between 1999 and 2012, the sales of prescription opioids have increased by at

least three fold.[10] During that same time span, the Center for Disease Control (CDC) estimates a five-fold increase in opioid related deaths.[13] The Department of Health and Human Services (HHS) estimates that, in 2016, 17,087 deaths were attributable to prescription opioid overdoses along with $504 billion in economic costs. [14] However, according to the 2016 National Survey on Drug Use and Health, the majority of the estimated 11.5 million Americans who misuse prescription pain medication did so to relieve physical pain. Only 12.9% reported misuse to "feel good or get high." [14]Thus, physicians continue to face the age-old dilemma of how to treat pain without putting patients at risk for addiction.

Surgeons, in particular, face this dilemma on a daily basis. Pain after surgery is nearly universally experienced and is often the element of surgery that gives patients the most anxiety. [15] Adequate control of acute pain in post-surgical patients is not only humane and ethical, but also important for early mobilization and rehabilitation, prevention of surgical complications and lowering the risk of developing chronic post-surgical pain.[16,17] The exact percentage of patients who develop chronic post-surgical pain is not well studied. Retrospective or epidemiologic studies, with potential for significant recall bias, estimate the rate to be anywhere between 5% and 50%. [16,18-20] In reviewing nearly 80,000 surgical patients treated at their institution over the course of 2 years, researchers at the University of Pennsylvania found that 9.2% of surgical patients were still using opioids 3 months after surgery. [21] Another recent study found that the risk of chronic opioid use after surgery does not differ between minor and major surgical procedures. [22] Since many patients are exposed to opioid medications for the

first time after a surgical procedure, reducing narcotic use during this period of time may be important to reversing the opioid crisis at a societal level.

BACKGROUND and SIGNIFICANCE

Pain specialists and anesthesiologists advocate the use of multimodal pain regimens to reduce narcotic requirements after surgery. The clinical practice guidelines from the American Pain Society, American Society of Regional Anesthesia and Pain Medicine and the American Society of Anesthesiologists strongly recommends multimodal analgesia, defined as "use of a variety of analgesic medications and techniques that target different mechanisms of action in the peripheral and/or central nervous system" for postoperative pain. [23] A systematic review of randomized controlled trials comparing acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase 2 (COX-2) inhibitors to each other or placebo in patients with a morphine patient-controlled analgesia (PCA) found a significant decline in 24-hour morphine use when the non-steroidal medications were used. [24] The benefit of adding each agent ranged from a decrease of 6.3mg to 10.9mg of morphine but benefit of multiple agents was not assessed. [24] An earlier meta-analysis found similar results reporting a morphine dose reduction ranging from 7.2 to 27.8mg with the addition of various single agents. [25] A large-scale review of patients after total hip replacement and knee arthroplasties looking at effect of multiple modalities of pain control found that addition of analgesic modes had fewer respiratory and gastrointestinal complications and a decrease in opioid prescriptions in a stepwise fashion. [26]

The authors recommended the combined use of multiple modalities in perioperative analgesic protocols but also noted that the optimal regimen is not known.

Multimodal analgesia studies and recommendations have largely focused on general surgery and orthopedic procedures. [23] However, the benefits of multimodal pain strategies have been extrapolated to head and neck (H&N) procedures and recommended by the Enhanced Recovery After Surgery (ERAS) Society. [27] H&N surgical procedures may differ from general surgery or orthopedic procedures in several important respects. First, mucosal injury and pain may be different from soft tissue or visceral pain. Second, surgery of the neck often transects numerous sensory nerves and thus may also result in a different post-surgical pain experience. To date, few studies have assessed the efficacy and safety of multimodal analgesia in post-surgical H&N surgery patients (Appendix I). A randomized controlled trial of mucosal H&N surgery patients found that perioperative gabapentin (300mg twice daily) had no effect on narcotic usage but some benefit in terms of pain score. [28] Another recent retrospective, matched-control study showed that postoperative treatment with celecoxib decreased narcotic usage after H&N procedures requiring free tissue reconstruction. [29] Only one study has specifically looked at multimodal analgesia. Oltman et al found that at their institution, 64 of 222 (29%) of patients undergoing outpatient H&N surgical procedures elected multimodal analgesia. Of these patients, 39 were able to avoid postoperative narcotic medications. The objective

of this study was to see if implementation of a multimodal analgesic protocol would reduce narcotic usage in patients undergoing H&N surgeries.

METHODS

Patient Selection

A prospective continuous quality improvement (CQI) initiative with institutional review board (IRB) approval from the University of North Carolina – Chapel Hill was used to collect data between May 2017 and May 2018. All adult patients undergoing surgery with one of six H&N surgeons during this time period were included. H&N procedures included all soft tissue neck surgeries (i.e. thyroidectomy, parathyroidectomy, parotidectomy, neck dissection and lymph node excision) as well as surgeries involving the oral cavity, pharynx and larynx. The surgeries were not limited to the H&N region, however, as free tissue transfer or local flap reconstruction after oncologic ablative procedures were also included. Surgeries that involved tonsillectomy alone or endoscopic procedures such as direct laryngoscopy were excluded. Baseline data were collected between May 2017 and November 2017. A multimodal pain protocol was implemented for all H&N surgery patients on November 1st, 2017. We allowed for a period of two months for adjustment and for house staff and floor nurses to become familiar with the protocol. The medications for the protocol were incorporated into our pre-surgery and post-surgery electronic medical record (EMR) order sets. During this two-month period, we met with house staff and floor nurses and nurse managers to inform them of the protocol and to address

any concerns that arose. Post-implementation data were collected between January 2018 and May 2018.

Multimodal Analgesia Protocol

In collaboration with a pain management specialist from our Department of Anesthesia, a multimodal analgesia plan was developed and agreed upon among all surgeons in the Division of Head and Neck Surgery. Given the diverse range of surgical procedures encompassed by this protocol, we attempted to stratify procedures by extent of surgery and anticipated length of stay. Procedures such as thyroidectomy, parathyroidectomy, parotidectomy, lymph node excision and neck mass excision were defined as “minor” H&N procedures. These procedures are shorter in duration and can either be done on an outpatient basis or with short inpatient hospitalizations of 1-3 days. Procedures such as glossectomy, partial or total pharyngectomy, mandibulectomy, total laryngectomy and modified or radical neck dissection were defined as “major” H&N procedures. These procedures, often performed in combination with one another, are longer in terms of operative time and are associated with longer hospitalizations. This division also correlated with intermediate and high levels of anticipated post-operative pain. [30]

The multimodal analgesia protocol included acetaminophen (1000 mg IV or 650 mg PO every 4-6 hours as needed for mild pain, 4gm/24hr limit) and ketorolac (15 mg IV every 6 hours for 48 hours) for all patients after surgery. Initially, the protocol also included injection of bupivicaine at the end of surgery.

However, this was abandoned due to inconsistent availability of the medication in our operating suites. In addition, for major H&N surgery patients, pregabalin (100 mg PO) was given in pre-op on the day of surgery and then continued at a dose of 50mg PO twice daily for 10 days. As needed (PRN) opioid pain medication was ordered at the discretion of the provider. At our institution, this often consisted of oxycodone (5 mg PRN every 4-6 hours) and morphine (2-4 mg IV) for breakthrough pain. Major H&N surgery patients received a hydromorphone patient controlled analgesia (PCA) pump for the first 24-48 hours post-surgery before transitioning to oxycodone. The protocol did not restrict the amount of pain medication patients could receive, and medications could be modified or increased at the discretion of the clinical care team. Ketorolac was not given to patients with kidney disease. All medications were held when contraindicated or if there was concern for side effects.

Data Collection

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools at the University of North Carolina. [31] REDCap is a secure, web-based application designed to provide an interface for valid data entry, audit trails for tracking and data manipulation, export and import procedures. It also allows for automated and timed survey gathering through email. An initial survey, given to patients during their pre-operative clinic visit, queried prior chronic pain, baseline levels of pain, baseline narcotic medication use and anticipated level of post-surgical pain (Appendix II).

A post-operative survey was administered to patients 1-2 days after surgery (Appendix III). This was either obtained in person if the patient was still admitted or via a REDCap generated email if the patient had provided an email address for contact in their pre-operative survey.

Patient's age at time of surgery, sex, race, smoking status, past medical history, medication use at time of surgery, pathology from surgery and surgical procedures were abstracted from the EMR. Patient was also asked about chronic pain and baseline narcotic use on the pre-operative survey. The patient was designated to have chronic pain if they had a diagnosis of chronic pain on EMR or reported it on the pre-operative survey. Similarly, patients were considered to take opioid medication if it was listed on their medication list pre-operatively or if they reported it on the pre-operative survey. Surgical procedures were categorized as either "minor" or "major" in the following fashion. All procedures involving ablation of a mucosal malignancy (e.g. glossectomy, pharyngectomy, laryngectomy) were considered "major." Similarly, all neck dissections for malignancy were considered "major." All salvage procedures for persistent or recurrent tumor, as well as osteoradionecrosis were categorized as "major." Soft tissue neck procedures (e.g. parotidectomy, parathyroidectomy, thyroidectomy, neck mass excision) were categorized as "minor."

Outcomes

The primary outcome of this study was inpatient narcotic use as measured by morphine milligram equivalent (MME) in the first 24 hours after surgery and

MME per day averaged throughout the hospitalization (MME/HD). Our secondary outcomes measured were average documented pain scores (scale 1-10) in the first 24 hours after surgery and on the day of discharge. The relationship between narcotic usage, pain scores and patient's reported satisfaction with pain control (scale of 1-4 with 4 being extremely satisfied) was also analyzed. Patient reported satisfaction scores were only available for patients who completed a post-operative survey.

Statistical Analysis

Descriptive statistics were used to describe patient, disease and treatment characteristics. Bivariate analysis for pain score was performed using the 2-Sample T-Test for categorical variables and Pearson's Correlation for continuous variables. Bivariate analysis for MME and MME/HD was performed using Wilcoxon Rank-Sum test for categorical variables and Spearman's Correlation for continuous variables. Pre-protocol and post-protocol narcotic use and pain scores were analyzed with intention-to-treat based on the date of surgery. Multivariate analysis assessing opioid usage and pain scores between the two groups was performed with adjustment for all assessed covariates. Statistical analysis was performed using STATA™ version 15.1 (College Station, Texas).

FINDINGS

A total of 365 patients were initially captured in our database of patients treated by the division of H&N surgery department between May 2017 and May 2018. Ninety-three patients were excluded from study analysis for the following reasons: 9 (9.7%) due to surgery cancellation, 37 (39.8%) due to nature of procedure and 47 (50.5%) because they occurred in the two months immediately after protocol implementation. The washout period, November and December 2017, allowed for providers to become familiar with the protocol so that the post-intervention results would better reflect clinical practice when protocol was actively utilized. Two hundred and seventy-two patients met inclusion criteria and were included for study analysis: 167 before protocol implementation and 105 after protocol implementation. Two hundred and thirty-nine patients completed a pre-operative survey and 126 completed a post-operative survey for a survey response rate of 88% and 46%, respectively.

The characteristics of these patients are shown in Table 1. Utilization of various medications that comprise the multimodal analgesia regimen before and after protocol implementation is shown in Table 2. The cohorts of patients before and after protocol implementation were similar in age, sex and race distribution. There were more patients with benign disease in the post-implementation cohort (66% vs 55%) but more underwent major H&N procedures (64% vs 36%). There was no significant difference between the two groups in terms of mean length of hospitalization or complications requiring return to operating room rates.

Narcotic use as measured by Morphine Milligram Equivalents (MME) in the first 24 hours after surgery and averaged over the course of the hospitalization (MME/HD) was examined for 220 patients who were hospitalized for more than 24 hours. One patient had an extremely complicated hospitalization course spanning an 86-day admission and thus was excluded from analysis of narcotic use. The distribution for both MME in the first 24 hours and MME/HD were both positively skewed. The median opioid use in the first 24 hours was 48.0 mg (IQR 22.5-90.0) with 16 patients not receiving any opioid medications post-operatively. When averaged over the length of hospitalization, the median opioid use was 38.4 mg/day (IQR 15.0-74.0). Bivariate analysis showed that age, race, smoking status, history of chronic pain, pre-operative narcotic use, anticipated post-operative pain score and extent of surgery were significantly associated with opioid use in the first 24 hours after surgery (Table 3). On multivariate analysis, age, prior narcotic use and extent of surgery remained significantly associated. Age, smoking status, pre-operative history of chronic pain, narcotic use and anticipated post-operative pain were significantly associated with average MME over the course of hospitalization. After multivariate adjustment, only age, prior narcotic use and anticipated post-operative pain remained significant. After adjustment for all covariates, patients after protocol implementation had a significant decrease in opioid use in the first 24 hours (93.7mg vs 58.6mg, p=0.026) and but not averaged over the course of hospitalization (57.9mg/day vs 46.8mg/day, p=0.211, Table 5).

In the first 24 hours after surgery, patient's average pain score was 3.8 (SD 2.1). On the day of discharge, patient's average pain score was 2.7 (SD 2.6) and did not depend on length of stay. Bivariate analysis showed that the average pain score in the first 24 hours after surgery was significantly associated with age, sex and patient's preoperative anticipation of pain (Table 4). Similarly, bivariate analysis showed that patient's average reported pain score on day of discharge was significantly associated with age, pre-operative diagnosis of chronic pain, prior narcotic use and post-operative anticipated pain score. After multivariate adjustment, only age and pre-operative anticipation of pain remained significantly associated with pain scores in both the first 24 hours after surgery and at time of discharge. Aggregate patient reported pain scores did not change after implementation of multimodal analgesia plan, even when adjusting for covariates. The adjusted average 24-hour pain score before and after protocol implementation were 3.6 and 3.7, respectively (p=0.780). The adjusted average discharge pain score before and after protocol implementation were both 2.7 (p=0.868) (Table 5).

DISCUSSION

Our study, to our knowledge, is the first to study the effect of multimodal analgesia in Otolaryngology with an intention to treat study design. Different aspects of the multimodal analgesia protocol were implemented with different degrees of success. Post-protocol, the utilization of ketoralac in our patient population increased from 10% to 57%. Use of acetaminophen at our institution

was high at baseline (69%) and increased to 88% after the protocol. For patients undergoing a major H&N procedure, use of pregabalin on day of surgery increased from 11% to 76%. Certain medications may have been omitted due to contraindications, adverse reactions or simply because the ordering provider forgot. By comparing our outcomes pre- and post-protocol implementation, we wanted to assess both the feasibility of implementing such a multimodal analgesia plan and its effectiveness. H&N patients, especially ones undergoing surgical treatment for upper aerodigestive tract malignancies are often medically complex. Therefore, we did not expect that perfect implementation of the protocol would be feasible. Unfortunately, it was not possible to reliably ascertain the reason a specific medication was not ordered. We cannot determine what proportions of missed ordered medications were omitted due to patient factors and which were omitted by error. Nevertheless, including all post-protocol patients for analysis (rather than just the ones who received the medications according to protocol) allows us to get a better sense of the effect implementation of such a protocol has in actual clinical practice.

Our data showed a roughly one third reduction in the amount of narcotic pain medication used in the first 24 hours after implementation of a multimodal analgesic protocol. Adjustment for patient and surgical characteristics were made as the two cohorts differed in terms of age distribution, history of chronic pain and extent of surgery. Given that these variables all significantly modify patient's reported pain and tolerance of narcotic medications, the adjusted values are more likely to reflect the actual effect of the regimen implementation.

Interestingly, this reduction in narcotic use did not carry throughout the hospitalization course. This may be due to a few reasons. First, the use of ketoralac was limited to 48 hours in our protocol. For patients with longer hospitalizations, their choice of analgesia would have been limited to acetaminophen for mild pain or various narcotic medications for moderate to severe pain. Thus, we may not see as much of a benefit from the protocol over the hospital course simply because patients had fewer non-narcotic pain relief options later in their admission. Future studies assessing narcotic use at various post-surgical time points may help pinpoint strategies for improving the multimodal analgesia plan to further reduce opioid use during the entire hospital course. Second, a patient's analgesia requirements are not evenly distributed throughout their post-operative course. Thus, differences in cumulative opioid use may be missed when averaged over the length of hospitalization.

Our study findings are in line with previous studies that have shown that non-narcotic medications decrease morphine use.[24,25] It is difficult to make direct comparison, however, given that there is no standard multimodal regimen. Previous systematic reviews and meta-analyses have shown the benefit of adding single and sometimes two agents whereas our protocol describes a more comprehensive order set and strategy.[24,25] A drawback of this strategy is that it is more difficult to parse out the contributions of the individual pain medications in terms of opioid use reduction. Review of a large database of orthopedic patients found that NSAIDs and COX-2 inhibitors seemed to be the most effective modalities used [26]. An important concept that underpins multimodal non-opioid

analgesia is the concept of preventative analgesia. The goal of administering alternative modes of analgesia is to modify the transmission and processing of painful stimuli to decrease the central nervous system's experience of pain.[32,33] Our study was not designed to assess the individual components of the multimodal analgesia plan and thus the incremental benefit of adding each additional medication utilized remains unclear.

While there was a significant reduction in the amount of opioids used in the first 24 hours, it is important to note that opioid consumption even after protocol implementation remained high. Our reported post-operative opioid usage is higher than reported in other Otolaryngology studies. [28,34] This may be due to our inclusion of narcotic medications given immediately in the post anesthesia care unit (PACU) and surgical salvage patients who are more likely to have high baseline chronic opioid use related to their disease. Nearly a third of our patients reported chronic pain before surgery and a fifth had baseline narcotic use. Nevertheless, the CDC advises caution with opioid dosages of more than 50 MME/day and avoiding 90 MME/day whenever possible. [35] The CDC recommendations are specific for opioid prescriptions for chronic pain but it does raise the question of how much opioid is too much for episodic use. Given that some patients are opioid naïve, the post-surgical cohort ought to be more sensitive to both the analgesic and the adverse effects of narcotic medications. We do not know if there is an opioid dose threshold below which the risk of developing addiction is significantly decreased. In this study 16/220 (7.3%) patients did not receive any narcotic medications post-operatively. In the study by

Oltman et al, 39/222 (17.6%) patients were managed post-surgically without any narcotic medications. The goal of opioid-sparing analgesia should not only be to decrease opioid use but to better understand clinical scenarios in which post-operative narcotic use can be avoided altogether.

The side effects of opioid medications have been well documented. However, it is important to keep in mind that medications utilized in the multimodal analgesia protocol also have potential adverse effects. The main concern in using NSAIDs after surgery, especially in the H&N region, is the risk of post-operative bleeding. We did not find any increase in hematoma or bleeding requiring reoperation after protocol implementation. A meta-analysis of 27 studies of randomized control trials did not find any increase in postoperative bleeding with ketorolac [36]. Though other studies have also shown no significant difference in bleeding rates after H&N procedures or tonsillectomies with NSAIDs, [37,38]there continues to be concern that NSAID administration may increase the severity of hemorrhage when it does occur or the ooziness of surgical wounds [39]. Meticulous control of hemostasis and diligent monitoring of patients' post-operative course will continue to be important in order to ensure that routine use of NSAIDs in post-operative care won't lead to deleterious outcomes. Gamma-amiobutyric acid (GABA) agonists, such as gabapentin and pregabalin, have been used in numerous surgical populations safely.[34,40] Side effects include dizziness, drowsiness, nausea, extremity swelling and constipation and appear to be dose dependent. [41,42] GABA-agonists are considered to have low addictive potential but there are some reports of

individuals self-administering extremely high doses of these medications, often in conjunction with opioids or other narcotic medication.[43,44] Finally, numerous studies have shown that being prescribed numerous medications – polypharmacy – can independently increase a patient's risk of adverse health outcomes, particularly in the elderly.[45,46] We must be cautious that by using multiple non-narcotic medications to decrease use of opioids we do not simply substitute one problem for another.

In this study, we found that a decrease in narcotic consumption in the first 24 hours after surgery was not associated with any change in pain scores. This may indicate that the level of pain control did not change despite less opioid use. However, it may also reflect the fact that pain scores and narcotic dose measure different outcomes. On multivariate analysis, we find that older patients and males reported lower pain scores. We also see that the severity of post-operative pain anticipated by patients has the strongest association with pain scores reported in the first 24 hours. While we see that older patients also utilized less narcotic medications, multivariate analysis of 24h opioid use showed no significant association with sex or anticipated pain levels. Rather, pre-operative narcotic use and extent of surgery were significantly correlated with narcotic use. Post-surgical narcotic use is partly dictated by physician orders and may also reflect surgeon's expectations of how much pain patients will experience after surgery. Additional studies are needed to parse out this distinction so as to target future efforts to decrease unnecessary opioid use in the post-surgical setting.

There are numerous limitations of this study that have not already been mentioned. First, the study results are limited to the inpatient course. While decreasing narcotic use in the hospital is of value, it will be important to understand the long-term ramifications of a multimodal analgesia protocol. Second, pain score and MME were measured in the first 24 hours after surgery because they were available for all patients. However, the immediate post-operative period may not be the optimal time to assess for changes resulting from multimodal analgesia. Immediately after surgery, patient's pain experience may still be altered by medications given intraoperatively. A previous study looking at pain assessments after H&N surgery found that median pain score was highest on postoperative day 6.[47] Opioid usage, similarly, may vary throughout the hospital course. This variability in the postoperative course experience of pain limits our ability to compare our findings to other similar studies. Finally, this study included a wide range of surgical procedures spanning from relatively simple neck mass excisions to complex multi-component ablative and reconstructive procedures. Given the difficulties in predicting the exact degree of pain associated with each surgical procedure, the division of surgical procedures into "minor" and "major" ones may be somewhat arbitrary. The addition of non-narcotic medications may be of substantial benefit in one subset and simply unnecessary in another. The goal of grouping all H&N patients under a single multimodal analgesia protocol was to show its feasibility and assess its general effects.

Our findings suggest that multimodal analgesia may be helpful in decreasing opioid use after H&N surgery. However, there is a great deal regarding the optimal role of multimodal analgesia that needs further investigation. Additional studies are needed to assess the safety and cost effectiveness of multimodal analgesia strategies. Future studies are also needed to assess whether such strategies are sufficient to decrease the long-term use of chronic opioid use.

CONCLUSIONS

A multimodal analgesia protocol was successfully initiated at our institution for use after H&N surgical procedures. Implementation of the protocol was associated in a decrease in narcotic use immediately after surgery but did not alter patients' pain scores. Patient's experience of pain is largely influenced by their age and anticipation of pain. Although these variables also influence opioid doses, the quantity of narcotic medications used after surgery is also associated with baseline narcotic use and the extent of surgery. The experience at our institution suggests that multimodal analgesia protocols may be a valuable tool for post-operative pain control amid the current opioid epidemic. However, the optimal combination of these medications, their long-term effectiveness and safety, and the cost effectiveness of these strategies compared to existing analgesia strategies merit further research and evaluation.

REFERENCES

1. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions. *Experimental and clinical psychopharmacology.* 2008;16(5):405-416.
2. Corbett AD, Henderson G, McKnight AT, Paterson SJ. 75 years of opioid research: the exciting but vain quest for the Holy Grail. *British Journal of Pharmacology.* 2006;147(Suppl 1):S153-S162.
3. Porter J, Jick H. Addiction rare in patients treated with narcotics. *NEJM.* 1980;302(2):123.
4. Leung PTM, Macdonald EM, Stanbrook MB, Dhalla IA, Juurlink DN. A 1980 Letter on the Risk of Opioid Addiction. *NEJM.* 2017;376(22):2194-2195.
5. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain.* 1986;25(2):171-186.
6. McQuay H. Opioids in pain management. *Lancet.* 1999;353(9171):2229-2232.
7. Melzack R. The tragedy of needless pain. *Scientific American.* 1990;262(2):27-33.
8. Phillips DM. JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations. *JAMA.* 2000;284(4):428-429.
9. Max MB. Improving outcomes of analgesic treatment: is education enough? *Annals of internal medicine.* 1990;113(11):885-889.
10. Baker DW. History of The Joint Commission's Pain Standards: Lessons for Today's Prescription Opioid Epidemic. *JAMA.* 2017;317(11):1117-1118.
11. Von Korff M, Saunders K, Ray GT, et al. Defacto Long-term Opioid Therapy for Non-Cancer Pain. *The Clinical Journal of Pain.* 2008;24(6):521-527.
12. Frenk SM, Porter KS, Paulozzi LJ. Prescription opioid analgesic use among adults: United States, 1999-2012. *NCHS data brief.* 2015(189):1-8.
13. Control CfD. Opioid Overdose. Center for Disease Control; 2017.
14. Key Substance Use and Mental Health Indicators in the United States: Results from the 2015 National Survey on Drug Use and Health, published 2016.
15. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Current medical research and opinion.* 2014;30(1):149-160.
16. Bruce J, Quinlan J. Chronic Post Surgical Pain. *Reviews in pain.* 2011;5(3):23-29.
17. Yeung JK, Harrop R, McCreary O, et al. Delayed mobilization after microsurgical reconstruction: an independent risk factor for pneumonia. *The Laryngoscope.* 2013;123(12):2996-3000.
18. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet.* 2006;367(9522):1618-1625.
19. Macrae WA. Chronic post-surgical pain: 10 years on. *British Journal of Anaesthesia.* 2008;101(1):77-86.
20. Tawfic Q, Kumar K, Pirani Z, Armstrong K. Prevention of chronic post-surgical pain: the importance of early identification of risk factors. *Journal of Anesthesia.* 2017;31(3):424-431.

21. Jiang X, Orton M, Feng R, et al. Chronic Opioid Usage in Surgical Patients in a Large Academic Center. *Annals of Surgery.* 2017;265(4):722-727.
22. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA surgery.* 2017;152(6):e170504.
23. Greuter MJE, Schouten CS, Castelijns JA, et al. Cost-effectiveness of response evaluation after chemoradiation in patients with advanced oropharyngeal cancer using (18)F–FDG-PET-CT and/or diffusion-weighted MRI. *BMC Cancer.* 2017;17:256.
24. McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. *Health technology assessment.* 2010;14(17):1-153, iii-iv.
25. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology.* 2005;103(6):1296-1304.
26. Memtsoudis SG, Poeran J, Zubizarreta N, et al. Association of Multimodal Pain Management Strategies with Perioperative Outcomes and Resource UtilizationA Population-based Study. *Anesthesiology.* 2018;128(5):891-902.
27. Dort JC, Farwell DG, Findlay M, et al. Optimal Perioperative Care in Major Head and Neck Cancer Surgery With Free Flap Reconstruction: A Consensus Review and Recommendations From the Enhanced Recovery After Surgery Society. *JAMA otolaryngology-- head & neck surgery.* 2017;143(3):292-303.
28. Townsend M, Liou T, Kallogjeri D, et al. Effect of Perioperative Gabapentin Use on Postsurgical Pain in Patients Undergoing Head and Neck Mucosal Surgery: A Randomized Clinical Trial. *JAMA otolaryngology-- head & neck surgery.* 2018.
29. Carpenter PS, Shepherd HM, McCrary H, et al. Association of Celecoxib Use With Decreased Opioid Requirements After Head and Neck Cancer Surgery With Free Tissue Reconstruction. *JAMA otolaryngology-- head & neck surgery.* 2018.
30. Sommer M, Geurts JW, Stessel B, et al. Prevalence and predictors of postoperative pain after ear, nose, and throat surgery. *Archives of otolaryngology--head & neck surgery.* 2009;135(2):124-130.
31. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics.* 2009;42(2):377-381.
32. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. *Canadian Journal of Anaesthesia* 2001;48(10):1000-1010.
33. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesthesia and analgesia.* 2005;100(3):757-773.

34. Chiu TW, Leung CC, Lau EY, Burd A. Analgesic effects of preoperative gabapentin after tongue reconstruction with the anterolateral thigh flap. *Hong Kong Medical Journal.* 2012;18(1):30-34.
35. Dowell D HT, Chou R. . *CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016.* CDC;2016.
36. Gobble RM, Hoang HL, Kachniarz B, Orgill DP. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. *Plastic and reconstructive surgery.* 2014;133(3):741-755.
37. Chin CJ, Franklin JH, Turner B, Sowerby L, Fung K, Yoo JH. Ketorolac in thyroid surgery: quantifying the risk of hematoma. *Journal of otolaryngology - head & neck surgery* 2011;40(3):196-199.
38. Pfaff JA, Hsu K, Chennupati SK. The Use of Ibuprofen in Posttonsillectomy Analgesia and Its Effect on Posttonsillectomy Hemorrhage Rate. *Otolaryngology--head and neck surgery.* 2016;155(3):508-513.
39. Mudd PA, Thottathil P, Giordano T, et al. Association Between Ibuprofen Use and Severity of Surgically Managed Posttonsillectomy Hemorrhage. *JAMA otolaryngology-- head & neck surgery.* 2017;143(7):712-717.
40. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *The Journal of Pain.* 2016;17(2):131-157.
41. Semel D, Murphy TK, Zlateva G, Cheung R, Emir B. Evaluation of the safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies. *BMC family practice.* 2010;11:85.
42. Toth C. Pregabalin: latest safety evidence and clinical implications for the management of neuropathic pain. *Therapeutic Advances in Drug Safety.* 2014;5(1):38-56.
43. Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. *European neuropsychopharmacology.* 2017;27(12):1185-1215.
44. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? *CNS drugs.* 2014;28(6):491-496.
45. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert opinion on drug safety.* 2014;13(1):57-65.
46. Salvi F, Rossi L, Lattanzio F, Cherubini A. Is polypharmacy an independent risk factor for adverse outcomes after an emergency department visit? *Internal and Emergency Medicine.* 2017;12(2):213-220.
47. Hinther A, Nakoneshny SC, Chandarana SP, Wayne Matthews T, Dort JC. Efficacy of postoperative pain management in head and neck cancer patients. *Journal of Otolaryngology - Head & Neck Surgery.* 2018;47:29.

TABLE 1: Characteristics of Patients pre and post pain protocol implementation

Characteristics	**Pre-Protocol (N=167)** Mean (SD) or %	**Post-Protocol (N=105)** Mean (SD) or %
Age (years)	57.8 (1.1)	59.0 (1.4)
Sex		
Female	46%	41%
Male	54%	59%
Race		
Caucasian	73%	78%
Non-Caucasian	27%	22%
BMI (kg/m2)	28.1 (0.5)	26.7 (0.7)
Smoking Status		
Never	35%	42%
Ever	65%	58%
Pre-operative status		
Chronic Pain	26%	32%
Narcotic usage	21%	20%
Anticipated post-operative pain	6.1 (0.2)	6.3 (0.3)
Final Pathology		
Benign	55%	66%
Malignant	45%	34%
Extent of surgery		
"Minor" procedures	48%	36%
"Major" H&N procedure	52%	64%
Length of Hospitalization	5.2 (0.7)	4.7 (0.4)
Post-operative complication requiring RTOR	6%	3%

SD: Standard deviation. RTOR: Return to Operating Room. BMI: Body Mass Index

TABLE 2: Postoperative Non-Narcotic Pain Medication Utilization

% Utilization	Pre-Protocol (N=167)	Post-Protocol (N=105)
Acetaminophen	69%	88%
Ketorolac	10%	57%
	Pre-Protocol (N=87)	**Post-Protocol (N=68)**
Pregabalin	11%	76%

TABLE 3: Bivariate Analysis of Patient and Surgical Characteristics and Opioid Use in First 24 Hours After Surgery and Averaged Throughout Hospitalization

Characteristics	Total n	Median 24h MME (mg)	P value	Median MME/HD (mg/day)	P Value
Age (years)	220	r=-0.2505	**<0.001**	r=-0.3425	**<0.001**
Sex					
Female	92	45.0	0.246	37.5	0.481
Male	128	52.5		44.0	
Race					
Caucasian	159	45.0	**0.038**	37.4	0.079
Non-Caucasian	52	63.8		45.0	
Smoking Status					
Never	77	37.5	**<0.001**	30.0	**0.001**
Ever	142	56.3		45.2	
Pre-operative status					
Chronic Pain					
No	157	43.5	**0.003**	33.7	**<0.001**
Yes	63	75.0		51.8	
Narcotic usage					
No	140	37.5	**<0.001**	30.0	**<0.001**
Yes	80	81.0		64.9	
Anticipated post-operative pain	185	r=0.3434	**<0.001**	r=0.3715	**<0.001**
Final Pathology					
Benign	143	46.5	0.619	37.5	0.297
Malignant	77	48.0		41.3	
Extent of surgery					
"Minor" procedure(s)	77	45.0	**0.044**	40.0	0.880
"Major" procedure(s)	143	51.0		37.5	

TABLE 4: Bivariate Analysis of Patient and Surgical Characteristics and Average Pain Scores in First 24 Hours After Surgery and on Day of Discharge.

Characteristics	Total n	Average Pain Score in First 24hrs	P value	Average Pain Score on Day of Discharge	P Value
Age (years)	272	r=-0.1833	**0.003**	r=-0.1829	**0.003**
Sex					
Female	116	3.9	**0.045**	2.9	0.369
Male	150	3.3		2.6	
Race					
Caucasian	194	3.5	0.680	2.6	0.482
Non-Caucasian	62	3.6		2.8	
Smoking Status					
Never	101	3.5	0.423	2.5	0.242
Ever	164	3.7		2.8	
Pre-operative status					
Chronic Pain					
No	190	3.4	0.123	2.5	**0.046**
Yes	76	3.9		3.2	
Narcotic usage					
No	221	3.5	0.156	2.4	**0.001**
Yes	55	4.0		3.9	
Anticipated post-operative pain	272	r=0.2606	**<0.001**	r=0.3388	**<0.001**
Final Pathology					
Benign	160	3.5	0.780	2.7	0.988
Malignant	106	3.6		2.7	
Extent of surgery					
"Minor" procedure(s)	114	3.7	0.630	2.7	0.802
"Major" procedure(s)	152	3.5		2.7	

TABLE 5: Pain Scores and Opioid Usage Pre and Post Protocol Implementation

	Pre-protocol	Post-protocol	P Value
Average 24h pain score			
unadjusted	3.5	3.6	0.867
adjusted	3.6	3.7	0.787
Average pain score on discharge			
unadjusted	2.8	2.6	0.635
adjusted	2.7	2.7	0.952
Median 24h MME (mg)			
unadjusted	90.2	61.9	0.057
adjusted	93.7	58.6	**0.026**
Median MME/HD (mg/day)			
unadjusted	61.0	46.5	0.118
adjusted	57.9	46.8	0.211

APPENDIX I

LIMITED SYSTEMATIC REVIEW

A limited systematic reviewed was performed to identify studies that assess effect of multimodal analgesia on opioid use after head and neck surgery. A PubMed search was performed using the search terms *Otolaryngology multimodal pain management*, *head and neck post-surgical pain management, neck surgery multimodal analgesia, opioid sparing head and neck surgery, Otolaryngology narcotic requirement* and *Otolaryngology opioid use*. The search was filtered to human studies published in English.

A total of 228 articles were identified through PubMed search (Figure 1). Sixty-five full text articles were reviewed. The majority of articles were excluded as they focused on pediatric tonsillectomy patients or endoscopic sinus surgery procedures. Studies were also excluded if they did not specifically assess a non-narcotic analgesic medication or did not report opioid dosages. Three studies assessed a non-narcotic analgesic medication and its affect on opioid doses in this surgical population but only assessed a single medication. One article met inclusion criteria of studying multimodal analgesia effects on opioid use after head and neck surgical procedures.

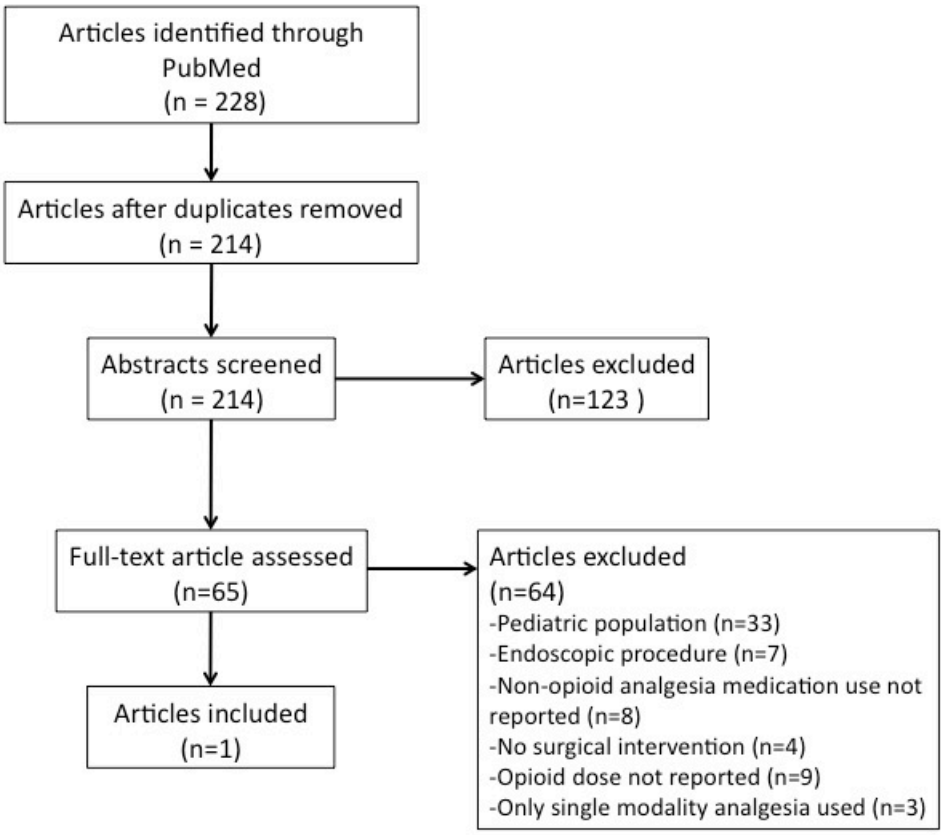

Figure 1: PRISMA Flow Diagram of Limited Systematic Review of Multimodal Analgesia for Post-surgical Pain Control of Head and Neck Surgery Patients.

APPENDIX II

PRE-OPERATIVE PATIENT SURVEY

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

□ YES □ NO

2. Chronic pain is pain that disrupts sleep or your normal daily functions on a regular basis. Do you have chronic pain unrelated to the problem that you are having surgery for?

□ YES □ NO

3. Please rate your average level of pain in the past 24 hours.

□ 0 (no pain) □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 (worst pain imaginable)

4. Do you take pain medication every day? If yes, please specify medication and quantity.

□ YES if yes, which one and how much _____ □ NO

5. How much pain are you expecting to experience the first day after your surgery?

□ 0 (no pain) □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 (worst pain imaginable)

APPENDIX III

POST-OPERATIVE PATIENT SURVEY

1. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

□ 0 (no pain) □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 (worst pain imaginable)

2. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

□ 0 (no pain) □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 (worst pain imaginable)

3. Please rate your pain by marking the box beside the number that best describes your pain on **average**.

□ 0 (no pain) □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10 (worst pain imaginable)

4. Please rate your current pain at rest on a scale between 0 and 4.

□ 0 (minimal pain) □ 1 □ 2 □ 3 □ 4 (maximum pain imaginable)

5. Please grade any distress and bother from vomiting in the past 24 hours.

□ 0 (not at all) □ 1 □ 2 □ 3 □ 4 (very much)

6. Please grade any distress and bother from itching in the past 24 hours.

□ 0 (not at all) □ 1 □ 2 □ 3 □ 4 (very much)

7. Please grade any distress and bother from sweating in the past 24 hours.

□ 0 (not at all) □ 1 □ 2 □ 3 □ 4 (very much)

8. Please grade any distress and bother from freezing in the past 24 hours.

□ 0 (not at all) □ 1 □ 2 □ 3 □ 4 (very much)

9. Please grade any distress and bother from dizziness in the past 24 hours.

□ 0 (not at all) □ 1 □ 2 □ 3 □ 4 (very much)

10. How satisfied are you with your pain treatment during the past 24 hours.

□ 0 (not at all) □ 1 □ 2 □ 3 □ 4 (very much)