PAINFUL CONDITIONS IN OLDER ADULTS WITH DEMENTIA:

ARE ANALGESICS AND PSYCHOTROPICS INAPPROPRIATELY PRESCRIBED?

by

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Painful Conditions in Older Adults with Dementia: Are analgesics and psychotropics inappropriately prescribed?

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Abstract

This thesis examines prescription of analgesics and psychotropics among older adults with painful conditions, focusing on the relationship between medication use and cognitive status. Previous research suggests that pain is undertreated among older adults with cognitive impairment and that the consequences of undertreated pain include 'problem' behaviours, potentially misidentified as dementia-related. This thesis hypothesizes that among older adults with arthritis, the presence of Alzheimer's disease, is a barrier to prescription of analgesics, specifically non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Unrelieved pain manifests as behaviours which are managed with psychotropics, specifically neuroleptics and benzodiazepines.

The data used in this thesis were obtained from the Canadian Study of Health and Aging (1991/1992). The study sample consisted of 1,475 older adults categorized on the basis of the presence or absence of arthritis or rheumatism and cognitive status: cognitively intact; probable, or possible Alzheimer's disease.

Logistic regression analyses indicated that likelihood of NSAID use was lower among those with Alzheimer's disease (*OR* = .56) and those taking benzodiazepines (*OR* = .60). Likelihood of acetaminophen use was lower with benzodiazepine use (OR = .60), higher among institutional residents (*OR* = 1.4) and increased with age (*OR* = 1.04). Likelihood of neuroleptic use increased with frequency of dementia-related behaviours (*OR* = 1.02), but decreased with age (*OR* = .95). Likelihood was higher among those with moderate (*OR* = 5.6) and severe (*OR* = 20) compared with mild dementia and

among institutional residents (*OR* = 2.5). Likelihood of benzodiazepine use was greater among institutional residents (*OR* = 2.3) and lower among those with severe dementia (*OR* = .36). Neither presence of arthritis nor prescription of analgesics emerged as a statistically significant predictor of prescription of either psychotropic.

Results suggest reasons to be both encouraged and concerned. It is encouraging that pain does not seem to be misidentified and treated inappropriately with psychotropics, but the high use of neuroleptics among those with severe dementia raises some concerns.

Dedication

This thesis is dedicated in loving memory

of my father,

Gordon Douglas Fisher

March 1, 1920 – November 8, 1973

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Chapter One: Background

Chronic pain is a reality for many older adults. Estimates of the prevalence of chronic pain among community dwelling older adults range from 25 % to 50% (Scudds & Robertson, 2000; Millar, 1996; Cook, Rideout & Browne, 1984). Among nursing home residents, the prevalence of chronic pain is estimated to be as high as 80% (Ferrell, Ferrell, & Osterweil, 1990). Musculoskeletal conditions are the predominant cause of pain among both populations (Ferrell, 1991; Roy, Thomas & Cook, 1999; Lansbury, 2000), though other painful conditions such as headache, herpes zoster and neuropathies are also common. According to the 1994-1995 National Population Health Survey, the prevalence of arthritis and rheumatism among Canadians over 64 years of age is 40% (Millar, 1996). The prevalence of musculoskeletal conditions in nursing home residents has been estimated to range from 49% to 70% (Parmalee, Smith and Katz, 1993; Sengsten & King, 1993; Ferrell, Ferrell & Rivera, 1995).

Some evidence exists to suggest that the treatment of pain differs depending on the age of the patient. Ferrell (1995) contends that 45% to 80% of nursing home residents may suffer decreased quality of life and diminished functional ability as a result of inadequately treated pain. Researchers have proposed various explanations for the differential treatment of pain. The first concerns pain assessment. For pain to be treated effectively, first it must be recognized that the patient is experiencing pain. Much of pain assessment involves self-report. However, elderly patients underreport pain and many people consider pain in later life to be inevitable (Cook & Thomas, 1994; Parmalee, 1994) that is a natural consequence of aging *that must be borne.* Furthermore, some older adults are reluctant to admit to pain because they interpret this as a sign of terminal illness (AGS Panel on Chronic Pain in Older Persons, 1998). The perceptions of healthcare providers may also influence the assessment of pain in an elderly patient as some share the view that, because of age-related neurological changes, older patients do not experience pain as acutely as younger patients (Harkins & Price, 1992).

Older patients with cognitive loss are potentially at increased risk for undertreatment of pain. Deterioration of language skills, such as the ability to conceptualize and express feelings or to find words can hinder verbal self-reporting of pain (Parmalee, Smith & Katz, 1993; Clavel, D.S. 1999; Buffman et al., 2001). Impaired abstraction may render comparative evaluation of the pain experience difficult, if not impossible. Also, the patient may deny experiencing pain because he or she cannot remember being in pain. In addition, labeling of the patient as cognitively impaired may result in caregivers or healthcare professionals considering all aggressive or agitated behavior as manifestations of dementia, such that no other cause is investigated (Olson, 2000, Kitwood, 1990)

The consequences of unrelieved pain in the older person are many and serious. There is a considerable body of evidence linking unrelieved pain with decreased health and well-being, increased rates of depression and sleep disturbances, decreased socialization and increased costs (Ferrell et al., 1990; Parmalee, Katz & Lawton, 1991). Some researchers have suggested that untreated pain may be the underlying cause of aggressive behavior and other behavioral symptoms in cognitively impaired patients (Miller et al., 1995; Olson, 2000; Huffman et. al., 2001). Behavioral symptoms such as aggression and agitation are frequently treated with psychotropic medications, specifically neuroleptics and benzodiazepines (Draper et al., 2000; Salzman, 2001; Sourial et al., 2001). Such pharmacological agents are associated with numerous serious adverse effects, including extra pyramidal effects (e.g. dystonia or spasms; akathesia or restlessness), tardive dyskinesia, and increased cognitive loss. The symptoms of tardive dyskinesia include involuntary oral movements such as lip smacking, jaw and tongue movements, and abnormal movements of the extremities and difficulty swallowing (Draper et al., 2000; Hagen & Armstrong-Esther, 2000; Salzman, 2001). The potential exists, therefore, for serious negative consequences for older patients with cognitive loss who suffer from unrelieved pain.

There is a small body of evidence suggesting that cognitively impaired older adults with pain are inappropriately prescribed psychotropic drugs i.e., benzodiazepines and neuroleptics (Hanlon et al., 1996; Willis et al., 1997; Olson, 2000; Sorensen et al.,

2001). The question arises, are elderly with painful conditions at increased risk for inappropriate use of psychotropic medications if they are cognitively impaired? The objective of this thesis will be to explore the relationship between painful conditions, cognitive impairment and prescription of psychotropic medications.

Chapter Two: Theoretical Framework

2.1 Pain Mechanisms

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience which we primarily associate with tissue damage or describe in terms of such damage, or both" (Merskey & Bogduk, 1994, p. 210). This definition recognizes the complexity of the experience of pain. The perception of pain is not merely sensory that is the direct outcome of exposure of the body to noxious stimuli but a conscious expression only partly determined by the sensory stimulus which activates the neural mechanism (Portenoy & Kanner, 1996). In other words, pain is a "subjective experience that is generated within the brain and integrally associated with emotional, cognitive and learned behaviours" (Bausbaum & Woolf, 1999, p. R429).

Fordyce (1988) emphasizes the importance of differentiating among four aspects of the perception of pain: *nociception; pain; suffering;* and *pain behaviours.* Nociception refers to the physiological stimulation of sensory nerve endings which is then carried by the A-delta and C fibres to the central nervous system. Pain is generally understood to be the sensation arising from this physiological mechanism. Fordyce (1988) believes this to be an oversimplification and instead, argues that pain should be understood in terms of suffering and pain behaviour. Suffering is the emotional response that is triggered by the aversive event whereas pain behaviours are the outward visible signs of the suffering the individual is experiencing. These pain behaviours arise as the result of the synthesis of the sensory input including, but not limited to, the original nociceptive signal, with a multitude of other affective and cognitive functions. Nociception and pain can be considered as the input, suffering and pain behaviours are the output (Fordyce, 1988).

Loeser (2000) defines three basic types of pain: transient; acute; and chronic or ongoing pain. *Transient* pain ceases once the stimulus is withdrawn and causes no lasting local tissue damage. Clinical examples include the pain resulting from procedures such as injection. *Acute* pain results from injury to body tissues. The injury is such that it does not overwhelm the body's ability to repair itself, although acute pain often prompts

the sufferer to seek healthcare. *Chronic* or persistent pain is usually the result of injury that as a result of various physiological and psychological factors overwhelms the body's ability to heal itself. Traditionally, the difference between acute and chronic pain has been defined in terms of duration: that is, pain that lasts longer than one month or that continues beyond the time after which physical healing is deemed to have occurred is 'chronic' pain (Portenoy & Kanner, 1996). However, Loeser (2000) has proposed that the distinction between acute and chronic pain is not duration but the body's ability to heal the site of injury and restore normal processing of sensory input.

2.2 Pain Theories

A theory of pain mechanism must be consistent with both the physiological evidence and the way in which pain is experienced by patients and described to healthcare practitioners. Pain theory must also be able to explain the three basic types of pain. Several theories have been proposed: The first of these is Specificity Theory.

2.2.1 Specificity Theory

Specificity Theory explains pain in terms of a linear relationship between sensory stimulation and outcome: that is, tissue injury activates specific pain receptors and the sensation is then transmitted via an afferent neural pathway in the spine. The theory inspired research into the physiological aspects of pain including the search for the pain pathway and a pain centre in the brain, and the exploration of the characteristics of sensory nerve fibres.

Afferent sensory nerve fibres can be classified into three main groups on the basis of their size and degree of myelination: A-beta, large myelinated fibres, A-delta, small, thinly myelinated, and C-fibres, unmyelinated. C fibres constitute sixty to seventy percent of all sensory fibres. A specific type of sensation was ascribed to each class of fibre; touch to A-beta, cold to A-delta and warmth and pain to A-delta and C fibres.

Noxious stimuli activate nociceptors in the periphery of the body. According to Specificity Theory, the impulses generated by the stimulation of these pain receptors

ascend to the brain via multiple pathways in the spinal cord. Two major systems have been identified: medial and lateral systems. The spinoreticular system, paleospinothalalmic tract, dorsolateral spinomesencephalic pathway and propriospinal system comprise the medial system, and are generally, slow conducting fibres. In contrast, the pathways of the lateral system are rapidly conducting and highly organized. There are three pathways in the lateral system: the spinocervical tract; the neospinothalalmic tract; and the dorsal column postsynaptic system. The spinothalmic tract became known as the 'pain pathway' (Horn & Munafo, 1997). It is now believed that all seven pathways play a role in the perception of pain (Melzack & Wall, 1996). The 'pain centre' was held to be in the thalamus while the cortex was believed to exhibit inhibitory control (Horn & Munafo, 1997).

The notion of a specific pain centre has now been disputed by experimental evidence. Cortical mapping using techniques such as positron emission tomography (PET) has demonstrated that multiple areas of the brain are involved in processing 'pain' information (Melzack and Wall, 1996; Hofbauer et al., 2001).

While the research inspired by the specificity theory provided valuable insight into the physiological mechanism of pain transmission, the theory itself is flawed. Its primary weakness is the assumption of a direct and invariant relationship between peripheral stimulation and sensation. The very naming of sensory receptors as 'pain receptors' implies that stimulation of these receptors always and only causes the same sensation of pain. The role of determining what is experienced as pain is ascribed to the peripheral receptor, not the brain.

This basic assumption is not supported by empirical evidence or clinical experience. Equivalent levels of tissue damage or sensory stimulation are not always perceived at the same level of 'pain', or even *as* pain at all. Classic examples are soldiers in battle or athletes who do not 'feel' the pain of a severe injury (Melzack & Wall, 1996; Horn & Munafo, 1997). Alternatively, *pain* may be perceived when there is no apparent tissue damage, or may continue long past the time of apparent healing of the original injury. Clinical examples of such phenomena are neuralgia and causalgia in which the

patient experiences severe pain though there is no apparent physiological tissue damage. Another classic example is phantom limb pain in which the patient continues to experience pain in an amputated limb (Melzack & Wall, 1996; Horn & Munafo, 1997).

Specificity theory thus fails to adequately explain the pain phenomena. Also, such a theory is potentially very damaging. The basic assumption of a linear relationship between sensation and perception leads to the belief that without detectable tissue damage no pain exists. Patients who suffer pain such as that from neuralgia and causalgia may be seen as not having 'real' pain, i.e., psychosomatic pain or malingering. Their suffering may be ignored or not taken seriously, and consequently, not treated.

2.2.2 Patterning Theories

Patterning theories arose in response to the deficiencies of specificity theory. The work of Goldscheider in 1894 marked the beginning of the development of such theories. Goldscheider observed the situation of people with *tabes dorsalis*, a condition occurring in late stage syphilis in which successive applications of a warm test tube to the skin is felt as increasingly hot until the patient cries out in pain as if being burned. Such observations led Goldscheider to formulate the idea of patterning of sensory input and led to the development of a number of theories (Melzack & Wall, 1996; Horn & Munafo, 1997).

The first and simplest of these is that of *peripheral summation*. Excessive peripheral stimulation of non-specific receptors results in the experience of pain. This theory assumes that all nerve fibre endings are alike. However, empirical evidence indicates that this is not true; physiological specialization is the norm (Melzack & Wall, 1996; Horn & Munafo, 1997).

A more complex theory, *central summation*, takes the fact of physiological specialization into account. This theory, based on the work of Livingston in the mid 1940's, assumes a central neural mechanism of pain. Pathological stimulation of sensory nerves activates reverberating circuits. This mechanism can, once established, be triggered by normal, non-noxious input. The process then becomes self-sustaining such

that removal of the peripheral source of stimulation does not eradicate the pain. This offers an explanation for the phenomena of phantom pain.

Under normal conditions, however, summation does not take place because a control mechanism is maintained by a balance between two systems. These two systems have been described variously as, fast versus slow, epicritic versus protopathic, myelinated fibres versus unmyelinated. In the 1950's, the existence of a balance between small and large fibres was proposed. The small fibres carry the nerve impulse pattern that causes pain whereas the large fibres inhibit transmission of the impulse. These fibres exist in a ratio such that a greater proportion of small fibres result in increased neural transmission, summation and pathological pain. This explanation has been termed the *sensory interaction theory* of pain (Melzack & Wall, 1996; Horn & Munafo, 1997).

Patterning Theory presents several improvements over the linear model assumed by Specificity Theory. Nevertheless, it does not adequately explain the control mechanism that maintains the balance between the two systems, nor does it provide a framework whereby individual differences in the perception of pain can be explained. Rather, it assumes a standard ratio between small and large fibres, implying a consistent level of pain perception across individuals.

2.2.3 Gate Control Theory

Gate Control Theory was first proposed by Melzack and Wall in 1965 in response to the limitations of existing pain theories. Melzack and Wall presented a three-stage mechanism of pain transmission and perception:

1. nerve impulses arrive from injured tissue to the dorsal horn of the spinal cord and excite the Transmission (T) cells which then transmit the impulse to reflex circuits and the brain;

2. the above mechanism is modulated by low-threshold afferents which excite inhibitory interneurons decreasing the injury related discharge of the T cells;

3. activity of the descending pathway from the central nervous system further modulates the transmission of the sensory neurons;

Two mechanisms function synergistically to modulate transmission of the impulse: reduced release of neurotransmitter substances which blocks impulse transmission at the nerve terminals; or reduced excitability of cells in response to arriving impulses. The exact mechanisms were not fully elucidated in the original theory.

The basic assumption of the Gate Control Theory is the presence of a 'gate', a central neural mechanism, where sensory input is 'screened'. The transmission must 'pass' through this gate for the sensation to be registered as *pain.* This *gate* is believed to be located in the dorsal horn of the spinal cord, in the *substantia gelatinosa Rolandi,* which is a clear zone of the dorsal horn, comprised of two laminae (layers). Ascending signals from peripheral nerves, carried by A-beta, A-delta and C fibres and descending signals from the central nervous system arrive at the dorsal horn. The extent the gate is open or closed depends upon these signals. Incoming nerve impulses excite the T cells of the dorsal horn which then transmit the impulse to reflex circuits and the brain. Transmission is modulated by low-threshold afferents that excite inhibitory interneurons thereby decreasing the rate of firing of the T cells. Transmission is further modulated by the activity of the descending pathway (from the central nervous system) which also decreases the firing of the T cells. The experience of pain, therefore, can be influenced by the input of sensory nerves (the ascending signals) and input from the central nervous system (descending pathways).

2.2.4 Modifications to Gate Control Theory

The most important contribution of Gate Control Theory to pain research was that it marked a conceptual change in the understanding of pain mechanisms. The concept of a simple and invariant relationship between sensory input and the sensation felt was discarded. In contrast, the experience of pain was recognized to be a complex process, integrating psychological, behavioural and physiological components. The basic theory provides a framework whereby the experience of pain can be understood as the result of the synthesis of input from sensory neurons (including but not limited to) nociceptors and

input from brain structures that are involved in affect and cognitive function. How an individual perceives pain therefore is influenced by a multitude of factors.

Gate control theory opened the door to research into the psychological and behavioural mechanisms of pain experience. With the expansion of the body of knowledge regarding pain mechanisms, Gate Control Theory underwent modifications and revisions to produce new models of pain. These, described below, can be seen as elaborations of Gate Control Theory.

2.2.5 A Three Dimensional Model of Pain

Melzack (1983) proposed a three dimensional model of pain: sensory-discriminative; affective – motivational; and cognitive - evaluative.

2.2.5.1 Sensory-Discriminative

When Melzack and Wall first introduced the Gate Control Theory, the body of knowledge regarding pain physiology was inadequate to explain the mechanisms of pain modulation. The quest to elucidate these mechanisms inspired research primarily focused on the physiological mechanism of nociception.

Three important advances of recent research have been:

1. identification of the neurotransmitters primarily responsible for the transmission of pain impulses;

2. isolation of endogenous opioids that act as a self-regulatory pain blocking mechanism;

3. evidence of central neural changes following peripheral tissue or nerve damage, termed "central neural plasticity".

2.2.5.2 Neurotransmitters

Neurotransmitters are substances that are released when the axon terminal of the presynaptic neuron is depolarized. The neurotransmitter diffuses across the synaptic cleft

to act on target cells. Neurotransmitters enhance or enable the transmission of the impulse from the neuron to target cells.

First identified in 1930, 'Substance P' is postulated to be the prototype for other peptides in peripheral sensory nerve fibres responsible for conveying pain sensation information to the central nervous system (Horn & Munafo, 1997). Substance P is believed to modulate sensitivity to pain. Glutamate and another peptide, aspartate, act at N-methyl-D-aspartate receptor sites and have been implicated in pain transmission. Recent research has identified glutamate as the predominant excitatory neurotransmitter and is now believed to be the principal transmitter signaling pain of all intensities (Julius & Basbaum, 2001). .

Unmyelinated C fibres appear to be of two classes: peptidigenic; and non-peptidigenic. Those of the former class synthesize and release neuropeptides substance P, neurokinin A, and calcitonin gene-related peptide (CGRP) and express TrkA (high affinity tyrosine kinase receptor for nerve growth factor). Those of the latter class express fewer peptides and express a surface lectin IB4 and P_2X_3 receptors, specific subtypes of an ATP gated ion channel and respond to the glial[1] derived neurotropin factor family of growth factors (Bennett, 2001; Julius & Basbaum, 2001).

The release of neurotransmitters such as substance P, CCRP and other peptides promotes the release of chemicals and other factors from neighbouring non-neuronal cells and vascular tissue. These products of tissue damage create an 'inflammatory soup' made up of extra cellular protons, arachidonic acid and other lipid metabolites, serotonin, bradykinin, nucleotides and nerve growth factor. This is part of the process of *allodynia*, or persistent pathological pain, whereby pain can be produced by the activity of non-nociceptive peripheral sensory fibres. Allodynia results from two mechanisms: *central sensitization*, or increased responsiveness of spinal cord pain transmission neurons; and

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[1] Glial cells are the supporting cells of the nervous system, supplying nutrients and oxygen to neurons, holding the neurons in place, and removing dead neurons. Recent research suggests that glia may play an important role in pain modulation (Watkins, Milligan & Maier, 2001).

peripheral sensitization[2], or decreased activation thresholds of the nociceptive terminals. The latter mechanism is the result of exposure of the nociceptive terminals to the chemicals and other factors in the inflammatory soup.

Experimental research has further elucidated the role of neurotransmitters in the modulation of pain by the descending pathways. These pathways appear to exert their action through the release of serotonin, noradrenalin and possibly, peptides. The cells of the midline *nucleus raphe magnus* and the reticular formation contain serotonin; those of the *dorsolateral pons* contain noradrenalin. The release of serotonin and noradrenalin causes the release of inhibitory compounds by the cells of the spinal cord, including GAMMA, endogenous opioids and possibly, dopamine.

2.2.5.3 Endogenous Opioids

Endogenous opioids play an important role in pain modulation by the descending pathways. These substances are peptides, all pharmacologically related to morphine. Endogenous opioids have multiple functions linked to basic survival mechanisms. They may also be important in the regulation of emotion and higher integration functions, and mediation of analgesia. Endogenous opioids bind to specific receptors. Three types of receptors are important in analgesia. These are the: mu, with two subtypes; delta, with two subtypes; and kappa, with at least three subtypes. Enkephalins are most active at the mu and delta receptors, dynorphin at kappa and mu (Drolet, et al., 2001). Mu_1 receptors have been implicated in the mediation of supraspinal analgesia. Delta receptors mediate

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[2] The molecular and biochemical processes through which peripheral sensitization occurs are complex. Local tissue injury results in acidosis. Such acidic conditions promote sustained discharges in the nociceptors and can augment the responsiveness of dorsal root ganglia (DRG) neurons to chemical stimuli. Bradykinin seems to produce membrane depolarization and sensitization to other noxious and even innocuous stimuli via a variety of processes. Nerve growth factor is released by mast cells, fibroblasts and other cells at the site of the tissue damage which acts on the primary sensory nerve terminals to promote hypersensitivity to temperature. Arachidonic acid is a lipid messenger that is converted into various inflammatory products. Chief among these is prostaglandin E2. PGE_2 is postulated to increase levels of cyclic AMP in nociceptors by binding to specific receptors (G-protein-coupled). PGE_2 may increase the excitability of DRG neurons by hyperpolarizing a specific subclass of voltage gated sodium (Na^+) channels expressed by nociceptors. The extent to which a stimulus must depolarize the membrane to produce a discharge is decreased, thereby favouring repetitive firing of the neuron (Coderre et al., 1993; Price, 1999).

enkephalin induced antinociception and selection for analgesic systems at the spinal level (Portenoy & Kanner, 1996).

2.2.5.3 Central Neural Plasticity

Theoretical frameworks of pain mechanism have attempted to explain why tissue injury sometimes but not always, results in persistent, pathological pain. The answer would appear to be that neural processes are dynamic. Changes in both spinal and peripheral sites appear to be important in the mechanism of pathological pain. These changes are the result of interactions between excitatory amino acids, endogenous opioids, monoamines and non-opioid peptides and persist long after the actual tissue damage has occurred. Tissue injury results in an increase in the sensitivity of the peripheral neurons, resulting in spontaneous activity, decreased threshold and increased responsiveness to stimuli (Dickenson, 1991).[3] The physical pathology only resolves slowly providing the opportunity for central neural changes to occur.

It has been postulated that excitatory amino acids (EAA) and C fibre neuropeptides interact to contribute to central sensitization. Activity in small diameter primary afferents in response to noxious stimulation results in the release of EAA's such as glutamate and aspartate and neuropeptides (e.g., substance P) into the spinal cord dorsal horn. These chemicals cause an increase in intracellular calcium (Ca^{++}) which then increases the excitability of the cell membrane. Glutamate acts on the AMPA receptor to produce a fast excitatory potential. Glutamate and aspartate stimulate the influx of Ca^{++} via NMDA receptor operated channels to produce an elongated synaptic potential. This occurs after the activity of glutamate at the AMDA receptor results in the removal of magnesium (Mg^{++}) from the NMDA receptors. Substance P mobilizes Ca^{++} from intracellular stores. Substance P produces a slow depolarization of the cell membrane and may also contribute to the sensitization of the membrane indirectly by stimulating the release of glutamate or enhancing the activation of NMDA receptors by removing the

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[3] It has been postulated that a relative reduction in the quantity of C fibres versus A-delta fibres disrupts the self-regulatory mechanism of the peripheral neurons.

Mg^{++} block. Calcitonin gene dependent protein increases intracellular Ca^{++} via the voltage-gated channels (Dickenson, 1991; Coderre et al., 1993).

A second component of the mechanism involves intracellular second messengers, specifically, the phospolipase C (PLC) second messenger system. PLC is an enzyme that catalyzes the hydrolysis of polyphophatidylinositol into inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 stimulates the release of Ca^{++} from intracellular stores. DAG stimulates the translocation and activation of protein kinase (PKC) which in turn, phosphorylates specific substrate proteins that are involved in neurotransmitter release and transduction. In addition, PKC seems to enhance Ca^{++} currents and may also directly increase neuron excitability. Substance P is believed to play a role in this mechanism by stimulating PLC activity (Coderre et al., 1993; Hökfelt, Zhang & Wiesenfeld-Hallin, 1994).

2.2.5.4 Affective-Motivational and Cognitive-Evaluative Components

The conceptual change in the understanding of pain mechanisms brought about by the advent of the Gate Control Theory and subsequent modifications and elaborations of this model notwithstanding, the influences of the affective and cognitive components have not received the attention given to the investigation of the physiological mechanisms of pain transmission (Fernandez, Clark, & Rudick-Davis, 1999).

Although the Melzack model identifies affect and cognition as two distinct dimensions, the two components are closely integrated. The emotional feeling an individual ultimately experiences is the outcome of a cognitive appraisal integrating his or her experience, memories and expectations. The appraisal may be deliberate, controlled and conscious, or automatic. In the latter circumstance, the individual may be unaware of the process of appraisal (Fernandez et al., 1999).

Price (1999) notes that a precise quantification of the cognitive factors underlying the emotional feelings experienced with pain unpleasantness is lacking in current research. He proposes that the intensity of the affective experience of pain can be explained on the basis of the interplay between two basic issues: the desired outcome;

and the perceived likelihood or expectation of the occurence. The nature of the interaction is influenced by the ultimate goal; avoidance of a negative outcome (avoidance goal); or attaining a pleasurable outcome (approach goal). The individual's past experience, his or her memories, and preconceived notions of the meaning of the pain he or she is experiencing will influence this interaction.

Price (1999) further proposes that there are two dimensions to the affective component of pain, the immediate and the secondary stage. The immediate affective dimension is closely linked with the intensity of the painful sensation. The intensity of the sensation may be modulated by the context in which the pain occurs, its source and immediate implications. Well known pain, such as that of recurrent migraine headaches or ongoing arthritic joint pain, may be understood and therefore perceived as less unpleasant than a new pain, the source and implications of which are unknown and which consequently are viewed as more threatening.

The secondary stage of the affective component of pain, which some term 'suffering', is based on a complex process which integrates memory and imagination about the implications of the pain and its long term consequences (Price, 1999). Over time, ongoing pain continues to interfere with life and may come to be viewed as a burden to be endured. The sufferer will experience anxiety, frustration, depression, anger and fear in varying degrees, depending upon the nature of his or her appraisal of the pain, expectations of future pain, and the time frame. Personality traits such as extraversion and neuroticism have been found to influence the nature of this appraisal (Price, 1999).

The individual's established coping style also influences their experience of pain Three essential components of coping mechanisms are locus of control, (external vs. internal), focus (emotion vs. problem), and perceived self-efficacy (Melding, 1997). Overall, a strong external locus of control, that is, viewing one's circumstances as residing in the hands of fate, is associated with increased pain-related disability and depression. Similarly, a focus on management of the emotional consequences of pain rather than on modifying the source of the pain (problem based focus) tends to be maladaptive and is associated with poorer pain outcomes. Low self-efficacy is also

associated with poorer outcome as lack of confidence leads to decreased ability to engage in pain reducing coping strategies (Melding, 1997).

2.3 Pain and the Elderly

Does the experience of pain change over the lifespan? Clinicians have observed that some acute medical conditions present with atypical patterns of pain in elderly populations. For example, silent (painless) myocardial infarction is more common in elderly than younger patients. Does this reflect a generalized age-related hyposensitivity to pain?

2.3.1 Anatomical and Physiological Changes

Senescent physiological changes to the sensory components of pain present the potential for differential perceptions of pain and suggest an increased tolerance to pain with advancing age. Three such changes are the loss of nerve cells, a decrease in the impulse conduction rate and an increase in the time for an impulse to cross the synapse (Spence, 1995).

Whether brain neurons undergo mitosis is a matter currently under debate. If nerve cells are not replaced as they die in the natural course of aging, a decrease in the number of peripheral neurons with age may potentially affect the transmission of the signal from peripheral nociceptors to the central nervous system. Reduction in the number of neurons in cortical areas (up to 45%) and the cerebellum (about 25%) as well as atrophy of convolutions of the brain occurs as a result of normal aging. The brain loses an average of 100 gm of weight between ages 25 to 70 years (Street & Earles, 1984; Spence, 1995).

Slower conduction rates and increased time to transmit impulses across the synapse may also affect pain transmission. A mild loss of myelin from the neuronal sheaths has been noted with aging and is believed to be responsible for the reduced rate of conduction. Substantial metabolic changes within the synaptic complexes related to neurotransmitter production, and reduced norepinephrine in the brain have been noted in

the elderly. In addition, a significant decrease in the number of postsynaptic receptors has been observed. The combination of reduced number of receptors and decreased neurotransmitter substances may be responsible for the increased time for nerve impulses to cross a synapse (Street & Earles, 1984; Spence, 1995).

Changes to the sensory system also occur with age. A decrease in tactile sensation and reduced ability to discriminate temperature changes may also occur with aging (Street & Earles, 1984; Spence, 1995). Since the experience of pain is understood to be a complex integrative process incorporating input from all the sensory systems, such changes could impact nociception in the elderly.

Yet, changes in the opiate system suggest a decrease in pain tolerance. Yehunda and Carasso (1997) observe that the ability of opiates to stimulate receptors decreases with age, the number of opiate receptors declines and the affinity of opiates for the receptors is also reduced. In addition, the level of endogenous opiates decreases with age. The decrease in pain tolerance with increased age observed in some studies may be related to these age related changes in the opiate system (Yehunda & Carasso, 1997).

A key question, however, is do senescent physiological changes result in true age related differences in pain perception? Despite physical changes to the nervous system, the EEG of normal older adults remains basically unchanged and within the normal limits of other age groups (Street & Earles, 1984; Spence, 1995). While a loss of nerve cells does occur with age, the body has a surfeit of neurons; the loss may not be sufficient to interfere with normal functioning. Moreover, there is some question as to whether the changes in neurotransmitter levels are the result of senescence or of pathology.

2.3.2 Empirical evidence

Harkins and colleagues (1996) summarize research investigating the effect of senescence on pain perception. The results of studies on the effects of aging on the perception of pain have been equivocal. The findings of some studies suggest that pain perception decreases with age whereas others suggest an increase. Still others indicate that there are no age related changes.

Pain research presents multiple challenges. The contradictory findings of the current research can be understood in the context of these issues. Experimental research has involved producing 'laboratory pain', transient pain which ceases once the stimulus is reversed and does not result in lasting tissue damage. Obviously, there are ethical reasons for this as researchers cannot permit permanent injury to their human subjects. The clinical applicability of such research is limited, therefore. Certainly, one cannot equate the pain caused by pinpricks or immersing the subject's arm in cold water with the real agony of terminal cancer pain or the ongoing pain of osteoarthritis.

As a result of such ethical concerns, many of the recent advances in understanding the molecular and biochemical mechanisms of nociception have involved research with other species. Studies of the sensory systems of invertebrates have provided important information regarding the transduction mechanisms of nociception. Invertebrates do not experience the sensation of 'pain' in the same manner as mammals, however. Researchers have, therefore, also studied the sensory systems of other animals, such as mice (Julius & Basbaum, 2001). While such research does provide important insights into the physiological mechanisms of pain, the validity of extrapolating the results of such research to explain the clinical phenomena of pain experience remains questionable. Given such challenges, it is not surprising that pain research has continued to focus on the physiological mechanisms of pain.

The empirical investigation of the effects of senescence on pain perception presents all of the above challenges, and others, specific to the challenge of research with aging populations. In their review article, Harkins and colleagues (1996) discuss many of the methodological deficiencies of the current research.

Firstly, whereas chronic pain is predominant in older age, research has tended to focus on acute pain. The endpoint of many studies of pain threshold bear limited relation to clinical or chronic pain. Clinical practice is concerned with the dynamic properties of pain, including a wide range of intensities. Laboratory studies focus on superficial pain and response to the brief stimuli of experimentally induced pain, a very different mechanism than that involved in persistent, chronic pain.

There have been no longitudinal studies of age effects on pain perception, making the separation of potential biases such as cohort effects, very difficult. In addition, valid comparison between studies is hampered by marked variability among studies in terms of methodology, terms of reference, and the endpoints used. Moreover, the nature of the stimulus may affect pain threshold and levels of pain tolerance. Older subjects may respond differently to thermal stimuli than to other types of laboratory pain such as electrical shock, due to specific properties and characteristics of their skin structure and composition and to age related changes in hypothalamic functioning with consequent changes in body temperature thermostatic processes (Yehunda & Carasso, 1997). Therefore, generalization among the results of various studies utilizing different experimental stimuli is limited.

Most studies have been concerned with young-old. It is uncertain if results obtained in such studies can be generalized to the old-old, or to those with co-morbid conditions. Harkins and colleagues (1996) note several important considerations. While there is no empirical evidence to support a significant difference, for example, in the density of nociceptive receptors, between middle aged and young old adults, without a systematic study it is not possible to establish whether this holds for the old-old population as well. Similarly, co-existing medical conditions, such as Parkinson's disease or diabetic neuropathy, impact the physiological process of pain perception (Harkins et al., 1996). Differentiating the confounding effects of disease processes from senescence is impossible without systematic investigation. Overall, there is little empirical evidence of a significant age effect on nociception.

2.3.3 Psychosocial and Cognitive Changes in Pain Perception

There is some evidence in the literature however suggesting age related differences in the affective and cognitive components of pain perception. A study by Riley and colleagues (2000) of three age cohorts of chronic pain sufferers found that the older subjects (age 65 and older) reported significantly less emotional distress related to their pain and exhibited fewer pain behaviours than the young (18-44) and middle aged

(45-64) patients. The authors attribute these results to differences in attitudes and beliefs about pain and aging, and age cohort differences in coping mechanisms.

Certainly, the expectation of experiencing pain is greater in older patients because they are aware that the prevalence of painful conditions increases with age (Thomas & Roy, 1999). Whereas chronic pain violates the life expectations of a younger person, an older pain sufferer may interpret pain as an inevitable outcome of advancing years (Thomas & Roy, 1999; Riley et al., 2000).

The older pain sufferer also brings into the experience many years of adaptation and problem solving mechanisms (Melding, 1997; Lansbury, G. 2000). Pain may be seen as heralding the loss of good health and function, mobility and independence, and be viewed as highly threatening (Melding, 1997). Consequently, the older patient may be reluctant to report pain, or to exhibit pain behaviours.

There is some clinical evidence supporting the hypothesis that older people under-report pain. Ferrell and colleagues (1990) provide indirect evidence. Their study of nursing home residents found that 85% of those with pain had not received analgesic medications within the previous 24 hours. Many of the patients cited a desire to 'not bother' the nursing staff as the reason they did not request pain medication. Indirect evidence also comes from a qualitative study involving 72 community dwelling elderly persons with chronic pain (Lansbury, 2000). Many of the participants expressed concerns that healthcare professionals did not take the time to listen to their complaints, or when they did, did not truly hear what the patient was saying. Concern not to bother busy doctors and nurses was also a prominent barrier to adequate pain management for these patients. The desire to maintain independence and control over their lives was also important and medical intervention viewed as a threat to these goals. In addition, fear of the side effects of drugs prevented many of the sufferers from requesting or taking analgesics.

2.4 Pain in the Cognitively Impaired Older Patient

A major subgroup and the population of interest for this research, is older persons with cognitive impairment. The neurological changes that occur with advancing dementia potentially impact all components of the pain experience included in the three dimensional model of pain: the sensory – discriminative; affective-motivational; and cognitive- evaluative.

Dementia is characterized by the progressive and ongoing decline of multiple cognitive functions that impair daily activities, while preserving consciousness (i.e., distinct from delirium). According to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV, APA, 1994) criterion, cognitive deficits include memory impairment and one or more of aphasia, apraxia, agnosia or disturbance of executive function which may be the result of multiple etiologies (Klein & Kowall, 1998). The Canadian Study of Health and Aging (CSHA Working Group, 1994) identified 252,600 Canadians living with some form of dementia in 1991 (Hill et al., 1996).

The two most common forms of degenerative dementia are Alzheimer's disease and vascular dementia. Alzheimer's disease is the most prevalent (Rogan & Lippa, 2002), accounting for 50 to 75 % of all cases of dementia (Katzman, 1985; Bachman et al., 1993; Ebly et al., 1994; Hill et al., 1996). Vascular dementia accounts for about 19% of dementia cases (Hill et al., 1996). Within the clinical subset of the study population of the CSHA-1, 749 participants (25.3%) received a final diagnosis of Alzheimer's disease (probable or possible) and 116 (6.9%) of vascular dementia. Alzheimer's disease, as the most prevalent degenerative dementia, is the focus of this thesis.

Another issue concerns the potential homogeneity of the population under study and possible confounding variables. The neuropathology of Alzheimer's disease is characterized by diffuse atrophy of the cerebral cortices which typically results in a gradual and insidious deterioration of cognitive function (Klein & Kowall, 1998). In contrast, vascular dementia which is the result of multiple small and/or large brain

infarcts tends to result in a progressive yet stepwise deterioration of cognitive function. The sudden onset of dysfunction in one or more cognitive domains with a patchy distribution of deficits is characteristic. The cognitive function affected depends on the location of the damage (Klein & Kowall, 1998). Therefore, the subgroup of patients with vascular dementia is characteristically more heterogeneous than that of those with Alzheimer's disease. In addition, it is possible that vascular dementia patients will be taking acetylsalicylic acid (ASA) for reasons other than analgesia since ASA is frequently prescribed for stroke prevention in such patients.

2.4.1 Anatomical and Physiological Changes

The pathogenesis of Alzheimer's disease continues to be the subject of considerable research. It is generally recognized, however, that the progressive decline in cognitive function that characterizes this disease correlates with the pathological changes evident in the brain (Smith et al., 2001; Rogan & Lippa, 2002). These anatomical and physiological changes potentially impact both pain sensation and perception.

2.4.2 Sensory and Affective components

Alzheimer's disease is associated with atrophy of areas of the brain that are involved in pain processes including the septohippocampal region, amygydala, hypothalamus, intralaminar nucleus of the thalamus, prefrontal region, the nucleus raphe dorsalis (NRD) and the locus coeruleus (LC) (Katzman & Jackson, 1991; Huffman & Kunik, 2000; Scherder, 2000). The somatosensory complex tends to remain intact, however; therefore pain sensation is likely to be preserved.[4] Moreover, an additional pathway for the transmission of noxious stimuli, the direct spinoseptal and spinohypothalamic projections, is also preserved (Geisler, 1994).

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[4] Specifically, the portion of the spinothalamic tract responsible for the sensory discriminative components of pain projects to the ventroposterior and posterior thalamus and ends in the somatic cortical regions which generally do not undergo substantial deterioration (Katzman & Jackson, 1991; Huffman & Kunik, 2000; Scherder, 2000).

Alterations have been observed in regions that are associated with the major neurotransmitter systems. The septohippocampal region, cholinergic and ascending and descending serotonergic and noradrenergic pathways which originate from the septohippocampal region, the NRD and the LC respectively deteriorate in Alzheimer's disease (Scherder, 2000). There is substantial loss of large cholinergic neurons of the basal nucleus of the forebrain (Katzman & Jackson, 1991). The cholinergic pathway plays an important role in the neuroendocrine and affective components of pain experience. Similarly, the serotonergic and noradrenergic pathways are important to pain and pain suppression. A decreased level of cortical somatostatin, another neurotransmitter involved in the pain process, has also been noted in patients with Alzheimer's disease. The deterioration of the regions of the brain involved in these important neurotransmitter systems implies a reduction in the ability to transmit pain impulses. In addition to the effect of the deteriorating septohippocampal cholinergic pathway, the affective component of pain experience is compromised by deficits in the spinoreticular tract which projects to the limbic areas.

2.4.3 Changes in Cognitive Function

Memory impairment is a hallmark of dementia. The temporal lobes which are particularly important for new learning and recent memory are damaged in most, and probably all cases of dementia (Jacques, 1992). Memory deficits occur at the initial encoding of the information, the transfer into intermediate memory, and the retrieval of stored information (Tuokko & Crockett, 1989). Memory plays an essential role in the perception of pain. Memory of past pain is an important determinant in the cognitive processing of painful sensation. Current pain is compared with past pain in order to make a relative judgment regarding the intensity, degree of unpleasantness and potential consequences of the current pain and to shape pain behaviour (Parmalee et al., 1991; Morley, 1993). As memory deficits increase over the course of the illness, the ability to integrate the memory of past pain into the interpretation of current pain is increasingly impaired.

Lacking the ability to compare current pain to that experienced in the past, the individual may misinterpret the pain: For instance, a painful knee may not be understood as ongoing discomfort that can be endured and need not be feared. Moreover, the refinement and adaptation of problem solving mechanisms and skills developed with maturity that permits older chronic pain sufferers to cope with ongoing pain may become lost as memory deficits increase. Furthermore, with increasing loss of cognitive functioning, the individual loses the ability to think abstractly, integrate information from a variety of sources and generate logical conclusions, thus impeding the ability to problem solve and make judgements regarding the implications of the pain being experienced (Jacques, 1992; Mahoney et al, 2000).

Other associated factors related to memory such as attention deficits which prevent the individual from maintaining focus long enough for the brain to transcribe the information into memory are likely to affect pain perception by interfering with the individual's interpretation of pain. Attention deficits are particularly problematic in the presence of multiple stimuli; pain experienced when engaged in activity, for example. The affected brain is unable to isolate one stimulus, giving equal attention to all or jumping randomly from one to another (Mahoney et al., 2000). The individual may be unable, therefore, to focus on the pain long enough to realize that the movement and pain are associated, understand why he or she is experiencing pain and draw logical conclusions regarding the context and implications of that pain.

Progressive language deficits compound the effects of impaired memory and the deterioration of other cognitive functions on pain perception. Both receptive and expressive language decline as the dementing illness advances. The complex processes of understanding meaning decline first. The individual's vocabulary gradually decreases, sentences becoming simpler and shorter. He or she may become muddled when attempting to convey more complex messages, have difficulty shifting from one mental set to another and excluding irrelevant information (Jacques, 1992). Thus, he or she may not understand when questioned about the presence of pain or be unable to convey the message of being in pain

In summary, on the basis of the anatomical and physiological alterations that occur as a result of Alzheimer's disease, there is some reason to believe that changes in the perception of pain may occur. Patients continue to perceive painful stimuli, but the experience of pain may change as a result of a decline in the affective components. Progressive cognitive deficits may also influence the perception of pain. Memory loss and declining ability to think abstractly and logically which may result in the misinterpretation of pain and the loss of well established coping skills suggest increased suffering in persons with dementia.

2.4.4 Empirical Evidence

While the number of studies is limited, several lines of empirical research suggest that cognitively impaired elderly may experience less pain.

Benedetti and colleagues (1998) found no difference in pain *threshold* between Alzheimer's patients and cognitively normal subjects, but pain *tolerance* was found to be negatively correlated with cognitive status. Tolerance to pain, induced either by electrical stimuli or ischemia, was also found to increase with the severity of dementia, as measured by MMSE scores and spectral analysis of the electroencephalogram (EEG). The authors conclude that these findings are consistent with neuroanatomical evidence that the regions of the brain associated with sensation are preserved in Alzheimer's disease whereas those areas involved in the affective and cognitive components of pain perception suffer deficits. Furthermore, the researchers assert that their findings support the hypothesis that the sensory-discriminative component of pain is maintained, although the cognitive and affective counterpart may be altered (Beneditti et al., 1998).

There is some clinical evidence consistent with the findings of Beneditti and colleagues. Fisher-Morris and Gellaty (1997) describe several cases in which Alzheimer's patients with significant, painful conditions were seemingly pain free. In one such case, the patient was able to walk with no apparent pain, only hours after surgical repair of a fractured femur (Fisher-Morris & Gellaty, 1997). The data are largely anecdotal, however, and considered only a small number of subjects. Blennow, Wallin and Hager (1993) report a lower occurrence of headache following lumbar puncture in

patients with dementia (2%) when compared with non-demented elderly (4-9%) and with all patients (24-39%). Feldt and colleagues (1998) studied elderly patients undergoing hip fracture surgery, demonstrating a significant negative correlation between cognitive status and pain.

Researchers have found a similar association with chronic pain among nursing home residents. Cohen-Mansfield and Marx (1993) found a significant negative relationship between pain as measured by a simple numerical pain assessment tool and cognitive status in elderly nursing home residents (n=408).

Parmelee, Smith and Katz (1993) examined self-reported pain in 758 frail elderly residents of a nursing home and congregate apartment complex. They found a small but statistically significant negative correlation between both pain intensity and number of localized pain complaints and cognitive status. This relationship held when the effects of physical health and functional ability were statistically controlled. When specific types of pain complaints were analyzed, however, the relationship held for backaches and joint pains only. No differences in either intensity of pain or number of complaints were demonstrated for other types of pain including headaches, gastrointestinal and cardiac pain. Specific pain complaints were consistent with the identified possible physical cause, regardless of cognitive status, implying that pain complaints of cognitively impaired patients are genuine and accurate. The authors note that the pain complaints elicited in this study were in response to a structured assessment instrument. Their findings may not be generalizable to spontaneous reporting of pain or to patients with marked communication deficits.

It should also be noted that the authors of all of the studies cited above conclude that while their findings support the hypothesis that cognitive impairment interferes with reporting of pain it is not known whether the experience of pain is truly attenuated.

The inadequacy of pain assessment tools that rely on verbal self-report in cognitively impaired patients has been recognized by a number of researchers (Ferrell, 1995; Hadjistavropoulos et al., 1998; Krulewitch et al., 2000; Epps, 2001). There are

only a very limited number of studies of pain in dementia patients using non-verbal pain assessment tools.

Scherder and Bouma (2000) used visual analog scales to assess pain intensity and pain affect in three groups of subjects, early stage Alzheimer's disease (AD), midstage AD and cognitively intact. Those with both early and midstage AD reported experiencing less intense pain and less pain affect than control participants. The conclusions that can be taken from this study are limited by a small sample size of 20 in each group. Another limitation of the study is that, while the scales used to measure pain intensity were readily understood by those with Alzheimer's disease the instruments used to measure pain affect were not as well understood.

Hadjistavropoulos and colleagues (1998) used the Facial Action Coding System (FACS) to examine pain reactions in cognitively impaired and intact elderly patients. The FACS is a comprehensive and anatomically based coding system that offers an objective description of patterns of facial expressions (e.g., tongue show, eye blinks). Distinct patterns of facial activity have been demonstrated among patients experiencing pain (Hadjistavropoulos et al., 1998). Hadjistavropoulos and colleagues (1998) videotaped 59 elderly patients during a routine blood sampling procedure at baseline, swabbing and venepuncture. Their facial responses were then coded using the FACS to identify frequency and intensity of each facial movement. In contrast to the findings of Scherder and Bouma (2000), no significant difference in pain reactions was observed between the two groups.

In summary, there is little valid empirical evidence to support the hypothesis that pain is truly attenuated in patients with Alzheimer's disease. The evidence that exists in the literature involves small, often anecdotal case studies or is based on the assessment of pain by verbal self-report. In view of the well established understanding that cognitive deficits compromise verbal self-report, it seems unreasonable to assume that such self-reporting of pain accurately reflects the true experience of pain. Until there are a greater number of methodologically rigorous empirical studies using non-verbal pain assessment

tools, it cannot be said that pain is truly attenuated among patients with Alzheimer's disease.

2.4.5 Treatment of pain in cognitive impairment

There is, however, a small body of evidence suggesting that pain is treated differently in patients with dementia as compared to those who are cognitively intact.

Feldt, Ryden and Miles (1998) examined the treatment of pain in cognitively impaired versus intact patients following surgical repair of hip fracture (n=88). While *prescribed* amounts of both opioid analgesics and acetaminophen did not differ significantly, cognitively impaired patients were *administered* significantly less analgesic; the cognitively impaired patients received less than 25% of the mean prescribed opioid dosage. Cognitive status was found to have a significant main effect on the amount of opioid analgesic administered in the first 48 hours following surgery when controlling for age, illness severity, and creatinine clearance, which controls for dose reduction in response to decreased kidney function.

Bell and colleagues (1997) obtained similar findings. Retrospective chart review of 18 impaired and 18 intact older patients following orthopedic surgery demonstrated that the cognitively impaired patients received significantly less analgesic during the first 24 hours following surgery, and slightly less during the second and third 24 hour post-operative periods.

Horgas and Tsai (1998) studied analgesic use in 339 nursing home residents with a mean age of 87 (range 66-104). Residents with diagnosed cognitive impairment were significantly less likely to be prescribed and administered analgesic drugs than cognitively intact residents. Moreover, among residents who did receive analgesic agents, cognitively impaired residents were prescribed and administered significantly lower dosages than cognitively intact residents.

A study by Marzinski (1991) found that only 3 out of 26 patients with Alzheimer's disease were taking analgesic medication despite suffering from a variety of

painful conditions including metastatic colon cancer and degenerative joint disease. A large scale (n= 49,971) study by Won and colleagues (1999) examined the correlates and management of non-malignant pain in nursing homes in four US states from 1992-1995. Of those with documented daily pain, almost 25% were taking no analgesics. Regression analysis demonstrated that cognitive impairment was associated with a decreased likelihood of receiving analgesic medications.

Sengstaken and King (1993) examined pain in 100 nursing home residents. The study found that significantly fewer non-communicative than communicative residents received acetaminophen and other analgesics. Treating physicians identified chronic pain in 43% of the communicative patients and only 17% of the non-communicative patients. The only difference noted between those whose pain was identified and those whose pain was missed by the physician was a higher prevalence of neurological diagnoses among those whose pain was missed.

In their study of 217 nursing home patients, Ferrell and colleagues (1995) noted that while 62% of the patients reported pain complaints during the interview and on the pain questionnaire, none of the patients was systematically and routinely evaluated for pain. Moreover, while acetaminophen was ordered for 81% of those who reported pain, the exact order could not always be determined from the chart. They further observed that 21% of patients were unable to express their needs, and of those who did complain of pain, 17% were unable to complete any of the qualitative assessment scales. Cognitive impairment was a substantial barrier to pain assessment in this study. The researchers concluded that elderly patients with mild to moderate cognitive impairment often require time to assimilate questions about pain and to respond appropriately to such questioning due to their limited attention spans and distractibility. Unfortunately, facility staff frequently either does not take such time, or may not have the time.

Kaasalainen and colleagues (1998) report similar findings. They examined pain and pain management in 83 nursing home residents. Controlling for pain-related diagnoses, residents with cognitively impairment were both prescribed and administered significantly less pain medication than those who were cognitively intact. Moreover,

more cognitively intact (47%) than cognitively impaired (25%) residents had a scheduled pain medication. Administration of pain medication as a routine, scheduled dose is recognised to provide more effective analgesia than on an as needed basis (AGS Panel on Chronic Pain in Older Persons, 2002).

The findings are similar in studies of community dwelling older adults. Hanlon and colleagues (1996) conducted a survey of 4,110 subjects aged 65 and older in urban and rural North Carolina. Multivariate analysis revealed that participants with cognitive impairment were significantly less likely to take analgesics than those who were cognitively intact ($OR = 0.66, p = .001$).

The studies discussed above suffer from multiple methodological limitations. A number of the studies, including that of Marzinski (1991), Scherder and Bouma (1997), Bell and colleagues (1997), and Feldt and colleagues (1998) involved small samples. While the study by Horgas and Tsai (1998) included more than 300 participants, the findings must be interpreted with some caution because the amount of variance explained by the regression models is modest, (i.e., ranging from 2% to 6%). Factors, such as the presence of co-morbid conditions may play an important role in the prescription and administration of analgesics but were not included in the regression models. Similarly, while the study by Won and colleagues (1999) involved a large sample of almost 50,000, conclusions are limited by the fact that only those with mild cognitive impairment were included.

The limitations of the above studies notwithstanding, collectively they suggest that older patients with cognitive impairment receive fewer pain medications than others, despite the presence of chronic pain conditions.

2.4.6 Explanations of Lower Analgesic Use in Dementia

Scherder (2000) discusses three explanations that may underlie lower analgesic administration to cognitively impaired elderly:

1. decreased communication about pain;

2. fewer painful conditions;

3. decreased actual pain experience.

The latter two proposed mechanisms suggest that lower use of analgesic medication in persons with dementia is appropriate whereas the first points to a true undertreatment of pain.

The issue of decreased actual pain experience has been discussed above. As previously stated, while the physiological, psychological and cognitive changes that occur as a result of the disease process raise the possibility that changes in experience of pain may occur in patients with Alzheimer's disease, there is little valid empirical evidence in support of this hypothesis.

There is some evidence suggesting that the prevalence of some painful conditions, in particular, arthritis and other musculoskeletal diseases, is lower among Alzheimer's disease patients than others. Parmalee and colleagues (1993) note that a lower percentage of the subjects with marked cognitive impairment (29%) experienced joint pain than those who were cognitively intact (45%). Wolf-Klein and colleagues (1988) found a significant negative correlation between Alzheimer's disease and arthritis. Similarly, Schmader and colleagues (1998) reported that 58% of those in their study with Alzheimer's disease had arthritis compared with 70% who were cognitively intact.

A lower prevalence of painful conditions and arthritis in particular, does not, however, adequately explain the lower use of analgesics in dementia patients. Among elderly with arthritis and other painful conditions, use of analgesics is still found to be significantly lower among patients with dementia (Parmelee et al., 1993; Horgas and Tsai, 1998; Kaasalainen et al., 1998; Scherder et al., 1999).

Treatment of pain requires that the individual be recognized to be in pain. He or she must convey suffering, either verbally or in some other manner. Language deficits hinder self reporting of pain by interfering with either verbal expression or comprehension. An individual with memory deficits may simply not remember that he or

she is in pain, or having lost the memory of past pain, may not understand what he is experiencing. The memory and language deficits increase the risk that the individual's pain will be unrecognized and therefore, untreated.

Turk and colleagues (1985) observed that in the assessment of pain in all persons inadequate attention has been paid to the characteristics and range of behaviours (i.e. pain indicators) that should be included. Moreover, preconceived attitudes and beliefs about elderly persons with dementia may affect the assessment and treatment of pain in the residents. Kitwood (1990) observed a tendency to consider a person with dementia as a 'non-person'; to be properly considered a person, and of value, the individual must be seen as a sentient being. Once a person has the label of dementia, even normal behaviour can be interpreted in terms of the dementing process. Therefore, if a person with dementia becomes agitated or displays aggressive behaviour because he or she is suffering pain, such behaviour may be identified as a behavioural manifestation of the dementing illness and no further explanation is sought.

2.4.6.1 Greipp model of ethical decision making

The Greipp model of ethical decision making provides a framework for understanding the interaction between nurse and client. In this model, both nurse and client are seen as biological essences with physical and mental characteristics that have been shaped by their background and previous experiences, which for nurses will include professional education. The interaction is further influenced by a set of psychosocial and cultural variables which Greipp terms learned potential inhibitors: belief system; culture; personal and professional experiences. Nurses are also influenced by the ethical framework of their profession which includes principles of autonomy, beneficence, nonmaleficence, justice, responsibility and accountability for competence and the nursing process. The model is built on a deontological base (i.e. a fundamental belief in one's duty to other human beings).

Greipp (1992) has applied this model to pain management. The nurse's learned beliefs regarding pain and suffering and personal and professional experiences with pain management influence his or her approach to the client in pain. Yet these learned beliefs

are not necessarily based in fact. Misconceptions about pain medications may place the nurse's belief system in conflict with professional ethical standards. For instance, misplaced fear of the addictive potential or respiratory depression of opioid analgesics may cause the nurse to deny the client adequate analgesia by not offering medication, administering lower or less frequent doses, not reporting ineffective pain relief or not seeking more effective treatment for the client (Greipp, 1992). A positive professional experience with pain management (i.e. patients who receive pain relief) is likely to predispose the nurse to expect a positive outcome. In contrast, nurses who work with chronic pain sufferers may develop a pessimistic attitude, believing that pain management is not possible (Greipp, 1992). Cultural biases about pain include the attitude that everyone should suffer some pain in life, to build character.

The Greipp model offers a framework for understanding the treatment of pain in older persons with cognitively impairment. Moreover, while the model was developed with respect to nurses, it can apply equally to other healthcare professionals including physicians. Kane (2002) contends that multiple factors, including ageism, motivational issues and countertransferance have the capacity to affect the relationship between practitioner and patient.

2.5 Behavioural Disturbances in Dementia

Disturbances of behavior are common in dementia and are often the precipitating factor in nursing home placement (Dyck, 1997; Volicer et al., 1998). Cohen-Mansfield and Billig (1986) define disruptive behaviour as inappropriate behavior that is the result of unmet needs or confusion. They divide problem behaviors into four categories: aggressive; physically nonaggressive; verbally agitated; and hiding/hoarding behaviors. Aggressive behaviour is particularly disruptive as there is potential for harm to the individual or to others, but all of the above behaviours have a negative impact on the quality of life of the patient, family, and other residents in nursing homes and are a source of concern and increased burden to professional caregivers (Sourial et al., 2001).

Sourial and colleagues (2001) observed that over a two week period, 94.7% of the long term patients with dementia in their study (n=56) exhibited one or more agitated behaviours. This observation corroborated the findings of Cohen-Mansfield and colleagues (1989) who reported that 93% of those in the nursing homes they studied exhibited agitated behaviour (n=408). Dyck (1997) identifies four models of causation of dementia behavioural disorders: diminished adaptive capacity; stress; characterology; and neurobiology. The diminished adaptive capacity model suggests that the person with dementia becomes increasingly frustrated with his or her deteriorating ability to cope with everyday life and this frustration leads to agitation. The stress model focuses on the impact of multiple stressors in the lives of elderly patients with dementia, including the loss of status and autonomy. In contrast, the characterologic model suggests the cognitive losses that occur with dementia result in the breakdown of the socially imposed inhibitions. The individual can no longer use his established repertoire of learned social behaviours to moderate responses to irritation, annoyance and frustration. Finally, the neurobiologic model focuses on the neurochemical changes that take place as a result of the progression of the disease. Acetylcholine levels drop up to 90% in advanced cases; norepinephrine and serotonin and possibly dopamine levels are also affected. The implications of the imbalances in these neurochemical are not fully understood, but are believed to play a role in the expression of behaviour distrubances.

Each of the models identified above is consistent with the suggestion that untreated pain may present as disruptive behaviour. Closs (1996) identifies two types of behaviour that are seen in dementia that may indicate pain: vocal behaviour, including language, crying, screaming or moaning; and nonvocal behaviours including grimacing, posturing, guarding or rubbing.

Ryden, Bossenmaier and McLachlan (1991) observed that most of the aggressive behaviours observed among nursing home residents occurred with physical content or movement. The researchers concluded that pain triggered by the physical content or movement precipitated the aggressive behaviour.

Feldt, Warne and Ryden (1998) explored pain and pain assessment in residents of three nursing homes. The researchers found that residents with diagnoses of painful conditions had significantly higher aggressive behaviour scores than those with no pain-related diagnoses. Persons with arthritis had significantly higher aggression scores than those without. Patients with two or more pain-related diagnoses had a significantly higher mean aggression score. Huffman and colleagues (2001) reported similar results. In a study of 33 nursing home residents they found a significant positive correlation between discomfort and agitation scores ($r = 0.50, p = .003$). Multiple regression analysis revealed that after controlling for severity of dementia, agitation was significantly associated with discomfort ($R^2 = 0.14, p = 0.02$). Douzjian and colleagues (1998) conducted an informal study of residents in a 60 bed skilled nursing facility. They found that 650 mg of acetaminophen administered three times daily to residents with difficult behaviour decreased behavioural symptoms by 63%, suggesting that untreated pain was the underlying cause of the patients' behavioural symptoms.

Miller and colleagues (2000) suggest that lack of knowledge and inadequate pain assessment skills compromise the ability of health professionals to identify the source of much aggressive and agitated behaviour in dementia patients. Aggressive and agitated behaviour is distressing to caregivers, patients, families and other institutional residents. In their efforts to relieve such distress, caregivers and families may view sedative medication as the most practical management of such behaviours

2.6 Psychotropic Drug Use and Cognitive Status

The broad drug classification of psychotropic or psychoactive drugs includes over 1,500 agents that modify thought, mood or emotion and may be prescribed to treat disorders of mental function (Byck, 1975). Neuroleptics and anxiolytics, specifically, benzodiazepines, are two classifications of psychotropic agents commonly prescribed to manage behaviour symptoms exhibited by persons with dementia.

2.6.1 Neuroleptics

2.6.1.1 Mechanism of Action

An imbalance in neurotransmitters, in particular an increased level of dopamine, is believed to be responsible for clinical symptoms of psychoses such as hallucinations and delusions (Hagen & Armstrong-Esther, 1999; Comaty & Advocat, 2001). Neuroleptics or antipsychotic agents exert their effects by decreasing dopamine levels in the brain. Their primary mechanism of action is believed to be the blockade of dopamine (D_2) receptors. Blockade of D_2 receptors of the mesolimbic pathway is believed to be responsible for the therapeutic effects, especially decreasing hallucinations, delusions (Comaty & Advocat, 2001), distorted thinking and aggression (Jenike, 1988). Blockade of receptors of the nigrostriatal pathway may be responsible for some of the adverse effects, specifically the parkinsonian or extrapyramidal symptoms (EPS) and tardive dyskinesia (TD).[5] All neuroleptics also block serotonin ($5HT_2$) receptors resulting in a reduction in serotonin release. Serotonin acts on the D_2 receptors of the nigrostriatal pathway to inhibit the release of dopamine. Blockade of the $5HT_{2A}$ receptors may therefore, result in an increased release of dopamine within this pathway. The role this action plays in the therapeutic effects of the neuroleptics is uncertain. It is believed, however, to be important in the mechanism of adverse effects, especially EPS (Comaty & Advocat, 2001).

All neuroleptics also act on other neurotransmitter receptors. Blockade of muscarinic (cholinergic) receptors is responsible for numerous adverse effects, including blurred vision, urinary retention, sinus tachycardia, delirium and confusion (Jenike, 1988; Hagen & Armstrong-Esther, 1999; Comaty & Advokat, 2001) Adverse cardiovascular effects such as postural hypotension and reflex tachycardia result from antagonism of α_2 adrenoceptors. Blockade of histamine receptors causes sedation and drowsiness (Comaty & Advokat 2001). Individual agents vary in the degree to which they act on these

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[5] Decreased levels of dopamine are believed to be responsible for the clinical symptoms of Parkinson's disease.

neurotransmitter receptors. This variability is responsible for the differing side effect profiles of the drugs.

Neuroleptics are classified as either typical (traditional) or atypical (second generation). Typical neuroleptics are further classified into:

- phenothiazines (e.g. chlorpromazine, thioridazine, perphenazine)
- thioxanthenes (e.g. thiothixene)
- butyrophenones (e.g. haloperidol)

Atypical neuroleptics include the newer agents, clozapine, risperidone, olanzapine, and quetiapine. The primary difference between the typical and atypical neuroleptics is that the atypicals appear to produce fewer extrapyramidal symptoms and less tardive dyskinesia and appear to be more effective in the treatment of negative psychoses symptoms. The reason is believed to be that in contrast to the typical neuroleptics, the atypicals block the $5HT_2$ receptors to an equal or greater extent than they do the D_2 receptors (Pickar, 1995; Stoppe, Brandt & Staedt, 1999).

The adverse effects of the neuroleptics limit their clinical effectiveness, particularly in older patients who are particularly vulnerable to many of these side effects. For instance, sedation and orthostatic hypotension increase the risk of falls and hip fracture (Hagen & Armstrong-Esther, 1999; Ebly et al., 1997). Co morbid conditions of the gastrointestinal, urinary and sensory systems may compound the anticholinergic effects. Alzheimer's patients have a preexisting loss of cholinergic cells and decreased levels of choline acetyltransferase which is responsible for the production of acetylcholine. Therefore, they are especially vulnerable to the central anticholinergic effects of the neuroleptics (i.e. cognitive impairment and confusion; Jenike, 1988; Hagen & Armstrong-Esther, 1999; Comaty & Advokat, 2001). McShane and colleagues (1997) report a rate of cognitive decline in older demented patients taking neuroleptics twice that of those not taking these medications. Moreover, physiological changes which alter pharmacokinetics, (i.e., drug distribution, metabolism and excretion) may impact the

blood level and half life of the drugs (Jenike, 1988), increasing the risk of adverse effects in older patients.

The elderly are at particular risk for developing EPS and TD, particularly distressing and potentially dangerous adverse effects (Jenike, 1988; Comaty & Advokat, 2001). EPS are symptoms of movement, posture, equilibrium and muscle tone, including: dystonia (spasms and stiffness); parkinsonism (generalized rigidity and tremors); akathesia (restlessness including pacing); and akinesia (decreased or absent movement; Jenike, 1988). Tardive dyskinesia is a serious condition characterized by choreoathetoid movements of the face, tongue and jaw, (e.g., pill rolling) the limbs and trunk (Comaty & Advokat, 2001).[6] The effects may not be reversible on discontinuation of the drug and the syndrome may actually be masked by the effects of the drugs and become apparent only upon withdrawal of the medication or dose reduction (Garland, 1998).

The more favorable side effect profiles of the atypical agents, in particular the lower incidence of EPS and TD make them potentially more attractive for use with older patients (Comaty & Advokat, 2001; Salzman, 2001). These agents are not devoid of side effects, however. Because they all act, to varying degrees, on muscarinic, adrenergic and histamine receptors, the atypical agents share the side effect profiles of the classic agents which are the result of their action on these receptors (Comaty & Advokat, 2001).[7]

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[6] In some instances, the ability of the individual to eat, speak, walk and breathe is compromised While the onset of TD is usually gradual and related to long term, high dose therapy, it can occur regardless of dose (Jenike 1988). The early symptoms which include fine movements of the tongue, lip smacking, facial tics and mild movement of the fingers or toes are frequently missed or misinterpreted by caregivers (Jenike, 1988; Hagen & Armstrong-Esther, 1999).

[7] Clozapine and olanzapine have a low binding affinity for nigrostriatal dopamine D_2 and high anticholinergic activity compared with the other atypical agents may limit their usefulness in patients with Alzheimer's disease. Clozapine is associated with agranulocytosis (1% to 2%) and seizures (5%) and requires weekly blood work (Garland, 1998), further limiting its usefulness.

2.6.1.2 Efficacy in Persons with Dementia

Helms (1985), Salzman (1987), Devand and colleagues (1988), and Sunderland and Silver (1988) have conducted qualitative reviews of studies examining the efficacy of neuroleptics in the treatment of agitation and related behaviour symptoms in dementia. They conclude that the cumulative body of evidence indicates that the neuroleptics are at best moderately effective in the treatment of selected behaviours (e.g. agitation), in geriatric patients with or without dementia.

Helms (1985) examined 21 studies. He considered only three of these studies to be methodologically rigorous. The remaining 18 studies suffered from such limitation as failure to include a control group or placebo comparison and the inclusion of widely differing diagnostic groups in the samples. Helms concluded that the three good quality studies failed to provide solid evidence that neuroleptics offer effective and efficient treatment for dementia related behaviour symptoms.

Devanand and colleagues (1988) and Sunderland and Silver (1988) respectively identified 15 and 20 double-blind studies examining the use of neuroleptics among older adults. Both sets of reviewers conclude that only limited evidence exists to support the hypothesis that neuroleptics are effective and efficient agents in this population. Ten of the 20 studies examined by Sunderland and Silver (1988) were placebo-controlled; five showed a positive effect, and three no effect for the neuroleptics used. Moreover, two of the studies demonstrated a negative effect for the drugs. Devanand and colleagues (1988) conclude that relatively low doses may be useful in selected patients who exhibit certain behavioural symptoms, although the evidence is weak that symptoms such as suspiciousness, hallucinations, sleeplessness, agitation, emotional lability and aggressiveness will respond to such treatment.

Salzman (1987) reviewed 69 reports, of which about 50% were controlled studies and 60% involving treatment in older patients with dementia. He concluded that, on the basis of these studies, there is evidence of modest therapeutic efficacy of the neuroleptics in the symptomatic management of agitation in elderly patients with or without dementia. He further concludes that all the neuroleptics studied were equally efficacious.

Schneider and colleagues (1990) conducted a meta-analysis of 33 studies. Seventeen of these studies were placebo controlled. A number of these studies had methological limitations, including non-randomized sample selection and diagnostic heterogeneity in the samples. Twenty of the 33 studies compared a neuroleptic with another agent, but only five compared two neuroleptics, in all cases, thioridazine and haloperidol. The reviewers conclude that the meta-analyses confirm the findings of Salzman (1987). Schneider and colleagues (1990) conclude that the relatively small effect size (*ES* = .18) is nevertheless clinically significant when considered in the context of the improvement rate of behavioral symptoms; 18 % of patients with dementia may be denied improvement if not treated with neuroleptics. Schneider and colleagues (1990) note that a high placebo response rate up to 67% is an important consideration, however, and they observe that a substantial number of older people with dementia may receive neuroleptics unnecessarily since they would have responded to those factors associated with placebo treatment or continued to receive the medications despite improvement in their symptoms. Moreover, the reviewers note that contrary to claims made by some of the authors of those studies examined, none demonstrated a statistically significant improvement over placebo.

Stoppe and colleagues (1999) note that the interpretation of clinical studies is further complicated by the heterogeneity of the study populations and use of questionable diagnostic criteria. Differing neuropathology may impact response to drugs. For example, Dementia of the Lewy Body Type is associated with a higher rate of sensitivity reactions to neuroleptics as compared to other forms of dementia (Stoppe et al., 1999). Thus, a lower benefit to risk ratio would be expected. Furthermore, since some symptoms such as verbal and physical agitation, hostility and hallucinations have been demonstrated to respond more favourably to neuroleptics than symptoms such as wandering, unsociability and screaming, distinction among behavioural symptoms is important, but is generally not evident in the current literature (Stoppe et al., 1999).

The review articles cited above examined the typical neuroleptics. Stoppe and colleagues (1999) and Comaty and Advokat (2001) review the current literature regarding the use of atypical neuroleptics in dementia.[8] The use of these agents in younger adults with schizophrenia has been studied extensively but there are limited numbers of clinical studies in the geriatric population.

Stoppe and colleagues (1999) reviewed 15 studies. Five studied clozapine and ten involved risperidone. The reviewers note numerous methodological limitations. For instance, only two of these studies were multicentre randomized double-blind, placebo controlled trials with large samples, (625 and 344 respectively and studied risperidone). Six of the remaining 13 studies were case reports involving small numbers of patients. Moreover, most failed to address other important issues such as the effect of the medication on different behaviours and whether the effect was immediate or delayed, short or long term. Stoppe and colleagues (1999) conclude that the evidence presented in these studies suggests that atypical neuroleptics may be useful in the treatment of behavioural disorders in dementia. They note, however, that due to the limited quantity and quality of the published data the tolerability and effectiveness of these agents for the treatment of dementia cannot be established unequivocally at this time.

Comaty and Advokat (2001) arrive at similar conclusions. They contend that the current literature suggests that risperidone produces the most favourable benefit: risk ratio for the treatment of behavioural symptoms in dementia, although some evidence exists to suggest that olanzapine and quetiapine may have similar profiles. They note, however, that more research is required to establish the efficacy of the atypical neuroleptics in the treatment of elderly dementia patients.

In summary, the modest efficacy of the neuroleptics must be considered within the context of the side effect profile of these agents. The adverse effects of neuroleptics can be distressing and in many cases, have serious consequences. Therefore, the potential

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[8] Atypical neuroleptics are included for completeness in the literature review, although availability was limited during 1991/1992 when data that was used in this thesis was collected.

benefits of treatment with neuroleptics must be carefully balanced with the potential adverse consequences of the medication.

3.6.2 Benzodiazepines

Benzodiazepines are also used to manage agitation and aggressive behaviour in persons with dementia.

2.6.2.1 Mechanism of Action

The precise mechanism of action of the benzodiazepines has not been determined but is believed to be related to their affinity for specific receptors within the central nervous system (CNS), that are binding sites for gamma aminobutyric acid (GABA). GABA, the primary inhibitory neurotransmitter in the CNS acts by increasing the influx of chloride ions into the neuron which hyperpolarizes and stabilizes the neuronal membrane. The result is a net inhibition of neuronal firing. The presence of the benzodiazepine molecule at the GABA receptor enhances the affinity of the receptor for GABA which then potentiates this inhibitory effect. The potency of the individual agent depends on its affinity for the binding sites. Varying areas of the CNS have different types of receptors; the actions of the drugs depend upon their affinity for these different receptors (Gillis, 1999).

Individual benzodiazepines differ with respect to potency and pharmacokinetics and are divided into three categories on the basis of half-life ($t_{1/2}$). Long acting benzodiazepines such as chlordiazepoxide, diazepam and flurazepam have half-lives of approximately 100 hours. Intermediate acting agents have half lives ranging from 5-15 hours (oxazepam) to 20-80 hours (clonazepam) and include alprazolam, lorazepam, clonazepam, oxazepam and temazepam. Midazolam ($t_{1/2}$ = 1 - 4 hours) and triazolam ($t_{1/2}$ = 1.5 - 5 hours) are examples of short acting agents (Gillis, 1999). Another important distinction among agents is the existence of an active metabolite. In general, longer acting agents also have active metabolites which contribute to the long half-lives. Benzodiazepines also differ in their lipophilic tendencies. All agents are lipophilic meaning that they tend to accumulate in lipid rich areas of the CNS and in adipose tissue.

The more lipophilic the drug is, the faster its rate of absorption and onset of action. Diazepam and triazolam have fast (less than one hour) onsets of action; alprazolam and lorazepam have intermediate onsets (one to three hours) and oxazepam is slow acting (more than 3 hours). Pharmacokinetic characteristics are primary determinants of both therapeutic and adverse effects of the benzodiazepines. Moreover, the half lives of these agents tend to be elongated in older as compared to younger adults which significantly complicates dosing.

2.6.2.2 Efficacy in the treatment of dementia behavioural disorders

Therapeutic uses of benzodiazepines include the management of anxiety and panic disorders, insomnia, seizure disorders and as skeletal muscle relaxants. Because of their efficacy as anxiolytics, benzodiazepines have been prescribed to manage agitation in persons with dementia (Banazak, 1996; Marsh, 1997; Rockwood, 1998). Several sources recommend the use of benzodiazepines as a temporary measure to treat agitation and anxiety in persons with dementia (Jenike, 1988; Marsh, 1997; Rockwood, 1998; Gillies, 1999). Agents with short half-lives such as lorazepam and oxazepam are frequently used on an 'as required basis' to control agitation occurring at specific times such as bathing (Marsh, 1997). There is, however, a paucity of empirical evidence supporting the efficacy of benzodiazepines in the management of agitation and aggression in dementia.

Sanders (1965) evaluated the use of oxazepam in elderly patients. A double-blind, placebo controlled randomized trial (n=94) found a significant reduction in target symptoms and improvement in overall function in the treatment group. This study which was conducted in the early 1960's did not identify the cognitive status of the participants nor differentiate specific behavioural symptoms. Target symptoms included a wide range of behaviours and problems, such as anxiety, tension, depression, agitation, lethargy, insomnia and obsessive thinking. It is questionable, therefore, whether this study can be taken as evidence of the efficacy of benzodiazepines in the treatment of dementia behaviour disorders.

Elderly patients are particularly vulnerable to the adverse effects of the benzodiazepines, in particular somnolescence and increased confusion. Drowsiness, for

example, can increase the risk of falls. Moreover, senescent changes in drug distribution and metabolism lengthen the duration of action and result in increased accumulation of the drug in the body. The long acting agents should be avoided in older patients for this reason (Jenike, 1988; Rockwood, 1998; Gillies, 1999).

In summary, the use of benzodiazepines with older adults with dementia for the management of behavioural symptoms must be carefully considered by examining the risk to benefit ratio.

2.6.3 Empirical evidence

There is some evidence of an inverse relationship between cognitive status and prescription of psychotropic drugs. Macdonald and colleagues (2002) investigated the prevalence of dementia and the use of psychotropic drugs in a sample of 445 nursing home residents. The researchers found a strong association between antipsychotic drug use and MMSE scores and dementia related behavioural problems. The rate of use of antipsychotic drugs was highest for those with severe cognitive impairment, moderate for those with moderate dementia and lowest for those with mild or no cognitive impairment.

A large scale population based study by Willis and colleagues (1997) of elderly residents of Stockholm demonstrated that 45% of the participants with dementia compared with 38% of those identified as cognitively normal used psychotropic agents. More patients with dementia (22%) than cognitively normal persons (3.5%) used antipsychotic drugs.

2.7 Research Questions

While studies have shown that cognitively impaired older persons receive fewer analgesic medications (Marzinski, 1991; Sengstaken & King, 1993; Ferrell, Ferrell & Rivera, 1995; Hanlon et al., 1996; Bell et al., 1997; Scherder & Bouma, 1997; Feldt et al., 1998; Horgas & Tsai, 1998; Won et al., 1999) and more psychotropics (Willis et al., 1997; Mort & Aparasu, 2001; Macdonald et al., 2002), few, if any have simultaneously examined the prevalence of prescription of both types of medications among persons with

dementia in relation to painful conditions. The Canadian Study of Health and Aging (CSHA Working Group, 1994), a randomized population based study, provides an opportunity to conduct such analyses.

Since language and memory deficits are associated with cognitive loss it is possible that pain will be misidentified in patients with cognitive loss. Untreated or under treated pain may manifest in behavioural symptoms which may be misdiagnosed as dementia related behavioural disturbance and consequently treated with psychotropic medications, in particular, neuroleptics and benzodiazepines. Figure 1 outlines a model of the above progression from the presence of pain to prescription of psychotropic medication.

Following from this, it is hypothesized that:

1. Among elderly people with painful conditions, specifically arthritis and rheumatism the use of analgesics will be significantly associated with cognitive status.

    1.1. Patients with cognitive impairment, specifically an Alzheimer presentation, will be less likely to receive analgesics as compared to those who are cognitively intact.

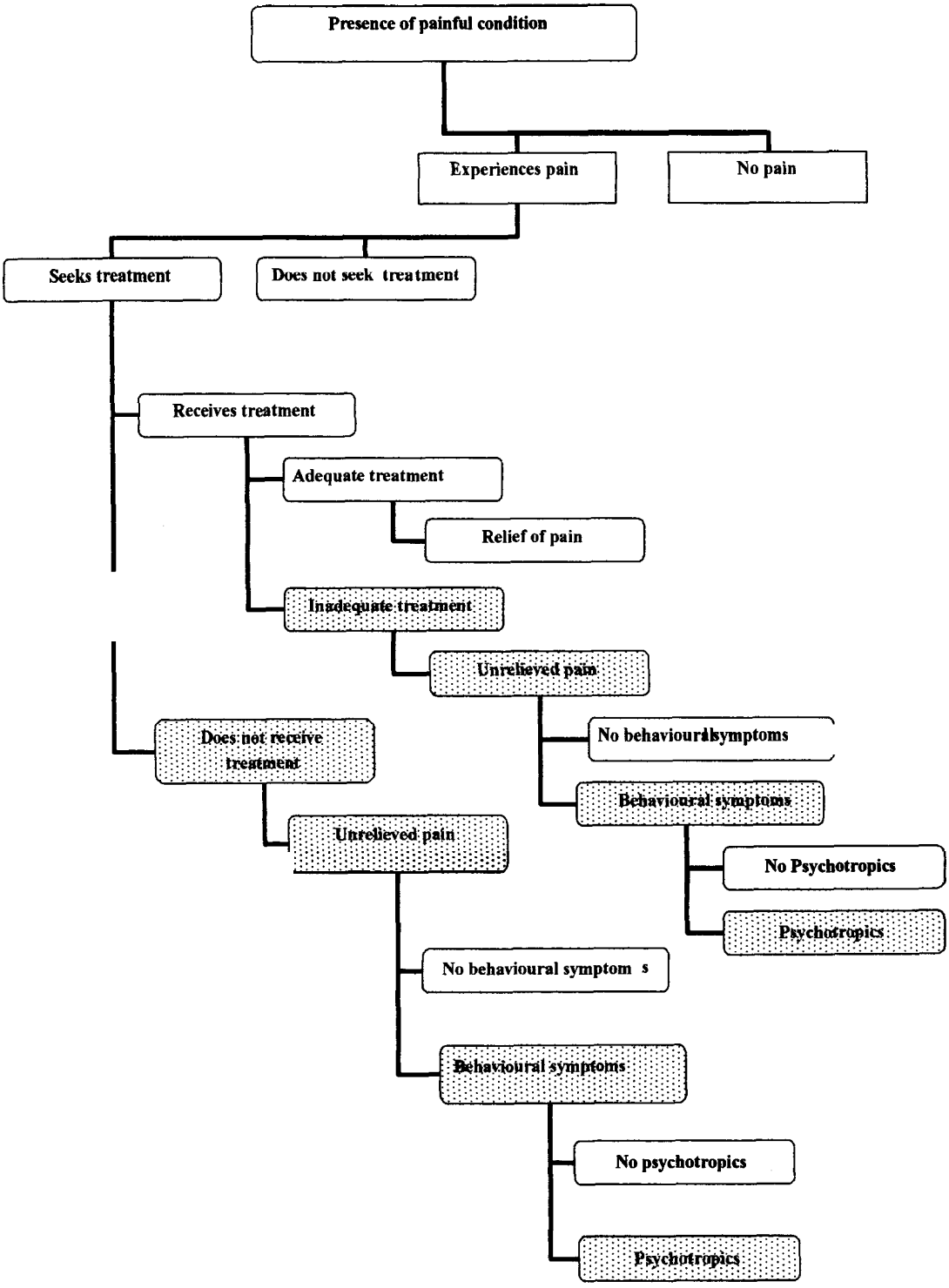
    1.2. The relationship between cognitive status and use of analgesics will vary according to the severity of cognitive impairment.

        1.2.1. More precisely, severe impairment will be associated with lower analgesic use.

2. Among elderly patients with Alzheimer's disease and a painful condition the use of psychotropic medications, specifically neuroleptics and benzodiazepines will vary with the severity of dementia.

    2.1 Psychotropic use will be highest among those with moderate severity and lowest among those with mild impairment.

Figure 1: Model



Chapter Three: Methods

3.1 Procedures

This thesis involves a secondary analysis of the data from The Canadian Study of Health and Aging (CSHA Working Group, 1994). The CSHA is a population based study developed in response to the challenges presented by the aging of the Canadian population, specifically to estimate the prevalence of dementia among elderly Canadians, identify risk factors for dementia of the Alzheimer type, describe current caregiving patterns and establish a data-base for further studies (Aylesworth, 1998).

The CSHA was a collaborative effort by the Department of Epidemiology and Community Medicine, University of Ottawa and the Division of Aging and Seniors, Health Canada, with funding from the federal Seniors' Independence Research Program, administered by the National Health Research and Development Program. There were 18 study centres across Canada in all ten provinces. The first phase of data collection, from which data used in this thesis is derived, took place between February, 1991 and May, 1992.

The CSHA included both a community and institutional component. The community sample (n =9,008) was drawn from both urban and rural areas of Canada in each province. Participants were selected randomly from the computerized records of the provincial health care plans, with the exception of Ontario where the sampling frame was the Enumeration Composite Record. Participants for the institutional component (n=1,255) included residents of nursing homes, chronic care facilities and collective dwellings. In three of the eighteen study centres, institutionalized participants were selected randomly from the provincial health insurance lists. In each of the remaining fifteen centres, participants were randomly selected from a stratified random sample of 17 institutions in each region (CSHA Working Group, 1994). The total number of participants was 10,263.

All subjects were over 64 years of age as of October 1, 1990. Participants were selected in the age groups 65 to 74, 75 to 84 and 85 and over, and due to oversampling for the older groups the sampling fraction among the oldest group was 2.5 times that among the youngest group. Individuals who were not fluent in either French or English or who had a life-threatening illness such as terminal cancer were excluded. The Yukon and Northwest Territories, Indian reserves and military units were not included in the sampling frame.

While all subjects took part in the screening phase of the study, a sub- sample of 3,659 individuals was selected for clinical assessment. Community residing participants were screened for cognitive status using the Modified Mini-Mental State (3MS; Teng & Chui, 1989) examination. Participants who scored below 78 on the 3MS (n=1,614), those unable to be screened for any reason (n=59) and all institutional participants (n=1,255) were invited to undergo the clinical assessment. In addition, a sample of 731 community dwelling individuals who screened above 78 on the 3MS was included. Complete clinical data were obtained for 2,914 participants.

The Modified Mini-Mental State (3MS) was chosen as a measure of cognitive status in the CSHA after a review of 18 cognitive screening tools determined that the 3MS offered optimal coverage of relevant aspects of cognitive impairment, quality of documentation and validity. The 3MS is believed to be superior to the MMSE in scope, sensitivity and sophistication of scoring system (CSHA Working Group, 1994). The cut-off point of 77/78 was determined based on the original work of Teng and Chui (1989) and the results of the CSHA pilot study (CHSA Working Group, 1994). Higher scores indicate a higher level of cognitive status. Responses to the 3MS have demonstrated high internal consistency. Tombaugh, McDowell, Kristjansson and Hubley (1996) obtained a Cronbach's alpha of $\alpha = .88$ for the subtests comprising the measure for the population of community dwelling Alzheimer's patients in the CSHA-1. Tombaugh and colleagues (1996) also demonstrated that the 3MS has a high level of specificity and sensitivity in detecting cognitive impairment.

The clinical assessment was conducted in four stages. A nurse conducted the first stage of the assessment which included a standardized history, a second administration of the 3MS, and a brief physical examination. A listing of all current medications, prescribed and non-prescribed was included in the clinical assessment with duration of use but not dosage or frequency or indications for use. This was obtained by self-report when possible, proxy and/or from the medical record in the case of institutionalized subjects. The American Hospital Formulary Service (AHFS) system was used to code medications. The nurse also administered an Informant Interview that consisted of Section H of the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX). Section H of the CAMDEX includes questions regarding personality, mental functioning, mood, sleep and behaviour.

In the second stage of the assessment, a psychometrician administered a series of neuropsychological tests of memory and new learning, including:

1. Buschke Cued Recall
2. Wechsler Memory Scale: information subtest
3. Rey Auditory – Verbal Learning Test
4. Benton Visual Retention Test (Revised)
5. WAIS-R Digit Span
6. Working Memory Test

Abstract thinking was assessed using the WAIS-R Similarities Short Form and judgment using the WAIS-R Comprehension Short Form. Tests of language fluency included:

1. Token Test (11 items)
2. Lexical Fluency (Words)
3. Semantic Fluency (Animals)
4. WAIS-R Digit Symbol
5. Buschke Visual Component

Only participants with a score of 50 or greater on the 3MS underwent these tests. The results of the above tests, the CAMDEX and the 3MS were reviewed by a neuropsychologist. A physician reviewed the data collected by the nurse, conducted a physical and neurological examination and made a preliminary diagnosis. Selected hematological and biochemical tests were performed on participants to arrive at a preliminary diagnosis. The final diagnosis of cognitive status was determined by

consensus at a multidisciplinary case conference, integrating data available for each individual.

At the case conference, all participants were categorized with no cognitive loss, cognitive loss but not dementia, Alzheimer's disease, vascular dementia, other specific dementia or unclassified dementia. Diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria for dementia. Consensus diagnoses are understood to be most accurate for cognitive status (Katzman & Jackson, 1991). The diagnosis of dementia was further classified as to severity based on the assessment of short and long term memory, verbal abstract thinking, judgment, and other higher cortical functioning including language, motor activities, recognition and identification of objects and construction of figures and designs. The categories of severity are defined as follows:

1. **Mild**: work and social activities are significantly impaired but capacity for independent living remains. Adequate personal hygiene and judgment are relatively intact
2. **Moderate**: independent living is hazardous. Some degree of supervision necessary
3. **Severe**: continual supervision is essential. Minimal personal hygiene not possible to maintain independently. Individual largely incoherent or mute.

(American Psychiatric Association, 1987)

The diagnosis of Alzheimer's disease (probable or possible) was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). According to these criteria, the diagnosis of probable Alzheimer's disease requires:

- Dementia as established by clinical examination and documented with the Mini-Mental test, Blessed Dementia Scale or similar examination and confirmed by neuropsychological tests
- Deficits in two or more areas of cognition
- Progressive deterioration of memory and other cognitive functioning
- No disturbance of consciousness
- Onset between age 40 and 90
- Absence of systemic disorder or other brain disease that could account for the progressive memory and cognitive deterioration

The diagnosis of possible Alzheimer's disease is made on the basis of:

- Presence of dementia syndrome in the absence of other neurologic, psychiatric or systemic disease that would cause dementia
- Presence of variations in the onset, presentation or clinical course
- Presence of another systemic or brain disorder that could produce dementia but is not considered to be the cause

(McKhann et al., 1984)

The diagnosis of cognitive loss, not dementia (CIND) included the following subcategories: delirium; chronic alcohol abuse; chronic drug intoxication; depression; psychiatric disease; age associated mental impairment; mental retardation; multiple diagnoses; cerebral vascular (stroke); general vascular; Parkinson's disease; brain tumor; epilepsy; socio-cultural; social isolation; multiple sclerosis; blindness or deafness.

The variables required for the analyses undertaken for this thesis were not contained in a single set of data. Rather, five data sets were utilized: the Screening, Doctor, Caregiver and Proxy Files from CSHA-1 and the Linking File. The Linking File which assimilates three phases of the CSHA study, CSHA-1, the Maintaining Contact study (MCS) and CSHA-2 provides basic demographics and data on clinical diagnosis. The screening questionnaire, administered to 8,949 participants gathered information regarding basic demographics and social support, activities of daily living, cognitive status, and health status. Health problems in the past year were assessed based on self-perception of the presence of common health problems e.g. arthritis or rheumatism. The Proxy questionnaire gathered similar information for an additional 2,560 participants incapable of self-reporting. The Doctor file contains the data from the clinical assessment. The Caregiver file contains the data from the Caregiver questionnaire which was administered to caregivers of participants with the diagnosis of dementia.

Table 1 outlines the source of the variables used in this analysis. The Linking file was chosen as the most complete data source for diagnostic category, indicators of severity of dementia and sociodemographic characteristics (Aylesworth, 1998).

Table 1: Source of Variables

Measure	*Source Data Set*	*CSHA source variable*
Diagnostic category	Linking File	SUMM1DX
Severity of dementia	Linking File	CLIN1SEV
Presence of arthritis	Screening File, Proxy File	ARTHRI, ARTHIT
Age	Linking File	CSHA1AGE
Problematic Behaviours	Caregiver File	DBDSCORE
Medications	Doctor File	Drug 1 – Drug 12
Other demographics	Linking File	MARSTAT, IC

3.2 Characteristics of the study sample

The study sample for this thesis consisted of 1,475 individuals, categorized on the basis of the presence or absence of arthritis or rheumatism (n= 856, arthritis or rheumatism; n = 619, no arthritis or rheumatism) who fell into one of three diagnostic categories, (cognitively normal [n = 863]; Probable Alzheimer's disease [n = 373]; and Possible Alzheimer's disease [n = 239]).

Figure 2 outlines the derivation of the study sample from the total CSHA-1 study sample. Complete clinical data exists for 2,914 individuals. Information regarding both

the presence or absence of arthritis or rheumatism[9] and the severity of dementia[10] was available for 2,492 individuals. Of these 2,492 individuals, 1,425 are identified as having, and 1,067 as not having arthritis or rheumatism. Of the 1,425 individuals with arthritis or rheumatism, 856 individuals fell into one of three target diagnostic categories (cognitively normal, [n= 532]; probable Alzheimer's disease, [n=198]; possible Alzheimer's disease, [n=126]). Of the 1,067 without arthritis or rheumatism, 619 individuals fell into one of these three categories (cognitively normal, [n=331]; probable Alzheimer's disease, [n=175]; possible Alzheimer's disease, [n=113]).

The study sample range in age from 65 to 106 years (M = 81.16, SD = 7.38). The number of years of education ranged from 0 to 25 years (M = 8.98, SD = 3.98). They were predominantly female (66.1%) with an overall male: female ratio of 500:975. The majority of the participants (53.0%) were widowed and lived in the community (68.8%). Slightly more than one-half of the study sample was cognitively intact (58.5%). Of the 612 individuals with Alzheimer's disease, the majority (76.9%) had either moderate (38.7%) or severe (38.2%) dementia, whereas slightly less than one-quarter had mild dementia (23.0%).

Tables 2 and 3 show the sociodemographic characteristics of the sample dichotomized by the presence of arthritis/rheumatism and cognitive status respectively. As shown in Table 2, the arthritis group contained a significantly greater proportion of women (arthritis, 71.3%; non-arthritis, 59.0%; $p<.001$), widows and widowers (arthritis, 55.6%; non-arthritis, 49.4%; $p<.05$) and of those identified as cognitively intact (arthritis, 62.1%; non-arthritis, 53.5%; $p<.05$) than the non-arthritis group.

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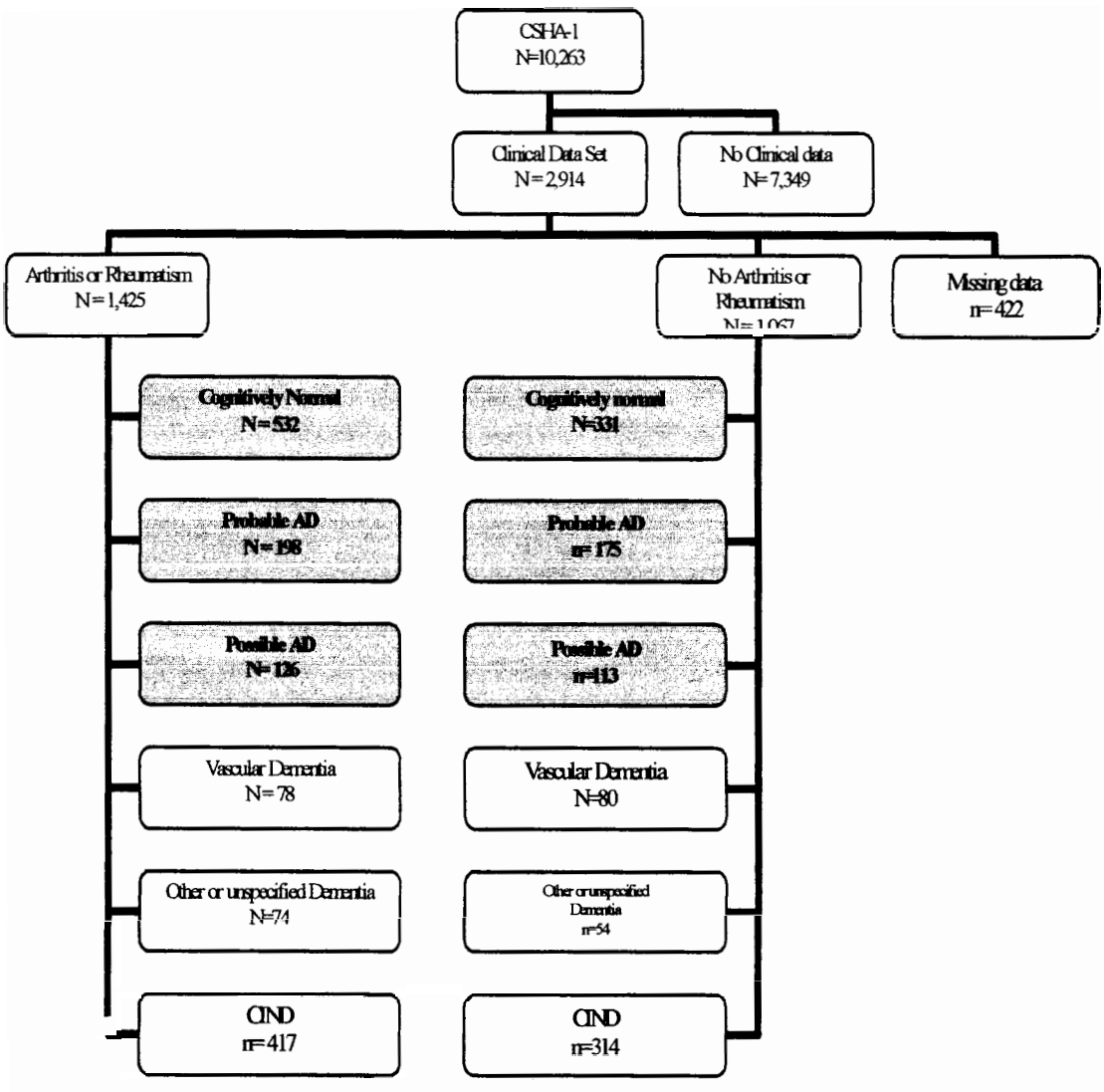
[9] From the screening and proxy questionnaires.

[10] From the Linking File.

As shown in Table 3, the Alzheimer's disease (AD) group[11] was significantly older than the cognitively intact group, ($p<.001$) and contained a significantly greater proportion of women (AD, 73.0%; cognitively intact, 61.2%; $p<.001$), and widows or widowers (AD, 62.9%; cognitively intact, 46.0%; $p<.001$) and institutional residents (AD, 57.0%; cognitively intact, 12.9%; $p<.001$). A significantly lower proportion of those in the AD group were identified as having arthritis or rheumatism (AD, 52.9%; cognitively intact, 61.6%; $p<.01$) than those in the cognitively intact group.

[11] Henceforth, Alzheimer's disease includes those with probable and possible Alzheimer's disease.

Figure 2: Derivation of Study Sample



Shaded boxes indicate inclusion in study population
AD = Alzheimer's Disease
CIND = Cognitive impairment, not dementia

Table 2: Sociodemographic Characteristics of Study Sample by Presence or Absence of Arthritis or Rheumatism

	Arthritis or Rheumatism *n*= 856	**No Arthritis or Rheumatism *n*=619**	*p*
Age (years); Mean	81.23	81.06	
SD	7.24	7.56	*ns*
Education (years)			
Mean	8.85	9.15	
SD	3.96	4.00	*ns*
Gender			
Female	610 (71.3%)	365 (59%)	$p<.001$
Residence			
Institution	264 (30.8%)	196 (31.7%)	*ns*
Marital status			
Never married	91 (10.6%)	63 (10.2%)	$p<.05$
Married/common-law	258 (30.2%)	231 (37.0%)	
Divorced/separated	26 (2.8%)	14 (2.2%)	
Widowed	476 (55.6%)	306 (49.4%)	
Missing	7 (0.8%)	5 (0.8%)	
Cognitive status			
Intact	532 (62.1%)	331 (53.5%)	$p<.05$
Mild AD	73 (8.5%)	68 (11.0%)	
Moderate AD	124 (14.5%)	113 (18.3%)	
Severe AD	127 (14.8%)	107 (17.3%)	

Table 3: Sociodemographic Characteristics of Study Sample by Cognitive Status

	Cognitively Intact *n*= **863**	**Probable or Possible Alzheimer's Disease** *n*= **612**	*p*
Age (years)			
Mean	79.00	84.21	
SD	6.96	6.85	$p<.001$
Education (years)			
Mean	9.28	8.49	
SD	4.07	3.77	*ns*
Gender			
Female	528 (61.2%)	447 (73.0%)	$p<.001$
Residence			
Institution	111 (12.9%)	349 (57.0%)	$p<.001$
Marital Status			
Never married	84 (9.7%)	70 (11.4%)	
Married/common-law	343 (39.7%)	146 (23.9%)	$p<.001$
Divorced/separated	29 (3.2%)	9 (1.5%)	
Widowed	397 (46.0%)	385 (62.9%)	
Missing	10 (1.1%)	2 (0.4%)	
Arthritis or rheumatism			
yes	532 (61.6%)	324 (52.9%)	$p<.01$
no	331 (38.4%)	288 (47.1%)	

3.3 Data Analysis

The data were analyzed using the statistical software program SPSS. Univariate analysis was performed to describe the socio-demographic characteristics, health and cognitive status characteristics of the study sample and patterns of medication use within the sample. Bivariate analyses were then undertaken to examine the relationships between the dependent variables, the independent variables of primary interest and the control variables. Finally, logistic regression was performed to test study hypotheses.

3.3.1 Dependent Variables

Four medication variables were chosen as the dependent variables. These included two types of analgesics, non-steroidal anti-inflammatory agents (NSAIDs)[12] and acetaminophen, and the two classes of psychotherapeutic agents of interest, neuroleptics and benzodiazepines. Each medication variable was computed by counting occurrences of each of the drugs in these categories in the current drug variables, Drug 1 through Drug 12 in the nurse's component of the clinical assessment. A detailed description of the individual drugs included in each medication variable is found in Appendix B.

3.3.1.1 Analgesics

Non-steroidal anti-inflammatory agents (NSAIDs) and acetaminophen were chosen as the analgesics of interest because each is usual and recommended treatment for arthritis and rheumatism (Goodman & Gilman, 1975; Paton & Bell, 1998; Peloso, 1998; Sloane et al., 2002). Three additional types of analgesics, opioids, muscle relaxant and analgesic compounds, and acetylsalicylic acid compounds were not included in the analyses. Opioid analgesics and muscle relaxants were excluded because of the low frequency of use within the study population. While the frequency of use of the acetylsalicylic acid compounds was higher than that of the opioid and muscle relaxant

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[12] Note: Acetylsalicylic Acid (ASA) was not included in NSAIDs.

combinations, these agents were also excluded from the final analyses. Bivariate analyses failed to demonstrate statistically significant relationships between this type of analgesic and either cognitive status or the presence of arthritis or rheumatism. Moreover, a number of agents such as Anacin^{R,} Fiorinal^{R,} Midol^{R}, 692^{R} and 217^{R} were included in this category, each of which is a combination of different drugs, with differing therapeutic indications including conditions other than arthritis or rheumatism. Unfortunately, differentiation amongst the individual agents was impossible because the same code (N02BA61) was used for all of these agents. Therefore, all agents coded with N02BA61 were excluded from the multivariate analyses.

3.3.1.2 Psychotropics

Neuroleptics and benzodiazepines were chosen as the psychotropic agents of interest on the basis of clinical indications for use and frequency of usage within the study population.[13]

3.3.2 Independent Variables

The variables of primary interest were the presence of arthritis or rheumatism, cognitive status, the level of severity of dementia, and dementia related behavioural problems. Sociodemographic variables and type of residence (institution vs. community) were included based on the findings of previous research suggesting significant associations between drug use and sociodemographic characteristics (Paterniti et al., 1999; Phillips et al., 2000) and higher drug use among older adults living in insititutions as compared with those living in the community (Furniss, Craig & Burns, 1998).

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[13] Other agents that are recommended for the management of agitation and aggression in patients with dementia including carbamezepine, valproic acid, buspirone and trazadone have other therapeutic indications such as seizure disorders and depression and would therefore introduce numerous confounding variables.

3.3.2.1 Cognitive status and severity of dementia

The consensus diagnosis was the measure of cognitive status. Similarly, the measure of severity of dementia used in the analyses was that determined during the case conference and recorded in the Linking File.

3.3.2.2 Dementia Behaviour Disorder Score

The Dementia Behaviour Disorder Score was the measure of frequency of dementia related behaviours. In CSHA-1, problematic behaviours were measured using the Dementia Behavior Disturbance Scale (DBD) (Baumgarten, Becker & Gauthier, 1990). The DBD scale consists of 28 questions pertaining to behaviours such as verbal abuse and physical attacks and rates the frequency of such behaviours on a 5 point Likert-type scale from never (0) to all the time (4). The items are listed in the Appendix A. Responses to this scale have previously demonstrated internal consistency, test-retest reliability. Construct validity of responses to the DBD has been demonstrated relative to the Behavior and Mood Disturbance (Tuokko, Kristjansson, & Miller, 1995). The items of the DBD focus on specific manifestations of dementia rather than functional and somatic symptoms and cognitive deficits. Internal consistency of responses to the DBD by participants in the current study was measured as $\alpha = .87$.[14] Therefore, responses to this scale may be considered a reliable measure of problematic behaviours.

A total score was computed for each individual with higher scores indicating more frequent and more numerous problematic behaviours. Detailed instructions for the computation of the total score or DBDSCORE are available in Appendix A, Program 5 of the Caregiver Coding Manual for CSHA-1.

This measure was administered to caregivers of participants with a diagnosis of dementia. The respondent was the person most closely involved in assisting and

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[14] SPSS Reliability analysis (Scale- Alpha), Correlation matrix.

providing care for the participant, usually a spouse or adult daughter. In some cases, the respondent was a paid professional such as a nurse. Because the DBD was only administered as part of the Caregiver Study, values were available for only 262 of the 619 individuals in the study population. Therefore, imputed values estimated using the PRELIS program (Jöreskog & Sörbom, 1996) were incorporated to supplement the actual values such that a DBD score was available for a total of 470 individuals. The PRELIS program imputes values based on like-responses, a method considered preferable to mean substitution which can obscure group differences (Little & Rubin, 1987). Table 4 presents the mean, standard deviation, range, skewness and kurtosis of the DBD scale for the two variables of primary interest in this thesis: the presence or absence of arthritis or rheumatism; and severity of dementia. These statistics are consistent with univariate normality.[15]

The interval form of the variable was used for the regression analyses. For the bivariate analyses an ordinal variable with three categories was constructed: 0 – 12 (33.2%), 13 – 23 (36.4%) and 24 and over (30.4%). These points of delineation were chosen to construct three categories of approximately equal size that reflected low, moderate and high frequency of dementia related behaviours.

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[15] For skewness and kurtosis, absolute values of less than 3 indicate univariate normality (Lomax, 2001).

Table 4: Dementia Behaviour Scale

	n	Mean	*SD*[16]	Range	Skewness	Kurtosis
Arthritis						
yes	248	19.04	12.84	0 – 76	1.23	2.49
no	219	19.33	13.35	0 – 66	.81	.24
Total	467	19.18	13.07	0 - 76	1.02	1.32
Severity						
Mild	117	10.62	8.43	0 – 39	.80	.25
Moderate	178	21.35	13.75	0 – 73	.80	.29
Severe	172	22.76	12.40	2 – 76	1.30	2.43
Total	467	19.18	13.07	0 - 76	1.02	1.32

3.3.3 Rationale for selection of arthritis or rheumatism as pain indicator

The presence of arthritis or rheumatism was chosen as an indicator of the presence of pain on the basis of prevalence of the condition and usual pharmacological pain management. Arthritis and rheumatism are chronic conditions highly prevalent in the older population (Parmalee, Smith & Katz, 1993; Sengsten, & King, 1993; Ferrell, Ferrell, & Rivera, 1995; Millar, 1996). Arthritis/rheumatism was the most common chronic condition (48.9%) identified by participants who received the clinical assessment. It is reasonable to assume that individuals suffering from these conditions will experience disease-related pain. Furthermore, analgesics such as non-steroidal anti-inflammatory

[16] Standard deviation

agents and acetaminophen are indicated in the management of chronic pain of musculoskeletal origin (Paton & Bell, 1998; Peloso, 1998).

The two next most common ailments, high blood pressure (32.8%) and heart disease (30.5%) do not satisfy the above mentioned conditions. High blood pressure is typically painless. Pain related to heart disease is managed primarily with nitroglycerin, beta blockers and calcium channel blockers rather than standard analgesics (Parker & Parker, 1998).

It would have been desirable to include a direct measure of pain; however, this was not available in CSHA-1. The screening questionnaire for the follow up study, CSHA-2 conducted in 1996 included two measures of pain:

- Variable S20: How much bodily pain have you had during the past 4 weeks?
- Variable S21: During the past 4 weeks, how much did pain interfere with the following things? Mood; Ability to move about; Sleep; Normal tasks; Recreational activities; Enjoyment of life

As a result of attrition, mostly due to death, the size of the population of primary interest decreases substantively in CSHA-2. As a result, the numbers of individuals in subgroups of interest also decreases. Furthermore, it is questionable whether the above measures of the presence and severity of pain would be useful for this analysis given that lower usage of analgesics in cognitively impaired individuals is related to communication deficits and consequent under-reporting due to cognitive impairment and decreased recognition of pain in these patients. As a result of the above considerations, the data from CSHA-1 were chosen for this analyses and the presence of a painful condition (i.e., arthritis or rheumatism) was chosen as an indicator of pain.

3.3.4 Residence

The sampling frame of CSHA-1 included participants in both institutions and the community. Because a greater percentage of the participants with dementia were institutionalized, it was desirable to include both components in the analyses for this thesis. It was necessary to control for residence (i.e., institution vs. community) in the

regression analysis, since the patterns of use of the medications may differ by type of residence. For example, since acetaminophen is an over- the- counter medication, individuals living in the community may self-medicate, whereas in an institution, all medications must be prescribed by a physician and administered by institutional staff. In addition, the bivariate analysis indicated that the patterns of use of the other medications vary according to type of residence.

3.3.5 Sociodemographic variables

Age, gender and education were included as control variables in the analyses. As discussed earlier, evidence in the literature suggests that the pharmacological treatment of pain varies with the age of the patient. In addition, there is some evidence of significant associations between demographic factors and cognitive status (Swanwick et al., 1999; Fillingim, Edwards & Powell, 2000; Fillingim & Ness, 2000). The interval forms of the variables for age and education in years were included in the logistic regression analysis. For the bivariate analysis, however, 'age' was recoded into three groups, 65-74, 75-84 and 85 +. Table 5 presents the mean, standard deviation, range, skewness and kurtosis for the interval variables, age and education.[17]

[17] For skewness and kurtosis, absolute values of less than 3 indicate univariate normality (Lomax, 2001).

Table 5: Age and Education (n = 1,475)

	Mean	***SD***	**Range**	**Skewness**	**Kurtosis**
Age (years)	81.2	7.4	65 – 106	-.005	-.29
Education (years)	9.0	4.0	0 – 25	.36	.31

SD = standard deviation

3.4 Missing Values

Valid values were missing for 57 cases on the education variable and on 152 cases for the DBD score. These cases were therefore excluded from the logistic regression analyses reducing the working sample size for the two sets of regressions to 799 and 403 respectively.

3.5 Power and effect size

The regression analyses conducted to predict analgesic use included eight independent variables. The sample size of 799 is sufficient to detect a small effect size at the alpha = .05 level, assuming power of .80 (Cohen, 1992). The regression analyses conducted to predict psychotropic use included ten independent variables. The sample size of 403 is sufficient to detect a large to medium effect size at the alpha = .05 level (Cohen, 1992)

Chapter 4: Results

This chapter presents and interprets the results of the data analyses. A summary of medication use for the total sample is first presented, including bivariate analyses. Results of bivariate analyses and logistic regression analyses conducted to test the hypotheses follow. Finally, a summary description of the individual benzodiazepine agents and neuroleptic classes is presented.

4.1 Medication use in total study sample

Table 6 summarizes the medication use of the study sample.

Table 6: Frequency (%) of Medication Use in Study Sample

Medication	N = 1,475	%
Analgesics		
Acetaminophen		
One	297	20.1
Two +	23	1.6%
ASA compounds		
One	290	19.7
Two	7	0.5%
NSAIDs		
One	161	10.9
Two	2	0.1
Opioids		
One	11	0.7
Two	11	0.7
Psychotropics		
Neuroleptics		
One	136	9.2
Two	8	0.5
Benzodiazepines		
One	285	19.3
Two	25	1.7

4.2 Analgesic use in study sample

Of the 1,475 individuals in the study sample, 593 (40.2%) took at least one analgesic medication. As is evident in Table 3, the most common analgesic was acetaminophen, followed by ASA compounds. The least common class of analgesic was the opioid class.

4.2.1 Bivariate analysis

Bivariate analyses were conducted to investigate the direction and magnitude of the associations between the dependent variables and the independent variables. Correlations ranging from zero to $r = .20$ indicate a weak association, those between $r = .20$ and $r = .40$ a moderate association and those where over $r > .40$ a moderate to strong association. In this thesis, the dependent variables are the use of each of the four medications. The independent variables used in the bivariate analyses are nominal and ordinal. Likelihood ratio chi-square and Kendall's tau-c have been used to indicate the magnitude of association between the independent and dependent variables. Likelihood ratio chi-square is used when one of variables is nominal. Fisher's exact test of significance is used when the expected frequency is small (Vogt, 1999). Kendall's tau-c is used for ordinal variables when the number of rows and column cells is unequal.

This section presents a summary of the bivariate analyses conducted to examine the relationships between the two analgesic medications of primary interest and the independent variables to be considered in the hypothesis testing.

4.1.1 Analgesic use by presence of arthritis or rheumatism

Two by two chi-square tests demonstrated statistically significant relationships between the presence of arthritis or rheumatism and the use of each of the analgesic medications of interest. There was a weak positive relationship between acetaminophen

use and having arthritis (Likelihood ratio[18] χ^2= 27.422, *df* = 1, *p*<.001). A larger proportion of those with arthritis (26.4%) took acetaminophen than those without (15.2%). There was a weak positive relationship between the use of NSAIDs and having arthritis, (χ^2 = 69.340, *df* = 1, *p*<.001). A larger proportion of those with arthritis (16.5%) took NSAIDs than those without arthritis (3.6%).

4.2.1.2 Analgesic use by cognitive status

Two by two chi-square tests demonstrated weak, statistically significant relationships between cognitive status and analgesic use. The relationship between NSAID use and cognitive status was in the expected direction; a higher proportion of cognitively normal participants (14.0%) took NSAIDS than those with dementia[19] (6.9%), χ^2= 19.642, *df* = 1, p<.001. The relationship between the use of acetaminophen and dementia, however, was in the opposite direction (χ^2= 64.962, *df* = 1, *p*<.001). A larger proportion of participants with dementia (32.0%) took acetaminophen than those who were cognitively normal (14.4%).

Statistically significant relationships were demonstrated between severity of dementia and analgesic use, although the relationships were different for the two analgesics.

The use of acetaminophen was positively associated with severity of dementia, (Kendall's tau-c = .206, *p*<.001). A greater proportion of those with severe dementia (43.2%) took acetaminophen than those with moderate (28.3%) or mild (19.9%) dementia or who were cognitively intact (14.4%).

The relationship between NSAID use and severity of dementia was statistically significant but appeared to be non-linear (Kendall's tau-c = -.080, *p*<.001). NSAID use

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[18] Likelihood ratio χ^2 henceforth referred to as χ^2.

[19] In this thesis, those with dementia includes persons with a diagnosis of Probable or Possible Alzheimer's disease.

was highest among the cognitively normal group (14.0%) and lowest among the group with severe dementia (2.6%). However, NSAID use was higher among those with moderate (10.1%) than mild dementia (8.5%).

4.2.1.3 Analgesic use by age group

A weak, inverse relationship between age and NSAID use was indicated (Kendall's tau-c = -.037, $p<.05$). NSAID use was higher among the youngest group (13.2%) than either the middle (11.6%) or the oldest group (8.5%). The weak positive relationship between acetaminophen use and age (Kendall's tau-c, $p<.001$) was contrary to expectation. A greater proportion (31.2%) of the oldest age group, 85 and older took acetaminophen than either the middle age group, 75 to 84 (19.9%) or the youngest group, 65 to 74 (12.9%).

The results of the above bivariate analyses are summarized in Table 7 and illustrated in Chart 1.

Chart 1: Analgesic Use (%)

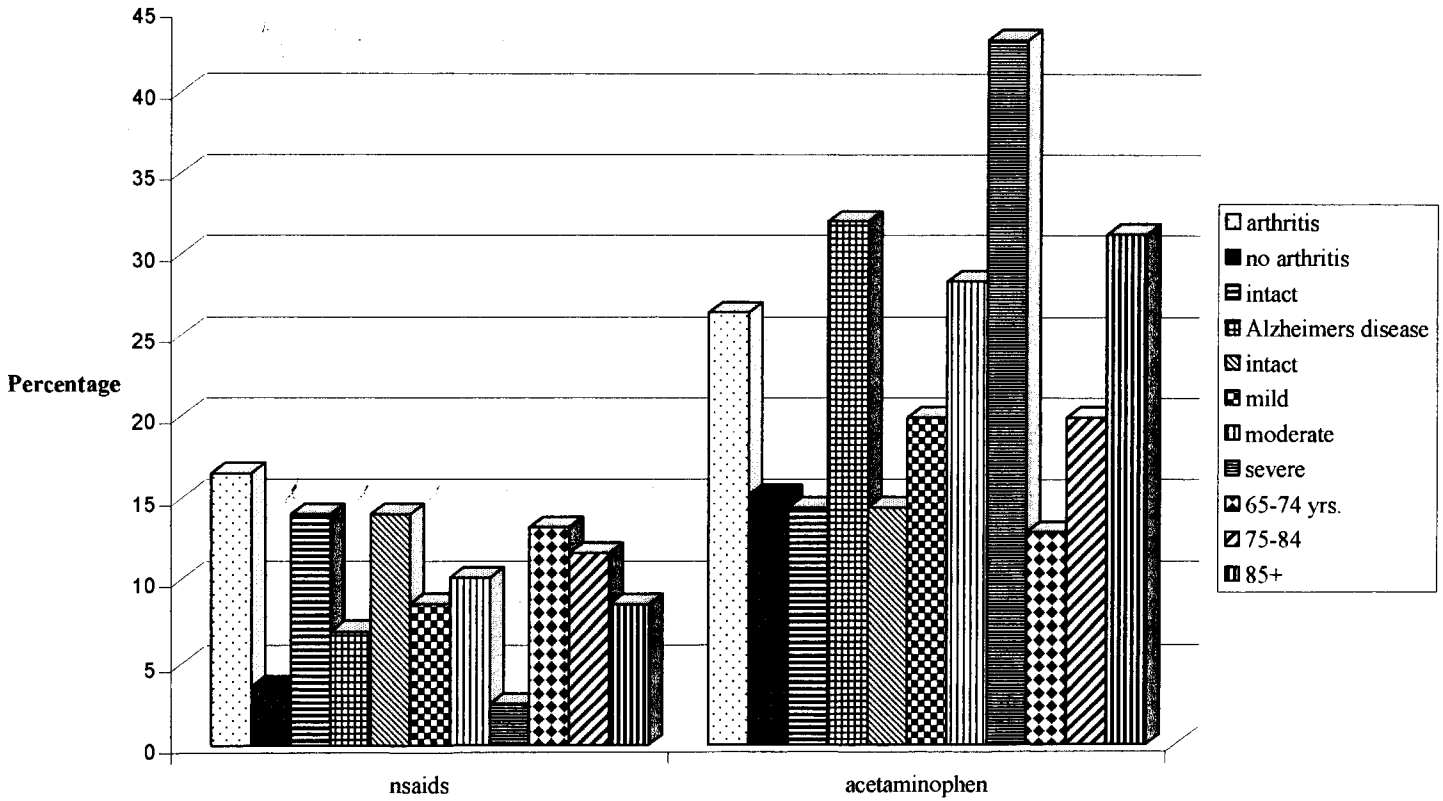

Table 7: Frequency (%) of analgesic use by the presence of arthritis, cognitive status, severity of dementia and age group (n= 1,475)

	Medication	
Variable	**NSAIDS**	**Acetaminophen**
Presence of Arthritis or Rheumatism		
Yes	141 (16.5%)[20]	226 (26.4%)
No	22 (3.6%)	94 (15.2%)
Likelihood Ratio χ^2	69.340***	27.422***
df	1	1
Cognitive Status (Diagnosis)		
Intact	121 (14.0%)	124 (14.4%)
Alzheimer's Disease	42 (6.9%)	196 (32.0%)
Likelihood Ratio χ^2	19.642***	64.962***
df	1	1
Severity of Dementia		
Intact	121 (14.0%)	124 (14.4%)
Mild Dementia[21]	12 (8.5%)	28 (19.9%)
Moderate Dementia	24 (10.1%)	67 (28.3%)
Severe Dementia	6 (2.6%)	101 (43.2%)
Kendall's tau-c	- .08***	.21***
Age Group		
65 to 74	43 (13.2%)	42 (12.9%)
75 to 84	83 (11.6%)	143 (19.9%)
85 +	37 (8.5%)	135 (31.2%)
Kendall's tau-c	-.037*	

***p<.001, ** p<.01, * p<.05

[20] Row %: Columns cannot be added

[21] Includes those with a diagnosis of probable or possible Alzheimer's disease

4.2.1.4 Analgesic use by diagnosis (cognitive status) controlling for the presence of arthritis

To further examine the relationship between analgesic use and cognitive status the relationship was reanalyzed controlling for the presence of arthritis or rheumatism. The results are presented in Table 8.

Table 8: Frequency (%) of Analgesic Use by Diagnosis controlling for Presence of Arthritis or Rheumatism

	Acetaminophen		**NSAIDS**	
Arthritis or Rheumatism	Intact (*n*=863)	Alzheimer's Disease (*n*=612)	Intact (*n*=863)	Alzheimer's Disease (*n*=612)
Yes (*n*=856)	108 (20.3%)	118 (36.4%)	111 (20.9%)	30 (9.3%)
χ^2	26.408***		21..131***	
df	1		1	
No (*n*=619)	16 (4.8%)	78 (27.1%)	10 (3.0%)	12 (4.2%)
χ^2	62.694***		.588, ns	
df	1		1	

Note: *df* = degrees of freedom; $p<.05$*, $p<.01$**, $p<.001$***

4.3 Psychotropic use in total study sample

Of the 1,475 individuals in the study sample, 414 (28.1%) took at least one psychotropic medication. As indicated in Table 3, a higher percentage of the sample took benzodiazepines (21.0%) than neuroleptics (9.7%).

4.3.1 Bivariate analysis of psychotropic use

Bivariate analyses were conducted to examine the relationships between each of the two psychotropic medications and the independent variables.

4.3.1.1 Psychotropic use by cognitive status and severity of dementia

It was expected that psychotropic use would be positively associated with the presence of dementia. Contrary to expectation, only the relationship between neuroleptics and dementia was statistically significant. A 2 x 2 chi-square test indicated that the relationship between benzodiazepines and a diagnosis of Alzheimer's disease was not statistically significant (χ^2= 2.290, *df* = 1, *ns*).

A 2 x 2 chi-square test indicated a moderate positive association between neuroleptic use and a diagnosis of Alzheimer's disease (χ^2= 173.042, *df* = 1, $p<.001$). A greater proportion of those with Alzheimer's disease (21.4%) took neuroleptics than those who were cognitively intact (1.5%). This result was observed as hypothesized.

It was also expected that psychotropic use would be associated with severity of dementia such that drug use would be highest among those with moderate dementia and lowest among those with mild dementia. Contrary to expectation, the relationship between benzodiazepine use and severity of dementia was not statistically significant (Kendall's tau-c = .023, *ns*). However, the relationship between neuroleptic use and severity of dementia was statistically significant (Kendall's tau-c = .247, $p<.001$). Neuroleptic use was highest among those with severe dementia (38.9%). The results of the analyses are summarized in table 9.

Table 9: Frequency (%) of Psychotropic Use by Diagnosis and Severity of Dementia[22]

	Neuroleptics	**Benzodiazepines**
Diagnosis		
Cognitively intact	13 (1.5%)	193 (22.4%)
Alzheimer's Disease	131 (21.4%)	117 (19.1%)
χ^2	173.042***	2.290, ns
df	1	1
Severity of Dementia		
Cognitively intact	13 (1.5%)	193 (22.4%)
Mild Dementia	4 (2.8%)	25 (17.7%)
Moderate Dementia	36 (15.2%)	39 (16.5%)
Severe Dementia	91 (38.9%)	53 (22.6%)
Kendall's tau-c	.247***	.023, *ns*

Note: *df* = degrees of freedom; * $p<.05$, ** $p<.01$, *** $p<.001$

[22] Row %; Columns cannot be added

4.3.1.2 Psychotropic use by presence of arthritis

Two by two chi-square tests indicated statistically significant relationships between psychotropic use and the presence of arthritis. A weak positive relationship was demonstrated between benzodiazepine use and the presence of arthritis, ($\chi^2 = 8.3$, $df = 1$, $p < .01$). A larger proportion of the arthritis group (23.6%) took benzodiazepines than the non-arthritis group (17.4%). A weak inverse relationship was demonstrated between neuroleptic use and the presence of arthritis, ($\chi^2 = 4.2$, $df = 1$, $p < .05$). A slightly smaller proportion (8.4%) of the arthritis group took neuroleptics than the non-arthritis group (11.6%).

4.4 Hypothesis One

4.4.1 Analgesic Use in Arthritic Group

For the purpose of testing the hypothesis, the analyses of analgesic use were restricted to the arthritis group (n=856). The small number of NSAIDs used by non-arthritics made interpretation of the results difficult. Moreover, restriction of the analysis of analgesic use to arthritics allows more meaningful analysis. It is a reasonable assumption that those with arthritis or rheumatism will experience pain and that analgesic use will be related to that pain, as suggested by the statistically significant relationship demonstrated between the use of both acetaminophen and NSAIDs and the presence of arthritis. While it is possible that some analgesic use is related to pain from conditions other than arthritis, excluding non-arthritics reduces this possibility.

Of the 856 individuals identified as having arthritis or rheumatism, slightly more than one-half (56%) were taking at least one analgesic medication. The most common analgesic taken was acetaminophen (26%), followed by ASA compounds (20%),

NSAIDs (16.5%) and opioids (1.5%). The analysis will focus on acetaminophen and NSAIDs to test the hypotheses.[23]

4.4.2 Analgesic use by cognitive status and severity of dementia

It was hypothesized that analgesic use would be associated with cognitive status such that analgesic use would be lower among those with dementia than those who are cognitively intact. Two by two chi-square tests demonstrated statistically significant relationships between cognitive status and the use of both acetaminophen and NSAIDs. Contrary to expectation, however, the relationships were in opposite directions.

The weak inverse relationship between the presence of dementia and NSAID use was consistent with expectation (χ^2= 21.13, df =1, p<.001). A smaller proportion of those with Alzheimer's disease (9.3%) took NSAIDs than those who were cognitively normal (20.3%).

Whereas a weak positive relationship between the presence of dementia and acetaminophen use was observed (χ^2=26.41, df=1, p<.001). A larger proportion of those with Alzheimer's disease (36.4%) took acetaminophen than those who were cognitively normal (20.3%). This result was contrary to the one hypothesized.

It was further hypothesized that analgesic use would vary by severity of dementia such that more severe dementia would be associated with lower analgesic use. Small cell size, specifically in the severe dementia category precluded meaningful analysis of NSAID use by severity of dementia.

Contrary to expectation, a 2 x 4 cross tabulation demonstrated a weak positive relationship between severity of dementia and acetaminophen use (Kendall's tau-c =.18,

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[23] Opioids were excluded because of low usage. ASA compounds were excluded for two reasons. Firstly, this classification included a variety of different agents (e.g. Fiorinal ®) with various therapeutic indications other than arthritis or rheumatism. These agents were indistinguishable from one another since the same code was used for all. Secondly, preliminary bivariate analysis failed to demonstrate a statistically significant association between use of this class of analgesic and cognitive status.

$p<.00$). A greater proportion of those with severe dementia (45.7%) took acetaminophen than those with moderate (33.9%) or mild dementia (24.7%) or with no cognitive impairment (20.3%).

4.4.3 Analgesic use by age group

It was expected that analgesic use would be inversely associated with age; older patients would use fewer analgesics than younger patients. Two by three cross tabulation analyses demonstrated statistically significant relationships between age and the use of both analgesics. Contrary to expectation, however, the direction of the relationships differed by medication.

Consistent with hypothesis one, a weak inverse relationship between NSAID use and age was found (Kendall's tau-c = -.076, $p<.01$). A smaller proportion of the oldest age group, those age 85 and over (11.0%) took NSAIDS than either middle age group, those age 75-84 (17.9%) or the youngest group, age 65-74 (20.7%).

Contrary to expectation, a weak positive relationship between acetaminophen use and age was indicated (Kendall's tau-c = .16, $p<.01$). A larger proportion of the oldest age group (36.6%) took acetaminophen than either the middle age group (24.9%) or the youngest group (15.8%).

4.5 Hypothesis Two

4.5.1 Psychotropic use among Alzheimer's disease patients

For purposes of testing the hypotheses, analysis of psychotropic use was restricted to the Alzheimer's group (n=612). The small numbers of cognitively intact individuals who took neuroleptics made interpretation of the analysis difficult. Indeed, it would not be expected that cognitively normal individuals, unlike patients with Alzheimer's disease, would be prescribed neuroleptics for the purpose of controlling dementia related problem behaviours. Comparing neuroleptic use between the two groups is therefore, suspect. Moreover, valid DBD scores were available only for a very limited number (7.2%) of the cognitively normal individuals.

4.5.2 Psychotropic use by Dementia Behavior Disorder Score

It was expected that the use of psychotropic drugs would be associated with the presence of dementia behaviour disorder such that drug use would be highest among those who exhibited the most problem behaviours. Consistent with expectation, a weak positive relationship was indicated between neuroleptic use and DBD score (Kendall's tau-c = .19, $p<.001$). A higher proportion of those in the group with the highest DBD scores (32.4%) took neuroleptics than those in either the middle group (17.1%) or the group with the lowest scores (10.3%).

Contrary to expectation, a 2 x 3 cross tab test of benzodiazepine use by DBD score failed to attain statistical significance, (Kendall's tau-c = -.044, *ns*).

It was hypothesized that an interaction effect between the presence of arthritis or rheumatism and problem behaviours would be observed such that the psychotropic use would be higher among those with arthritis than those with no arthritis. To test for this interaction effect, the above analyses were repeated controlling for the presence of arthritis.

The analyses failed to detect an interaction effect. The original relationship between dementia behaviour and the use of neuroleptics was replicated for both the arthritis and non-arthritis groups ($\chi^2= 8.65$, $df= 3$, $p<.05$ [arthritis]; $\chi^2= 15.67$, $df= 3$, $p<.001$ [no arthritis]). The relationship between dementia behaviour and the use of benzodiazepines failed to achieve statistical significance for both the arthritis and the non- arthritis group ($\chi^2= .170$, $df= 3$, *ns* [arthritis]; $\chi^2= 3.24$, $df= 3$, *ns* [no arthritis]).

4.5.3 Psychotropic use by severity of dementia

It was hypothesized that psychotropic use would be associated with the level of severity of dementia such that use would be highest among those with moderate dementia. Consistent with expectation, a 2 x 3 cross tabulation test indicated a statistically significant relationship between neuroleptic use and severity of dementia (Kendall's tau-c = .311, $p<.001$). Contrary to expectation, however, a higher proportion

of those with severe dementia (38.9%) than those with mild (2.8%) or moderate dementia (15.2%) used neuroleptics.

A 2 x 3 cross tab test failed to demonstrate a statistically significant association between benzodiazepine use and severity of dementia (Kendall's tau-c = .049, *ns*).

4.5.4 Psychotropic use by age

Since both the likelihood and consequences of adverse drug effects increase with age, it was expected that physicians would prescribe fewer psychotropics for their oldest patients resulting in an inverse association between age and psychotropic use. Consistent with expectation, a 2 x 3 cross tab test indicated a statistically significant relationship between age and neuroleptic use (Kendall's tau-c = -.094, $p<.05$). A higher proportion of the youngest age group (40.9%) took neuroleptics than either the middle (19.6%) or the oldest group (18.5%).

Contrary to expectation, a 2 x 3 cross tabulation test failed to demonstrate a statistically significant relationship between age and benzodiazepine use (Kendall's tau-c = -.007, *ns*).

4.5.5 Psychotropic use by residence

Two by two chi-square tests indicated statistically significant relationships between residence and prescription of both neuroleptics and benzodiazepines. The association was moderate in strength for neuroleptics and weak for benzodiazepines. A higher proportion of institutional residents (32.7%) took neuroleptics than community dwellers (6.5%), ($\chi^2 = 68.6$, $df = 1$, $p<.001$). Similarly, a greater percentage of institutional (23.8%) than community (12.9%) residents took benzodiazepines, ($\chi^2 = 11.8$, $df = 1$, $p=.001$).

Since the relationship between neuroleptic use and residence is likely to be the result of an interaction between severity of dementia and residence, the analysis was repeated controlling for severity of dementia. Small numbers of mild dementia patients taking neuroleptics and severe dementia patients in the community make analysis of the

results somewhat difficult. Neuroleptic use was higher among institutional than community residents with mild (12.0% [institutions], 0.9% [community]) and moderate dementia (22.3% [institutions], 8.8% [community]) and the relationships are statistically significant ($\chi^2 = 6.5$, $df = 1$, $p < .05$ [mild]; $\chi^2 = 8.5$, $df = 1$, $p < .01$ [moderate]). While the relationship appeared to hold for those with severe dementia also, (0.9% [institutions], 22.7% [community]) it failed to retain statistical significance ($\chi^2 = 2.9$, $df = 1$, *ns*).

4.6 Summary of bivariate analysis

4.6.1 Hypothesis one

The bivariate analyses provided mixed support for the hypothesis that analgesic use would be lower among older patients with dementia than those who are cognitively intact. A weak inverse relationship was indicated between NSAID use and the presence of dementia; a lower percentage of those with dementia took NSAIDs than those who were cognitively intact. This finding supports the hypothesis; however, a weak positive relationship was indicated between acetaminophen use and the presence of dementia as a higher percentage of those with dementia took acetaminophen than those who were cognitively intact. This finding does not support the hypothesis.

The bivariate analyses also failed to support the hypothesis that analgesic use would be inversely associated with severity of dementia. A weakly positive linear association between acetaminophen use and dementia severity was indicated by the bivariate analyses. Small cell size precluded analysis of NSAID use using cross tabulation.

4.6.2 Hypothesis two

The bivariate analyses appear to provide mixed support for the hypothesis that psychotropic use would be associated with severity of dementia and the presence of a painful condition. The analyses indicated a positive association between neuroleptic use and severity of dementia. The relationship was not as expected as neuroleptic use was highest among those with severe dementia. Moreover, the relationship between

neuroleptic use and dementia severity was the same regardless of the presence of arthritis. Furthermore, the relationship between dementia behaviour disorder and neuroleptic use also remained the same regardless of the presence of arthritis. This finding does not appear to support the hypothesis that the symptoms of unrelieved pain are misdiagnosed as dementia behaviour disorder and treated with neuroleptics.

Bivariate analyses failed to demonstrate statistically significant relationships between benzodiazepine use and any of the explanatory variables of interest. The hypothesis does not appear to be supported for the use of benzodiazepines.

4.7 Multivariate Analyses

Logistic regression was chosen because it is considered a rigorous statistical technique for multivariate analysis involving dichotomous dependent variables, and in particular, those with skewed distributions as indicated by the four medication variables [24] (DeMaris, 1995). An extension of linear (OLS) regression, logistic regression relates one or more explanatory variables to a dependent variable yielding regression coefficients, predicted values and residuals[25] (Wright, 1995). This technique overcomes the problems encountered when modeling a dichotomous dependent variable using OLS regression by transforming the dependent variable (Y) into a log (DeMaris, 1995; Wright, 1995; Wister & Dean, 1998). This transformation produces an S shaped or sigmoid curve such that the predicted values always fall between 0 and 1 (Wright, 1995; Wister & Dean, 1998). DeMaris (1995) states that the logit formulation expresses the probability of Y = 1 as a closed-form expression: $P(Y=1) = \pi = \exp(\alpha + \beta_k X_k / 1 + \exp(\alpha + \beta_k X_k)$ which can be linearized by using a logit transformation on the probability π. Thus, the equation becomes: $\log(\pi/1-\pi) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_k X_k$, such that the right hand side of the equation is now a linear function of the explanatory variables. The beta coefficients (β)

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[24] NSAIDs, not taking (88.9%), taking (11.1%); Acetaminophen, not taking (78.3%), taking (21.7%); Neuroleptics, not taking (90.2%), taking (9.8%); Benzodiazepines, not taking (79%), taking (21%).

[25] Residuals are computed as the actual minus predicted value of the dependent variable (Wright, 1995).

are "maximum likelihood estimates for the linear regression of the latent dependent variable in log form on the explanatory variables" (Wister & Dean, 1998, p. 10).

The exponential of the logistic regression beta coefficient (β) becomes an odds ratio (*OR*), which is easier to interpret than the raw coefficient. The *OR* estimates the change in the odds of membership in one group (the target group) for each one-unit change in the explanatory or predictor variable (for continuous variables) or compared with a reference group (for categorical variables), while statistically controlling for all other variables (DeMaris, 1995; Wright, 1995; Wister & Dean, 1998). Negative beta coefficients become odds ratios with values from one to (but never reaching) zero, whereas positive betas result in odds ratios ranging from one to infinity (Wister & Dean, 1998).

The statistics generated by logistic regression using SPSS and presented in thesis were: the model and block chi-square (χ^2) with their level of significance; the beta coefficient (β) and its standard error (*SE*); the odds ratio (*OR*) and the 95% confidence interval (*CI*) of the *OR*. The model χ^2 represents the overall fit of between the regression model and the data. A statistically significant model χ^2 indicates that at least one β is nonzero (DeMaris, 1995). The block χ^2 and its corresponding significance level indicate the contribution of that block of explanatory variables to the model.

Four hierarchical logistic regressions were performed using each of the four medication variables, NSAIDs, acetaminophen, neuroleptics and benzodiazepines as dependent variables. Each dependent variable was coded as a dichotomy (i.e., 0 = not taking, 1 = taking the medication). The odds ratio was the likelihood of prescription of each of the medications for one category of an explanatory variable compared to the reference, or for one unit change in the interval variables.

4.7.1 Evaluation of the assumptions of multiple regression analysis

Multiple regression analysis makes a number of assumptions regarding the variables in the regression. Before conducting the analysis it is important to address these assumptions.

The three interval variables, age, education and dementia behaviour disorder score, were evaluated for the presence of outliers. Two cases were identified in the age variable that exceeded three standard deviations from the mean. Five cases were identified among the education variable. These cases were eliminated and the analyses were repeated. As the results were essentially replicated, the cases were included in the analyses. No univariate outliers outside three standard deviations were identified. As noted previously, skewness and kurtosis for each of the three interval variables indicate near normal distributions.

A correlation matrix of all the independent variables was run to test for multicolinearity. The greatest inter-item correlation was .48 between severity of dementia and the dementia behaviour disorder score. It was concluded that multicolinearity would not affect the estimates.

4.7.2 Hypothesis one: Analgesic Use

It was hypothesized that among elderly people with painful conditions, specifically arthritis and rheumatism, the use of analgesics would be associated with cognitive status such that patients with dementia would be less likely to take analgesics than those who are cognitively intact. It was further hypothesized that this relationship would vary with the severity of dementia such that more severe cognitive impairment would be associated with lower analgesic use.

To test this hypothesis, hierarchical logistic regressions were performed using prescription of each of the two analgesic medications of primary interest, NSAIDS and acetaminophen as dependent variables. Prescription of the two analgesics was examined separately because bivariate analysis demonstrated different patterns of use. Since the relationship between NSAIDs and cognitive status differed from the relationship between acetaminophen and cognitive status, combining the two analgesics into a composite analgesic variable would have obscured the relationships. The sub-sample for these analyses was those identified as having arthritis or rheumatism (n=856).

4.7.2.1 NSAID Use

The independent variables were entered in five hierarchically ordered blocks into the regression analysis. These were:

Block 1: diagnostic category; cognitively intact or probable or possible Alzheimer's disease with cognitively intact as the reference category;

Block 2: place of residence; institution or community, with community as the reference category;

Block 3: sociodemographic characteristics, age, gender and education;

Block 4: prescription of acetaminophen with taking the drug as the reference;

Block 5: prescription of each of the psychotropic drugs (neuroleptics and benzodiazepines) entered separately with taking the drug as the reference.

The presence of dementia is the predictor of primary interest and is expected to be the strongest predictor of analgesic use among older people with a painful condition. Therefore, diagnostic category is entered in the first block. Consistent with evidence in the literature and as demonstrated by the bivariate analysis, the presence of dementia was considered to influence the likelihood of institutionalization. Therefore, place of residence was entered in the second block. Sociodemographic characteristics, age, gender and education have been demonstrated in the literature to influence medication use (Robbins & Clayton, 1989; Swanwick et al., 1999); therefore, the sociodemographic block precedes the two medication blocks. Prescription of the other analgesic of interest was included to control for multiple prescription of analgesics and was entered prior to the psychotropic block since prescription of analgesic is hypothesized to influence prescription of psychotropics.

Model 1 is statistically significant (model $\chi^2 = 14.12$, $p<.001$). The likelihood of taking NSAIDS is decreased by a factor of .45 for those who have a diagnosis of

Alzheimer's disease compared to those who are cognitively intact ($\beta = -.80, p<.001$, $SE = .22$, odds ratio = .45).

Model 2 includes the 'place of residence' variable and is statistically significant (model $\chi^2 = 14.28, p<.01$). Place of residence was not found to be a significant predictor of NSAID use but inclusion in the model slightly weakens the effect of diagnostic category ($\beta = -.76, p<.01$, $SE. = .24$, odds ratio = .47).

Model 3 includes the sociodemographic variables and is statistically significant (model $\chi^2 = 15.47, p<.01$). None of the sociodemographic variables demonstrate a statistically significant relationship with NSAID use. The inclusion of these variables further weakens the main effect of diagnostic category ($\beta = -.70, p<.01$, $SE. = .25$, odds ratio = .50). Controlling for place of residence, age, gender and education, the likelihood of taking NSAIDs for people with a diagnosis of Alzheimer's disease is decreased by a factor of .5 compared with those who are cognitively intact.

Model 4 includes the prescription of acetaminophen and is statistically significant (model $\chi^2 = 15.94, p<.01$). Acetaminophen use is not significantly associated with NSAID use, controlling for all other variables. The main effect of diagnostic category is replicated with the inclusion of acetaminophen use ($\beta = -.70$, $p<.01$, $SE = .25$, odds ratio = .50).

Model 5 includes the prescription of the two psychotropic medications, neuroleptics and benzodiazepines and is statistically significant (model $\chi^2 = 23.35$, $p<.01$). Of the two psychotropic medications, only benzodiazepine use resulted in a statistically significant association with NSAID use ($\beta = -.52, p<.05$, $SE=$ .21, odds ratio = .59). Controlling for all other variables, the likelihood of taking NSAIDs is decreased by a factor of .6 for those taking as compared with those not taking benzodiazepines. The inclusion of the prescription of psychotropics weakens the main effect of diagnostic category ($\beta = -.58, p<.05$, $SE = .26$, odds ratio = .56). The likelihood of taking NSAIDs is decreased by a factor of .6 for those with a diagnosis of Alzheimer's diseases compared with those who are cognitively intact.

In the final model, the strongest predictor of prescription of NSAIDs was cognitive status as measured by diagnostic category. The presence of dementia compared with no cognitive impairment reduces the likelihood of taking NSAIDs by a factor of about .6, controlling for all other variables. This finding supports the hypothesis. The only other predictor identified in the model was prescription of benzodiazepines. Controlling for all other variables, benzodiazepine use reduces the likelihood of taking NSAIDs by a factor of .6.

The overall estimated explained variance of the model is low, 3% (Cox and Snell $\hat{R}^2 = .03$). The results of the regression are summarized in table 10.

Table 10: Summary of Logistic Regression Results, NSAIDs (n = 856)

	β	*O.R.*	95% *CI* of *O.R.*	Model χ^2	Block χ^2	$\hat{R}^2$ [26]	ΔR^2
Diagnosis	-.80***	.45	.29 -.70	14.12**	14.12**	.018	
Diagnosis	-.76**	.47	.29 -.75	14.28**	.16	.018	0
Institution	-.096	.91.	.56 -1.46				
Diagnosis	-.70**	.50	.30 -.81	15.47**	.89	.019	.001
Institution	-.07	.93	.58 -1.5				
Gender	-.07	.94	.63 -1.40				
Age	-.012	.99	.96 -1.02				
Education	-.001	1.00	.95 -1.05				
Diagnosis	-.70**	.50	.30 -.81	15.94**	.77	.020	.001
Institution	-.004	.99	.60-1.65				
Gender	-.055	.95	.63 -1.41				
Age	-.011	.99	.96-1.02				
Education	-.001	1.00	.95-1.05				
Acetamin	.21	1.24	.76-2.01				
Diagnosis	-.58*	.56	.34 -.93	23.35**	7.4*	.029	.009
Institution	-.025	.98	.58 -1.64				
Gender	-.081	.92	.62 -1.38				
Age	-.012	.99	.96 -1.02				
Education	.005	1.01	.96 -1.05				
Acetamin.	.28	1.32	.81- 2.15				
BDZ	-.52*	.60	.39-.90				
Neuroleptics	.69	1.99	.67-5.9				

Note: acetamin. = acetaminophen; BDZ = benzodiazepines;
O.R. = odd's ratio, *CI* = confidence interval
* $p<.05$, ** $p<.01$, *** $p<.001$

[26] Cox and Snell $R^{\wedge 2}$ (approximated R^2)

4.7.2.2 Acetaminophen Use

Using the sub-sample of only those with arthritis, the independent variables were entered in five hierarchically ordered blocks into the regression analysis. The blocks were identical to those described above with two exceptions. Higher frequency of acetaminophen than NSAID use permitted the inclusion of severity of dementia. Therefore, Block 1 included the variable 'severity of dementia' which has four categories, cognitively intact and mild, moderate and severe dementia with cognitively intact as the reference category rather than the dichotomous variable cognitively intact versus probable or possible Alzheimer's disease. In Block 4, the prescription of NSAIDS was entered rather than acetaminophen.

Model 1 included the measure of severity of dementia and was statistically significant (model $\chi^2 = 34.56, p<.001$). Both moderate and severe dementia compared with no cognitive impairment were significant predictors of acetaminophen use [$\beta = .68, p<.01$, $SE= .22$, odds ratio = 1.97 (moderate dementia); $\beta = 1.38, p<.001$, $SE= .25$, odds ratio = 3.98 (severe dementia)]. Having moderate compared with mild dementia increased the likelihood of prescription of acetaminophen by a factor of two, whereas severe compared with mild dementia increased the odds by a factor of four.

Model 2 includes the variable 'place of residence' and is statistically significant (model $\chi^2 = 95.56, p<.001$). Place of residence was a statistically significant predictor of acetaminophen use ($\beta = 1.62, p<.001$, $SE = .21$, odds ratio = 5.03). The odds of taking acetaminophen (compared with not taking acetaminophen) are increased by a factor of five among residents of institutions compared to community dwellers, controlling for the level of cognitive impairment. With the inclusion of the residence variable, the main effect of presence and severity of dementia became non-significant.

Model 3 includes the sociodemographic variables, age, gender and education and is statistically significant (model $\chi^2 = 110.47, p<.001$). Only age demonstrated a statistically significant relationship with acetaminophen use ($\beta = .045, p<.01$, $SE= .211$, odds ratio = 1.05). The odds of taking acetaminophen are increased by an increment of

.05 for each year of age. The inclusion of the sociodemographic variables reduced the main effect of institutionalization ($\beta = 1.53, p<.001, SE. = .21$, odds ratio = 4.61). Controlling for cognitive status and sociodemographic variables, the odds of taking acetaminophen were greater by a factor of 4.5 among people living in institutions compared with those living in the community.

Model 4 includes prescription of NSAIDs and is statistically significant (model $\chi^2 = 111.21, p<.001$). However, NSAID use was not significantly associated with acetaminophen use. The effects of both place of residence and age are maintained.

Model 5, the final model, includes prescription of the two psychotropic medications of interest and is statistically significant (model $\chi^2 = 121.44$, $p<.001$). Benzodiazepine use demonstrated a statistically significant relationship with acetaminophen use ($\beta = -.64, p<.01, SE= .20$, odds ratio = .53). Controlling for all other variables, the likelihood of taking acetaminophen is decreased by a factor of .5 for people taking benzodiazepines as compared with those not taking benzodiazepines. Controlling for psychotropic use slightly reduces the main effect of both place of residence ($\beta= 1.42, p<.001, SE= .21$, odds ratio = 4.13) and age ($\beta = .046, p<.001, SE= .014$, odds ratio = 1.04). The likelihood of taking acetaminophen is increased by a factor of four among people living in institutions as compared with the community, and by an increment of .04 for each year of age, controlling for all other variables.

In the final model, controlling for all other variables, the predictors of acetaminophen use were demonstrated to be place of residence, age and benzodiazepine use. Elderly people with arthritis or rheumatism were more likely to take acetaminophen if they lived in an institution compared with the community and less likely if they were also taking benzodiazepines. The odds of taking acetaminophen increased with age. The estimated overall variance of acetaminophen use explained by the final model is 14% (Cox and Snell $^R^2 = .14$). The results of the regression analysis are summarized in Table 11.

Table 11: Summary of Logistic Regression Results, Acetaminophen (n = 856)

	β	*O.R.*	95% *CI* of *OR*	model χ^2	block χ^2	$\hat{}R^2$	ΔR^2
Dementia							
mild	.226	1.25	.70-2.25	34.56	34.56***	.042	
moderate	.676**	1.97	1.27-3.05	***			
severe	1.38***	3.98	2.46-6.45				
Dementia							
mild	.164	1.18	.64-2.18	95.56	61.00***	.11	.071
moderate	.225	1.25	.77-2.03	***			
severe	.206	1.23	.70-2.17				
Institution	1.62***	5.03	3.35-7.55				
Dementia							
mild	-.102	.903	.47-1.73	110.47	14.91**	.13	.016
moderate	-.010	.99	.60-1.65	***			
severe	-.001	1.00	.55-1.80				
Institution	1.53***	4.61	3.05-6.97				
Gender	.355	1.43	.95-2.15				
Age (years)	.045**	1.05	1.02-1.07				
Education	-.001	1.00	.95-1.04				
Dementia							
mild	-.118	.889	.46-1.70	111.21	.74	.13	.001
moderate	-.022	.978	.59-1.63	***			
severe	-.041	.960	.53-1.74				
Institution	1.53***	4.64	3.07-7.02				
Gender	.355	1.43	.95-2.15				
Age (years)	.045**	1.05	1.02-1.07				
Education	-.001	.999	.95-.04				
NSAIDs	.212	1.24	.76-2.01				
Dementia							
mild	-.092	.91	.47-1.76	121.44	10.22**	.14	.011
moderate	.030	1.03	.61-1.73	***			
severe	.087	1.09	.58-2.06				
Institution	1.42***	4.13	2.70-6.31				
Gender	.33	1.39	.92-2.10				
Age(years)	.046***	1.04	1.02-1.08				
Education	.005	1.01	.96-1.05				
NSAIDs	.27	1.31	.80-2.14				
BDZ	-.64**	.53	.36-.78				
Neuroleptics	.014	1.01	.52-1.97				

Note: Reference for severity of dementia is cognitively intact *OR* = odds ratio, *CI* = confidence interval, BDZ = benzodiazepines, NSAIDs = non-steroidal anti-inflammatory drugs *$p<.05$, ** $p<.01$, *** $p<.001$

4.7.3 Hypothesis two: Psychotropic Use

It was hypothesized that among elderly people with dementia conditions, the use of psychotropic medications (i.e., neuroleptics and benzodiazepines) would be associated with the presence of a painful condition. Unrelieved pain are assumed to be manifest as behaviours that would be misidentified as dementia-related and subsequently treated with psychotropic drugs. This relationship would vary with cognitive status such that psychotropic use would be highest among those with moderate dementia and lowest among those with mild dementia.

To test these hypotheses, hierarchical logistic regressions were performed using prescription of each of the two psychotropic medications, neuroleptics and benzodiazepines, as dependent variables. Prescription of each psychotropic was examined separately. Bivariate analysis demonstrated that the relationship between neuroleptics and cognitive status differed from the relationship between benzodiazepines and cognitive status. Combining the two drugs into a composite 'psychotropic' variable would have obscured the unique relationships.

The analyses were restricted to the sub-sample consisting of those having Alzheimer's disease (n=612). The independent variables were entered in seven hierarchically ordered blocks. These were:

Block 1: DBD score (frequency and number of problem behaviours);

Block 2: presence of arthritis/rheumatism, having arthritis/ rheumatism as the reference category;

Block 3: place of residence, living in the community as the reference

Block 4: severity of dementia, mild dementia as the reference category;

Block 5: sociodemographic variables, age, gender and education;

Block 6: prescription of the other psychotropic drug of interest;

Block 7: NSAIDS and acetaminophen, entered separately, taking the drug is the reference category.

Since management of problem behaviours is the primary indication for prescription of neuroleptics, it was expected to be the strongest predictor of psychotropic use and was entered into the regression in the first block.

4.7.3.1 Neuroleptic Use

Model 1 includes the Dementia Behaviour Disorder Score and is statistically significant (model $\chi^2 = 15.17, p<.001$). There was a statistically significant relationship between DBD score and neuroleptic use ($\beta = .037, p<.001, SE. = .0095$, odds ratio = 1.04). The likelihood of taking neuroleptics increases by an increment of .04 for each point of increase in DBD score. Model 2 includes the presence of arthritis or rheumatism and is statistically significant (model $\chi^2 = 15.17, p<.001$). The presence of arthritis or rheumatism was not a significant predictor of neuroleptic use, controlling for dementia related behaviours. The main effect of DBD score was replicated with the inclusion of the presence of arthritis.

Model 3 includes place of residence and is statistically significant (model $\chi^2 = 45.53, p<.001$). Residence was identified as a significant predictor of neuroleptic use ($\beta = 1.64, p<.001, SE = .33$, odds ratio = 5.16). The odds of taking neuroleptics are increased by a factor of five among institutional compared to community residents, controlling for frequency and number of problem behaviours (as measured by the DBD score) and the presence of arthritis. The main effect of the DBD score was maintained.

Model 4 includes severity of dementia and is statistically significant (model $\chi^2 = 70.50, p<.001$). A statistically significant relationship was indicated between the level of severity of dementia and neuroleptic use. The odds of prescription of neuroleptics are increased by a factor of five among those with moderate dementia ($\beta = 1.64, p<.05, SE = .770$, odds ratio = 5.14) and by a factor of 16 among those with severe dementia ($\beta = 2.80, p<.001, SE = .79$, odds ratio = 16.37) compared to those with mild dementia, controlling for frequency and number of problem behaviours, the

presence of arthritis and place of residence. Inclusion of the level of severity weakens the main effect of place of residence, such that the relationship becomes non-significant.

Model 5 includes the sociodemographic variables and is statistically significant (model $\chi^2 = 79.16$, $p<.001$). Of the sociodemographic variables, only age demonstrated a statistically significant relationship with neuroleptic use ($\beta = -.05$, $p<.05$, $SE = .021$, odds ratio = .94). The likelihood of taking neuroleptics is decreased by an increment of .06 for each year of age. The inclusion of the sociodemographic variables strengthens the main effect of place of residence and the relationship with neuroleptic use regains statistical significance ($\beta = .92$, $p<.05$, $SE. = .40$, odds ratio = 2.50). The odds of taking neuroleptics are increased by a factor of 2.5 among those in institutions compared to those living in the community, controlling for the other variables. The inclusion of the sociodemographic variables also strengthens the main effect of severity of dementia. The odds of taking neuroleptics increased by a factor of 5.5 among those with moderate dementia ($\beta = 1.7$, $p<.05$, $SE. = .80$, odds ratio = 5.44) and by a factor of 18 among those with severe dementia ($\beta = 2.91$, $p<.001$, $SE. = .80$, odds ratio = 18.28) compared to those with mild dementia, controlling for the other variables. The effect of the DBD score weakens with the inclusion of the sociodemographic variables ($\beta = .023$, $p<.05$, $SE = .012$, odds ratio = 1.02). The odds of taking neuroleptics increases by an increment of .02 for each increment in the DBD score, controlling for the other variables.

Model 6 includes prescription of the other psychotropic, benzodiazepines and is statistically significant (model $\chi^2 = 81.77$, $p<.001$). Benzodiazepine use was not demonstrated to be a significant predictor of neuroleptic use. The inclusion of benzodiazepine use slightly weakens the effect of both place of residence ($\beta = .87$, $p<.05$, $SE. = .40$, odds ratio 2.35) and age ($\beta = -.05$, $p<.05$, $SE = .02$, odds ratio = .95). Controlling for the other variables, the likelihood of taking neuroleptics is increased by a factor of 2 among those living in institutions compared to those living in the community and decreases by an increment of .05 for each year of age. The effect of severity of dementia is strengthened. The likelihood of taking neuroleptics is increased by a factor of approximately 5.5 among those with moderate dementia ($\beta = 1.73$, $p<.05$, $SE = .80$,

odds ratio = 5.66) and almost 19.5 among those with severe dementia ($\beta = 2.98$, $p<.001$, *SE.* = .80, odds ratio = 19.48) compared with those with mild dementia, controlling for the other variables. The main effect of the DBD score is maintained.

Model 7, the final model, includes analgesic use and is statistically significant (model $\chi^2 = 82.63$, $p<.001$). The use of neither NSAIDs nor acetaminophen was a significant predictor of neuroleptic use. The effects of the DBD score, age and moderate compared to mild dementia are maintained. The effect of severe dementia was strengthened ($\beta = 3.03$, $p<.001$, *SE* = .81 odds ratio = 20.6). The odds of taking a neuroleptic are increased by a factor of more than 20 among people with severe dementia compared to those with mild dementia, controlling for all other variables. The effect of place of residence strengthens slightly with the inclusion of analgesic use ($\beta = .91$, $p<.05$, *SE* = .42, odds ratio = 2.47). Controlling for all other variables, the likelihood of taking a neuroleptic is increased by factor of 2.5 among institutional residents compared to community dwellers.

In the final model, the predictors of neuroleptic use are frequency and number of problem behaviours (measured by the DBD score), residence, severity of dementia and age. Controlling for all other variables, the likelihood of taking neuroleptics is increased by a factor of 2.5 among those living in institutions compared with those living in the community, and by a factor of 5.5 among those with moderate and of 20 among those with severe dementia than mild dementia. The likelihood of taking neuroleptics is increased by an increment of .02 with each increase in DBD score and decreased by an increment of .05 with each year of age, controlling for all other variables.

The estimated overall variance explained is 18.5% (Cox and Snell $^R^{2)}$. The results of the regression are summarized in Table 12.

Table 12: Summary of Logistic Regression Results, Neuroleptics (n = 612)

	β	O.R.	95% CI of OR	model χ^2	block χ^2	$\hat{}R^2$	ΔR^2
DBD	.037***	1.04	1.02-1.06	15.17***	15.17***	.037	
DBD	.037***	1.04	1.02-1.06				
Arthritis	.003	1.00	.59-1.70	15.17***	.000	.037	0
DBD	.040***	1.04	1.02-1.06				
Institution	1.64***	5.16	2.71-9.82	45.53***	30.36***	.107	.07
DBD	.026*	1.03	1.00-1.05				
Dementia			1.14-	70.50***	24.97***	.160	.053
Moderate	1.64*	5.14	23.24				
Severe	2.80***	16.37	3.5-76.55				
DBD	.023*	1.02	1.00-1.05				
Institution	.915*	2.50	1.14-5.45	79.16***	8.65*	.178	.018
Dementia			1.18-				
Moderate	1.69*	5.44	24.98				
Severe	2.91***	18.28	3.80-87.8				
Gender	-.360	.70	.36-1.37				
Age	-.057*	.94	.91-.99				
Education	-.023	.98	.90-1.06				
DBD	.023*	1.02	1.00-1.05				
Institution	.86*	2.35	1.07-5.17	81.77***	2.61	.184	.006
Dementia							
Moderate	1.73*	5.66	1.23-26.1				
Severe	2.98***	19.72	4.10-95.2				
Age	-.053*	.948	.910-.981				
BDZ	-.59	.553	.907-1.13				
DBD	.024*	1.02	1.00-1.04				
Institution	.91*	2.47	1.10-5.57	82.63***	.86	.185	.001
Dementia							
Moderate	1.72*	5.61	1.21-25.9				
Severe	3.03***	20.6	4.2-100.0				
Age	-.052*	.95	.91-.99				
NSAIDS	-.49	.610	.19-1.95				
Acetaminophen	.17	1.18	.62-2.24				

Note: Reference for dementia severity = mild dementia; Non-significant variables removed in subsequent blocks; SE = standard error, OR = odds ratio, CI = confidence interval, BDZ = benzodiazepines. *p<.05, **p<.01, ***p<.001

4.7.3.2 Benzodiazepine use

The independent variables were entered in seven hierarchically ordered blocks into the regression analysis. The blocks were identical to those described above with the exception of Block 6 in which neuroleptic use was included rather than benzodiazepine use. Model 1 is not statistically significant (model $\chi^2 = 1.46$, *ns*). Model 2 includes the presence of arthritis. The model is not statistically significant (model $\chi^2 = 5.26$, *ns*).

Model 3 which includes place of residence, is statistically significant (model $\chi^2 = 10.42$, $p<.05$). Place of residence is found to be a statistically significant predictor of the use of benzodiazepines ($\beta = .59$, $p<.05$, *SE.* = .26, odds ratio = 1.81). The odds of taking benzodiazepines are increased by a factor of two among institutional compared to community residents, controlling for problem behaviours and the presence of arthritis or rheumatism.

Model 4 includes severity of dementia and is statistically significant (model $\chi 2 = 13.62$, $p<.05$). Severity of dementia is not a significant predictor of benzodiazepine use. With the inclusion of severity of dementia, the main effect of place of residence strengthens ($\beta = .89$, $p<.01$, *SE* = .31, odds ratio = 2.43). The odds of taking benzodiazepines are increased by a factor of almost 2 among those in institutions compared to those living in the community, controlling for the other variables.

Model 5 includes the sociodemographic variables and is statistically significant (model $\chi^2 = 21.46$, $p<.01$). Of the sociodemographic variables, only age was found to be a significant predictor of benzodiazepine use ($\beta = -.038$, $p<.05$, *SE.* = .02, odds ratio = .96). The likelihood of taking benzodiazepines is decreased by an increment of .04 with each year of age. With the inclusion of the sociodemographic variables, the main effect of place of residence strengthens ($\beta = 1.07$, $p<.01$, *SE* = .33, odds ratio = 2.92). Controlling for the other variables, the likelihood of taking benzodiazepines is increased by a factor of almost three among those living in institutions compared to those living in the community. Severe compared with mild dementia becomes a statistically significant predictor of benzodiazepine use with the inclusion of the sociodemographic variables

($\beta = -.82, p<.05, SE = .43$, odds ratio = .44). Controlling for the other variables, the likelihood of taking benzodiazepines is decreased by a factor of .five among those with severe compared with mild dementia.

Model 6 includes prescription of the other psychotropic of interest, neuroleptics and is statistically significant (model $\chi^2 = 24.04, p<.01$). Neuroleptic use was not demonstrated to be a significant predictor of benzodiazepine use. With the inclusion of neuroleptic use, the main effect of age weakens and become non-significant. The effect of place of residence also weakens, but the relationship retains significance ($\beta = 1.03, p<.01, SE. = .34$, odds ratio = 2.79). The likelihood of taking benzodiazepines is increased by a factor of almost 3 among those institutional compared with community residents, controlling for the other variables. The effect of severe compared with mild dementia strengthens slightly ($\beta = -1.02, p<.05, SE = .45$, odds ratio = .36). The likelihood of taking benzodiazepines is decreased by a factor of almost .4 among those with severe compared with mild dementia, controlling for the other variables.

Model 7 includes prescription of the two analgesics and is statistically significant (model $\chi^2 = 27.56, p<.01$). Analgesic use was not demonstrated to be a statistically significant predictor of benzodiazepine use. With the inclusion of analgesic use, the effect of place of residence weakens slightly ($\beta = .82, p<.05, SE = .35$, odds ratio = 2.28). The odds of taking benzodiazepines increase by a factor of two for those living in institutions compared with those living in the community, controlling for all other variables. The effect of severe compared with mild dementia is maintained.

In the final model, the predictors of benzodiazepine use are place of residence and severe dementia. Controlling for all other variables, the likelihood of elderly people with Alzheimer's disease taking benzodiazepines is increased by a factor of two among institutional residents compared with those living in the community and is decreased by a factor of .4 among those with severe compared with mild dementia. The estimated variance explained by the final model is 7% (Cox and Snell $\hat{R}^2 = .07$). The results of the regression are summarized in Table 13.

Table 13: Summary of Logistic Regression, Benzodiazepines (n = 612)

	β	*O.R.*	95% *CI* of *OR*	model χ^2	block χ^2	$\wedge R^2$	ΔR^2
DBD score	-.012	.988	.97-1.01	1.46	1.46	.004	
Arthritis	.50*	1.65	.99-2.75	5.26	3.80*	.013	.009
Arthritis	.48	1.61	.97 -2.70	10.42*	5.16*	.026	.013
Institution	.59*	1.81	1.08-3.03				
Institution	.89**	2.43	1.31-4.51	13.62*	3.20	.033	.007
Dementia							
Moderate	-.42	.659	.33 -1.29				
Severe	-.75	.475	.21 -1.08				
Institution	1.07**	2.92	1.52-5.61	21.46**	7.83*	.052	.019
Dementia							
Moderate	-.46	.633	.32 -1.26				
Severe	-.82*	.440	.19 -1.01				
Gender	.45	.698	.84 -2.94				
Age (years)	-.038*	.962	.93-1.00				
Education	-.060	.942	.88 -1.01				
Institution	1.03**	2.79	1.44-5.41	24.04**	2.59	.058	.006
Dementia							
Moderate	-.512	.600	.30 -1.20				
Severe	-1.02*	.361	.15 -.874				
Neuroleptics	-.586	.557	.28 -1.13				
Institution	.82*	2.28	1.14-4.56	27.56**	3.52	.066	.008
Dementia							
Moderate	-.504	.60	.30-1.22				
Severe	-1.01*	.36	.15-.89				
NSAIDs	-.127	.88	.36-2.15				
Acetaminophen	-.544	.58	.32-1.04				

Note: Reference for dementia severity is mild dementia; Non-significant variables removed in subsequent blocks; NSAIDs = non-steroidal anti-inflammatory; *OR* = odds ratio; *SE* = standard error; *CI* = confidence interval
* $p<.05$, ** $p<.01$, *** $p<.001$

4.8 Summary of multivariate analysis

The analyses appear to offer mixed support for hypothesis one which contends that analgesic use will be lower among patients with dementia than those who are cognitively intact and lowest among those with most severe dementia. The multivariate analyses indicate that analgesic use is predicted by cognitive status. The hypothesis is supported for the use of NSAIDs; the presence of dementia does predict lower NSAID use. However, the hypothesis does not appear to be supported for the use of acetaminophen; the presence of dementia predicts higher acetaminophen use.

The analyses do not appear to support the second hypothesis which contends that psychotropic use will be higher amongst patients with dementia who have co- morbid arthritis. The presence of arthritis did not predict use of either neuroleptics or benzodiazepines. The hypothesis that psychotropic use will be associated with cognitive status received mixed support, although the patterns of the relationship were not as expected. More severe dementia was associated with higher neuroleptic use. Contrary to expectation, however, severe dementia was a stronger predictor of neuroleptic use than was moderate dementia. Also contrary to expectation, severe compared with mild dementia was associated with lower benzodiazepine use.

4.9 Summary of Psychotropic drug use by individual agents and classes

The most common benzodiazepine was lorazepam (8.8%), followed by triazolam (4.0%), oxazepam (3.6%), flurazepam (2.2%), temazepam (1.5%), diazepam (1.4%), and alprazolam (1.0%). A small number of individuals (1.6%) took chlordiazepoxide, clonazepam, nitrazepam and chlorazepate.

The most common class of neuroleptic was the phenothiazine class, e.g., thioridazine (13.0%), followed by butyrophenones, e.g., haloperidol (3.5%), and dibenzodiazepines, e.g., loxapine (1.6%). Two other classes of neuroleptics, thioxanthenes, e.g. flupenthixol and dibenzodiazepines, e.g., pimoxide were taken rarely (0.2%)

The patterns of psychotropic drug use vary somewhat by dementia severity and the presence of arthritis. Charts 2 through 5 summarize the patterns of psychotropic use in both the total study sample and in the group with a diagnosis of Alzheimer's disease.

Chart 2: Frequency of Benzodiazepine Use (%) , Total Study Sample (n=1,475)

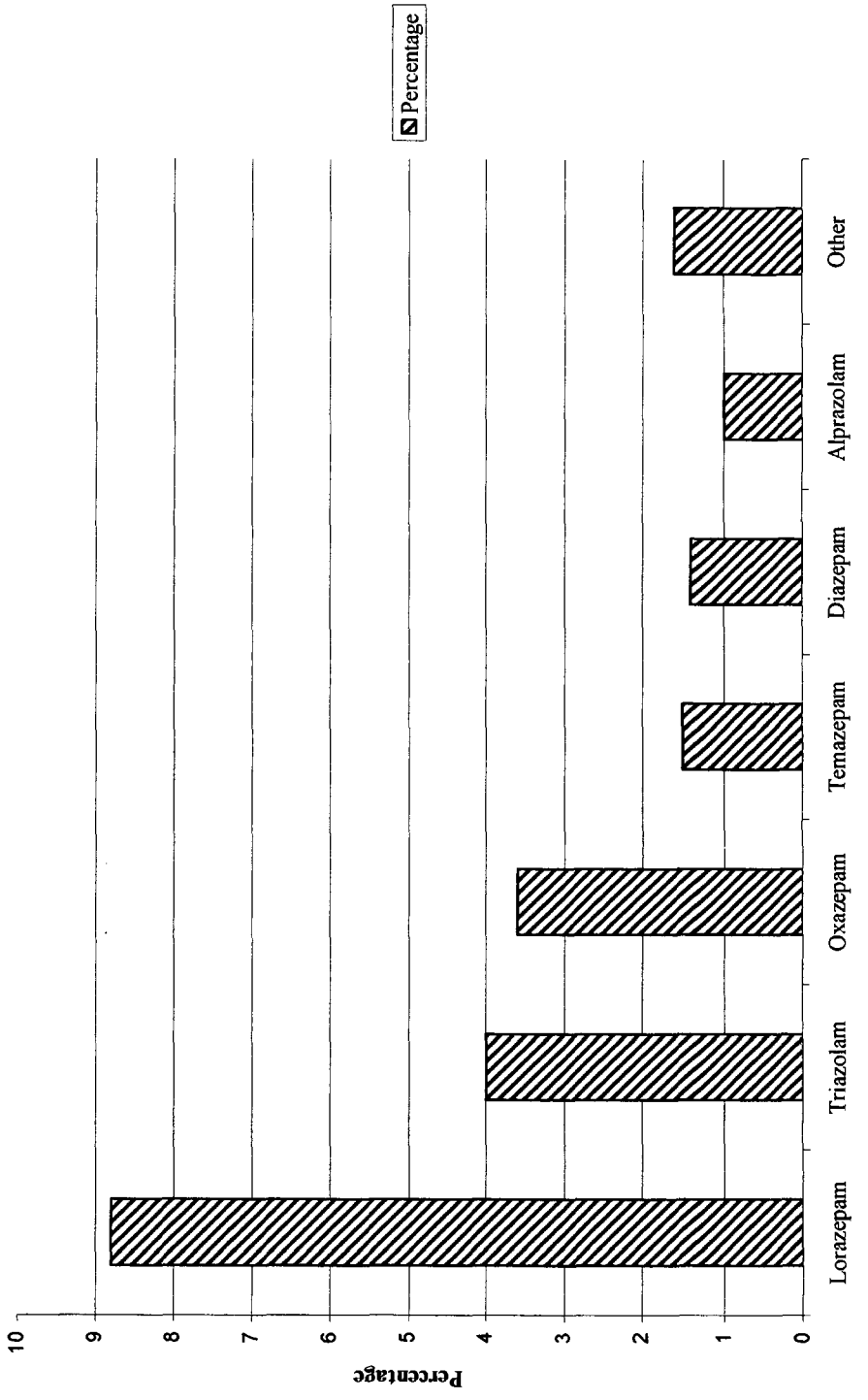


Chart 3: Frequency of Neuroleptic Use (%), Total Study Sample (n=1,475)

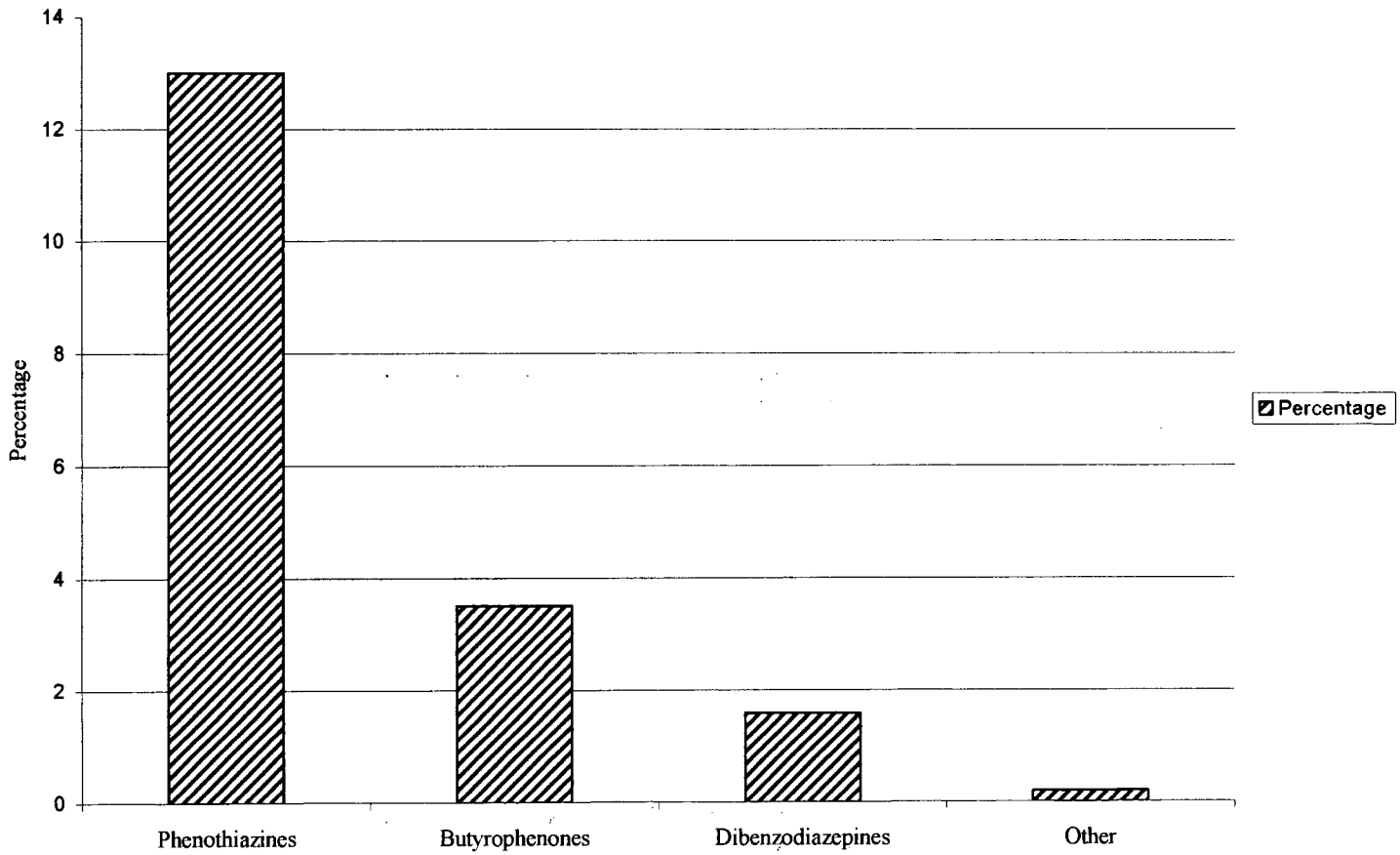


Chart 4: Benzodiazepine Use (%) by severity of dementia and arthritis (n=612)

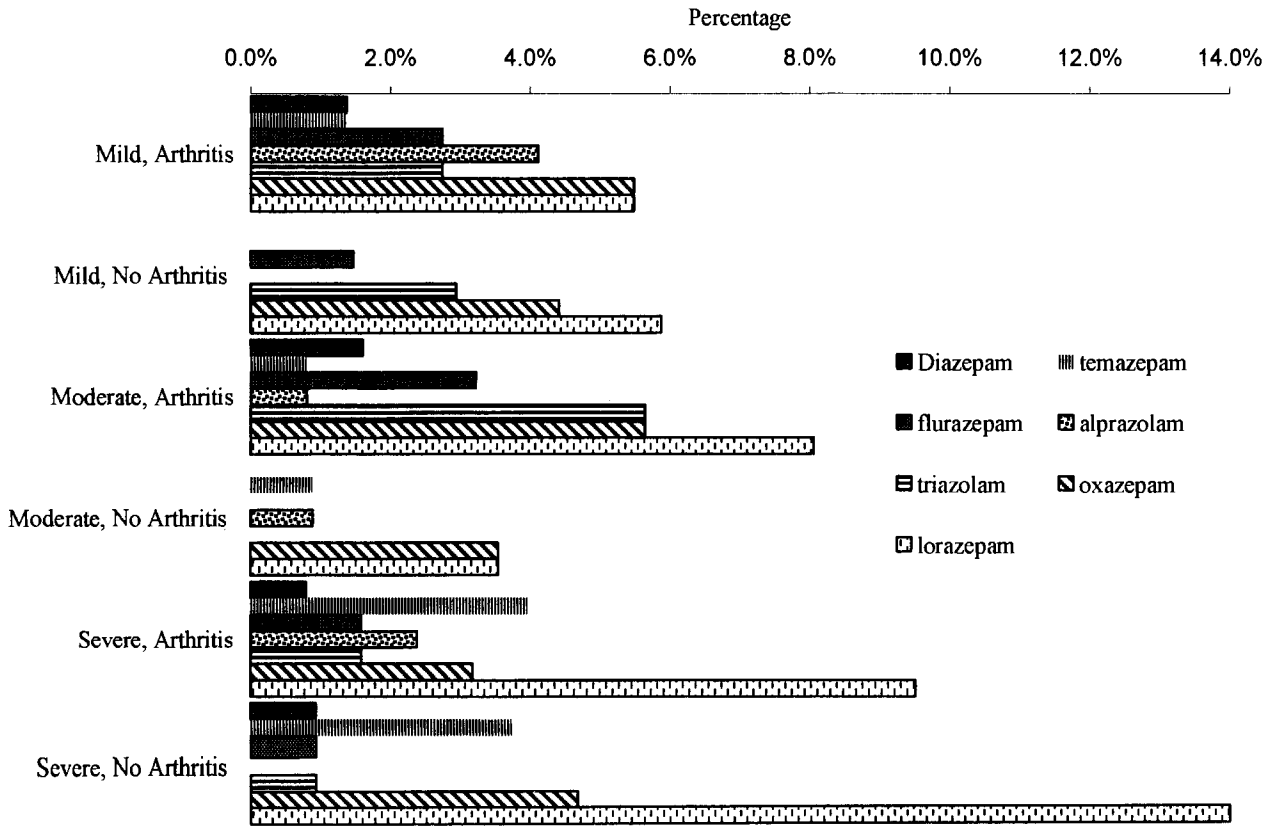
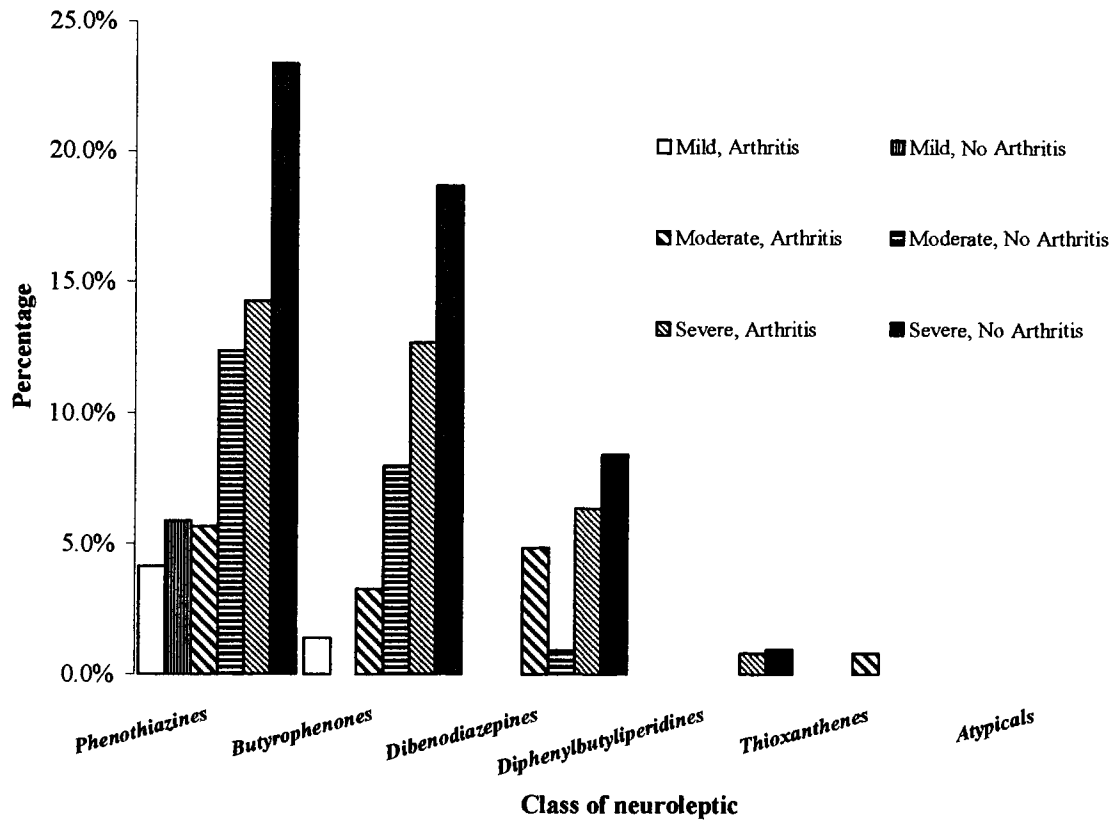


Chart 5: Neuroleptic Use (%) by severity of dementia and presence of arthritis (n=612)



Chapter 5: Discussion

The primary purpose of this thesis was to investigate the relationship between the treatment of pain in elderly people with dementia and the use of psychotropic medications. A secondary purpose of this thesis was to describe the patterns of analgesic and psychotropic drug use in an elderly population.

This chapter entails a review of the research issues followed by a presentation of the findings related to the hypotheses and discussion of the implications of the findings as related to theoretical considerations and possible implications of the patterns of drug use indicated by the findings.

5.1 Research Issues

Current pain theory describes the experience of pain as a highly complex process. How an individual ultimately experiences pain is the result of the integration of many sensory, affective and cognitive processes. Many factors modify, attenuate or exacerbate the sensations the individual feels and how he or she interprets those sensations.

The treatment of pain is an equally complex process. The perceptions and interpretations of not only the pain sufferer, but also those of the potential provider of treatment influence the intervention the sufferer receives. Greipp (1992) provides a framework for understanding the many factors that affect the interaction between the person in pain and the care provider. In this model, the care recipient and provider are affected by both personal experience and external factors. The outcome (the treatment) the pain sufferer receives is the product of the interaction of these many factors.

Treatment of pain in older persons with dementia introduces yet another layer of complexity. Perceptions, attitudes and understanding concerning the experience and process not only of pain, but also of dementia, may influence how such patients are treated when they suffer pain. Moreover, the physiological, psychological and cognitive

changes that are part of the disease process have the potential to influence the experience and expression of pain.

There is a cumulative body of evidence suggesting that pain is indeed treated differently in patients with dementia (Marzinski, 1991; Sengstaken & King, 1993; Ferrell et al., 1995; Hanlon et al., 1996; Bell et al., 1997; Horgas & Tsai, 1998; Kaasalainen et al., 1998). Some researchers have suggested that under treated pain may present as aggressive and agitated behaviour in persons with dementia (Miller et al., 1996; Olson, 2000; Buffman et al., 2001). This thesis has explored the issue of pain treatment among elderly patients and the relationship between pain treatment and the use of psychotropic medications. Two hypotheses were formulated to examine this relationship and to investigate the following issues. Among elderly people with a painful condition, specifically arthritis/rheumatism, is the presence of dementia a barrier to the adequate treatment of pain? Is pain behaviour misdiagnosed as problem behaviours resulting from dementia and subsequently treated with neuroleptic and benzodiazepine medication as opposed to analgesics?

5.2 Hypothesis number one

The first hypothesis states that among elderly people with painful conditions, specifically arthritis or rheumatism, the use of analgesics will be associated with cognitive status and will vary with the severity of cognitive impairment. It was assumed that analgesic use would be lower among patients with dementia as opposed to those who are cognitively intact and lowest among patients with severe dementia.

The findings provide mixed support for this hypothesis. The hypothesis was supported for the use of NSAIDS, but was not supported for the use of acetaminophen.

Bivariate analysis demonstrated an inverse relationship between NSAID use and the presence of dementia. The prescription of NSAIDS was lower among patients with Alzheimer's disease than those who were cognitively intact. Multivariate analysis indicated that prescription of NSAIDS was predicted by cognitive status; patients with

Alzheimer's disease were less likely to take NSAIDS than those who were cognitively intact.

Conversely, bivariate analysis demonstrated a positive relationship between acetaminophen use and the presence of dementia. Moreover, this trend was evident across all levels of dementia severity; acetaminophen use increased with the level of severity. Multivariate analysis indicated that, when controlling for all other variables, the presence and severity of dementia did not predict the use of acetaminophen. These results fail to support the hypothesis.

The observation that patients with Alzheimer's disease who have arthritis are receiving acetaminophen, suggests that the presence of dementia is not an absolute barrier to the receipt of analgesic medication. While language and memory deficits may result in a decreased ability to communicate the presence of pain to caregivers and request treatment, such deficits can be overcome. This result is consistent with the findings of Hadjistavropoulos and colleagues (1998), Krulewitch and colleagues (2000) and Epps (2001) who suggest that with the use of non-verbal pain assessment tools, pain can be identified among cognitively impaired patients when verbal self-reporting is compromised. The finding that institutional residents were more likely to be taking acetaminophen than community residents suggests that professional caregivers may be adept at identifying the presence of pain among older adults, regardless of cognitive status.

An alternative interpretation may be that this finding reflects the difference in documentation of medication use in institutions compared with the community. In an institution, all medication administered to a patient must be prescribed by a physician and documented in the patient's records, regardless of the status of the medication (i.e., prescription versus over-the-counter). Therefore, acetaminophen use would be documented for institutional residents. This may not be true for community residents. If, however, this finding reflects a true difference in acetaminophen use among older adults with arthritis in facilities as compared with the community, the question of undertreatment of pain among community residents persists.

Nevertheless, the hypothesis was supported with respect to NSAID use, suggesting that treatment of arthritic pain is different for patients who are cognitively impaired than for those who are cognitively normal. It is true that NSAIDs, in particular the traditional agents available at the time when the data analyzed in this thesis were collected, must be used with caution in frail elderly patients. These agents can be associated with serious adverse effects such as gastrointestinal bleeding (AGS panel on Chronic Pain in Older Persons, 1998). Consequently, the most recent guidelines published by the AGS Panel on Persistent Pain in Older Persons (2002) recommend acetaminophen as first line treatment for mild to moderate musculoskeletal pain. NSAIDs are recommended when treatment with maximum safe doses of acetaminophen (4,000 mg daily, with normal renal and hepatic function) fails to adequately control pain. However, these cautions and recommendations apply regardless of cognitive status. That the presence of dementia is associated with lower NSAID use suggests that factors other than concerns regarding adverse consequences influence the treatment of pain in elderly patients with arthritis.

The relationship between age and each of the two analgesics, however, suggests good practice corresponding to the AGS guidelines. Bivariate analysis demonstrated an inverse relationship between NSAID use and age whereas both bivariate and multivariate analysis indicated a positive relationship between age and acetaminophen use.

The question of the adequacy of the treatment remains, however. Because dose information was not available in the data set, it was not possible to determine if the patients taking acetaminophen received therapeutic doses. Single, as required, doses of acetaminophen were not distinguishable from a regularly scheduled and administered, around the clock dosing of acetaminophen such as that recommended in the AGS guidelines.

The results are consistent with the Greipp model of ethical decision making (1992) which suggests that healthcare providers bring a set of biases and attitudes formed by their personal and professional experience to their relationship with their patients. The lower use of NSAIDs among persons with Alzheimer's disease compared with those who

are cognitively intact may reflect such a decision making process by practitioners. Beliefs that persons with Alzheimer's disease suffer less pain than those who are cognitively intact or that there is little that can be done for those with dementia may be affirmed by experience if a patient with Alzheimer's disease is unable to provide feedback following successful treatment with an analgesic or conversely, explain that the pain is still present. This may lead the practitioner to erroneous conclusions regarding the efficacy of the pain treatment, perpetuating misconceptions regarding pain treatment with this patient population. The data did not, however, permit an examination this issue.

The multivariate analysis also demonstrated an inverse relationship between analgesic and benzodiazepine use. People taking benzodiazepines were less likely to take either of the two analgesics studied, (i.e., acetaminophen and NSAIDs). While this finding does not provide direct support for the hypothesis since the effect is evident regardless of cognitive status, it does raise the specter of inappropriate use of benzodiazepines. Is benzodiazepine use among those who are not taking analgesics related to unrelieved arthritic pain?

The model explained only 3% of the variance in NSAID use among elderly patients with arthritis or rheumatism. Clearly, there are many important factors influencing the prescription of NSAIDs in this population that were not addressed by this model, including the presence of comorbid conditions such as gastrointestional disease.[27]

Two final issues remain regarding analgesic use among elderly persons with arthritis or rheumatism. A number of people who were identified as having arthritis or rheumatism (n=372, 44%) were not taking an analgesic of any kind, raising the question of whether or not these individuals are suffering from unrelieved pain. Answering this question definitively is difficult without further data on the presence or severity of pain. It is a reasonable assumption, however, that the presence of arthritis or rheumatism will result in some degree of pain. This result is consistent with evidence in the literature

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[27] Active peptic ulcers or active inflammatory disease of the gastrointestinal tract is a contraindication to the use of NSAIDs.

indicating that pain is under identified and under treated among older people, regardless of cognitive status (Ferrell et al., 1990; Harkins, 1996; Bernabei, 1998).

The second issue concerns the very low use of opioids in this population. While opioids are powerful drugs with the potential to cause serious adverse effects, particularly in older patients, these drugs can be used safely and effectively when their use is warranted for severe pain and monitored effectively. The AGS Panel on Persistent Pain in Older Persons (2002) notes that there has been a reluctance among medical practitioners to use opioid drugs based on misconceptions regarding their safety in this population and in particular, regarding their abuse potential. True addiction is rare and tolerance slow to develop when opioids are used in older patients to manage persistent pain syndromes (AGS Panel, 2002). Indeed, the AGS Panel notes that such problems are "probably rare in comparison with the known prevalence of undertreated debilitating pain" (p.S213). Concern regarding the safety of these drugs in older populations is good practice. Such concern must, however, be weighed against the possible benefits of treating severe, debilitating pain among older adults.

5.3 Hypothesis number two

The second hypothesis contends that among patients with dementia, the presence of arthritis or rheumatism will be associated with an increased use of psychotropic drugs, specifically neuroleptics and benzodiazepines. Inadequately treated arthritic pain will be misdiagnosed as dementia related problem behaviours. The hypothesis was not supported for either of the two psychotropic medications.

5.3.1 Neuroleptic use

The multivariate analyses indicated that neither the presence of arthritis nor the prescription of analgesics was predictive of neuroleptic use among patients with dementia. The analysis does not support the hypothesis that pain is misdiagnosed as dementia behaviour disorder and subsequently treated with neuroleptic medication. Similarly, the bivariate analyses failed to provide support for this hypothesis; no interaction effect was observed between dementia behaviour and the presence of arthritis.

It is possible that the effect was too small to be detected by the analysis. While a sample of 400 is sufficient to detect a moderate effect when there are 10 variables, it is insufficient to detect a small effect (Cohen, 1992).

Lack of support for the hypothesis can be interpreted, however, as good news. The finding that elderly people with dementia are not being treated with neuroleptic drugs when analgesics would be the appropriate treatment is encouraging.

As expected, the dementia behaviour disorder score predicted the use of neuroleptics. The DBD score was a strong predictor of neuroleptic use; the odds of taking a neuroleptic increased by an increment of .02 for each additional point scored on the DBD scale. This finding confirms the well established understanding that problem behaviours are an important therapeutic indication for the use of neuroleptics among patients with Alzheimer's disease and is consistent with the literature (Macdonald et al., 2002).

It was hypothesized that the use of neuroleptics would be highest among patients with moderate dementia. This hypothesis was based on findings in the literature that patients at the most severe level of dementia have low levels of functional ability and are therefore, less likely to be able to exhibit disruptive behaviours, whereas patients at the moderate level of dementia are more ambulatory and therefore more likely to exhibit such behaviours (Vitaliano et al., 1991; Auer et al., 1994; Volicer et al., 1998; Sherman, 1999). Problem behaviours are generally rare among patients with mild dementia (Volicer & Hurley, 1999). This hypothesis received mixed support. The multivariate analysis indicated that the presence of moderate and severe dementia did predict neuroleptic use. However, the presence of severe dementia was a stronger predictor than moderate dementia; the odds of taking a neuroleptic are increased by a factor of 20 for people with severe dementia as compared with mild dementia whereas the odds increased for those with moderate dementia (as compared with mild) by a factor of 5. This finding, while it does not support the hypothesis, is consistent with prior research (Sloane et al., 1999). One interpretation of this finding could be that it reflects a methodological limitation of the analysis. There was a higher proportion of those with severe dementia

(49%) among the cases missing data on the DBD score, than either moderate (30%) or mild dementia (18%). It is possible that the missing cases with severe dementia are those with very low functional ability who may have low DBD scores whereas those included, have higher functional ability. Since cases with missing data are automatically removed from the analysis, the remaining severe cases may reflect an abnormally high level of functioning, problem behaviours and neuroleptic drug use.

The effect of moderate and severe dementia on the use of neuroleptics is evident after controlling for the frequency and number of problem behaviours, as measured by DBD scores. This finding suggests three possible interpretations. One is that patients with dementia, especially severe dementia, are treated with neuroleptic drugs as matter of course, for reasons unrelated to the management of problem behaviours. Another interpretation is that problem behaviours continue despite treatment with neuroleptics. Both of these interpretations raise concerns. Neuroleptic drugs are powerful agents with serious adverse effects. The evidence supporting their efficacy in dementia patients is modest at best (Lanctot, 1998; Salzman, 2001); their use is justified only when the benefits of their use outweigh the hazards of their side effects.

Institutional as opposed to community residence increased the likelihood of taking a neuroleptic, controlling for age, problem behaviours and severity of dementia. This suggests that patients with dementia are treated differently in institutions than in the community. Staff in institutions may be more familiar with neuroleptic drugs and hence, less reluctant to prescribe and administer these agents. Moreover, similar behaviours may be viewed as more disruptive in an institutional setting than in the community. A behaviour that may be tolerated and accommodated by a spouse or adult child caregiver may be highly disruptive to the life and activity of a unit in a long term care facility. Facility staff may more readily seek pharmacological means of managing the behaviour in the interests of their other patients and their families. Lack of sufficient staff may mean that care providers have little time to devote to individual patients; medication may provide a solution to 'problem' behaviours. In addition, conditions within an institution may increase the frequency of problem behaviours. Numerous unfamiliar care providers, inflexible daily routines and sterile hospital environments may contribute to the residents'

feelings of frustration and confusion, resulting in agitation and aggressive and other disruptive behaviours (Clavel, 1999; Sherman, 1999; Talerico, 2002).

A final issue concerns the specific types of neuroleptics that are prescribed. Phenothiazines were the most commonly used category of neuroleptics. As a class, phenothiazines are poorly tolerated in older patients; they are highly hypotensive and anticholinergic (Comaty & Advokat, 2001). Haloperidol, which was taken by the next highest percentage of individuals may also be a poor choice. Higher potency neuroleptics such as haloperidol are associated with a high level of EPS and TD (Comaty & Advokat, 2001). Although loxapine and risperidone are recommended as better choices (Lanctot, 1998; Salzman, 2001), these agents were used infrequently or not at all. This result may be partially explained by the fact that the data was collected in 1991/1992 when these drugs were relatively new.

5.3.2 Benzodiazepine Use

The hypothesis is also not supported for benzodiazepine use. Bivariate analysis failed to establish a statistically significant relationship between benzodiazepine use and either the presence of arthritis or the dementia related behaviour. In the multivariate analysis, neither the presence of arthritis nor analgesic use predicted benzodiazepine use. This finding fails to provide support for the hypothesis that unrelieved pain among patients with dementia is misinterpreted as dementia related behaviour disturbance and subsequently treated with benzodiazepines.

The multivariate analysis identified two predictors of benzodiazepine use: institutional residence; and severe dementia. Residents in institutions were more likely to take benzodiazepines than community dwelling people with dementia, a not unexpected finding. Institutions are typically noisy and busy places, even at nighttime. Such an environment is associated with substantial sleep disruption (Steinweg, 1997). It is unsurprising that many older residents of institutions take benzodiazepines, possibly to treat sleep disturbances. It is, however, of some concern, since benzodiazepines are associated with serious adverse effects including ataxia which may increase the risk of falls and fractures (Earthy et al., 2000).

The finding that patients with severe dementia are significantly less likely to be taking benzodiazepines is encouraging as this class of medications has anti-cholinergic properties. Even at therapeutic levels, benzodiazepines can cause cognitive impairment in older adults (Salzman et al., 1992; Miller, 1995). Such an effect would be particularly problematic for patients with significant cognitive loss.

While it is encouraging that patients with severe dementia are less likely to take benzodiazepines, it is of some concern that almost one-fifth (19%) of the patients with Alzheimer's disease were taking benzodiazepines. It is also encouraging that the use of agents such as flurazepam and diazepam which have long half-lives and active metabolites is lower than that of those with shorter half-lives, such as lorazepam, oxazepam and temazepam. However, a total of 3.6% of the study population did take either flurazepam or diazepam. Moreover, triazolam (Halcion^{R}) is the second most common agent. This drug is known to cause higher rates of antegrade amnesia and next day memory loss than any of the other benzodiazepines (CPS, 1999) and is currently contraindicated for use when the individual cannot be certain of a full seven to eight hours sleep. This agent is a very poor choice of sedative-hypnotic among elderly patients, and especially, those with pre-existing cognitive impairment.

5.4 Limitations

This thesis utilized a secondary data source. Secondary data analysis has both advantages and limitations. The CSHA-1 provided a large, well developed database, which oversampled for the oldest age group, especially helpful since the study population of interest was frail older people, those diagnosed with dementia. Moreover, clinical assessment followed by case conference ensured generally reliable and valid assignment to diagnostic category. Furthermore, the CSHA includes both an institutional and community component allowing comparison between the two groups.

Analyses were somewhat restricted by the data available in the original study, however. A primary limitation was lack of information regarding the dose of the medications. As discussed, without dosing information it was not possible to determine

if therapeutic levels of the drugs were administered or to compare treatment with different agents.

The database also lacked a measure of the presence and severity of pain. Such information would have aided the assessment of the adequacy of analgesic treatment, in addition to permitting a comparison of treatment by severity of pain and severity of pain by cognitive status. Furthermore, there was no measure of the severity of the arthritic condition, making it impossible to compare treatment by severity of disease.

Lack of a true measure of pain also meant that it was not possible to definitively delineate the presence and absence of pain. Although it is a reasonable assumption that people with arthritis will experience some degree of disease related pain, it cannot be assumed that those without arthritis will be pain-free.

Because the Dementia Behaviour Disorder scale was administered as part of the Caregiver questionnaire, data were missing for a large number of cases. It would have been ideal to have data for all individuals, or at least for all with Alzheimer's disease. As was discussed earlier, the missing cases were skewed towards those with severe dementia, which may have influenced the outcome.

Furthermore, the variance explained for NSAID use was less than 3%, indicating that many factors determine the prescription of NSAIDs that were unaccounted for by the study variables. Those factors could include the presence of gastrointestinal disease or reduced kidney function, both of which are contraindications for NSAID use. Laboratory tests, including creatinine clearance and blood urea nitrogen levels to measure kidney function were performed on some of the participants. The number of cases for which there are valid values is minimal, however, and insufficient to adequately assess the role of kidney function in explaining the variance in NSAID use. While information on the presence of gastrointestinal complaints was available, no measures of severity of the complaints were available; therefore, it was not possible to determine whether the 'stomach' ailment was a contraindication to NSAID therapy. Moreover, the cross-sectional nature of the data precluded a determination of whether the gastrointestinal complaint was actually the result of NSAID use.

A final limitation is that the information is becoming somewhat dated. Data for CSHA-1 was collected in 1991/1992. Since then, new drugs have become available that offer greater treatment options. The cyclooxygenase (COX)-2 selective NSAIDs, (e.g. Vioxx^{R}) may prove to be safer than the traditional NSAIDs (AGS, 2002). Additional atypical neuroleptics have also become available since the early 1990's which show promise as safe, effective treatment for controlling severe agitation in elderly patients with dementia (Stoppe et al., 1999; Comaty & Advocat, 2001).

5.5 Future Research

Future research should address the limitations described above. Key components of future research should be the inclusion of the doses of medications, both prescribed and administered and measures of the presence and severity of pain. Future studies should utilize non-verbal pain assessment tools, such as the Facial Action Coding System (FACS) employed by Hastjistavropoulos and colleagues (1998). It remains to be determined whether or not the higher use of acetaminophen among elderly persons with dementia reflects truly adequate and rational pain management. The inclusion of dose and measures of pain would significantly aid the evaluation of this issue.

A study that specifically addresses pain behaviours rather than dementia related behaviours could help to determine whether or not pain elicits unique types of behaviour in patients who are cognitively impaired. If so, do differences in reaction to pain affect pain management?

In view of the advent of new agents such as the COX-2 selective non-steroidal anti-inflammatory agents (e.g. rofecoxib) and new atypical neuroleptics (e.g. olanzapine) a new study of the issues investigated in this thesis is warranted to assess the impact of recent additions to the pharmacological arsenal on the management of arthritic pain and dementia related behaviours among older adults.

The CSHA is an ongoing, longitudinal study. Follow-up with the second and third waves of this study is therefore possible. Attrition due to mortality may be

problematic. However, panel studies could assist in the elucidation of a number of issues such as the extent to which medication use hastens cognitive decline.

The role of social support was not examined in this thesis. Does the presence of a spouse or other significant family member affect the adequacy of pain treatment? The effect of patient-partner interactions on pain behaviours has been studied by some researchers (Romano, 2000). For elderly patients with cognitive impairment, particularly those in institutional care, the presence of a caring advocate may play a key role in their receiving adequate pain relief.

Finally, the focus of this thesis was the pharmacological treatment. Non-pharmacological measures are vital components of management of both pain and dementia related behaviours. Future studies should also focus on the use of these measures, the patterns and extent of their use.

Chapter 6: Summary and Conclusion

The principal goal of this thesis was to examine the prescription of analgesic and psychotropic medication among older adults with a painful condition. Of particular interest was the relationship between the prescription of these medications and cognitive status.

The review of literature presented in Chapter 2 demonstrated that there is reason to suggest prescription of analgesic and psychotropic drugs is influenced by the cognitive status of the patient. Chapter 2 also presented a review of the development of pain theory. In addition, a summary of the mechanism of action and the therapeutic and adverse effects of neuroleptics and benzodiazepines was presented. Two hypotheses were developed and investigated as a result of the literature review.

Chapter 3 described the research methodology, including the data source, the derivation of the study sample, the outcome measures and the explanatory factors. Information about missing data is presented and the statistical power of the analyses are discussed.

Chapter 4 presented the results of the bivariate and multivariate analyses. At the bivariate level the main findings were that: 1) prescription of NSAIDs was inversely associated with the presence of dementia but prescription of acetaminophen was positively associated with the presence and severity of dementia, and that; 2) prescription of neuroleptics was positively associated with the severity of dementia whereas the relationship between prescription of benzodiazepines and the presence and severity of dementia was not statistically significant. Multivariate analyses (i.e., logistic regression) revealed that after controlling for all other independent variables the presence of dementia and prescription of benzodiazepines were predictive of NSAID use whereas institutional residence, age and prescription of benzodiazepines were predictive of acetaminophen use. After controlling for all other independent variables, dementia behaviour disorder score, institutional residence, severity of

dementia, and age were identified as statistically significant predictors of neuroleptic use, whereas only institutional residence and severe (when compared with mild) dementia emerged as significant predictors of benzodiazepine use.

A discussion of the main findings and their integration with the research issues were provided in Chapter 5. There was partial support for the hypothesis that among older adults with a painful condition, the presence of dementia acts as a barrier to the prescription of analgesics. However, neither the presence of pain, nor prescription of either acetaminophen or NSAIDs was predictive of prescription of either class of psychotropic medication. This finding fails to support the hypothesis that untreated pain is misidentified and treated with psychotropic medications.

Limitations of the research and suggestions for future research were also discussed. It was suggested that the inclusion of information regarding dose of each of the medications and the severity of pain would offer further insights into issues under study. This thesis attempted to provide a greater understanding of the complex issues of the experience of pain among older adults, in particular, those with dementia.

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Appendices

Appendix A: Components of DBD Scale

1. Lack of interest in daily activity
2. Unwarranted accusations
3. Verbally abusive, curses
4. Empties drawers or closets
5. Dresses inappropriately
6. Exposes himself indecently
7. Screams for no reason
8. Physical attacks
9. Inappropriate sexual advances
10. Paces up and down
11. Moves arms in restless way
12. Lost outside
13. Incontinent of urine
14. Incontinent of stool
15. Wakes up at night for no reason
16. Wanders in the house at night
17. Sleeps excessively during the day
18. Overeats
19. Refuses to eat
20. Cries or laughs inappropriately
21. Refuses to be helped
22. Throws food
23. Wanders aimlessly outside

24. Hoards things for no reason

25. Destroys property, breaks things

26. Loses, misplaces, or hides things

27. Asks same question again

28. Repeat the same action.

Appendix B: Derivation of Medication Variables

NSAIDS (non-steroidal anti-inflammatory agents) includes:

- M01AB: Acetic acid and acetamide derivatives
    - Indomethacin
    - Suldinac
    - Diclofenac, and the combination of diclofenac with misoprostol
    - Ketoralac
    - Etochlorac
- M01AC: Oxicams
    - Piroxicam
    - Tenoxicam
- M01AE: Propionic acid derivatives
    - Ibuprofen
    - Naproxen
    - Ketoprofen
    - Flurbiprofen
    - Tiaprofenic acid
- M01AX: Other
    - Nabumetone
    - Choline
    - Magnesioum salicylate and choline salicylate
    - Sodium salicylate
    - Difunisal

Acetaminophen (anilides) includes:

- NO2BE01

Opioid Analgesics includes:

- N01A: Opioid Anesthetics
    - Leritine
- N02A: Opioids
    - Natural opium alkaloids
        - Morphine
        - Papavertum
        - Hydromorphone hcl
        - Codeine phosphate, codeine, caffeine and acetaminophen or acetylsalicylic acid compounds
    - Oxycodone and acetaminophen or acetylsalicylic acid compounds
- Phenylpiperidine derivatives
    - Fentanyl
- Diphenylpropylamine derivatives
    - Dextropropoxyphene
    - Propoxyphene napsylate
- Benzomorphan derivatives
    - Pentazocine
- Artificial opioids
    - Meperidine hydrochloride

ASA Compounds:

- M03: Muscle Relaxants (with ASA)
    - M03BA: Carbamic acid esters

- Methocarbamol compounds with acetylsalicylic acid
- Above compounds with codeine

- N02BA: Acetylsalicylic acid and caffeine compounds with butabital, cinnamedrine, dextropropoxyphene or orphenadrine
- N02BZ:Unknown analgesics and antipyretics

Neuroleptics include:

- Phenothiazines
  - N05AA: with demethylaminopropyl group
    - Chlorpromazine
    - Methotrimeprazine
  - N05AB: with piperazine structure
    - Perphenazine
    - Trifluoperazine
  - N05AC: with piperidine structure
    - thioridazine
    - mesoridazine
    - pipotiazine
  - N05AD: butyrophenone derivatives
    - Haloperidol
  - N05AF: thioxanthene derivatives
  - flupenthixol decanoate
  - thiothixene
- N05AG: diphenylbutylpiperidine derivatives
  - fluspirilene
  - pimoxide

- N05AH: dibenzodiazepine and dibenzooxazepine derivatives
    - loxapine hcl / succinate
- N05AX: other antipsychotics
    - Risperidone

Benzodiazepines include:

- diazepam
- chlordiazepoxide
- oxazepam
- chlorazepate dipotassium
- lorazepam
- alprazolam
- flurazepam
- nitrazepam
- triazolam
- temazepam
- clonazepam
- "unknown psycholeptics"

The following drugs were not included:

- prochloroperazine – primary indication as an antiemetic (CPhA., 1999)
- trifluoperazine and isopropamide combination – primary indication for gastro-intestinal disorders (CPhA., 1999)
- topical products for joint and muscular pain – only two occurrences
    - capsaicin
    - axsain
    - zostrix

- triethanolamine salicylate

- cyclobenzoprine – indication as a muscle relaxant, not analgesic (CPhA., 1999) and only two occurrences

- baclofen – indicated as a muscle relaxant, not analgesic (CPhA., 1999) and only one occurrence

- mefenamic acid – while indicated for the relief of moderate pain related to muscular aches and pains (CPhA., 1999) in clinical practice use is primarily for primary dysmenorrhea and there were no occurrences within the study population.

- Anti-migraine preparations which are indicated specifically for the relief of pain related to migraine headaches and are not indicated for the management of arthritic pain (CPhA., 1999).