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Reduction of Opioid Medication Use in Chronic Pain Patients by Adding Memantine: A Pilot Study

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Reduction of Opioid Medication Use in Chronic Pain Patients by Adding Memantine: A Pilot Study

A Thesis in Biomedical Science by Adam J. Bertino, B.S.

Submitted in Partial Fulfillment of the Requirements for the Degree of Masters of Science in Biomedical Sciences

July, 2017
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Research Study to Reduce Opioid Medication Use in Chronic Pain Patients by Adding Memantine: A Pilot Study

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Masters in Biomedical Sciences, July 2017
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An investigational clinical research pilot study is being conducted at a nursing facility and an academic primary care office to evaluate memantine as an adjunct to opioid therapy for treatment of chronic pain. Memantine can be beneficial in reducing pain because it is an N-methyl-D-aspartate receptor (NMDAr) antagonist with a pivotal action in the hippocampus: it initiates long-term potentiation in the anterior cingulate cortex and forebrain. These areas of action have a high probability for reducing the affective quality of pain.

This open-label, non-randomized pilot study is designed to observe any effects which may occur during addition of memantine to the therapeutic regimen of nursing home patients and office patients who take daily opioids (oxycodone, oxycodone/acetaminophen combination or hydromorphone) on an as-needed basis (prn) for chronic pain. The objective is to gauge, preliminarily, whether patients benefit from using memantine as an adjunct to their daily oxycodone/acetaminophen or hydromorphone treatment by increased analgesia, a reduction of opioid used, and increased bowel movements.
Memantine efficacy was assessed using pain diaries where patients recorded on a daily basis the amount of opioid used, pain scores (from ‘0’ [no pain] to ‘10’ [worst pain ever]), and number of bowel movements. Data are collected for six weeks; initially a two-week, no-memantine observation period, followed by a four-week treatment phase. Collected data are then analyzed.

With the first patient to complete the study, a trend of decreased pain scores over the six-week study was observed. There was also an indication of decreased opioid use but may be due to inconsistencies; bowel movements fluctuated and did not show a trend. The second patient showed trends of a decreased pain score with a decrease in opioid dosage over the course of the study and slightly lower bowel movements per week.

This pilot study presented insight to the plausible use of memantine as an adjunct to treat chronic pain patients. Although the number of patients that participated in this pilot was small, the trends observed may help to launch this type of study into a larger scale. Thus, these initial data present insight to the plausible use of memantine as an adjunct to treat chronic non-malignant pain patients who take an opioid daily.
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Chapter 1

INTRODUCTION

Approximately 20 percent of adults live with moderate to severe chronic pain that lasts for six months or longer [15]. Opioids may be considered to be the first drug of choice to combat severe chronic pain; over the past decade there has been an exponential increase in opioid prescriptions in the United States, Australia, and Europe [15]. Typical opioids available to treat chronic pain include morphine, codeine, oxycodone, fentanyl, and buprenorphine that are administered in multiple forms, e.g., tablet, skin patch, sublingual liquid. For individuals with persistent severe pain (“high impact pain”), high levels of opioid dosage result in improved analgesia but also increase the frequency and/or intensity of adverse effects; these reactions include sedation, impaired cognitive function, depression, constipation, and bladder dysfunction [15]. Endocrine dysfunction can develop such as hypogonadism/hypotestosteronism caused by central depression of hypothalamic secretion [9]. Furthermore, despite an increase in dosage, it is common for opioids to become ineffective over time due to tolerance, which, consequently, increases adverse effects. There is a risk that the patient may abuse, misuse or divert these medications. According to the American Society of Addiction Medicine, “Of the 21.5 million Americans 12 or older that had a substance use disorder in 2014, 1.9 million had a substance use disorder involving prescription pain relievers and 586,000 had a substance use disorder involving heroin” [1]. Patients develop tolerance to many pharmacological properties such as sedation, respiratory depression and nausea but not to
gastrointestinal hypomotility. With increased opioid dosage, this adverse effect becomes a major problem in the life of a chronic pain patient which can decrease the quality of living.

Pain can be described as a dynamic phenomenon, influenced by various mechanisms of excitatory and inhibitory control. Gender can factor into the amount of pain a patient experiences, due to varied levels of hormones in each system that are produced by the ovaries and testes. The different amount of hormones produced by each sex may have a direct impact on the perception of pain. Estradiol which is produced by the testes and more so in ovaries, can potentiate glutamate binding to NMDAr [18].

A retrospective cohort study was performed to determine if a gender difference exists in the incidence of severe postoperative pain episodes. Pain scores were collected from various types of non-ambulatory surgical procedures (e.g. coronary artery bypass graft, heart valve procedures, and laminectomy) using the Numeric Rating Scale (NRS), which is an 11 point scale (0-10) with 0 being no pain at all and 10 being the worst pain ever experienced. In addition, the incidence of severe pain events was determined by employing a SPE (Sudden Painful Events) scale; which is how many episodes of sudden-onset pain were experienced post-surgery. Evaluation of 333,000 pain scores between males and females, in similar procedural categorizations, resulted in a statistical difference. At post-operative day (POD) 1, the female averaged pain score was 4.20 with males at 3.98 (mean difference 0.22, 99% CI 0.16-0.28, p<0.0001). At POD 5, the female average pain score was 4.11, and male average of 3.74 (mean difference 0.36, 99% CI 0.33-0.40, p<0.0001). With these data, it was concluded that, on average, females report higher numeric pain intensity ratings within a clinical environment and that they
experience a greater incidence of SPEs on POD 1. Also, through the NRS pain scores, females had increasing pain through POD 5, which shows that males had a quicker decrease in pain than females [24].

A survey was performed to determine differences between females and males during a painful stimulus by studying the relationship between gonadal hormones and the central nervous system. When considering the epidemiology of sex differences in pain, researchers found that females tend to report more severe pain and longer lasting pain than their male counterparts with similar disease processes such as irritable bowel syndrome, chronic pelvic pain and interstitial cystitis. Females also have a more frequent prevalence of pain when the pain is related to musculoskeletal, visceral origin or autoimmune diseases like lupus and rheumatoid arthritis. Also, females are more likely to visit a physician when experiencing pain and use significantly more pain-relieving medications, even when the frequency and severity of pain was equated for the sexes. To explain this finding, there was a consideration of gonadal steroid hormones produced by the ovaries and testes. The testes mainly produce androgens, testosterone, and dihydrotestosterone, whereas, the ovaries mainly produce estrogens and progesterin. The precise roles of these biological substances in relation to pain are not yet well understood.

Effects on pain and analgesia were first thought to be caused by release of gonadal hormones and are possibly due to de novo hormone synthesis in the affected tissues. The hypothesis that gonadal hormones can affect sensitivity to pain when an organism is developing and throughout adulthood has also been tested in this research by examining the endogenous opioid neurotransmitters and μ opioid receptors. Females and males differ in their concentration of μ opioid receptors, which may be due to age and the
amount of circulating gonadal steroids [18]. According to the researchers, in various human experiments, females are generally found to have a greater amount of μ opioid receptors in the periaqueductal gray (PAG), including descending projections to the rostral ventral medulla (RVM) and dorsal horn of the spinal cord, when measured with positron emission tomography. Researchers used the individual gender role expectations of pain (GREP) on experimental pain report and VAS to rate pain intensity. Males showed significantly higher pain endurance than females with similar disease, but females indicated a greater willingness to report pain. These investigators performed another study to assess the difference between genders regarding response to interdisciplinary chronic pain management. Females were found to have a greater benefit from pain management than males, although the investigators did not discuss why this occurred. Interdisciplinary chronic pain management is a series of therapies relating to pain and distress at three time points (immediately prior, on completion, and three months following intervention). This includes PT/OT, psychology, pharmacology, etc. Also reported was greater morphine analgesia in men than women, and women needed about 30% more morphine to have the same level of analgesia as men after surgical removal of the third molar tooth [18].

In a study comparing effects of patient-controlled analgesia (PCA) with morphine between women and men from trauma-related pain (not specified), as the PCA duration was increased, there was also a positive correlation in the morphine effect between the sexes, the morphine effect also increased (n=11, 95% c.i. 0.01-0.69, p=0.047). When considering μ opioid receptors in experimental pain studies, women had a larger decrease of painful stimulus by sensory neurons while taking opioids when compared to men, as
seen from performing a sensitivity analysis (n=11, effect size=0.36, 95% c.i. 0.17-0.56, p=0.003). Although there are no pharmacokinetic gender differences, morphine was more effective in women at lower dosages, but had a slower onset of action. Researchers are still uncertain about the reasoning behind the latter effect, but it may be explained by slower progression though the blood-brain barrier or to the sex differences in receptor-ligand kinetics. Although there is greater morphine effectiveness in women once the relatively delayed effect is appreciated, men exhibit an analgesic greater effect directly after injection [17].

To improve safety, efficacy and reduce the potential for addiction and abuse, chronic pain can be treated through a variety of different categories of non-opioid medications instead of, or in conjunction with, opioids. Medications that can be used to complement opioids include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants, and benzodiazepines. The most common non-opioid medications used to treat chronic pain that can result from trauma, arthritis, surgery, or cancer are acetaminophen and NSAIDs; they are effective when taken alone or in combination with opioids. Acetaminophen is a non-salicylate that has analgesic and antipyretic effects similar to aspirin. Although acetaminophen does not irritate the gastric mucosa, use of this drug must be monitored in patients who consume alcohol daily and/or have underlying liver disease due to the fact that they can develop acetaminophen-induced hepatotoxicity. The disadvantage of NSAIDs is that they have a ceiling effect, i.e., once a therapeutic ceiling level has been established, any further increases in dosage will increase side effects without additional analgesia. Physicians must be cautious when prescribing NSAIDs in conjunction with opioid therapy, especially in elderly patients.
with certain medical co-morbidities as they can cause gastrointestinal (GI) bleeding, impairment in renal function and, most importantly, have been linked to cardiovascular events. The most common side effects are GI consisting of anorexia, dyspepsia, nausea, abdominal pain and diarrhea. Tricyclic antidepressants (TCAs) when administered with opioids, improve analgesia. Patients who received opioid medications with intramuscular amitriptyline after a cholecystectomy [6] or cesarean section [25] showed a reduction in the amount of opioid needed to improve analgesia. TCA analgesic effects are shown to work in as little as 24 hours of use, while antidepressant actions can take up to a week or more to appear [11]. It is believed that the mechanisms of TCAs are related to blocking serotonin and norepinephrine reuptake, and stabilizing nerve membranes [11].

Anticonvulsants such as gabapentin and pregabalin can be used successfully when treating pain if opioid medication therapy is not effective, e.g., in diabetic neuropathy or trigeminal neuralgia. This is due the main actions of anticonvulsants that decrease voltage-gated calcium or sodium channels, and improved performance of the gamma-aminobutyric acid (GABA) inhibitory system [11].

Patients in chronic pain who are on opioids can experience anxiety and mood disorders. Adding benzodiazepines in this situation can be useful; however, it can increase the chance of respiratory depression, and also misuse or addiction [11].

A recent study was conducted in patients with post-operative stump pain after major lower limb amputation. This research involved 198 patients over a four-year period; 102 received a perineural catheter and were compared to 96 patients who did not receive the perineural catheter. The catheter was used to bathe the nerve endings with analgesic medications. By multiple regression analyses, perineural catheter use was
shown to lower cumulative post-op opioid consumption over the first 72 hours. Researchers compared the amount of morphine needed between the two groups in the first 72 hours post-op, along with the post-operative pain intensity within the first 24 hours. Analgesic medications were converted to morphine equivalents and patients who received a perineural catheter required less cumulative post-operative opioid medication over the first 72 hours (catheter 81.23 ± 90.77 mL/hr vs. non-catheter 134.51 ± 145.49 mL/hr, \( p = 0.03 \)), leading to a lower adverse effect rate of sedation and nausea, leading to a greater quality of life for the patients [2].

Other effective adjuncts to opioid therapy for the treatment of chronic pain are N-methyl-D-aspartate receptor (NMDAr) antagonists. Ketamine is such an agent but has serious adverse drug reactions including dysphoria and hallucinations which limit clinical use (Parsons et al. 2013). Memantine can be a useful alternative to ketamine because the former is an NMDAr antagonist that has a pivotal action in the hippocampus of the brain.

Glutamate activates the NMDAr, causing calcium (Ca\(^{2+}\)) ions to move into the postsynaptic neuron, triggering a signal cascade leading to long-term potentiation (LTP), producing a greater order of learning and memory [19]. NMDA can impair LTP in the hippocampus, but the action of memantine can prevent that effect [19]. This led to the theory that memantine could be used as a possible treatment for neuropathic pain due to an effect on the NMDA receptor, since the neurotransmitter glutamate is associated with neuropathic pain.

Glutamate acting on an NMDA receptor causes the postsynaptic cell to become more sensitive to input signals. Memantine blocks excessive NMDA receptor activity without disturbing normal activity. The properties of memantine that allow such an effect
are that it is a noncompetitive, low-affinity, open-channel blocker. When the NMDA receptor-associated ion channel is excessively open, memantine acts as a fast-shut off but will not accumulate in the channel, allowing for normal synaptic transmission [20].

Memantine is highly absorbed after oral administration. Peak concentrations can be reached within 3-7 hours after administration and the intake of food does not affect the absorption of memantine. Memantine has a half-life of 60-80 hours and is mostly excreted by tubular secretion [4]. The majority of the administered memantine (57-82%) is excreted unchanged in the urine and the remaining percentage is converted primarily into three polar metabolites which possess minimal NMDA receptor antagonist activity [22].

Minimal inhibition of CYP450 enzymes including CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4 (most involved in biotransformation of opioids) have been observed in in vitro studies with memantine. Due to this low activity here, pharmacokinetic interactions with other medications metabolized by these enzymes are not likely [14].

An unpublished pilot investigational study on three geriatric patients taking a daily regimen of oxycodone/acetaminophen combinations for non-specific chronic pain for more than two months revealed that adding memantine orally for 28 days, following the approved FDA regimen for Alzheimer’s Disease, allowed patients to reduce the amount of their pain medication [5] (Figure 1).
In a comprehensive randomized clinical trial, memantine was administered to improve post-operative pain from a breast cancer surgical treatment. This study was performed as a pilot clinical trial. Half of the patients received memantine both before and after surgery at an increasing dosage following the FDA approved schedule for Alzheimer’s Disease (i.e., 5 mg a.m. on Week One, 5 mg a.m. and p.m. on Week Two, 10 mg a.m. and 5 mg p.m. on Week Three, 10 mg a.m. and 10 mg p.m. on Week 4), while the other group received a placebo (lactose) in the same time frame as the experimental group. At three months post-surgery, pain scores (0-10) were obtained and evaluated between control and memantine groups. Patients who received memantine reported less pain intensity, and less rescue analgesic (acetaminophen, NSAIDs, tramadol and morphine) dosage when matched with patients receiving only placebo. Pain scores were significantly lower in the memantine group (placebo: 1.3 ± 1.8; memantine: 0.2 ± 0.4, p= 0.017). It was concluded that patients who underwent mastectomy had less
neuropathic pain and an improved state of well-being when memantine was added both before and after surgery compared to control [16].

This correlates with an earlier study performed where six patients were treated with memantine for eight weeks after they had developed complex regional pain syndrome in the upper extremity following traumatic injury. In this investigation, memantine was given orally starting with 5 mg per day and increasing doses 5 mg every second day until a final target dose of 30 mg/d was achieved; it was also administered twice a day once the target dose was reached (15 mg/morning and 15 mg/evening). After six months post-treatment with memantine, all patients showed a significant decrease in pain scores dropping from an average score of 9.78 to 1.17 (p = 0.0001) [23].

In 2010, Gustin et al. performed a study in patients presenting with regional pain syndrome. They were given memantine as an adjunct to morphine to try to reduce their VAS pain score. Memantine was titrated from 5 to 40 mg over 15 days and maintained at 40 mg for another 34 days in order to minimize side effects due to this combination therapy. Patients who received memantine showed a significant difference in their VAS pain score at the affected limb by completing a numeric pain intensity scale (0—no pain, 10—maximum pain) after active clenching of the hand (five times) and during rest (5.47 to 1.40, p < 0.001). This indicates that using memantine as an adjunct to morphine improved analgesia. The mood of patients receiving memantine was also shown to significantly improve when compared to those who received a placebo (0.90 to 5.08, p < 0.001). This was measured using the Center for Epidemiologic Studies Depression Scale, which is a numerical questionnaire and can be related to the reduction of pain [8].
A more recent similar study involved adding memantine to methadone as an adjunct. Patients were chosen according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for opioid-dependence. They were divided into randomized groups where one received a placebo plus methadone while the other group was administered memantine (5 mg memantine sustained-release capsule) for 12 weeks with methadone. Results showed that the dosage of methadone required by patients also receiving memantine was significantly lower than the placebo group (p = 0.034); it decreased in patients by 0.950 mg over the 12-week study period [12].

Results of these studies show that using memantine as an adjunct lowered the amount of pain, improved mood and decreased opioid dosage.

In this pilot study, memantine was added to patients taking immediate-release opioids, oxycodone, oxycodone/acetaminophen or hydromorphone, for at least two months; both office-based and nursing home patients were recruited. As a result of decreased opioid use, patients were hypothesized to experience fewer and/or less intense adverse effects; this outcome would be expected to improve their quality of life.
Chapter 2

METHODS

This pilot study was conducted to determine whether the addition of memantine to an established opioid analgesic regimen had measurable effects on analgesia, need for rescue pain medications or laxation. Objectives were to determine any reduction of daily dose of opioid medication, pain scores and constipation. This adjunctive agent was added to patients taking a combined oxycodone/acetaminophen formulation or hydromorphone for a minimum of two months.

Approval to conduct this research was obtained from the Institutional Review Board (IRB) at Philadelphia College of Osteopathic Medicine (PCOM) for two nursing homes located in Philadelphia (Bala Nursing and Rehabilitation Center [B]; St. Ignatius Nursing Home [S] on August 10, 2016. Additional IRB approval was obtained to recruit patients from the PCOM office-based practices of Katherine Galluzzi, DO, and Larry Finkelstein, DO on January 8, 2017. This study was an AB Design study, in which the patient initially did not receive treatment (A) and then was given the study drug (B). Inclusion criteria for this study were patients who are at least 18 years of age or older, taking opioids daily for two months for chronic pain, and able to sign the consent form. Patients were not able to participate in this study if they were taking certain antidepressants (TCAs and SNRIs) for less than 6 weeks, antipsychotics, or Alzheimer’s Disease medication. Other exclusion criteria included non-English speaking patients or
those with, gastric motility problems, pregnancy, or planned pregnancy during the 6 weeks of participation in this study.

A screening process was performed by the attending physician and student investigators. Student investigators performed a Mini Mental State Exam (MMSE) (Appendix C) on patients that were reported to be on short-acting opioid therapy in order to gauge their cognitive function. The physician then contacted patients who were cognitively capable of participating to ask them to volunteer to be potential study subjects. After consulting with the potential study subject, the physician asked the patient to explain this study back to them in order to assure complete understanding of what was expected. Patients that were asked to volunteer for this study were then given a consent form (Appendix A) in which they could review with their families and significant others. After one week, patients were asked for their decision and if they had any questions that may have arisen; these were answered by their physician. To maintain confidentiality, signed consent form documents and pain diary documents were kept in a locked file cabinet, as required by the IRB. Patients who decided not to be part of the study or decided to stop in the middle of this investigation were assured that they would continue to receive the same care from the staff and their physician.

Since this investigation was a pilot study with a small sample size and administration of memantine was off-label, it was not randomized, and a placebo was not used. Patients were allowed to use as much of their opioid daily as needed. Due to the fact that pain is variable from person to person, the amount of pain medication that each patient would require differs, therefore, each study subject served as his/her own control.
Memantine, provided from Verree Pharmacy located in Northeast Philadelphia, was given daily for 28 days in a row after a two-week pre-memantine phase to determine if the study patient could comply with all study requirements and to also obtain a baseline for the amount of opioid patients were taking, as well as their baseline pain score (Day 1-Day 14). A baseline was important in order to identify existing patterns of the opioid use by the patient and allow for a more accurate interpretation of the results. Memantine was delivered in a kit prepared by Verree Pharmacy with five bottles in each to be administered to the patients by nursing staff at the nursing facility. Office out-patient memantine kits were delivered to PCOM and each weekly corresponding bottle was given to the patient each week when they came into the office. All bottles were labeled with the corresponding week, and a number. Week 3: Bottle 1: 7 tablets of 5 mg each, Week 4: Bottle 2: 14 tablets of 5mg each, Week 5: Bottle 3: 7 tablets of 5 mg each Week 5: Bottle 4: 7 tablets of 10 mg each, Week 6: Bottle 5: 14 tablets of 10 mg each. Each bottle label also contained the date; subject ID, memantine dose per day, instructions, week number and physician name. Each was placed in a prescription bag with a unique kit number, with a label that included the number followed by Memantine-Opioid Clinical Investigation for research study use only.

The first part of this study was the pre-memantine phase, in which memantine was not administered and patients were asked a series of questions in a weekly pain diary (Appendix B). The questions were, 1.) How much of your pain medicine you are taking every day? 2.) How much pain you are having every day? 3.) How many bowel movements you are having every day? Pain was assessed by using an 11 point scale, zero being no pain at all and 10 being the worst possible pain. During the two-week pre-
memantine phase student investigators came in for a brief visit every day to learn how the patient was feeling. The patient then had a short discussion with their doctor regarding the desire to continue with this study. If the patient wanted to remain in the study, part two began immediately. During this phase, the patient took memantine for 28 days as follows, Week 3 – 5 mg in the morning for the first 7 days, Week 4 – 5 mg in the morning and 5 mg in the evening for the next 7 days, Week 5 – 10 mg in the morning and 5 mg in the evening for the next 7 days, Week 6 – 10 mg in the morning and 10 mg in the evening for the next 7 days (Appendix D). This titrated dosage regimen is exactly the dosage regimen approved by the FDA for treatment of Alzheimer’s Disease. It was important to conduct a titration scale for this medication because patient comfort was of utmost importance. The risk of adverse effects from this medication is increased if not titrated properly. Administering memantine through this process to reach a target dose allowed physicians and nursing staff to monitor any adverse effects that may occur while taking the medication. Due to the fact that this was an off-label use of memantine, after the four week administration period, the patients did not receive continual administration of this medicine through this study. The cost of memantine for a four-week supply is $50.00 which was covered by the PCOM Center for Chronic Diseases of Aging for the duration of the investigation. If the patient wanted to continue to use memantine off-label after the study was completed, a prescription had to be written by the primary physician of the patient.

For patients that resided in a nursing home, the first visit was a normal one where there was an initial identification of them for the study and discussion of the study; then the consent form was given. The next visit was for pre-study evaluation; if inclusion and
exclusion criteria were met, the patient was asked to sign the consent form, and Weeks one and two pain diary sheets were started. During the first week, student investigators visited the study subject in the afternoon and evening to ensure that the patient was compliant with the procedure (Day 1 – Day 7). The second week followed the schedule of the first week, in which the student investigators visited the patients to ensure they were remaining compliant with their daily pain diary logs (Day 8 - Day 15). On Day 15, if the patient remained compliant, the treatment phase was started where memantine was administered and the pain diary sheets for Weeks three and four were started. Student investigators continued to meet with patients at the same time in the afternoon and evening (Day 16 – Day 28). On Day 29 the treatment phase continued and diary sheets for Weeks five and six were started and student investigators continued to visit in the afternoon and evening (Day 29 – Day 42). Day 43 was the last visit and the end of participation for patients in this study. Student investigators visited the patient in the afternoon and evening to collect final data.

The study subject was visited two times per day by student investigators, once at noon and once in the evening. There were a total of 84 visits over the six week study period and each visit took approximately three minutes, leading to a total of 4.2 hours of time spent with each study subject. At the nursing home, student investigators were granted access to their Millennium Database to gain access to patient records for data collection. Data was collected from the morning by the patient directly writing in the pain diary. Mid-day and evening data were collected via one-on-one interviews between patients and Student Investigators.
PCOM office out-patient data were collected on a weekly basis; however, the pain dairy information remained the same. The first visit was a normal visit where there was an initial identification for the study, discussion of the study and the consent form was given. The next visit, a week later, was the pre-study evaluation visit, where, if inclusion and exclusion criteria are met, the patient was asked to sign the consent form and week one pain diary was started. The patients came into the office each week of the study to hand in their pain diary for the previous week and start the pain diary for the next week. After the two week pre-memantine phase was completed to a satisfactory level, memantine was distributed to the patient in weekly bottles. The patient returned to the office each week to submit pain dairy data and to collect the next weekly dose of memantine until completion of the study. After the six-week study, all the data collected were combined.
Chapter 3

RESULTS

3.1. PART A

Patients who volunteered were given designated codes to de-identify them except to the investigators. Seven patients were involved, four from one of the nursing homes (B) and three office out-patients. Patients from the nursing home were designated as M [Male]-01-B, M-02-B, M-03-B and M-04-B. Office out-patients were designated as M-01-R, M-02-R and F [Female]-01-R. However, three nursing home patients, M-02-B, M-03-B and M-04-B, did not continue the study after the pre-memantine phase and did not receive any memantine.

Patients followed by this Student Investigator were M-01-B M-02-B, M-03-B, M-04-B and F-01-R; those followed by Student Investigator, Lisa English, were M-01-R and M-02-R.

3.1.1. Study Subject M-02-B

He was an 81 year-old male with chronic hand and leg pain due to osteopenia. He received oxycodone, 5 mg + acetaminophen (oxy/acet) orally *per os (p.o.)*, as needed *pro re nata (prn)*, every six hours *quaque sex hora (q6)*. This patient was removed from the study during the second week of the pre-memantine phase because he was not taking
enough of the generic combination of oxycodone, 5 mg + acetaminophen (oxy/acet) (Figure 2) and it would have been difficult to observe a reduction in his opioid intake throughout the study.

**Figure 2:** Average Pain Scores and Bowel Movements per Week. Average weekly pain scores and bowel movements per day during the Pre-Memantine Phase of M-02-B.

Once this patient was removed from the study, he started physical therapy and thought he would be using more oxy/acet. Extensive monitoring was initiated to observe if he could be reintroduced into the study. Unfortunately, he passed away from a heart condition four days before starting memantine.
3.1.2. Study Subject M-03-B

He was a 71 year-old male with chronic left side hip and leg pain due to an unspecified bone disorder and a fractured left femur. He received oxycodone 10 mg p.o. prn, every four hours *quaque quarta hora* (*q4*). This patient was able to complete the full-two week pre-memantine phase but when the memantine phase was to start, he was admitted to the hospital to undergo left hip surgery. Due to this unexpected event, the memantine phase was halted, and a decision was made remove the patient from the study. Another factor in his removal was a drop in pain scores from week one to week two (Figure 3). Due to this reduction without any intervention with memantine it would have been difficult to determine if the memantine caused the decrease or it was due to a different cause.

**Figure 3: Pre-Memantine Phase; Daily opioid Dosage (mg).** Daily opioid dosage (mg) for the length of time M-03-B was included in the study.
3.1.3. Study Subject M-04-B

He was a 65 year old male with chronic back and leg pain who was taking oxy/acet 5-325 p.o. prn q6. This patient was taken out of the study after the first week of the Pre-Memantine Phase because he was not able to keep an accurate pain diary (Figure 4). Also, he underwent surgery for a new pacemaker during the beginning of the second week of the Pre-Memantine Phase. Another factor in his elimination was his daily inquiry as to when he would be receiving the memantine even though the two week Pre-Memantine Phase was explained to him every time. This was perceived as though the patient did not fully understand the study.

![Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week](image)

**Figure 4: Pre-Memantine Phase; Daily opioid Dosage (mg)**. Daily opioid dosage (mg) for the length of time M-04-B was included in the study.

These instances of nursing home patients indicated that their health instability made it difficult to collect and analyze accurate data; the decision was altered to recruit
office out-patients who would likely be more compliant, which would permit collection of more accurate data.
Chapter 4

RESULTS

4.1 PART B

4.1.1. Study Subject M-01-B

The first patient receiving memantine in this study, was a good candidate for this study because and was taking oxy/acet; this was administered via percutaneous endoscopic gastrostomy (PEG) tube, prn q4 for a pressure ulcer on his left heel, phantom pain from an amputated right fifth digit phalanx, and chest pain from the PEG tube. However, due to unforeseen circumstances, data accumulated from M-01-B are not as accurate as possible; however, they served as preliminary information to determine if a trend could be observed.

The first circumstance was that the patient did not understand his oxy/acet prescription was prn and that he had to ask for it when needed. In the beginning, he assumed his opioid was given to him regularly. During the first week of the pre-memantine phase he did not receive any for four days straight due to this misunderstanding (Figure 5). After explaining what ‘as needed’ meant, the number of oxy/acet he received increased. Due to his confusion, it was decided to extend the pre-memantine phase an additional week to obtain better data; the first week was renamed Week 0. This increased the study period from six to seven weeks in total.
4.1.1.1. Overview of Week Zero:

Figure 5. Average Daily Pain Scores, Opioid Dosage (mg) and Bowel Movements for Week Zero. Average daily pain scores, opioid dosage (mg) and bowel movements for each day of week zero.

The second circumstance was a staff participation issue in the nursing home. There were times where oxy/acet given to the patient, but it was not recorded by the staff on their electronic medical records. On multiple occasions, the patient knew he had received oxy/acet even though it was not on the Medication Administration Record (MAR). When staff were questioned, it was confirmed that he was given oxy/acet but they failed to record the dosage in the MAR. Due to this circumstance the number of oxy/acet tablets the patient actually received may not be accurate; thus these data are likely skewed. The third circumstance happened when the patient used the emergency call button in his room to alert the staff that he needed an oxy/acet due to significant pain. However, the patient described that it took anywhere between one and two hours until
someone came to his room to give him an oxy/acet. It got to the point where the patient
gave up trying to get the attention of the staff and just dealt with the pain. This further
skews the data obtained from this patient because the actual amount of oxy/acet he
needed was not reflected in the amount he was given. These issues were brought to the
attention of the Director of Nursing which seemed to resolve the problems for a few days,
but eventually they returned.

There were also problems with the labels on the memantine bottles. Week 3
should have been labeled 10 mg in the morning and 5 mg in the evening. However,
unfortunately, the dosages were switched which resulted in the patient missing out on a
10 mg dose on the first day of Week 3. Also for an unexplained reason, on the last day of
Week 3, the memantine medication was discontinued which resulted in another missed
10 mg dose on the first day of Week 4.

Since there were many inconsistencies with this patient and his treatment plan, the
data collected from him cannot be used in the final overall results for this study.
However, they can be employed as preliminary results to observe if there were any
changes.

**4.1.1.2. Pre-Memantine Phase**

Daily morning pain scores stayed fairly constant over the two week pre-
memantine phase (Figure 6).
4.1.2.1. Pain Scores

**Figure 6: Pre-memantine phase; Daily Morning Pain Scores.** Daily morning pain scores over the two week pre-memantine phase.

However, afternoon (Figure 7) and evening (Figure 8) reports dropped slightly during the pre-memantine phase.
Figure 7: Pre-memantine phase; Daily Afternoon Pain Scores. Daily afternoon pain scores over the two week pre-memantine phase.

Figure 8: Pre-memantine phase; Daily Evening Pain Scores. Daily evening pain scores over the two week pre-memantine phase.
In the first two weeks there was a slight decrease in average daily pain scores from week one to week two (Figure 9).

**Figure 9: Pre-Memantine Phase; Average Daily Pain Scores**. Averages of Morning, Afternoon and Evening pain scores for each day over the two week pre-memantine phase.

There was also a decrease in the average opioid dosage (mg) from week one to week two (Figure 10) and cannot be used to explain the decrease in average daily pain scores for this week.
4.1.2.2. Oxy/acet Dosage

**Figure 10: Pre-memantine phase; Daily Opioid Dosage (mg).** Daily opioid dosages (mg) for each day over the two week pre-memantine phase. ? = discrepancies.

There was also a slight decrease in bowel movements from week one to week two (Figure 11).
4.1.1.2.3 Bowel Movements

Figure 11: Pre-memantine phase; Daily Bowel Movements. Daily bowel movements for each day over the two week pre-memantine phase.
4.1.1.2.4. Overview of Pre-Memantine Phase

**Figure 12. Average Pain Scores, Opioid Dosage (mg) and Bowel Movements per Week.** Average weekly pain scores, opioid dosage (mg) and bowel movements for the first two weeks of the study.
4.1.1.3. Week One of Memantine

4.1.1.3.1. Pain Scores:

**Figure 13: Week One of Memantine (5 mg a.m.); Daily Pain Scores**

Average daily pain scores for week one (Figure 14) remained fairly constant, as did opioid dosage (mg) (Figure 15).
Figure 14: Week One of Memantine; Average Daily Pain Scores. Averages of morning, afternoon and evening pain scores for each day over the first week of memantine.

4.1.1.3.2. Oxy/acet Dosage

Figure 15: Week One of Memantine; Daily Opioid Dosage (mg). Daily opioid dosages (mg) for each day of the first week of memantine.
Bowel movements for week one exhibited no remarkable characteristics (Figure 16) but decreased slightly from the pre-memantine phase (Figure 17).

4.1.1.3.3. Bowel Movements:

**Figure 16: Week One of Memantine (5 mg a.m.); Daily Bowel Movements.** Daily bowel movements for each day of the first week of memantine.
4.1.1.3.4. Overview through Week One of Memantine

![Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week](image)

Figure 17. Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week. Average weekly Pain Scores, Opioid Dosage (mg) and Bowel Movements for the first three weeks of the study. Arrow indicates when memantine was first introduced.

4.1.1.4. Week Two of Memantine

Week two of memantine (5 mg a.m. & 5 mg p.m.) followed the same trend of week one of memantine with the afternoon pain scores being generally lower than the morning and evening pain scores (Figure 18).
4.1.4.1. Pain Scores

**Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Daily Pain Scores**

![Daily Pain Scores Graph]

**Figure 18: Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Daily Pain Scores.** Morning, afternoon and evening pain scores for each day over the second week of memantine.

The average pain score during each day of Week Two of memantine did drop from the beginning to the end of the week (Figure 19).
Figure 19: Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Average Daily Pain Scores. Averages of morning, afternoon and evening pain scores for each day over the second week of memantine.

Daily opioid dosages (mg) for the second week of memantine were relatively constant with 5 or 10 mg throughout the week (Figure 20).
4.1.4.2. Oxy/acet Dosage

**Figure 20: Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Daily Opioid Dosage (mg)**

Bowel movements for this week exhibited no unique characteristics (Figure 21) but increased slightly from the previous week (Figure 22).
4.1.1.4.3. Bowel Movements

**Figure 21: Week Two of Memantine; Daily Bowel Movements**

![Bar chart showing daily bowel movements for each day of the second week of memantine.

<table>
<thead>
<tr>
<th>Days of the Week</th>
<th>Daily Bowel Movements</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Thursday</td>
<td>0</td>
</tr>
<tr>
<td>Friday</td>
<td>2</td>
</tr>
<tr>
<td>Saturday</td>
<td>0</td>
</tr>
<tr>
<td>Sunday</td>
<td>1</td>
</tr>
<tr>
<td>Monday</td>
<td>1</td>
</tr>
<tr>
<td>Tuesday</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 21: Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Daily Bowel Movements.** Daily bowel movements for each day of the second week of memantine.
4.1.1.4.4. Overview through Week Two of Memantine

**Figure 22. Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week.** Average weekly pain scores, opioid dosage (mg) and bowel movements for the first four weeks of the study. Arrow indicates when memantine was first introduced.

4.1.1.5. Week Three of Memantine

The trend followed into the third week of memantine (10 mg a.m. & 5 mg p.m.) (Figure 23).
4.1.1.5.1. Pain Scores

**Figure 23:** Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Daily Pain Scores. Morning, afternoon and evening pain scores for each day over the third week of memantine. (*) = missed memantine dose.

Afternoon pain scores were generally lower than both morning and evening pain scores but increased in the weekend. The average daily pain score for the third week stayed relatively constant, but were lower than that in week two (Figure 24).
Figure 24: Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Average Daily Pain Scores. Averages of morning, afternoon and evening pain scores for each day over the third week of memantine.

Opioid dosage (mg) was also constant in week three; the patient received 10 mg in five of the seven days (Figure 25).
4.1.1.5.2. Oxy/acet Dosage

**Figure 25: Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Daily Opioid Dosage (mg)**

Bowel movements for this week exhibited no unique characteristics (Figure 26) but decreased slightly from the previous week (Figure 27).
4.1.1.5.3. Bowel Movements

Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Daily Bowel Movements

Figure 26: Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Daily Bowel Movements. Daily bowel movements for each day of week three.

4.1.1.5.4. Overview through Week Three of Memantine

Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week

Figure 27. Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week. Average weekly pain scores, opioid dosage (mg) and bowel movements for the first five weeks of the study. Arrow indicates when memantine was first introduced.
4.1.1.6. Week Four of Memantine

Data in the final week of memantine (10 mg a.m. & 10 mg p.m.) were constant with previous trends. Afternoon pain scores were generally lower than the morning and evening pain scores with an increase during the weekend (Figure 28).

4.1.1.6.1. Pain Scores

**Figure 28: Week Four of Memantine (10 mg a.m. & 10 mg p.m.); Daily Pain Scores**

The average daily pain score for the fourth week stayed relatively constant again, but were lower than that in week three of memantine (Figure 29).
Figure 29: Week Four of Memantine (10 mg a.m. & 10 mg p.m.); Average Daily Pain Scores. Averages of morning, afternoon and evening pain scores for each day over the fourth week of memantine.

Opioid dosage (mg) was relatively consistent with the patient receiving either 5 or 10 mg throughout each day (Figure 30).
4.1.1.6.2. Oxy/acet Dosage

**Figure 30: Week Four of Memantine (10 mg a.m. & 10 mg p.m.); Opioid Dosage (mg)**

Bowel movements increased during week four of memantine (Figure 31).
4.1.1.6.3. Bowel Movements

**Week Four of Memantine (10 mg AM & 10 mg PM); Daily Bowel Movements**

![Graph showing daily bowel movements for each day of week four.]

**Figure 31: Week Four of Memantine (10 mg a.m. & 10 mg p.m.); Daily Bowel Movements**. Daily bowel movements for each day of week four.
4.1.1.6.4. Overview through Week Four of Memantine

**Figure 32. Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week.** Average weekly pain scores, opioid dosage (mg) and bowel movements for each week of the study. Arrow indicates when memantine was first introduced.

4.1.1.7. In-depth Overview of Study Subject M-01-B

When compiling data from all six weeks of the study, trends were easier to observe. Average morning pain scores per week showed a decrease as the memantine dosage increased (Figure 33).
4.1.1.7.1. Pain Scores:

**Figure 33. Average Morning Pain Scores Per Week.** Average weekly morning pain scores for each week of the study. Arrow indicates when memantine was first introduced.

The largest reduction in average pain score was in the afternoon (Figure 34).
Average evening pain scores were similar to average morning reports, i.e. approximately the same values but still a noticeable decrease from the first week to the last (Figure 35).
The overall average pain scores per week decreased from week to week as the dosage of memantine increased (Figure 36).
Figure 36. Average Pain Score Per Week. Average weekly pain scores for each week of the study. Arrow indicates when memantine was first introduced.

There was a 2.3 pain score decrease from week one to week six. Opioid dosage (mg) over the six weeks fluctuated slightly, however, there was a 3.5 mg decrease from week one to week six (Figure 37).
4.1.1.7.2. Oxy/acet Dosage

**Average Opioid Dosage (mg) Per Week**

![Bar chart showing average opioid dosage per week](image)

*Figure 37. Average Opioid Dosage (mg) per Day per Week. Average weekly opioid dosage (mg) per day for each week of the study. Arrow indicates when memantine was first introduced.*

The average bowel movements did not show an increase over the six weeks of the study (Figure 38). Week six average bowel movements were higher due to the one day where the patient recorded five bowel movements.
4.1.1.7.3. Bowel Movements

**Figure 38. Bowel Movements per Week.** Bowel movements for each week of the study. Arrow indicates when memantine was first introduced.

4.1.2. Study Subject F-01-R:

This patient was a good candidate for this study because she was taking 4 mg hydromorphone, *prn*, every eight hours *quaque octava hora* (q8) for joint pain from a motor vehicle accident decades ago; she was riding on her bike and was hit by a car. She presented with antalgic gait including pain when turning and the feeling of “walking through molasses”. This patient also experiences pain in the middle of the night, and stated that her joint pain appears to be weather-related. The weather that affects this
patient the most are rainy days and when the seasons are changing that brings along a barometric alteration. She also stated that she takes gabapentin 600 mg – 900 mg up to four times per day for restless leg, meclizine 50 mg per day for dizziness, Cymbalta 30 mg per day for depression, Atorvastatin 20 mg per day to lower cholesterol, Hydrochlorothiazide (HCTZ) 25 mg per day to treat edema and metoprolol 50 mg per day to treat angina.

4.1.2.1. Pre-Memantine Phase

Over the two week pre-memantine phase, this patient experienced consistent pain scores in the morning, evening and afternoon. Her morning pain scores were all 5 or 6 (Figure 39), afternoon pain scores were mostly 6 and 7, with only two pain scores of 8 (Figure 40), and evening pain scores were all 8 with one night being a 9 (Figure 41).
4.1.2.1.1. Pain Scores:

Figure 39: Pre-Memantine Phase; Daily Morning Pain Scores. Daily morning pain scores over the two week pre-memantine phase.
Figure 40: Pre-Memantine Phase; Daily Afternoon Pain Scores. Daily afternoon pain scores over the two week pre-memantine phase.

Figure 41: Pre-Memantine Phase; Daily Evening Pain Scores. Daily evening pain scores over the two week pre-memantine phase. * = patient not able to rest all day.
The trend observed from the two week pre-memantine phase was that the patient recorded an increased pain score as the day proceeded with the highest pain scores in the evening (Figure 42).

**Pre-Memantine Phase; Daily Pain Scores**

![Graph showing daily pain scores over two weeks](image)

**Figure 42: Pre-Memantine Phase; Daily Pain Scores.** Daily morning, afternoon and evening pain scores over the two week pre-memantine phase.

However when comparing the average daily pain score for each day of the pre-memantine phase, the average did not go lower than 6.3 or higher than a 7.3 (Figure 43).
Figure 43: Pre-Memantine Phase; Average Daily Pain Scores. Averages of Morning, Afternoon and Evening pain scores for each day over the two week pre-memantine phase.

The amount of hydromorphone consumed by this patient remained consistent with 12 mg total each day, except for one when the patient overslept and missed a hydromorphone dose in the morning (Figure 44).
4.1.2.1.2. Hydromorphone Dosage

**Pre-Memantine Phase; Daily Opioid Dosage (mg)**

![Bar chart showing daily opioid dosages over two weeks.](image)

**Figure 44: Pre-Memantine Phase; Daily Opioid Dosage (mg).** Daily opioid dosages (mg) for each day over the two week pre-memantine phase. * = patient overslept and missed a usual dose.

Bowel movements were unremarkable with only one bowel movement every couple of days (Figure 45).
4.1.2.1.3. Bowel Movements

**Figure 45: Pre-Memantine Phase; Daily Bowel Movements.** Daily bowel movements for each day over the two week pre-memantine phase.
4.1.2.1.4. Overview of Pre-Memantine Phase

![Graph showing average pain scores, opioid dosage, and bowel movements per week.]

**Figure 46. Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week.** Average weekly pain scores, average opioid dosage (mg) and bowel movements for the first two weeks of the study.

4.1.2.2. Week One of Memantine

Daily pain scores for morning, afternoon and evening for the first week of memantine (5 mg a.m.) showed a trend of the morning and afternoon being 6 with a slight increase in the evening to pain scores of 7 and 8 (Figure 47).
4.1.2.2.1. Pain Scores

Figure 47: Week One of Memantine (5 mg a.m.); Daily Pain Scores. Morning, afternoon and evening pain scores for each day over the first week of memantine.

Compared to the pre-memantine phase data, she had on average a reduction in pain score at all times of the day. It also decreased (Figure 48) when compared to the pre-memantine phase data.
For week one of memantine, the average daily pain score was either 6.3 or 6.7, whereas during the pre-memantine phase, there were a few days that reached a pain score of 7.3. However, daily opioid dosage (mg) remained constant at 12 mg (Figure 49).
4.1.2.2.2. Hydromorphone Dosage

**Figure 49: Week One of Memantine (5 mg a.m.); Opioid Dosage (mg)**

![Bar chart showing daily opioid dosages (mg) for each day of the first week of memantine.]

Daily bowel movements did decrease slightly (Figure 50) from three bowel movements per week during the pre-memantine phase to two for the first week of memantine.
4.1.2.2.3. Bowel Movements

**Figure 50: Week One of Memantine (5 mg a.m.); Daily Bowel Movements.** Daily bowel movements for each day of the first week of memantine.
4.1.2.2.3. Week Two of Memantine

In daily pain scores for morning, afternoon and evening for the second week of memantine (5 mg a.m. & 5 mg p.m.) there was a trend of the first two with a score of 6; there were two instances where a pain score of 8 was recorded in the afternoon. Evening pain scores were almost all 7 (Figure 52).
4.1.2.3.1 Pain Scores

Figure 52: Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Daily Pain Scores

When observing the average daily pain score over each day of week two of memantine and comparing it to data from week one, there were more averages of 6.3, however, one day it was a 7.0 (Figure 53).
Figure 53: Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Average Daily Pain Scores. Averages of morning, afternoon and evening pain scores for each day over the second week of memantine.

Daily opioid dosages (mg) for the second week of memantine dropped due to the patient taking one less hydromorphone on Thursday, Friday and Saturday (Figure 54).
4.1.2.3.2. Hydromorphone Dosage

**Figure 54: Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Opioid Dosage (mg)**

![Chart showing opioid dosages for each day of the second week of memantine.]

**Figure 54: Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Daily Opioid Dosage (mg).** Daily opioid dosages (mg) for each day of the second week of memantine.

Bowel movements for this week showed no special characteristics (Figure 55) but decreased by a factor of 0.1 when compared to the pre-memantine phase (Figure 56).
4.1.2.3.3. Bowel Movements

Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Daily Bowel Movements

![Bar chart showing daily bowel movements for each day of the second week of memantine.]

**Figure 55: Week Two of Memantine (5 mg a.m. & 5 mg p.m.); Daily Bowel Movements.** Daily bowel movements for each day of the second week of memantine.
4.1.2.3.4. Overview through Week Two of Memantine

**Figure 56. Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week.** Average weekly pain scores, average opioid dosage (mg) and bowel movements for the first four weeks of the study. Arrow indicates when memantine was first introduced.

### 4.1.2.4. Week Three of Memantine

When looking at daily pain scores for morning, afternoon and evening for the third week of memantine (10 mg a.m. & 5 mg p.m.) there was a decreasing trend with mid-week stabilization (Figure 57).
4.1.2.4.1. Pain Scores

Figure 57: Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Daily Pain Scores

Monday was the worst day with a pain score of 9 recorded all day. From Tuesday through Saturday the patient had an average daily pain score of 6, with a decrease to a pain score of 5 on Sunday (Figure 58).
Figure 58: Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Average Daily Pain Scores. Averages of morning, afternoon and evening pain scores for each day over the third week of memantine. Patient describes the highest pain score is due to weather.

This decrease in pain score was accompanied by a reduction in hydromorphone i.e., 4 mg less each day (Figure 59).
4.1.2.4.2. Hydromorphone Dosage

**Figure 59: Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Opioid Dosage (mg)**

![Bar chart showing daily opioid dosages for Week Three of Memantine.](image)

**Figure 59: Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Daily Opioid Dosage (mg).** Daily opioid dosages (mg) for each day of the third week of memantine.

Bowel movements stayed consistent with only two bowel movements this week (Figure 60), although the average bowel movements per day per week have only decreased by a factor of 0.1 (Figure 61).
4.1.2.4.3. Bowel Movements

**Figure 60: Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Daily Bowel Movements**

Daily bowel movements for each day of week three.

**Figure 60: Week Three of Memantine (10 mg a.m. & 5 mg p.m.); Daily Bowel Movements.** Daily bowel movements for each day of week three.
4.1.2.4.4. Overview through Week Three of Memantine

**Figure 61.** Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week. Average weekly pain scores, average opioid dosage (mg) and bowel movements for the first five weeks of the study. Arrow indicates when memantine was first introduced.

4.1.2.5. Week Four of Memantine:

In the final week, of memantine (10 mg a.m. & 10 mg p.m.) there was an improvement in morning pain scores, i.e., recorded pain scores were 5 for each day; afternoon and evening pain scores stayed relatively consistent from the previous week (Figure 62).
4.1.2.5.1. Pain Scores

Figure 62: Week Four of Memantine (10 mg a.m. & 10 mg p.m.); Daily Pain Scores. Morning, afternoon and evening pain scores for each day over the fourth week of memantine.

The average daily pain score for the fourth week were relatively the lowest of the whole study, i.e., five out of seven days the patient had an average pain score of only 5.7 (Figure 63).
Opioid dosage (mg) decreased further in that the patient needed to take only two 4 mg hydromorphone every day except for Easter Sunday due to lack of rest time (Figure 64).
4.1.2.5.2. Hydromorphone Dosage

Even with a decreased hydromorphone dose, pain scores continued to decrease.

Bowel movements stayed consistent during week four of memantine (Figure 65).
4.1.2.5.3. Bowel Movements

**Figure 65: Week Four of Memantine (10 mg a.m. & 10 mg p.m.); Daily Bowel Movements.** Daily bowel movements for each day of week four.

She stated that the only side effect was constipation, but bowel movements decreased by a factor of only 0.1 per day per week. (Figure 66).
4.1.2.5.4. Overview through Week Four of Memantine

**Figure 66. Average Pain Scores, Average Opioid Dosage (mg) and Bowel Movements per Week**

Average weekly pain scores, average opioid dosage (mg) and bowel movements for each week of the study. Arrow indicates when memantine was first introduced.

4.1.2.6. In-depth Overview of Study Subject F-01-R:

When compiling all data from the six weeks of the study trends are easier to observe. The average morning pain scores per week actually increased as the memantine dosage increased except for the last week when it was the lowest of the entire study (Figure 67).
4.1.2.6.1. Pain Scores

**Average Morning Pain Scores Per Week**

![Average Morning Pain Scores Per Week](image)

**Figure 67. Average Morning Pain Score Per Week.** Average weekly morning pain scores for each week of the study. Arrow indicates when memantine was first introduced.

Average afternoon pain scores decreased as memantine dosage was increased; they moved from an average of 6.9 during the pre-memantine phase to 6.1 (Figure 68).
Figure 68. Average Afternoon Pain Score Per Week. Average weekly afternoon pain scores for each week of the study. Arrow indicates when memantine was first introduced.

The largest reduction in pain score was the average evening result; it decreased from 8.1 to 6.6 (Figure 69).

Figure 69. Average Evening Pain Score Per Week. Average weekly evening pain scores for each week of the study. Arrow indicates when memantine was first introduced.
Overall average pain scores per week decreased from week to week as memantine dosage was raised (Figure 70).

Figure 70. Average Pain Score Per Week. Average weekly pain scores for each week of the study. Arrow indicates when memantine was first introduced.

The patient was at an average pain score of 6.9 during the pre-memantine phase but dropped to 5.9 after the fourth week of memantine. Although this is only a decrease in pain score by a factor of 1, the patient was taking less of her opioid. Opioid dosage (mg) over the six weeks decreased from an average of 12 mg to an average of 8.6 mg (Figure 71).
4.1.2.6.2. Hydromorphone Dosage

**Average Opioid Dosage (mg) Per Week**

![Graph showing average opioid dosage per week](image)

**Figure 71. Average Opioid Dosage (mg) per Day per Week.** Average weekly opioid dosage (mg) per day for each week of the study. Arrow indicates when memantine was first introduced.

The number of bowel movements did not show an increase over the six weeks of the study (Figure 72).
4.1.2.6.3. Bowel Movements

**Figure 72. Bowel Movements per Week.** Average bowel movements per day for each week of the study. Arrow indicates when memantine was first introduced.
Chapter 5

DISCUSSION

This pilot study demonstrated trends of positive effectiveness of memantine although there were only a limited number of patients. While patients can have different etiologies of pain, opioids work by targeting the μ-receptor, a sub-class of opioid receptor that is anti-nociceptive, thus making patients taking this medication comparable. The type of opioid medication used by each patient was different, however, the similarities between oxy/acet and hydromorphone made them suitable medications for this study. They mainly work on the μ1 and μ2 receptors. The former, when activated, is responsible for supraspinal analgesia whereas activation of the latter produces spinal analgesia, respiratory depression and constipation [10]. Memantine reduces glutamate activity at the NMDA receptor, and therefore has been shown to reduce pain. One mechanism of pain transmission involves glutamate activating the NMDA receptor, causing an influx of calcium ions into the post-synaptic neuron, making it more sensitive and more easily depolarized; adding memantine reduces calcium flow from excess glutamate, reducing the pain signal.

Oxycodone and hydromorphone are prescription opioids. Oxycodone is the main ingredient in Percocet® along with acetaminophen; brand names for hydromorphone are Dilaudid® and Exalgo®. Oxycodone and hydromorphone have similar properties; both can be administered in tablet form or available as a liquid. They are ideal for patients that have been taking opioids for an extended period of time and can benefit from a higher, controlled dose due to the fact that both are also available in extended-release forms.
However hydromorphone is stronger than oxycodone and are often prescribed for more severe pain that stems from surgery, broken bones, and cancer [21].

Dosage requirements for these drugs depend on a few factors. Elements that control the dosages are whether the drugs are in tablet form or liquid form, due to the liquid form having a faster absorption rate, type of pain, source of pain, and if the patient is in need of immediate-release or extended-release. If tolerance develops, both oxycodone and hydromorphone strength can be increased. Since cross-tolerance is incomplete among opioids, a common practice for physicians is to switch the type of opioid the patient is taking to extended-release if they have been on that drug for a long time with increasing dosages [21].

Side effects for each drug are similar due to similar shared properties. However, since hydromorphone is a more potent drug, side effects experienced when taking this drug can be more severe. The most common severe side effects for both of these drugs are shallow or light breathing, constipation (more severe with extended-release hydromorphone), drowsiness, dizziness and nausea. Less common severe side effects include respiratory depression, seizures, hallucinations and ataxia. Side effects that are relatively exclusive to hydromorphone when compared to oxycodone are heart palpitations, respiratory complications and skin rashes. It is recommended to avoid driving while taking these drugs due to the fact that both reduce judgment and physical skills. Withdrawal symptoms are also very likely if one was to suddenly stop taking the medication after a long-term use; they include gastrointestinal complications, cramping, nausea, depression and agitation. It is recommended to taper off the medication slowly. On the other end of the spectrum, both drugs can lead to overdose if too much is taken. A
child can have a fatal overdose on just one extended-release hydromorphone tablet due to high potency [21].

Hydromorphone has a black box warning on the label. This means that research has proven it can have serious and even life-threatening side effects. Respiratory depression causes the most concern. In addition, hydromorphone can cause hypotension. Oxycodone and hydromorphone can enhance the depressant effects of alcohol; both can also cause gastrointestinal complications such as nausea, vomiting, constipation, loss of appetite.

Potential side effects of memantine (Namenda®) with an incidence greater than 5% are confusion (6%), dizziness (7%) and headache (6%) [4]. In placebo-controlled trials in which dementia patients received doses of memantine up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the memantine group as in the placebo group, i.e. <1% [4].
Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Namenda and at a Higher Frequency than Placebo-treated Patients. [4]

<table>
<thead>
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<th>Body System</th>
<th>Placebo (N = 922) %</th>
<th>Namenda (N = 940) %</th>
</tr>
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<td></td>
</tr>
<tr>
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<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular System</td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Central and Peripheral Nervous System</td>
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<td></td>
</tr>
<tr>
<td>Dizziness</td>
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<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
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<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
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<tr>
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<td>3</td>
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<tr>
<td>Psychiatric Disorders</td>
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<td></td>
</tr>
<tr>
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<td>6</td>
</tr>
<tr>
<td>Somnolence</td>
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<td>3</td>
</tr>
<tr>
<td>Hallucination</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory System</td>
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<td>4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

5.1. Study Patient M-01-B

The first nursing home patient to complete this study was a 79 year-old male, taking oxy/acet for a pressure ulcer, phantom pain and PEG-tube discomfort. There were some small reductions in all measurements without the addition of memantine; this may have been to an expectation (mindset) that analgesia was going to occur as a result of being in the study [3]. Therefore, it was difficult to determine how much it contributed to
reducing parameters of this patient. However, some trends were observed over the remaining four weeks when memantine was administered.

Evaluation of daily morning, afternoon and evening pain scores for the first week of memantine (5 mg a.m.), showed that the former was lower after taking 5 mg of memantine in the morning. There was an anomaly; it occurred on the Friday of the first week of memantine (*) (Figure 13). The patient was taken to the hospital Thursday night because his PEG tube came out and it had to be replaced immediately. Due to the pain in his feet, it is hard for this patient to walk and he relies on a wheel chair to get around. He spent over six hours waiting in the hospital to be treated. The tape that the physicians used pulled his skin causing a rash and increased irritation and pain. The patient did not take an oxy/acet at the hospital because he did not want to stay there over-night; he just endured the pain. This likely caused pain scores to become higher on Friday when he returned to the nursing home.

Two noticeable differences were Saturday and Sunday of the third week of memantine, where pain scores were slightly elevated (Figure 23). This may have been due to the fact that weekend nurses are different than those on staff during the week; the former group may not know the patient as well. Since this group is changing weekend by weekend, they have less experience with the patient and did not recognize his situation at a deeper, meaningful clinical level. This may have led to the patient to not get his medication as quickly, resulting in increased pain.

Bowel movements increased during the final week of memantine. This may be attributed to the fact that his diet mainly consists of pureed food due to his PEG tube and
on Friday of that week he ate a piece of meatloaf by mouth that he received from another patient; his gastrointestinal tract may have not been able to handle it (Figure 32).

This patient decided not to continue memantine medication after the study was completed, due to the fact that he did not notice a difference in his way of life. However, with data collected from this patient, it was evident that his pain score decreased dramatically over the six-week study. Opioid dosage also decreased but may be attributed to anomalies that occurred during the study. Bowel movements fluctuated and did not show a certain trend.

5.2. Study Patient F-01-R

The second patient that completed this study was a female office-out patient who is 69 years old, taking hydromorphone for joint pain and altered gait.

The Sunday of the second week of the pre-memantine phase there was increase in pain score likely due to the patient not being able to rest because she was busy with friends and family (Figure 42). There was an increase in opioid dosage from week one of the pre-memantine phase to the second week due to a missed dose in the first week. However, instead of doubling up the dosage later, or taking the missed dosage too close to the second dose, the patient decided to refrain from taking the first one, resulting in a lower average for the first week (Figure 44).
This patient described significant improvement during this first week of memantine and stated that she “felt great”. She now wanted to participate in activities more of the time instead of always wanting to lay down to rest. F-01-R stated her pain was less in the evening (Figure 47), with less fatigue, more clear-headedness, more strength in her lower extremity, being able to sit up and stand faster after being seated for a while, less hip pain, and having a more positive attitude. She also recorded taking 25 mg less meclizine during this week (prescribed for her dizziness) and stated that no other drug has made her feel this great after taking it.

Sunday of the second week of memantine was another busy day for the patient where she was unable to rest as much as usual. This likely caused her pain scores to be slightly increased for that day (Figure 52). The patient started to decrease the amount of opioid she was taking this week and was able to take one 4 mg hydromorphone less on Thursday, Friday and Saturday (Figure 54). Although, there was not a decrease in average pain score, the patient experienced no increase in pain when taking less opioid along with memantine. At the end of the second week she described some dizziness and nausea, but attributed those symptoms to the re-occurring neck pain, concluding that they are nothing new and thus unrelated to memantine. This patient also noted that she still felt as if memantine was giving her a clearer head and the ability to feel pain differently such that she was able to isolate the exact location of the pain, instead of her whole body being in pain.

F-01-R described the third week of memantine as her best at that point in the study, and was amazed at how well she was feeling. All doses of gabapentin, meclizine and hydromorphone had decreased. Gabapentin was reduced from 600 mg, four times a
day to 300 mg three times per day, meclizine from 50 mg to 25 mg, and hydromorphone from 12 mg per day to 8 mg per day. Monday was the worst day with a pain score of 9 recorded at each point (Figure 58). The patient attributed this to the weather and the fused vertebrae in her neck. However, after taking the first 10 mg dose of memantine and waking up the next day, the patient felt like she had a “make-over”, every part of her body felt great. There was a decrease in pain score throughout the week, along with a decrease in hydromorphone dose (Figure 59). However, even with a decrease in hydromorphone, the patient described an increase in constipation which indicates that she may be part of the 5% of patients that experience constipation while using memantine. However, her bowel movements stayed constant at two per week during memantine treatment which is only one lower than the pre-memantine phase baseline of three bowel movements per week (Figure 61). This patient also reported no nausea or dizziness this week and felt as though she wanted to get more involved in daily activities due to her increase in well-being. Normally, F-01-R goes to bed early due to being in pain from the day, but this week she stayed out at a concert until 10 o’clock p.m. and was still alert. She even felt well enough to wake up early and make it to morning Mass, whereas she would usually wait to go to evening Mass.

Sunday of the fourth week of memantine there was an increase in pain score likely due to it being a holiday event and the patient was not able to rest as much as usual (Figure 62).

Pain score decreased slightly but was accompanied by a larger decrease in opioid dosage. This showed that memantine had a definitive effect on the pain the patient was experiencing. She also decided to continue with memantine after the study due to how
well this medication made her feel. A follow-up on this patient revealed that she is continuing to take only 8 mg of hydromorphone a day and her level of pain has stabilized to slightly lower than before the study. She claims memantine is “working better and better each day”.
Chapter 6

CONCLUSIONS

Adding memantine as an adjunct to daily opioid use in a chronic non-malignant pain condition reduced overall pain scores in two patients, whereas a decrease in opioid dosage and a slight reduction in bowel movements occurred only in one. It was the intention to observe differences between males and females but since only one of each gender was studied in the time-frame allotted for this study and the opioids were different, it was not possible to evaluate any distinction. However, this pilot study allowed insight to using memantine as an adjunct to treat chronic non-malignant pain patients who take an opioid daily.
Chapter 7

FUTURE DIRECTIONS

With the number of setbacks occurring at the beginning of this study, going forward some aspects will need to be changed. Future work will require a more in-depth review of the nursing homes to ensure that they have an adequate number of qualified staff to handle patients that are involved in a clinical study, allowing for more accurate data to be collected. In order to obtain a larger sample size, researchers could expand the type of opioid medication the patients are using, instead of limiting the study to only two types of opioids and expanding the amount of nursing home facilities or number of medical offices with out-patients. This may increase the prospective patient size and more patients may then be able to be recruited. With a larger patient sample size, comparing how memantine could affect both males and females may become possible.

Other data that would be interesting to obtain from this study in the future would be to try to observe if there is a certain amount of opioid dosage reduction in which it would increase gastric motility, and also to try to observe any differences over a larger age range. One thing to ask future test subjects would be to record any over-the-counter medications they are using and identify if they cause additional gastrointestinal problems. Researchers could then report if the complications from those medications are low or not a factor.
TITLE OF STUDY
Adding memantine as an adjunct to opioid therapy in adult patients presenting with pain of two months or longer: pilot study

TITLE OF STUDY IN LAY TERMS
Adding memantine to help treat pain in adults (18 years of age or older) taking oxycodone or an oxycodone/acetaminophen combination (for example, Percocet), for their pain which they have had for two months or longer

Principal Investigator
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Philadelphia, PA 19131
215-871-6859

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Department: Geriatric Medicine
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PURPOSE

The purpose of this research is to find out if giving you memantine every day for 28 days in a row can help reduce your pain, decrease the amount of the oxycodone or an oxycodone/acetaminophen combination you are now taking, and reduce side effects (like constipation) from your current pain medication. Previous research has shown that memantine has been helpful in relieving pain.

You are being asked to be a volunteer in this research study because you use opioid pain medication (oxycodone, or an oxycodone/acetaminophen combination [for example, Percocet]) every day.

You cannot be in this study if you are:
- 17 years of age or younger
- not taking oxycodone, an oxycodone/acetaminophen combination every day
- pregnant or plan to be in the next 8 weeks, or breastfeeding
- taking an antipsychotic drug
- taking a drug for Alzheimer’s Disease
- have been taking a drug for depression for less than 8 weeks

You also cannot be in this study if you have:
- Kidney disease
- Liver disease

If you have questions about this research, you can call Dr. Finkelstein at 215-871-6371. If you have any questions or problems during the study, you can ask Dr. Finkelstein who will be available during the entire study. If you want to know more about Dr. Finkelstein’s background, or the rights of research subjects, you can call the PCOM Research Compliance Specialist at (215) 871-6782.

DESCRIPTION OF THE PROCEDURES

If you decide to be in this study, you will be asked to fill out the Pain and Medication Diary every day for two weeks before starting to take memantine. Then you will be asked to take memantine, a medicine usually used to treat Alzheimer’s Disease, every day for 28 days in a row, in addition to your opioid pain medication. This daily activity will take about 6 minutes each time.

This means that you fill out the diary every day for 42 days during the total of 6 weeks you are in the study. As mentioned, it will take about 6 minutes to fill out the diary every day for a total of 4 hours during the 6 weeks you are in the study.

There will be 7 visits for the 43 days that you will be in the study.
Appendix A: Informed Consent Page

The total time for all 6 of your weekly visits is about 1½ hours. The total time for completing all of your diaries during 6 weeks is about 4 hours. Therefore, the total time you will spend in visits and completing all 6 diaries is about 5½ hours of your time. You will be given a weekly guide of this plan you are to follow.

There are two parts of this study.

I. PART ONE begins with your first office visit to Dr. Finkelstein at his office in Suite 533, Rowland Hall, 4190 City Avenue, Philadelphia, PA 19131.

Start of Week 1:
The study doctor or his staff will write down:
- how much of your opioid pain medicine you are taking every day
- how much pain you are having every day

They will also collect some information about you, or obtain it from your medical records (like your age, sex, your medical conditions, and other medicines you are currently taking.)

You will be given the Week 1 Pain and Medication Diary; you have to write in it every day. If you miss completing the Diary for two or more days you cannot continue to be in the study.

Start of Week 2:
You will come to the office for a brief visit. Bring your Week 1 Pain and Medication Diary, which the study doctor will collect. You will be given your Week 2 Pain and Medication Diary; you have to write in it every day. If you miss completing the Diary for two or more days you cannot continue to be in the study.

II. PART TWO begins the day after Part One ends. You will take doses of memantine for 28 days in a row (four weeks). You will also continue to take your opioid medication as you need. If you miss taking any study drug pills, you cannot continue to be in the study. If you miss completing the Diary for two or more days, you cannot continue to be in the study. In addition, you MUST attend your appointment as scheduled at the start of each Visit Week so that you do not miss taking any study drug pills.

The next part of the plan will be:

Start of Week 3:
You will come to the office for a brief visit so the staff can learn how you are feeling. Bring your Week 2 Pain and Medication Diary. The study doctor will collect your Week 2 diary. If you are female and are able to bear children, you will have a urine pregnancy test. If it is positive, you will be withdrawn from the study.

You will be given the Week 3 Pain and Medication Diary; you have to write in it every day. You will be given one bottle containing 7 pills of 5 mg memantine. You will take one pill of 5 mg every morning.
**Start of Week 4:**
You will come to the office for a brief visit so the staff can learn how you are feeling. Bring your Week 3 Pain and Medication Diary, which the study doctor will collect. Bring your pill bottle with you to this visit. Note in your diary if you have missed taking any pills or if you have lost any pills.

You will be given the Week 4 Pain and Medication Diary; you have to write in it every day. You will be given one bottle containing 14 pills of 5 mg memantine. You will take one pill of 5 mg every morning and one pill of 5 mg every night.

**Start of Week 5:**
You will come to the office for a brief visit so the staff can learn how you are feeling. Bring your Week 4 Pain and Medication Diary, which the study doctor will collect. Bring your pill bottle with you to this visit. Note in your diary if you have missed taking any pills or if you have lost any pills.

You will be given the Week 5 Pain and Medication Diary; you have to write in it every day. You will be given one bottle containing 14 pills of 5 mg memantine and one bottle containing 7 pills of 5 mg memantine. You will take one pill of 10 mg every morning and one pill of 5 mg every night.

**Start of Week 6:**
You will come to the office for a brief visit so the staff can learn how you are feeling. Bring your Week 5 Pain and Medication Diary, which the study doctor will collect. Bring your pill bottles with you to this visit. Note in your diary if you have missed taking any pills or if you have lost any pills.

You will be given one bottle containing 14 pills of 10 mg memantine. You will take one pill of 10 mg every morning and one pill of 10 mg every night.

**Visit 7, End of study visit**
You will come to the office for a brief visit so the staff can learn how you are feeling. Bring your Week 6 Pain and Medication Diary, which the study doctor will collect. Bring your pill bottles with you to this visit. Note in your diary if you have missed taking any pills or if you have lost any pills.

Your participation in this study will end at this visit.

**POTENTIAL BENEFITS**
You may be able to reduce the number of pain pills that you take every day and you may have less constipation. You may not benefit from being in this study. Other people in the future may benefit from what the researchers learn from the study.
RISKS AND DISCOMFORTS
The most frequent effects are feeling dizzy, being confused, having a headache, or being constipated. These effects are mild and may be due to memantine.

If you become pregnant, you must stop taking memantine immediately because there may be an unknown risk to your unborn child -- and you then must also call Dr. Finkelstein so he can take you out of this study.

ALTERNATIVES
The other choice is to not be in this study. If you decide not to be in this study, you will continue to receive the same care from Dr. Finkelstein without penalty or loss of benefits to which you are otherwise entitled and without any effect on your medical care.

PAYMENT
There is no payment for being in this study. PCOM will pay for the cost of the memantine.

CONFIDENTIALITY AND HIPAA
Your health information is protected under the Health Information Portability and Accountability Act (HIPAA). There is a risk of loss of confidentiality from your participation in this study. We will do our best to prevent the disclosure of your identity.

Records of your participation in this study will be held as confidential except if disclosure is required by law or as described in this informed consent document.

You will be given a study ID number. Your study documents will use this ID number, not your name or other identifying information. All information and records relating to your participation will be kept in a locked file or on a password-protected computer in the investigator’s office. The master list that links your name and other identifying information to your study ID will be kept in a separate file on the investigator’s password-protected computer. This linking list will be destroyed at the end of the study.

Information that will be collected: demographic data including your age, sex, medical history, medications you are taking, Daily Diary information. Your information will be used and/or shared with others in order to do the research, to study the results, and to see if the research was done right.

By signing this form you are giving permission to the following individuals and organization(s) to use and disclose your information for this research study:

- the PCOM Coordinating Center staff, the study doctor, and study staff at this site
- members of the PCOM Institutional Review Board (which is a group of people who are concerned with protecting the safety and rights of people who volunteer to participate as investigational research subjects)
- the U.S. Office of Human Research Protections
- the U.S. Food and Drug Administration.
If the results of this study are published, your name or other identifying information will not be included.

You may change your mind at any time. If you wish to withdraw, please tell the study doctor.

If you take back your permission, the research team may still keep and use any information about you that they already have. But they can’t obtain more health information about you for this research. If you take back your permission, you will need to leave the research study. Changing your mind will not affect any other treatment, payment, healthcare, enrollment in health plans or eligibility for benefits.

**REASONS YOU MAY BE TAKEN OUT OF THE STUDY WITHOUT YOUR CONSENT**

If health conditions occur that would make staying in the study possibly dangerous to you, or if other conditions occur that would damage you or your health, the study doctor may take you out of this study.

If you do not take the study drug as instructed, writing in the Diary, or keeping your visits with Dr. Finkelstein as scheduled, you will be taken out of the study. If you experience side effects that lead you to stop taking the study drug, you will be taken out of the study.

The entire study may be stopped if dangerous risks or side effects occur in other study participants.

The organization sponsoring this study, the Philadelphia College of Osteopathic Medicine (PCOM), may decide to terminate this study.

**NEW FINDINGS**

If any new information develops that may affect your willingness to stay in this study, you will be told about it.

**INJURY**

If you are injured as a result of this research study, you will be provided with immediate necessary care.

However, you will NOT be reimbursed for care or receive other payment. PCOM will not be responsible for any of your bills, including any routine care under this program or reimbursement for any side effects that may occur as a result of this program.

If you believe that you have suffered injury or illness in the course of this research, you should notify the PCOM Research Compliance Specialist at (215) 871-6782 and Dr. Finkelstein. A review by a committee will be arranged to determine if the injury or illness is a result of your being in this research.

You should also contact the PCOM Research Compliance Specialist at (215) 871-6782 if you believe that you have not been told enough about the risks, benefits, or other options, or that you are being pressured to participate in this study against your wishes.
VOLUNTARY PARTICIPATION

You voluntarily consent to be in this study with the understanding of the known possible effects or hazards that might occur during this study. Side effects may occur that are not yet known.

You may refuse to be in this study or you may leave this study at any time. If you drop out of this study, there will be no penalty or loss of benefits to which you are otherwise entitled.

SIGNATURE

I have had adequate time to read this form and I understand its contents. I have been given a copy for my personal records.

I agree to be in this research study.

Signature of Subject: ________________________________

Date: __/__/____  Time: ___________ AM/PM

Signature of Study Doctor ________________________________

Date: __/__/____  Time: ___________ AM/PM

Philadelphia College of Osteopathic Medicine

Institutional Review Board

Approval Date: 8/10/14
Expiration Date: 8/13/17
APPENDIX B: PAIN DIARY WEEK 1 (FRONT)

RESEARCH STUDY TO REDUCE OPIOID PAIN MEDICATION USE IN PATIENTS BY ADDING MEMANTINE

PAIN AND MEDICATION DIARY - WEEK ONE

If you have any questions or concerns about this research, please call Dr___________________ at ____________________.

Before you turn to the next page, please answer these questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN? ____No ____Yes. If ‘yes’ please write down what happened.

DID YOU HAVE BAD EFFECTS FROM THE DRUGS DURING THIS WEEK?
IF YOU DID, PLEASE WRITE DOWN WHAT THEY WERE.
**APPENDIX B: PAIN DIARY WEEK 1 (BACK)**

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<th>Week 1</th>
<th>How many oxycodone or oxycodone / acetaminophen tablets did you take today?</th>
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**PAIN SCORE**

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After you complete this page, please bring it with you to your weekly visit at the doctor's office.

*Thank you for joining our important study.*
APPENDIX B: PAIN DIARY WEEK 2 (FRONT)

RESEARCH STUDY TO REDUCE OPIOID PAIN MEDICATION USE IN PATIENTS BY ADDING MEMANTINE

PAIN AND MEDICATION DIARY - WEEK Two

If you have any questions or concerns about this research, please call Dr___________________ at___________________.

Before you turn to the next page, please answer these questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN? ____No ____Yes. If ‘yes’ please write down what happened.

DID YOU HAVE BAD EFFECTS FROM THE DRUGS DURING THIS WEEK?
IF YOU DID, PLEASE WRITE DOWN WHAT THEY WERE.
## APPENDIX B: PAIN DIARY WEEK 2 (BACK)

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<th>Week 2</th>
<th>How many oxycodone or oxycodone / acetaminophen tablets did you take today?</th>
<th>What was your pain score this morning?</th>
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I HAVE NO PAIN

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APPENDIX B: PAIN DIARY WEEK 3 (FRONT)
RESEARCH STUDY TO REDUCE OPIOID PAIN MEDICATION USE IN PATIENTS BY ADDING MEMANTINE

PAIN AND MEDICATION DIARY- WEEK THREE

If you have any questions or concerns about this research, please call Dr___________________ at ____________.

Before you turn to the next page, please answer these questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN?  ____No  ____Yes.  If ‘Yes’ please write down what happened.

DID YOU HAVE BAD EFFECTS FROM THE DRUGS DURING THIS WEEK?  IF YOU DID, PLEASE WRITE DOWN WHAT THEY WERE.
### APPENDIX B: PAIN DIARY WEEK 3 (BACK)

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<th>Week 3</th>
<th>How many oxycodone or oxycodone / acetaminophen tablets did you take today?</th>
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APPENDIX B: PAIN DIARY WEEK 4 (FRONT)
RESEARCH STUDY TO REDUCE OPIOID PAIN MEDICATION USE IN PATIENTS BY ADDING MEMANTINE

PAIN AND MEDICATION DIARY- WEEK FOUR

If you have any questions or concerns about this research, please call Dr___________________ at __________________.

Before you turn to the next page, please answer these questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN?  ____No  ____Yes.  IF ‘YES’ PLEASE WRITE DOWN WHAT HAPPENED.

DID YOU HAVE BAD EFFECTS FROM THE DRUGS DURING THIS WEEK? IF YOU DID, PLEASE WRITE DOWN WHAT THEY WERE.
**Appendix B: Pain Diary Week 4 (Back)**

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<th>Week 4</th>
<th>How many oxycodone or oxycodone / acetaminophen tablets did you take today?</th>
<th>What was your pain score this morning?</th>
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APPENDIX B: PAIN DIARY WEEK 5 (FRONT)

RESEARCH STUDY TO REDUCE OPIOID PAIN MEDICATION USE IN PATIENTS BY ADDING MEMANTINE

PAIN AND MEDICATION DIARY - WEEK FIVE

If you have any questions or concerns about this research, please call Dr___________________ at ________________.

Before you turn to the next page, please answer these questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN?  ____NO  ____YES.  IF ‘YES’ PLEASE WRITE DOWN WHAT HAPPENED.

DID YOU HAVE BAD EFFECTS FROM THE DRUGS DURING THIS WEEK?
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**APPENDIX B: PAIN DIARY WEEK 5 (BACK)**

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<th>Week 5</th>
<th>How many oxycodone or oxycodone / acetaminophen tablets did you take today?</th>
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If you have any questions or concerns about this research, please call Dr___________________ at ______________.

Before you turn to the next page, please answer these questions:

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DID YOU HAVE BAD EFFECTS FROM THE DRUGS DURING THIS WEEK?
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# Appendix B: Pain Diary Week 6 (Back)

<table>
<thead>
<tr>
<th>Week 1</th>
<th>How many oxycodone or oxycodone/acetaminophen tablets did you take today?</th>
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<tr>
<td>Day 3:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pain Score**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>

I HAVE NO PAIN

THIS IS THE WORST PAIN I EVER HAD

Date completed ___________________________

After you complete this page, please bring it with you to your weekly visit at the doctor's office.

*Thank you for joining our important study.*
### Mini-Mental State Examination (MMSE)

**Patient’s Name:** ________________________________  **Date:** __________

*Instructions: Score one point for each correct response within each question or activity.*

<table>
<thead>
<tr>
<th>Maximum Score</th>
<th>Patient’s Score</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>“What is the year? Season? Date? Day? Month?”</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>“Where are we now? State? County? Town/city? Hospital? Floor?”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient’s response is used for scoring. The examiner repeats them until patient learns all of them, if possible.</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>“I would like you to count backward from 100 by sevens.” (93, 86, 79, 72, 65, …) Alternative: “Spell WORLD backwards.” (D-L-R-O-W)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“Earlier I told you the names of three things. Can you tell me what those were?”</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Repeat the phrase: ‘No ifs, ands, or buts.’”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“Take the paper in your right hand, fold it in half, and put it on the floor.” (The examiner gives the patient a piece of blank paper.)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Please read this and do what it says.” (Written instruction is “Close your eyes.”)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Make up and write a sentence about anything.” (This sentence must contain a noun and a verb.)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Please copy this picture.” (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>TOTAL</td>
</tr>
</tbody>
</table>

![Diagram of a five-pointed star](image-url)
APPENDIX C: MINI MENTAL STATE EXAMINATION QUESTIONNAIRE

**Interpretation of the MMSE:**

<table>
<thead>
<tr>
<th>Method</th>
<th>Score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Cutoff</td>
<td>&lt;24</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;21</td>
<td>Increased odds of dementia</td>
</tr>
<tr>
<td></td>
<td>&gt;25</td>
<td>Decreased odds of dementia</td>
</tr>
<tr>
<td>Education</td>
<td>21</td>
<td>Abnormal for 8th grade education</td>
</tr>
<tr>
<td></td>
<td>&lt;23</td>
<td>Abnormal for high school education</td>
</tr>
<tr>
<td></td>
<td>&lt;24</td>
<td>Abnormal for college education</td>
</tr>
<tr>
<td>Severity</td>
<td>24-30</td>
<td>No cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>18-23</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>0-17</td>
<td>Severe cognitive impairment</td>
</tr>
</tbody>
</table>

**Interpretation of MMSE Scores:**

<table>
<thead>
<tr>
<th>Score</th>
<th>Degree of Impairment</th>
<th>Formal Psychometric Assessment</th>
<th>Day-to-Day Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-30</td>
<td>Questionably significant</td>
<td>If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.</td>
<td>May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.</td>
</tr>
<tr>
<td>20-25</td>
<td>Mild</td>
<td>Formal assessment may be helpful to better determine pattern and extent of deficits.</td>
<td>Significant effect. May require some supervision, support and assistance.</td>
</tr>
<tr>
<td>10-20</td>
<td>Moderate</td>
<td>Formal assessment may be helpful if there are specific clinical indications.</td>
<td>Clear impairment. May require 24-hour supervision.</td>
</tr>
<tr>
<td>0-10</td>
<td>Severe</td>
<td>Patient not likely to be testable.</td>
<td>Marked impairment. Likely to require 24-hour supervision and assistance with ADL.</td>
</tr>
</tbody>
</table>

**Source:**
# APPENDIX D: PATIENT STUDY SCHEDULE

<table>
<thead>
<tr>
<th>PART 1</th>
<th>Week 1</th>
<th>None</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 2</td>
<td>None</td>
<td>Daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PART 2</th>
<th>Week 3</th>
<th>5 mg Memantine AM - - - - - - - - - -</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 4</td>
<td>5 mg Memantine AM + 5 mg memantine PM</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>Week 5</td>
<td>10 mg Memantine AM + 5 mg memantine PM</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>Week 6</td>
<td>10 mg Memantine AM + 10 mg memantine PM</td>
<td>Daily</td>
</tr>
</tbody>
</table>
REFERENCES

1. American Society of Addiction Medicine, Opioid Addiction 2016 Facts and Figures. 201


5. Galluzzi K, Goldstein F.J. Memantine as an adjunct to opioid therapy in geriatric patients: Pilot study 2010; Personal communication


