Clinical Research Challenges: Insight from a Pilot Study at an Academic Healthcare Center

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CLINICAL RESEARCH CHALLENGES: INSIGHT FROM A PILOT STUDY
AT AN ACADEMIC HEALTHCARE CENTER

A Thesis in Biomedical Sciences by Gretchen Elizabeth Maurer
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Submitted in Partial Fulfillment of the Requirements for the Degree of
Master of Science
December, 2013
We the undersigned duly appointed committee have read and examined this manuscript and certify it is adequate in scope and quality as a thesis for this master’s degree. We approve the content of the thesis to be submitted for processing and acceptance.

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ABSTRACT

An investigational clinical research study was conducted at an academic healthcare center evaluating memantine as an adjunct to opioid therapy for treatment of chronic low back pain. The N-Methyl-D-Aspartate (NMDA) receptor is located in pain signaling neuronal synapses of the central nervous system. The receptor binds the excitatory neurotransmitter glutamate in addition to NMDA, to increase the magnitude of the perception of pain. Memantine (Namenda®) is a highly tolerated NMDA receptor antagonist which is currently prescribed in the treatment of Alzheimer’s disease. The purpose of the non-randomized pilot study without placebo was to evaluate the use of adding memantine as an adjunctive pain medication to the regimen of patients who use an oxycodone/acetaminophen combination daily for treatment of chronic low back pain (LBP). The effect of Memantine was evaluated using diaries where patients record on a daily basis the amount of oxycodone/acetaminophen used, pain scores, and number of bowel movements. Data was to be collected for six weeks with a two-week preliminary phase, followed by a four-week treatment phase, and then analyzed. The objective is to evaluate, on a preliminary basis, whether patients benefit from addition of memantine to their daily oxycodone/acetaminophen treatment by increased analgesia, a reduction of oxycodone/acetaminophen used, and less constipation. Consequently, limitations to the process of clinical research in an academic healthcare center are evaluated as a result of reduced protected time for researchers and lack of patient participation.
TABLE OF CONTENTS

ABSTRACT.................................................................................................................. iii
LIST OF FIGURES........................................................................................................ v
ACKNOWLEDGEMENTS............................................................................................... vi
I. INTRODUCTION ........................................................................................................... 1
II. LITERATURE REVIEW ............................................................................................. 7
III. METHODS ................................................................................................................ 12
IV. RESULTS .................................................................................................................. 17
V. DISCUSSION .............................................................................................................. 25
VI. CONCLUSION .......................................................................................................... 34
APPENDIX A: Consent Form ....................................................................................... 36
APPENDIX B: Patient Diary, Week One ..................................................................... 42
APPENDIX C: Patient Diary, Week Two ..................................................................... 44
APPENDIX D: Patient Diary, Week Three ................................................................. 46
APPENDIX E: Patient Diary, Week Four ..................................................................... 48
APPENDIX F: Patient Diary, Week Five ..................................................................... 50
APPENDIX G: Patient Diary, Week Six ..................................................................... 52
APPENDIX H: Patient Study Schedule ....................................................................... 54
APPENDIX I: Short Form Geriatric Depression Scale ............................................... 55
APPENDIX J: Mini Mental State Examination ........................................................... 57
REFERENCES .............................................................................................................. 59
LIST OF FIGURES

Figure 1. Recruitment flow chart..............................................................17
Figure 2. Table of averaged daily data per week for Patient One.........................20
Figure 3. Graph of averaged daily number of acetaminophen/oxycodone combination medication for Patient One.................................................................21
Figure 4. Graph of average daily number of acetaminophen/oxycodone combination medication on a weekly basis for Patient One.................................................................21
Figure 5. Average daily pain scores based off visual analogue scale for Patient One.....22
Figure 6. Average daily pain scores based off visual analogue scale on a weekly basis for Patient One.................................................................23
Figure 7. Daily number of bowel movements for Patient One.............................24
Figure 8. Clinical research interaction between AHC and institution.........................25
Figure 9. Including community engagement in the clinical research process............32
ACKNOWLEDGEMENTS

My sincerest gratitude to my thesis advisor and mentor, Dr. Frederick J. Goldstein, for his support and encouragement throughout this project. Through this experience, I have strengthened my commitment to clinical research endeavors and aspire to answer questions to increase quality of life for others in my career.

Thank you to my committee members, Dr. David Kuo and Dr. Katherine Galluzzi, for their support and guidance in the process. In addition, I would like to thank Dr. Larry Finkelstein for his contribution to the project. I look forward to following in all of your footsteps of clinical and academic integrity at PCOM.

Many thanks to Danielle LaSalle and Dr. Jane Dumsha for their continued insight and gracious assistance with this project. Also, thanks to Suzanne Walker-Garland and staff at the PCOM Roxborough Healthcare Center for their valuable time and help.

This journey of life off the beaten path is possible through the love and support of my family and friends who inspire compassion and benevolence in my life and remind me to be considerate and ever mindful of the needs of others. I thank my father for his unconditional support, nurturing care, and everlasting love throughout my life. I thank my mother for her teachings to discover happiness and appreciation in the love and beauty of this world. I am thankful for the time with all my grandparents, whom have taught me that wisdom comes with patience and perseverance in this life. Always, I am greatly appreciative of inspiration from my wonderfully eccentric, diverse, and interesting family. On the whole, I am most grateful to experience the love and kindness of my husband Jason. I am honored to have you as my love and my light, by my side, throughout all the adventures this life has to offer in all the years to come.
INTRODUCTION

Chronic pain has debilitating effects for patients across the United States, causing decreased quality of life, as well as increased disability and health-care related costs. Estimates of the prevalence of chronic pain reveals that 20% to 60% of the population are affected; the disparity in estimates is due to varied techniques employed to identify such patients, as well as substantial diversity among study populations and reporting formats (Clark, 2002). Chronic low back pain (LBP) is defined as persistent or fluctuating pain in and around the lumbar region that has persisted for a period over six months; 60% of patients with LBP seek a family physician for treatment (Last & Hulbert, 2009). In 2009, LBP was determined to be the second leading cause of disability in US adults, with total costs estimated to be between $100 billion to $200 billion annually, resulting from lost productivity and wages, as well as increasing healthcare related costs (Freburger et al., 2009). In many regards, it would prove most difficult to measure accurately the prevalence of nonspecific chronic LBP because of the ambiguity of causality in the population and varied diagnoses. Most studies focus on pharmacological or physiological treatments used by the population to manage the pain and subsequent outcomes. Most commonly, chronic LBP is treated via self-administration, where individuals monitor their own perception of pain and take prescribed medications to provide pain relief in the outpatient setting.

Within the past two decades, the proliferation and increased use of long-term opioid therapies and the associated epidemic of opioid abuse, misuse, and overdose have caused great concern leading to a more cautious approach to chronic pain management
and better monitoring of opioid use for patients with chronic pain (Korff, Kolodny, Deyo, & Chou, 2011). In addition, there remains a broad range of socio-economic effects of chronic LBP that may be evaluated through psychological, financial, and community considerations.

The persistence of pain influences domains such as depression by increasing fear of amplified pain and reduced confidence in the ability to perform daily activities (Slade, Molloy, & Keating, 2012). As a result, chronic LBP is associated with reduced productivity, availability to work, and increased financial stress leading to an elevated economic burden. Chronic LBP may affect an entire family and community; for example, an affected individual may not be able to pick up a child, complete household chores, or partake in other responsibilities associated with daily life. Currently, there is a broad range of interventions for management of chronic lower back pain, with a diversity of specialists approaching treatment through varied pharmacological and physical practices.

Approximately 90% of chronic LBP patients in primary care cannot attribute the pain to a specific cause, such as an infection, tumor, or fracture, making treatment for the disabling non-specific pain a difficult process (Lee, 2010). As a result of telephone surveys of a representative population of 4437 households in 1992 and 5357 households in 2006 in North Carolina, the prevalence of chronic LBP increased over a 14 year period from 3.9% to 10.2%; these data indicate that approximately 80% of the population is expected to suffer from LBP at some point in their lives, with 95% of these patients recovering within a few months from onset, and the remaining 5% continuing to suffer with chronic LBP (Freburger et al., 2009). As a consequence of the increasing prevalence and incidence of chronic LBP, healthcare professionals seek to incorporate evidence-
based medicine to improve identification of beneficial treatments and translate research findings to reduce pain and suffering associated with chronic LBP.

From a pharmacological standpoint, the first-line therapy for patients with chronic LBP is acetaminophen due to a high safety profile. Non-steroidal anti-inflammatory drugs (NSAIDs) are also commonly used due to their similar pain relief; however they frequently induce side-effects of a gastrointestinal or renovascular nature (Last & Hulbert, 2009). In a recent systematic review of 12 publications regarding the efficacy of pharmacological treatments for chronic LBP, NSAIDs such as aspirin, ibuprofen, and naproxen are recommended as the first-line of therapy due to their comparable effectiveness and lack of the serious side effects that are associated with opioids (White, Arnold, Norvell, Ecker, & Fehlings, 2011).

Opioid analgesics continue to be used extensively for analgesia in patients with mild to chronic pain. Opiates are naturally occurring alkaloids from the resin of the opium poppy, *Papaver somniferum*, and include morphine and codeine. Semi-synthetic opioids include oxymorphone, oxycodone and methadone. Regardless of the structure of such molecules, all opioids display the same basic pharmacological properties by binding to opioid receptors to reduce the perception of pain (Yaksh T.L., 2011).

Oxycodone, similar to morphine, produces analogous side effects involving nausea, vomiting, sedation, pruritus, and others, which are usually tolerated within few days of initial use; however, oxycodone-induced constipation (as occurs with all opioids) persists and usually requires additional medication, such as laxatives or stool softeners, for relief (Astolfi, 2011). This opioid is a useful oral analgesic for treatment of moderate
to severe, acute or persistent pain, and is usually combined with acetaminophen or ibuprofen, in immediate-release or controlled-released formulations (Baumann TJ, 2011). Recently, concerns of associated acetaminophen-induced hepatotoxicity warrant investigations to reduce the use of pain medications that combine oxycodone and acetaminophen, such as Percocet©. In addition, the rise of abuse among opiates such as oxycodone necessitates further research into adjunctive medications which may reduce the amount of pain medication required for analgesia.

In addition to the efficacy of prescribing analgesics, many patients are also treated pharmacologically for the psychological impacts of chronic LBP. The comorbidity of depression and chronic LBP is high; patients who are treated for the pain and depression together have better outcomes than those treated for pain alone (Lee, 2010). Patients coping with chronic LBP may develop behaviors to avoid pain or develop increased pain-related stress to cope with poor treatment outcomes and increasing disability. Antidepressants have been found to be no more effective than placebo for treating the pain associated with chronic LBP; however, they may be indicated to treat psychosocial outcomes such as anxiety and/or depression associated with a chronic pain state (White et al., 2011). In most cases, the complexity in which chronic LBP affects each individual is different; physicians must consider complementary treatments for the diversity of comorbid diseases or disorders that can present in patients.

There are many non-pharmacological complementary or alternative interventions for patients suffering from chronic LBP ranging from hands-on treatments such as osteopathic manipulative treatment (OMT), chiropractic adjustments, massage, and acupuncture, to practices such as exercise therapy, behavior therapy, yoga, and
meditation that prove beneficial in the management of pain. In most cases, multidisciplinary rehabilitation including a physician and at least one additional intervention reduces pain and alleviates disability to provide benefits lasting for years; patients frequently use non-pharmacologic treatments with or without consulting their physician (Last & Hulbert, 2009). Many of these methods aim to relieve the pain and stress of chronic LBP and increase self-awareness in the patient; each patient must be thoroughly evaluated to determine what type of complementary treatment may result in a favorable outcome.

Many investigations have been made into adjunctive medications that may reduce the side effects and tolerance produced by long-term opioid use. The demand for adjunctive medications in pain therapy is increasing, promoting investigations for innovative approaches to management of this condition. Therapeutic benefits could include reduction of opiate use, severity of dependence, and associated side effects. Identification of receptors in the pain signaling pathway has led to use of this information to increase efficacy of pain therapies. Some investigations of the role of NMDA-receptor antagonists in neuropathic pain have been promising; however there is limited research on the effects of these medications on patients who self-manage their chronic pain with opioids, as well as some conflicting evidence on benefits of added medication (Gustin et al., 2010; Weich et al., 2004).

The most commonly prescribed opioids are combined with acetaminophen for increased analgesia in pain management (Baumann TJ, 2011). Recently, increased concerns from the FDA and the healthcare community warranted investigation of hepatotoxicity associated with acetaminophen. A review of studies involving
opioid/acetaminophen combinations found that no conclusions could be made in regards to role of acetaminophen in acute liver failure; recommendations were made for further investigation since the impact of removal of these medications would substantially impact many patients in the management of pain (Michna et al., 2010).

Currently, the escalation of opioid misuse and abuse affirms investigations into adjunctive medications that can reduce the amount of opioids used for analgesia. This warrants the question: is there another class of drug that can provide increased analgesia for chronic pain and reduce the amount of opioid combination pain medications a patient must take to relieve their pain? In addition, will this drug further benefit the patient by reducing the intolerable side effects of opioid therapies?

In this study, the benefits of adding memantine (Namenda©), an N-Methyl-D-Aspartate (NMDA) receptor antagonist, to a daily regimen of oxycodone/acetaminophen (Percocet©) will be evaluated in patients with chronic LBP. The NMDA receptor is located in the pain signaling neuronal synapses of the central nervous system that bind the excitatory neurotransmitter glutamate in addition to NMDA, and is believed to increase the magnitude of the perception of pain. Therefore, by blocking this receptor, the perception of pain may be reduced, and less medication would be needed for analgesia. Memantine is a highly tolerated NMDA receptor antagonist with neuro-protective qualities and is currently prescribed in the treatment of Alzheimer’s disease. The proposed benefits of memantine as adjunctive pain medication are being investigated by determining if (1) patients take less opioid pain medication for daily analgesia, and (2) whether there is a reduction in opioid induced side effects such as constipation.
In the central nervous system, glutamate is an abundant excitatory neurotransmitter, occupying upwards of 90% of synapses; the N-Methyl-D-Aspartate (NMDA) receptor is an ionotropic receptor that binds glutamate in addition to the selective agonist NMDA in transmitter-gated and voltage-gated properties (Nolte, 2009). The NMDA receptors are found in addition to traditional glutamate receptors on the postsynaptic membrane; as well as allowing passage of Na$^+$ and K$^+$, the NMDA receptor channel allows passage of Ca$^{2+}$, a property associated with long-term potentiation (LTP) (Nolte, 2009). The activation of NMDA receptors is therefore necessary to induce LTP, which is the prolonged increase (hours to days) in the magnitude of post-synaptic response to presynaptic stimulus (Molinoff, 2011). In the pain processing neurons of the dorsal horn, both µ-opioid receptors and NMDA-receptors are present at the origins of the ascending pathways, and the association of these receptors has proposed investigations into the role of NMDA-receptor antagonists, and their role in reducing opioid-induced hyperalgesia and tolerance (Price DD, 2000). Hyperalgesia results from the combined release of substance P and glutamate in the nociceptive afferents in the spinal cord, causing increased activation of the NMDA receptors, and this wind-up progressively increases activity in pain transmission (Barrett KE, 2012). Together, the increased responsiveness of LTP in the CNS leading to hyperalgesia and allodynia, and the increased synaptic plasticity of wind-up, are proposed to be part of the diversity of mechanisms which lead to central sensitization and chronic pain (Chizh, 2007).
In vivo microdialysis and immunohistochemical analyses have been performed to investigate chronic tendinosis of the patellar tendon (Jumper’s knee) of five patients against a control group in 2001 (Alfredson, Forsgren, Thorsen, & Lorentzon, 2001). The study results revealed the increased presence of glutamate and NMDA receptors in patients who suffer with chronic pain without signs of inflammation, a fact which warrants future investigations regarding the role of NMDA receptors in peripheral pain pathways (Alfredson et al., 2001). Accumulating evidence signifies the role of the NMDA-receptor in the peripheral and central processing of nociceptive and neuropathic pain and how the activation of the NMDA receptor may increase the perception of pain.

Recent studies involving the role of N-Methyl-D-Aspartate (NMDA) receptor antagonists have produced interesting evidence for the role of blocking this receptor and subsequent attenuation of pain. Ketamine, a well-known NMDA receptor antagonist, has been used clinically for many years in the treatment of pain in the inpatient setting; however, ketamine produces many side effects. The parent analogue of ketamine is phencyclidine (PCP); both of these drugs are referred to as “dissociative anesthetics,” causing altered states of consciousness, hallucinations, and other central effects which limit the clinical use of ketamine (Chizh, 2007). The many limitations of ketamine include the fact that a steady state equilibrium blockade of NMDA receptors is difficult to achieve with a half-life of 15 minutes, and that the only routes of administration are intravenously or intramuscularly (Gilling, Jatzke, Hechenberger, & Parsons, 2009).

Memantine (Namenda©) is the only antiglutamatergic NMDA-antagonist currently on the market and is approved in the treatment of Alzheimer disease. Memantine retains 100% bioavailability, as it is not biotransformed by the liver, and has
been well tolerated by patients in clinical trials, with the most common adverse effects being constipation, confusion, dizziness, headache, hallucinations, coughing, and hypertension (Slattum PW, 2011). In addition, memantine displays a long half-life, ranging from 60 to 80 hours (Slattum PW, 2011). Although memantine and ketamine display similar IC$_{50}$ (half maximal inhibitory concentration) values and kinetics, the difference in the related side effects may be the result of ‘partial trapping’ of memantine versus ‘full trapping’ of ketamine. Nearly all the ketamine molecules remain trapped in the channel of the NMDA receptor following removal of the agonist, whereas some of the memantine molecules unbind and become untrapped; this may be due to memantine binding to a superficial site, as well as to a deep site in the channel (Kotermanski S, 2009). For this reason, memantine has been proposed to be of significance for clinical use due to oral efficacy, onset twice as fast, long half-life, and lack of associated side effects compared to ketamine (Gilling et al., 2009).

Studies investigating the benefits of NMDA receptor antagonists in combination with opioid therapies have revealed mixed results; some have used animal models in attempts to determine effects while other human studies are limited in their small sample size, lack of control group, and no placebo or blindedness to yield valid conclusions. With strength of research design, a randomized double-blind crossover trial of eight patients with chronic phantom limb pain (PLP) in 2004 concluded that the addition of memantine over four weeks (first week, 10mg/d; second week, 20mg/d; third and fourth weeks, 30mg/d) was ineffective for treatment of chronic PLP (Wiech et al., 2004). Other smaller open study clinical investigations evaluated the addition of memantine for a variety of pain conditions and reported contrasting results. Case reports of two
amputation patients with chronic PLP who received high dose opioids revealed a substantial decrease in pain intensity shortly after the addition of memantine to their daily regimens (Hackworth, Tokarz, Fowler, Wallace, & Stedje-Larsen, 2008). An unpublished pilot investigational study on three geriatric patients taking a daily regimen of oxycodone/acetaminophen combination for non-specific chronic pain revealed that the addition of memantine allowed patients to reduce the amount of pain medications needed for analgesia (Galluzzi & Goldstein 2009). For the most part, human studies involving memantine for analgesia have been limited in sample size and scale to present inferential results.

In addition to clinical studies evaluating analgesia, investigations have been made in regard to neuropathic mechanisms associated with NMDA receptor antagonists and the perception of pain. A double-blind randomized placebo-controlled study was performed using fMRI with memantine combined with morphine for patients with complex regional pain syndrome (CRPS) to revealed reduction in somatosensory-discriminative aspects of pain in cS1 and S2, which is presumed to be associated with the NMDA receptors, in addition to decreased activation in the anterior cingulate cortex (ACC), which also occurs with opioid therapy (Gustin et al., 2010). In like manner, an open study involving six patients with complex regional pain syndrome (CRPS) evaluated the effects of adding memantine following an established two week baseline; following eight weeks of memantine treatment, fMRI results concluded that the treatment normalized cortical reorganization associated with neuropathic pain, and that patients had significantly reduced perceived pain intensity at both eight weeks and six months following the addition of memantine (Sinis et al., 2007). Another investigation highlighted the
relationship of NMDA receptor antagonists and the development of opiate dependence in rodents; this study indicated that memantine was effective in reducing morphine-induced withdrawal hyperalgesia (Harris, Rothwell, & Gewirtz, 2008). Therefore, NMDA receptor antagonists may be useful to prevent or treat opioid dependence in humans, in addition to reducing the amount of pain medication to provide analgesia.
METHODS

Sample

The 6-week pilot study was designed to study 10 patients who take an oxycodone/acetaminophen combination (e.g., Percocet©) daily for chronic low back pain. Potential study subjects were recruited by their primary care physicians at an academic community healthcare center. These subjects were 18 years of age or older, displayed chronic lower back pain for a minimum of two months, and were taking stable doses of an oxycodone/acetaminophen combination for a minimum of six months.

Exclusion criteria were patients who were pregnant or planned to become pregnant, had a life expectancy less than 6 months, displayed moderately severe Alzheimer disease, moderate dementia, depression, and renal or hepatic disease. Furthermore, patients were excluded if they were currently taking NMDA-receptor antagonists, tricyclic antidepressants, antipsychotics, antiparkinson, or other possibly contradictory medications to avoid interactions with the memantine that may cause adverse effects to the subject or potentially influence the findings of the study.

During this study, participants were required to fill out daily diaries in which they wrote down their daily intake of an oxycodone/acetaminophen combination, a numeric score (0-10) of their pain perception in the morning, afternoon, and evening, and their number of bowel movements each day. Therefore, subject compliance was necessary. In addition, general weekly questions on the diaries involved causes for additional pain, added daily medications, as well as improvements in bowel movements. Participants were also required to come to the healthcare center at four sequential appointments on
specific days over the 6-week experimental period during the study, so they had to have transportation and the physical ability to maintain the visits.

Research Design

Approval was granted through the Institutional Review Board (IRB) at Philadelphia College of Osteopathic Medicine (PCOM). Before commencement of this study, certification of all participating researchers was achieved through the on-line Collaborative Institutional Training Initiative (CITI). Courses completed included the Biomedical Investigators Basic Refresher, Health Information Privacy and Security (HIPS) for Clinical Investigators, and Good Clinical Practice. Certification was mandatory for investigators performing clinical research involving human subjects to educate researchers on proper clinical practice and protection of the subjects’ private health information.

Following IRB approval, patient study packets were prepared for initial recruitment which included a copy of the dated and approved informed consent document, the first two weeks of diaries, and a study schedule. Following initial identification of potential participants, the primary care physician recruited and discussed the study with the patients, gave a copy of the informed consent to the patient for review, and set up a pre-study visit. At the following visit, participants who signed the informed consent were screened for dementia and cognitive impairment by completing a Mini-mental state examination (MMSE), as well as tested for the presence of depression with a short-form Geriatric depression scale (GDS). If required, a pregnancy test would also be administered at this pre-study visit. After obtaining a signed informed consent and
passing inclusion tests, the subject took home and completed the diaries for Weeks 1 and 2. The first two weeks acted as a control where each subject established a baseline prior to the treatment phase. After 14 days, the subject returned to the clinic with the completed diaries, and was given a sample pack of memantine (Namenda©) and diaries for Weeks 3 and 4. At this point, the patient was instructed to begin 5 mg in the morning for Week 3, and then 5 mg in the morning and 5 mg in the evening for Week 4. After 28 days, the subject returned to the clinic with the completed diaries, was given diaries for Weeks 5 and 6 and instruction to continue with the sample pack, taking 10 mg in the morning and 5 mg in the evening for Week 5, and 10 mg in the morning and 10 mg in the evening for Week 6. During each week of the study, subjects were contacted by phone to ensure compliance with the diaries and medication.

Instrumentation/Statistical Analysis

Study subjects were required to fill out diaries where they recorded a numeric score of their pain perception in the morning, afternoon, and evening, the total number of Percocet© taken each day, as well as the number of bowel movements each day. In addition, there are general weekly questions on the diary sheets that involve causes for additional pain, added daily medications, as well as improvements in bowel movements. Pain intensity was evaluated on a visual analogue scale (VAS) from 0-10 and recorded by patients in daily diaries throughout a six week period; first two weeks (Week 1 and Week 2) served as a control to establish baseline, and following four weeks were the treatment phase with increasing titration of memantine. After the first two weeks, the initial treatment with medication began in Week 3 and continued through Week 6 with the
following doses: Week 3, 5mg a.m.; Week 4, 5mg a.m. and 5mg p.m.; Week 5, 10mg a.m. and 5mg p.m.; Week 6, 10mg a.m. and 10mg p.m.

In addition, study subjects indicated the number of bowel movements each day to determine if the addition of memantine also reduced opioid-induced constipation. The data collected was averaged by day for the baseline and treatment phase to be plotted in a time course of pain rating (VAS) over time (day).

Since this study failed to obtain the total of ten subjects, statistical analysis could only be performed on the one subject who completed the study. If the study would have been successful in obtaining ten patients, descriptive statistics for each individual participant was to include measures of central tendency in numerical and graphical summaries. The alternative hypothesis (Hₐ) states that the addition of memantine will reduce the perception of pain corresponding to a reduction in the amount of Percocet® used. The null hypothesis (H₀) states that the addition of memantine will have no effect on the perception of pain or amount of Percocet® used. Individual subjects pre- and post-treatment were to be tested by a dependent Student’s t-test to evaluate whether treatment with memantine correlated with reduced VAS pain perception and oxycodone/acetaminophen use from control Weeks 1 and 2, to treatment Weeks 3 through 6, as well as if the number of bowel movements improved. Collectively, the data was to be evaluated through analysis of variance (ANOVA) to evaluate the effects of the added medication with VAS pain intensity, amount of oxycodone/acetaminophen used, and number of bowel movements. The hypotheses would have been tested at a level of significance less than or equal to 0.05.
Validity

As a pilot study, research design and sample size was to be limited to ten patients due to availability of patient base, inclusion/exclusion criteria, and ability for investigators to commit sufficient time to research endeavors.

In addition, reliance on the patients to self-report daily with diary entries at home leads to concerns of adherence as well as experimental mortality, with multiple testing effects as a result of three daily observations for a period of six weeks. Experimenter interaction effects must be considered due to the limited number of researchers and participants. This study was designed to investigate and contribute to understanding of an opioid adjunctive treatment and its effect on individual participants rather than generalizing the sample results to a population.

Ethical Considerations

Throughout this study, investigators and researchers involved maintained adherence to measures to protect the private healthcare information of all patients and study subjects. Only after recruitment from the primary care physicians did the researcher have contact with the patients. At all times, the researcher remained objective in interactions with patients involved in the study to reduce bias and the potential to influence results.
RESULTS

Recruitment of patients encompassed a period of six months; six patients were identified as potential study subjects based off inclusion criteria. Patient One was the only subject to progress through the control phase and subsequently complete the treatment phase (Figure 1).

Two of the six recruited patients were removed from the study by the researcher due to failure to meet inclusion criteria. Patient Two failed the GDS. To be included, participants must have had a score ≤ 5; this potential subject scored 7. When discussing the GDS score, Patient Two also stated some concerns about recent heart problems (atrial fibrillation) which caused additional stress. Although the participant was initially willing to commit to the study, Patient Two agreed with removal from the study and thought that...
it was not the right time to commit to such an endeavor. Patient Three was prescribed gabapentin (Neurontin®) by another physician which listed as an exclusion criteria on the IRB application. Although Patient Three was enthusiastic about participating, this participant was removed from the study.

Three patients encountered complications with participation and were not included in the study. Patient Four began the two-week control phase after passing the inclusion tests, but was physically and emotionally unable to continue. Recent complications from a fall and family problems at home caused this individual visible distress; this participant was crying during the appointment and felt overwhelmed with the commitment to the study and was consequently removed. Patient Five was recruited and signed the informed consent but could not participate due to a work schedule which would not allow the required appointments. Patient Six began the two-week control phase but was also unable to maintain regular appointment and did not show for a scheduled and rescheduled appointment on the same day. In addition, Patient Six stated concerns about additional daily medication added to the daily regimen which may have influenced motivation to participate since this individual was taking multiple prescriptions. This concern was discussed at the initial visit; Patient Six inspected the sample pack of Namenda® and determined that the additional medication would not be an issue since the dosage gradually increased through preset amounts.

Another factor contributing to the limited recruitment of patients was the promotion of the Principal Investigator from Medical Director of the Healthcare Center where the study took place, to another position which limited the investigator’s time in the healthcare center to recruit patients as needed. Although another primary care
physician/investigator continued to recruit when the Principal Investigator was not available, schedule constraints and limited protected time prevented recruitment of eligible participants.

Patient One, a 70 year old female with history of chronic low back pain was recruited by the Investigator/Primary care physician during a normally scheduled appointment based on inclusion criteria and daily use of acetaminophen/oxydode combination (Percocet® 5mg/325mg). This patient was enthusiastic to participate in the study due to her high admiration of her primary care physician. The patient returned to the office to review and sign the informed consent, and to take the short-form GDS and MMSE administered by the researcher. During this appointment, the patient was instructed on how to complete the diaries including the Visual Analog Scale (VAS) for pain intensity, number of oxycodone/acetaminophen combination medication used daily, number of bowel movements, and general weekly questions. Following this visit, Patient One was contacted by phone on Day 1 to begin the first two control weeks of the study by recording daily entries in the diaries. Patient One was contacted on Day 8 to ensure compliance, and then returned to the office with diaries of Weeks 1 & 2 to meet with the researcher on Day 15. At the appointment, the diaries were reviewed and the subject was given a sample pack for Namenda® and diaries for Weeks 3 & 4. Phone calls were made to address concerns and check compliance on Days 16 and 22. The patient was unable to attend the scheduled appointment on Day 29; the researcher picked up completed diaries and dropped off diaries for Weeks 5 & 6. Again, phone calls on Days 35 & 42 were made to address concerns and check compliance. The diaries for Weeks 5 & 6 were collected.
by the researcher at the subject’s home due to inability to get to the scheduled appointment at the academic healthcare center.

Based upon the collected diary data for Patient One (Figure 2), a small reduction of the daily averaged use of acetaminophen/oxycodone combination presents throughout the six weeks of the study (Figure 3 and Figure 4).

<table>
<thead>
<tr>
<th>Week</th>
<th>Average Daily Percocet® Used</th>
<th>Average Daily VAS Pain Intensity</th>
<th>Average Number of Bowel Movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.00</td>
<td>8.14</td>
<td>1.29</td>
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<td>4.43</td>
<td>8.05</td>
<td>0.86</td>
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<td>8.38</td>
<td>0.86</td>
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</tr>
<tr>
<td>6</td>
<td>4.71</td>
<td>8.57</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Figure 2. Averaged daily data per week including oxycodone/acetaminophen combination used (Percocet® 5mg/325mg), daily VAS pain scores, and number of bowel movements for Patient One.
Figure 3. Averaged daily number of acetaminophen/oxycodone combination medication for Patient One.

Figure 4. Average daily number of acetaminophen/oxycodone combination medication on a weekly basis for Patient One.
Concurrently, there was a slight increase of daily averaged VAS pain scores from Week 3 to Week 6 which appears to be in conflict with the reduction of daily acetaminophen/oxycodeone combination intake. Moreover, Patient One recorded high VAS pain scores (9 or 10) every morning and evening throughout the six weeks of control and treatment phases of the study (Figure 5 and Figure 6).

Figure 5. Average daily pain scores based off visual analogue scale (VAS) from 0-10.
Figure 6. Average daily pain scores based off visual analogue scale (VAS) on a weekly basis for Patient One.

This data suggests that Patient One was not using the opioid medication properly for analgesia, or Patient One may have had a fear of addiction as a result of opioid use. As a result, no conclusion can be drawn about the reduction of acetaminophen/oxycodone combination use during these six weeks due to the corresponding increase of daily pain intensity, which may have resulted from the decrease in pain medication rather than the use of Namenda©. Also, it is noted that the patient did not take the evening dosage of Namenda© on Day 34 (5 mg) and Day 40 (10 mg), which may have disrupted the steady state of the medication. Over the span of six weeks, there was no change in the daily number of bowel movements, thus no evidence in a reduction of constipation (Figure 7).
Figure 7. Daily number of bowel movements for Patient One.
DISCUSSION

Clinical research is vital for advancing progress in both the practice of medicine and education of healthcare professionals. To understand the methodology and impact of human research, participation in the process of research design and application is important. Gathering valid data from study patients can then be more efficiently translated from the scientific community to contribute to advances in medical practice.

An academic healthcare center (AHC) is a potential outpatient setting where clinical research can be promoted. Clinical research remains an interactive and dynamic process between an AHC and academic institution (Figure 8).

Figure 8. Clinical research interaction between AHC and institution.
Physicians in these AHCs see many patients and maintain direct contact with them. It is a collective community of healthcare professionals and patients which includes educating the next generation of physicians.

Difficulties can arise when trying to implement research in this setting, especially in smaller AHCs. Part of this is due to the lack ‘protected time’ for academic healthcare practitioners to participate in such endeavors apart from patient care and instruction of medical students, interns and residents. Therefore, research design must be appropriate for the demanding environment of an AHC; it needs to remain in harmony with community goals to inspire confidence and participation amongst the community.

Recent experience conducting our small pilot investigational an AHC revealed a major obstacle to be patient compliance. Also, as a result of having no protected time for our physicians, recruitment of patients was negatively impacted.

Our target patients were those with chronic low back pain who used daily an acetaminophen/oxycodeone combination medication for analgesia on as-needed (prn) basis. Six patients were initially recruited but only one completed the study in the allotted time-frame for the investigation.

The challenge was to develop a study that correlated with community needs, i.e., those patients presenting with chronic low back pain who desired improved analgesia, and reduced opioid use. This patient population demographic seemed to be appropriate for the targeted AHC. Some participants were enthusiastic about contributing to a research project being conducted by their primary care physicians; they wanted to share their time and health history to help others. Those who were less enthusiastic usually had
other priorities or conflicts in life; some had demanding schedules which prevented compliance with the required office visits every two weeks while others did not pass the MMSE or GDS for inclusion. Two patients who completed all inclusion tests did complete the first two weeks (control period) of diaries and confirmed compliance when contacted by phone; however, they did not show up for their respective scheduled appointments at the AHC.

From this experience, one recommendation would be to establish a group where patients can participate together in a supportive and educational setting. Since the patients involved with our study were receptive and appreciated sharing their stories of living with chronic pain, this approach may enhance recruitment. It would be beneficial for discussion and questions about the study, as well as provide a supportive environment of the shared experience. Through this experience, participants would benefit in collective motivation and guidance through a team-based approach to stay informed and maintain compliance. Group education can establish a dialogue in regards to clinical research studies involving a community; it would allow opportunity to a) explain informed consent, b) learn the schedule of data collection and office visits, c) address concerns of complications such as time and effort required to participate, and d) increase participant confidence in the process. In addition, by reaching out and discussing issues with the community, the AHC can educate about medical issues, research endeavors and answer questions about these issues. Patients may be more willing to participate in a clinical research study if it connects with their lives and community.

Clinical research is hindered by many obstacles that present in an AHC where the environment is committed to providing health profession students with the experience of
the hands-on demands of direct patient care, as well as the exposure to day-to-day operations of medical practice and administration. On the whole, lack of trained clinical researchers in practice results from previous limitations to participate in research in these clinical settings, especially at smaller, less-funded educational institutions.

Throughout the spectrum of healthcare professions, including medicine, nursing, dentistry, and pharmacy, the reduced amount of qualified clinical researchers results from discouraging factors such as lengthy training, lack of mentorship, and reduced potential salary compensations (Murillo, Reece, Snyderman, & Sung, 2006). Evidence-based medicine (EBM) remains a collaborative initiative to increase quality and efficacy in healthcare by sharing research insights of clinical research and decreasing the time for results to cause change in practice; by increasing protected time for experienced mentors to guide and train, investments can be made to increase the training experience at the AHC, and contribute to the quality of future clinical researchers (Murillo et al., 2006). Only through experience of research design and practice do future researchers gain hands-on application of knowledge; the AHC remains an excellent environment for investing in the training required to meet the demands in qualified researchers for future of clinical research endeavors.

As a result of limited time for research investigations, as well as reduced availability of study participants and lack of funding, the burden of daily clinical and ethical responsibilities of physician investigators and researchers in an AHC can restrict implementation of quality research in the academic setting. A study published in 2001 presents results from 478 surveys of department chairs and research administrators from medical schools in the United States and revealed that 93% regarded “pressure of faculty
to see patients” while simultaneously conducting clinical research as a moderate to large problem in academic investigational research; further, 48% reflected that the state of clinical research is not “healthy or robust” at their respective institutions (Campbell, Weissman, Moy, & Blumenthal, 2001). In addition to clinical pressures, respondents stated that identified major threats to clinical research to include reduced funding, inability to recruit experienced researchers, and competition from contract research organizations (CROs) (Campbell et al., 2001). Overall, respondents regarded the quality of clinical research performed at their institutions to be inferior to nonclinical research and that there remains an “inadequate supply of trained clinical researchers” (Campbell et al., 2001).

The Clinical Research Rountable (CRR) of the Institute of Medicine was established in June 2000 as a multifaceted group of persons involved in clinical research who were responsible for addressing issues that affect the nation’s clinical research endeavors. In addition to identifying holistic challenges to clinical research such as inadequate funding, scarcity of experienced researchers, lack of public participation, and fragmented information systems, the CRR presented two major “translational blocks” that prevent the flow of information; first is the application of knowledge from the laboratory environment to human studies in the clinical setting, and second is the sequentially use of knowledge gained in the clinical environment to then be employed used in clinical practice (Sung et al., 2003). In 2004, the CRR proposed the establishment of the National Clinical Research Enterprise (NCRE) in 2004 in efforts to establish to provide a diverse public and private partnership in efforts to improve a national “outdated infrastructure” when it comes to regarding clinical research (Crowley et al.,
This initiative was proposed to be funded by 0.25% of the nation’s health care budget; the agenda would be to help to increase public education for understanding and participation in clinical research, provide training and assistance for researchers, improve technologies to share clinical research data, and fund clinical research efforts that support safety, efficiency, and validity (Crowley et al., 2004). Unfortunately, such proposed initiatives to create a system to address national clinical research concerns have not been realized; however, the AHC remains an essential setting to implement and advocate change.

Benefits of increased clinical research in the primary care setting would include increased time and engagement between physician and patient, encourage involvement and participation in care, and perhaps allow access to newer treatments that are experimental and would otherwise not be available.

Research design in practice must align with the daily operations of an AHC where both increased clinical hours of patient time and decreased protected time to engage in research activities restrict healthcare professionals from participating in research. In our study, difficulties in recruiting patients were a result of physicians needing to identify patients from memory or being reminded of those that may be able to participate when acetaminophen/oxycodone combination prescriptions were refilled. With the help of the office manager and front desk staff at the AHC, the patient charts for potential recruits in our study were flagged to provide an additional reminder to the physicians to recruit. Through the implementation of advanced electronic medical records, software could assist to help physicians to identify potential recruits, flag their charts, and track their progress with increased efficiency.
The need for a commitment by academic medicine to focus on integration of different approaches of community-engaged research must be made as a progressive measure to increase the quality of healthcare experience by students and practitioners alike by involving patients more with their treatment and engaging them to participate in research that affects their community by addressing local concerns (Michener et al., 2012). These researchers also stated that efforts must be made to a) educate the community about research endeavors, b) disseminate findings to the community, and c) to establish active involvement and participation from members of the community to promote clinical research in an AHC (Michener et al., 2012). Ultimately, the beneficiaries of clinical research are the participants and the public who receive care in a healthcare system. Initiatives to increase community education and involvement in the process will be at the foundation of the collaboration needed to continue pursuits of change. In our study, monetary compensation was a substantial motivation for participation amongst recruits. However, every recruit did share a psychological motivation though the sense of contribution. Attempts to increase community engagement have potential to cultivate community appreciation and increase likelihood of success in the clinical research process (Figure 9).
Figure 9. Including community engagement in the clinical research process.

In many respects, clinical research in an AHC has the potential to gather vast amounts of knowledge that will not only contribute to increased wellness amongst a community, but will transcend beyond to national healthcare initiatives. By integrating appropriate research into medical practice, the physicians and patients can work together to answer questions in hopes of healing and wellness. Limited availability of primary care practitioners restricts the progression of clinical research in the AHC and beyond.
Strategies must be in place to develop, implement, and support clinical research. Hopefully, with advances in electronic records and web-based information systems, research can become more streamlined; efforts of increased staff teamwork will maintain coordination and efficiency of research endeavors to integrate research into primary care. Most importantly, research designs that acknowledge limitations of previous studies will support the academic environment to promote research in an AHC. At the level of the AHC, active discussion and debate among primary investigators, research investigators, faculty, staff, and students is vital for identifying complications and finding solutions throughout progression of the study. In many respects, AHC staff can provide valuable insight in regards to potential study patients and their ability to comply as a result of interactions of management, scheduling, billing, and general questions. By establishing a dialogue from the beginning amongst this the cooperative group of individuals at an AHC, strategies for recruitment and planning will increase efficiency and success of clinical research initiatives.
CONCLUSION

This pilot study offered insight to the processes of developing a clinical research study and conducting a human investigation at an AHC. It highlighted the need for institutional designation of sufficient ‘protected time’ for physicians and investigators in order for them to perform research in this setting. Only with adequate ‘protected time’ can investigators thoroughly participate in the process of design, recruitment, and completion of pilot investigational studies such as ours. In addition, engagement of the AHC community, including physicians, students, staff, and the public they serve, is necessary to increase efforts for recruitment of study subjects. Participation for a clinical research study can also be increased through establishment of an educational dialogue.

Clinical research must not be neglected in an environment such as the AHC since this setting promotes education and experience for the next generation of clinical researchers. The vitality of this next generation is of great concern. Only through active research development and implementation can future clinical researchers gain understanding of how a research process works. In addition, there will be an opportunity to determine how clinical research can be more efficient and transferred to improve medical care.

Through exposure to clinical research, medical professionals will develop appreciation for the process; they will also obtain valuable training to enhance future endeavors in the progression of medicine. In this view, even failure to complete a research study offers guidance on how research design and practice can be improved, and identifies where further investments should be made.
This study contributed to the education and training of those clinical investigators involved and shed light on limitations of design and institutional support. This experience served to highlight the importance and value of protected time for clinical researchers, especially in the educational environment of the AHC. The future of clinical research depends on investments made to increase protected time, engagement of the AHC community, and exposure to research training amongst health professional students.
Appendix A: Consent Form: Page 1

INFORMED CONSENT FORM

TITLE OF STUDY

Namenda (memantine) as an Adjunct to Opioid Therapy in Adult Patients With Chronic Low Back Pain: Pilot Study

TITLE OF STUDY IN LAY TERMS

Adding Namenda To Help Treat Pain in Adult (18 years of age or older) Patients Taking Every Day an Oxycodone/Acetaminophen Combination (for example, Percocet) for Their Constant Low Back Pain

PURPOSE

The purpose of this research is to find out if giving you Namenda every day for 28 days in a row can help to reduce your pain, decrease the amount of the oxycodone/acetaminophen pain medication you are now taking, and reduce side effects (like constipation) of your current pain medication.

You are being asked to be in this research study because you are an adult patient (18 years of age or older) who uses oxycodone/acetaminophen (for example, Percocet) pain medicine every day. If you not an adult patient, and not taking an oxycodone/acetaminophen narcotic pain medicine every day, and if you are pregnant or you are using sodium bicarbonate or a drug like Diamox (acetazolamide) or any other drugs to treat depression, Parkinson’s Disease, serious mental illness, severe Alzheimer’s Disease, epilepsy, glaucoma, or nerve pain, you can not be in this study.

INVESTIGATOR(S)

Principal Investigator: David Kuo, D.O.

Philadelphia College of Osteopathic Medicine
Department: Family Medicine
Address: 4190 City Avenue
Philadelphia, PA 19131

Co-Investigator: Frederick J. Goldstein, Ph.D.
Institution: Philadelphia College of Osteopathic Medicine
Department: Neuroscience, Physiology and Pharmacology
Address: 4170 City Avenue
Philadelphia, PA 19131

09/18/12
Appendix A: Consent Form: Page 2

Phone: 215-483-3800 Phone: 215-871-6859

Responsible (Student) Investigator: Gretchen Maurer, BA, Biomedical Graduate Student, PCOM, 2014

The treatment you are being asked to volunteer for is part of a research project.

If you have questions about this research, you can call Dr. David Kuo at (215) 483-3800.

If you have any questions or problems during the study, you can ask Dr. Kuo, who will be available during the entire study. If you want to know more about Dr. Kuo’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 take Namenda, a medicine usually used to treat Alzheimer's disease every day for 28 days in a row. You will be asked to fill out the Pain and Medication Diary every day. This daily activity will take about 6 minutes each time.

There are two parts of this study.

I. PART ONE begins with your first office visit to Dr. Kuo at the PCOM Healthcare Center in Roxborough, PA. It is 2 weeks long. Dr. Kuo or his staff will write down:
   - how much of your narcotic pain medicine you are taking every day
   - how much pain you are having every day
   WEEK 1 and WEEK 2: you will be asked to fill out the Pain and Medication Diary every day.

End of Week 2: You will then be asked to come to the PCOM Healthcare Center in Roxborough, PA for a brief visit so the staff can learn how you are feeling. Please bring your Pain and Medication Diaries for Weeks 1 and 2 to this visit.

   Dr. Kuo or his staff will write down:
   - how much of your narcotic pain medicine you are taking every day
   - how much pain you are having every day

II. PART TWO begins the day after Part One ends. You will take a dose of Namenda for 28 days in a row (four weeks). The plan will be:

   - WEEK 3: take 5 mg in the morning for the first 7 days

09/16/12
Appendix A: Consent Form: Page 3

- WEEK 4: take 5 mg in the morning and 5 mg in the evening for the next 7 days

Weeks 3 and 4: fill out the Pain and Medication Diary every day

End of Week 4: You will then be asked to come to the PCOM Healthcare Center in Roxborough, PA for a brief visit so the staff can learn how you are feeling. Please bring your Pain and Medication Diaries for Weeks 3 and 4 to this visit.

Dr. Kuo or his staff will write down:
- how much of your narcotic medicine you are taking every day
- how much pain you are having every day

- WEEK 5: take 10 mg in the morning and 5 mg in the evening for another 7 days

- WEEK 6: take 10 mg in the morning and 10 mg in the evening for the last 7 days

Weeks 5 and 6: fill out the Pain and Medication Diary every day

End of Week 6: You will then be asked to come to the PCOM Healthcare Center in Roxborough, PA for a brief visit so the staff can learn how you are feeling. Please bring your Pain and Medication Diaries for Weeks 5 and 6 to this visit.

Dr. Kuo or his staff will write down:
- how much of your narcotic medicine you are taking every day
- how much pain you are having every day.

You will continue to receive the same care every day from Dr. Kuo and his staff.

You will be given a weekly guide of the plan you are to follow.

You will fill out the diary every day for 42 days during the total of 6 weeks you are in the study. 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 4 visit(s) over the course of 43 days. The total time for all 4 of your visits is about 1 ½ hours, and the time for completing all of your diaries over 6 weeks is about 4 hours. Therefore, the total time you will spend in visits and completing all 6 diaries is about 5 ½ hours of your time.
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, or having a headache. These effects are mild and are due to Namenda. If you become pregnant, you must stop taking Namenda immediately because there may be an unknown risk to your unborn child – and you then must also call Dr. Kuo or Dr. Finkelstein so they 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. Kuo, Dr. Finkelstein and their staff.

PAYMENT

You will be paid for being in this study. At the end of this study when all diaries have been completed, there will be a lottery. Each study subject will have one ticket so there will be a total of 10 tickets for the drawing. First prize is $150. Second prize is $130. Third prize is $110. Fourth prize is $100. Fifth prize is $90. Sixth prize is $80. Seventh prize is $70. Eighth prize is $60. Ninth prize is $55. Tenth prize is $50.

CONFIDENTIALITY

All information and records relating to your participation will be kept in a locked file. Only the researchers, members of the Institutional Review Board, and the U.S. Food and Drug Administration will be able to look at these records. If the results of this study are published, no names or other identifying information will be used.

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 researchers may take you out of this study.
In addition, the entire study may be stopped if dangerous risks or side effects occur in other people.

**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. 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 if you believe that you have not been told enough about the risks, benefits, or other options, or that you are being pressured to stay in this study against your wishes.

**VOLUNTARY PARTICIPATION**

09/16/12
Appendix A: Consent Form: Page 6

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

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 entitled.

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 Investigator or Designee ________________________________ (circle one)

Date: ___/___/______ Time: ________ AM/PM

09/16/12
A RESEARCH STUDY TO REDUCE PAIN IN PATIENTS HAVING LOW BACK PAIN [NAMENDA® MEMANTINE STUDY]

PAIN AND MEDICATION DIARY - WEEK ONE

YOU WILL GET A SEPARATE DIARY FOR EVERY WEEK

If you have any questions or concerns about this research, please call the Principal Investigator for this study, Dr. David Kuo, Director, PCOM Roxborough Healthcare Center

5830 HENRY AVE, PHILADELPHIA PA 19128
215-483-3800

At the end of this week, please answer the following questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN?
FOR EXAMPLE, DID YOU FALL DOWN?

PLEASE CHECK ONE: ___No ___Yes

IF YOU CHECKED ‘YES’, PLEASE WRITE DOWN WHAT HAPPENED.

Did you have any improvement in your bowel movements? ___YES ___NO
If you answered ‘YES’, did you have less constipation? ___YES ___NO
During this week, have you taken any additional medications, ___YES ___NO
(For example, over the counter and/or prescription)
If you checked ‘Yes’, please list __________________________

After you complete these pages, please bring them with you — in the envelope we gave you — to each of your visits to the PCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
Appendix B: Patient Diary: Week 1 (Back)

Patient Name: ____________________________

[Please print]

Telephone Number(s): Home: ___________ Cell/Work: ___________

Date you started to write your information on this form: ___________

<table>
<thead>
<tr>
<th>WEEK ONE</th>
<th>Namenda used today: Please check</th>
<th>How many tablets of Percocet did you use today?</th>
<th>How would you score your pain this morning?</th>
<th>How would you score your pain this afternoon?</th>
<th>How would you score your pain tonight?</th>
<th>How many bowel movements did you have today?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>None</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pain Scale

0 1 2 3 4 5 6 7 8 9 10
I have no pain

I have the worst possible pain

Date completed: __________________________

After you complete these pages, please bring them with you — in the envelope we gave you — to each of your visits to the PCOM Foxborough Healthcare Center.

Thank you for choosing to be in our study.
A RESEARCH STUDY TO REDUCE PAIN IN PATIENTS HAVING LOW BACK PAIN
[NAMENDA® {MEMANTINE} STUDY]

PAIN AND MEDICATION DIARY- WEEK TWO

YOU WILL GET A SEPARATE DIARY FOR EVERY WEEK

If you have any questions or concerns about this research, please call the Principal Investigator for this study, Dr. David Kuo, Director, PCOM Roxborough Healthcare Center  
5830 HENRY AVE, PHILADELPHIA PA 19128  
215-483-3800

At the end of this week, please answer the following questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN?  
FOR EXAMPLE, DID YOU FALL DOWN?

PLEASE CHECK ONE: ___No ___Yes

IF YOU CHECKED ‘YES’, PLEASE WRITE DOWN WHAT HAPPENED.

Did you have any improvement in your bowel movements? ___YES ___NO
If you answered ‘YES’, did you have less constipation? ___YES ___NO
During this week, have you taken any additional medications, ___YES ___NO
(For example, over the counter and/or prescription)
If you checked ‘Yes’, please list ________________________________

After you complete these pages, please bring them with you— in the envelope we gave you— to each of your visits to the PCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
Appendix C: Patient Diary: Week 2 (Back)

Patient Name:  

[Please print]  

Telephone Number(s):  Home:  Cell/Work:  

Date you started to write your information on this form:  

<table>
<thead>
<tr>
<th>WEEK TWO</th>
<th>Namenda used today: Please check</th>
<th>How many Percocet did you use today?</th>
<th>How would you score your pain this morning?</th>
<th>How would you score your pain this afternoon?</th>
<th>How would you score your pain tonight?</th>
<th>How many bowel movements did you have today?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>□ None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>□ None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>□ None</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>□ None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>□ None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>□ None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>□ None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pain Scale*

0  1  2  3  4  5  6  7  8  9  10

I have no pain  I have the worst possible pain

Date completed:  

*After you complete these pages, please bring them with you – in the envelope we gave you – to each of your visits to the PCOM Roxborough Healthcare Center.*  

*Thank you for choosing to be in our study.*
Appendix D: Patient Diary: Week 3 (Front)

A RESEARCH STUDY TO REDUCE PAIN IN
PATIENTS HAVING LOW BACK PAIN
[NAMENDA® {MEMANTINE} STUDY]

PAIN AND MEDICATION DIARY- WEEK THREE

YOU WILL GET A SEPARATE DIARY FOR EVERY WEEK

If you have any questions or concerns about this research,
please call the Principal Investigator for this study,
Dr. David Kuo, Director, PCOM Roxborough Healthcare
Center
5830 HENRY AVE, PHILADELPHIA PA 19128
215-483-3800

At the end of this week, please answer the following questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN?
FOR EXAMPLE, DID YOU FALL DOWN?

PLEASE CHECK ONE: ___No   ___Yes

IF YOU CHECKED “YES”, PLEASE WRITE DOWN WHAT HAPPENED.


Did you have any improvement in your bowel movements? ___YES   ___NO
If you answered ‘YES’, did you have less constipation? ___YES   ___NO
During this week, have you taken any additional medications, ___YES   ___NO
(For example, over the counter and/or prescription)
If you checked ‘Yes’, please list

After you complete these pages, please bring them with you — in the envelope we gave you — to each of
your visits to the PCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
Appendix D: Patient Diary: Week 3 (Back)

Patient Name: [Please print]

Telephone Number(s): Home: ___________________ Cell/Work: ___________________

Date you started to write your information on this form: __________________

<table>
<thead>
<tr>
<th>WEEK THREE</th>
<th>Namenda used today: Please check</th>
<th>How many tablets of Percocet did you use today?</th>
<th>How would you score your pain this morning?</th>
<th>How would you score your pain this afternoon?</th>
<th>How would you score your pain tonight?</th>
<th>How many bowel movements did you have today?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>[ ] 5mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>[ ] 5mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>[ ] 5mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>[ ] 5mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>[ ] 5mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>[ ] 5mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>[ ] 5mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pain Scale

0 1 2 3 4 5 6 7 8 9 10

I have no pain

I have the worst possible pain

Date completed: __________________

After you complete these pages, please bring them with you — in the envelope we gave you — to each of your visits to the POCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
A RESEARCH STUDY TO REDUCE PAIN IN PATIENTS HAVING LOW BACK PAIN [Namenda® (Memantine) Study]

PAIN AND MEDICATION DIARY - WEEK FOUR

YOU WILL GET A SEPARATE DIARY FOR EVERY WEEK

If you have any questions or concerns about this research, please call the Principal Investigator for this study, Dr. David Kuo, Director, PCOM Roxborough Healthcare Center

5830 Henry Ave, Philadelphia PA 19128
215-483-3800

At the end of this week, please answer the following questions:

Did anything happen to you this week that gave you more pain? For example, did you fall down?

Please check one: ___ No ___ Yes

If you checked ‘YES’, please write down what happened.


Did you have any improvement in your bowel movements? ___ Yes ___ No

If you answered ‘YES’, did you have less constipation? ___ Yes ___ No

During this week, have you taken any additional medications, ___ Yes ___ No

(For example, over the counter and/or prescription)

If you checked ‘Yes’, please list__________________________

After you complete these pages, please bring them with you – in the envelope we gave you – to each of your visits to the PCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
Appendix E: Patient Diary: Week 4 (Back)

Patient Name: ____________________________

(Please print)

Telephone Number(s): Home: ____________________________ Cell/Work: ____________________________

Date you started to write your information on this form: ____________________________

<table>
<thead>
<tr>
<th>WEEK FOUR</th>
<th>Namenda used today: Please check</th>
<th>How many tablets of Percocet did you use today?</th>
<th>How would you score your pain this morning?</th>
<th>How would you score your pain this afternoon?</th>
<th>How would you score your pain tonight?</th>
<th>How many bowel movements did you have today?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>□ 5mg AM □ 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>□ 5mg AM □ 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>□ 5mg AM □ 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>□ 5mg AM □ 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>□ 5mg AM □ 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>□ 5mg AM □ 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>□ 5mg AM □ 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pain Scale

<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>
<tbody>
<tr>
<td>I have no pain</td>
<td>I have the worst possible pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date completed: ____________________________

After you complete these pages, please bring them with you — in the envelope we gave you — to each of your visits to the PCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
A RESEARCH STUDY TO REDUCE PAIN IN PATIENTS HAVING LOW BACK PAIN [Namenda® {Memantine} Study]

PAIN AND MEDICATION DIARY - WEEK FIVE

YOU WILL GET A SEPARATE DIARY FOR EVERY WEEK

If you have any questions or concerns about this research, please call the Principal Investigator for this study, Dr. David Kuo, Director, PCOM Roxborough Healthcare Center

5830 Henry Ave, Philadelphia PA 19128
215-483-3800

At the end of this week, please answer the following questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN?
FOR EXAMPLE, DID YOU FALL DOWN?

PLEASE CHECK ONE: ___No ___Yes

IF YOU CHECKED ‘YES’, PLEASE WRITE DOWN WHAT HAPPENED.


Did you have any improvement in your bowel movements? ___YES ___NO
If you answered ‘YES’, did you have less constipation? ___YES ___NO

During this week, have you taken any additional medications, ___YES ___NO
(For example, over the counter and/or prescription)
If you checked ‘Yes’, please list

After you complete these pages, please bring them with you — in the envelope we gave you — to each of your visits to the PCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
Appendix F: Patient Diary: Week 5 (Back)

Patient Name: ____________________________________________

[Please print]

Telephone Number(s): Home: ___________________ Cell/Work: ___________________

Date you started to write your information on this form: ________________________

<table>
<thead>
<tr>
<th>WEEK FIVE</th>
<th>Namenda used today: Please check</th>
<th>How many tablets of Percocet did you use today?</th>
<th>How would you score your pain this morning?</th>
<th>How would you score your pain this afternoon?</th>
<th>How would you score your pain tonight?</th>
<th>How many bowel movements did you have today?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>[ ] 10mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>[ ] 10mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>[ ] 10mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>[ ] 10mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>[ ] 10mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>[ ] 10mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>[ ] 10mg AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] 5mg PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pain Scale

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

I have no pain                                      I have the worst possible pain

Date completed: ______________________________________

After you complete these pages, please bring them with you — in the envelope we gave you — to each of your visits to the PCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
Appendix G: Patient Diary: Week 6 (Front)

A RESEARCH STUDY TO REDUCE PAIN IN PATIENTS HAVING LOW BACK PAIN [Namenda® (Memantine) Study]

PAIN AND MEDICATION DIARY - WEEK SIX

YOU WILL GET A SEPARATE DIARY FOR EVERY WEEK

If you have any questions or concerns about this research, please call the Principal Investigator for this study, Dr. David Kuo, Director, PCOM Roxborough Healthcare Center
5830 Henry Ave, Philadelphia PA 19128
215-483-3800

At the end of this week, please answer the following questions:

DID ANYTHING HAPPEN TO YOU THIS WEEK THAT GAVE YOU MORE PAIN?
FOR EXAMPLE, DID YOU FALL DOWN?
Please check one: ___ No ___ Yes
If you checked ‘Yes’, please write down what happened.

Did you have any improvement in your bowel movements? ___ Yes ___ No
If you answered ‘Yes’, did you have less constipation? ___ Yes ___ No
During this week, have you taken any additional medications? ___ Yes ___ No
(For example, over the counter and/or prescription)
If you checked ‘Yes’, please list ______________________________

After you complete these pages, please bring them with you — in the envelope we gave you — to each of your visits to the PCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
Appendix G: Patient Diary: Week 6 (Back)

Patient Name: 

[Please print] 

Telephone Number(s): Home: Cell/Work: 

Date you started to write your information on this form: 

<table>
<thead>
<tr>
<th>WEEK</th>
<th>Namenda used today: Please check</th>
<th>How many Percocet did you use today?</th>
<th>How would you score your pain this morning?</th>
<th>How would you score your pain this afternoon?</th>
<th>How would you score your pain tonight?</th>
<th>How many bowel movements did you have today?</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIX Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pain Scale

0  1  2  3  4  5  6  7  8  9  10
I have no pain

I have the worst possible pain

Date completed: 

After you complete these pages, please bring them with you — in the envelope we gave you — to each of your visits to the PCOM Roxborough Healthcare Center.

Thank you for choosing to be in our study.
## Appendix H: Patient Study Schedule

<table>
<thead>
<tr>
<th>PART</th>
<th>Week</th>
<th>Memantine</th>
<th>Pain and Medication Diary</th>
<th>Visit to Roxborough Healthcare Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PART 1</strong></td>
<td><strong>Week 1</strong></td>
<td>None</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Week 2</strong></td>
<td>None</td>
<td>Daily</td>
<td>End of week 2</td>
</tr>
<tr>
<td><strong>PART 2</strong></td>
<td><strong>Week 3</strong></td>
<td>5 mg Memantine AM + 5 mg memantine PM</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Week 4</strong></td>
<td>5 mg Memantine AM + 5 mg memantine PM</td>
<td>Daily</td>
<td>End of week 4</td>
</tr>
<tr>
<td></td>
<td><strong>Week 5</strong></td>
<td>10 mg Memantine AM + 5 mg memantine PM</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Week 6</strong></td>
<td>10 mg Memantine AM + 10 mg memantine PM</td>
<td>Daily</td>
<td>End of week 6</td>
</tr>
</tbody>
</table>
Appendix I: Short Form Geriatric Depression Scale Questionnaire

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week.

1. Are you basically satisfied with your life? yes no
2. Have you dropped many of your activities and interests? yes no
3. Do you feel that your life is empty? yes no
4. Do you often get bored? yes no
5. Are you in good spirits most of the time? yes no
6. Are you afraid that something bad is going to happen to you? yes no
7. Do you feel happy most of the time? yes no
8. Do you often feel helpless? yes no
9. Do you prefer to stay at home, rather than going out and doing things? yes no
10. Do you feel that you have more problems with memory than most? yes no
11. Do you think it is wonderful to be alive now? yes no
12. Do you feel worthless the way you are now? yes no
13. Do you feel full of energy? yes no
14. Do you feel that your situation is hopeless? yes no
15. Do you think that most people are better off than you are? yes no

Total Score ____________
Appendix I: Short Form Geriatric Depression Scale Instructions

Geriatric Depression Scale (GDS) Scoring Instructions

Instructions: Score 1 point for each bolded answer. A score of 5 or more suggests depression.

1. Are you basically satisfied with your life? yes no
2. Have you dropped many of your activities and interests? yes no
3. Do you feel that your life is empty? yes no
4. Do you often get bored? yes no
5. Are you in good spirits most of the time? yes no
6. Are you afraid that something bad is going to happen to you? yes no
7. Do you feel happy most of the time? yes no
8. Do you often feel helpless? yes no
9. Do you prefer to stay at home, rather than going out and doing things? yes no
10. Do you feel that you have more problems with memory than most? yes no
11. Do you think it is wonderful to be alive now? yes no
12. Do you feel worthless the way you are now? yes no
13. Do you feel full of energy? yes no
14. Do you feel that your situation is hopeless? yes no
15. Do you think that most people are better off than you are? yes no

A score of ≥ 5 suggests depression

Total Score

Appendix J: Mini Mental State Examination Questionnaire

### 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>
</tbody>
</table>

| 30 | TOTAL |
Appendix J: Mini Mental State Examination Interpretation

**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:**
REFERENCES


Galluzzi K, Goldstein F. (2010). Memantine as an Adjunct to Opioid Therapy in Geriatric Patients: Pilot Study (Unpublished Results).


