There is no doubt that people experience pain and that pain differs between individuals. It is a fact that most patients will consult with a general practitioner regarding their pain. In most cases a good assessment will reveal the nature of the pain and the appropriate treatment will be prescribed. The problem arises when the acute pain becomes refractory to standard therapy regimes or becomes chronic. The question then arises… To whom do I refer this patient?

When the cause of the pain is obvious then the referral is easy. When the cause of the pain is not known or the pain is masked by other complaints such as depression, sleep deprivation, or movement restriction the referral becomes problematic. This is where the concept of a pain clinic becomes useful but therein lies the problem.

What is a pain clinic? Who “manages” a pain clinic? It would be an impossible task for one individual practitioner to be able to diagnose and treat every pain condition. “Pain clinics” exist in South Africa but the vast majority of these are “pain treatment facilities” otherwise known as “pain units” or “modality oriented facilities”. Surely a multidisciplinary clinic is needed to fully evaluate and treat patients complaining of pain.

A practitioner cannot register for a diploma or degree in pain management in South Africa as such qualifications do not exist nor is any such qualification recognized by the HPCSA. This can give rise to the scenario “have needle…will treat!” This situation is obviously not optimal.

The IASP established a task team to investigate and recommend desirable characteristics for various pain treatment facilities. I have included the report of this task team in the Journal. This report should not only be digested by health practitioners but by the medical regulating and health funding boards as it has become clear to me that the there is a distinct lack of knowledge by the members of these boards not only in the diagnosis of the pain states, but of the very fact that pain is a disease and not a symptom and that pain can and must be treated. By quickly diagnosing and treating pain conditions there can be relief of a huge financial burden on the health budget of both the state and private healthcare industries.

Also included is a review of psychoneuroimmunology by Pienaar. This therapy is well researched and is another useful modality for treating patients suffering physical and psychological pain. She has clearly described the psychological and immunological mechanisms involved in this form of therapy. This treatment modality certainly has a place in the multidisciplinary clinic team approach to a suffering patient.

Dr. Milton Raff
BSc (WITS), MBChB (Pret), FFA (SA)
4 Science Direct:
PAIN TOP25 articles within the journal pain

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Task Force appointed by the President of IASP, Dr. Michael J. Cousins, and chaired by the Secretary of IASP, Dr. John D. Loeser

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   *Pain, Volume 127, Issue 3, 1 February 2007, Pages 199-203*

2. **Algorithm for neuropathic pain treatment: An evidence based proposal**
   *Pain, Volume 118, Issue 3, 1 December 2005, Pages 289-305*
   Finnerup, N.B.; Otto, M.; McQuay, H.J.; Jensen, T.S.; Sindrup, S.H.

3. **Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain**
   *Pain, Volume 127, Issue 3, 1 February 2007, Pages 276-286*
   Turner, J.A.; Holtzman, S.; Manci, L.

4. **Comparison of general exercise, motor control exercise and spinal manipulative therapy for chronic low back pain: A randomized trial**
   *Pain*

5. **The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain**
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   Linde, K.; Witt, C.M.; Streng, A.; Weidenhammer, W.; Wagenpfel, S.; Brinkhaus, B.; Willich, S.N.; Melchart, D.

6. **Pain relief by applying transcutaneous electrical nerve stimulation (TENS) on acupuncture points during the first stage of labor: A randomized double-blind placebo-controlled trial**
   *Pain, Volume 127, Issue 3, 1 February 2007, Pages 214-220*

7. **Gabapentin and postoperative pain - a systematic review of randomized controlled trials**
   *Pain, Volume 126, Issue 1-3, 1 December 2006, Pages 91-101*
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8. **Do the neural correlates of acupuncture and placebo effects differ? • Review article**
   *Pain, Volume 128, Issue 1-2, 1 March 2007, Pages 8-12*
   Dhond, R.P.; Kettner, N.; Napadow, V.

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   Cao, Y.Q.

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    *Pain, Volume 127, Issue 1-2, 1 January 2007, Pages 140-150*
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Desirable Characteristics for Pain Treatment Facilities

Task Force on Guidelines for Desirable Characteristics for Pain Treatment Facilities

IASP believes that patients throughout the world would benefit from the establishment of a set of desirable characteristics for pain treatment facilities. The principles set forth in this document can serve as a guideline for both health practitioners and those governmental or professional organizations involved in the establishment of standards for this type of health care delivery.

This Task Force has not addressed the issues of pain management in the postoperative or post-trauma setting. Such treatment programs may occur within a pain treatment facility, but they are not required for the assessment and treatment of patients with chronic pain.

Definition of Terms

The following terms will be briefly defined in this section; a more complete description of the characteristics of each type of facility appears in subsequent portions of this report.

1. Pain treatment facility:
A generic term used to describe all forms of pain treatment facilities without regard to personnel involved or types of patients served. Pain unit is a synonym for pain treatment facility.

2. Multidisciplinary pain center:
An organization of health care professionals and basic scientists which includes research, teaching and patient care related to acute and chronic pain. This is the largest and most complex of the pain treatment facilities and ideally would exist as a component of a medical school or teaching hospital. Clinical programs must be supervised by an appropriately trained and licensed clinical director; a wide array of health care specialists is required, such as physicians, psychologists, nurses, physical therapists, occupational therapists, vocational counselors, social workers and other specialized health care providers. The disciplines of health care providers required is a function of the variety of patients seen and the health care resources of the community. The members of the treatment team must communicate with each other on a regular basis, both about specific patients and about overall development. Health care services in a multidisciplinary pain clinic must be integrated and based upon multidisciplinary assessment and management of the patient. Inpatient and outpatient programs are offered in such a facility.

3. Multidisciplinary pain clinic:
A health care delivery facility staffed by physicians of different specialties and other non-physician health care providers who specialize in the diagnosis and management of patients with chronic pain. This type of facility differs from a Multidisciplinary Pain Center only because it does not include research and teaching activities in its regular programs. A Multidisciplinary pain clinic may have diagnostic and treatment facilities which are outpatient, inpatient or both.

4. Pain clinic:
A health care delivery facility focusing upon the diagnosis and management of patients with chronic pain. A pain clinic may specialize in specific diagnoses or in pains related to a specific region of the body. A pain clinic may be large or small but it should never be a label for an isolated solo practitioner. A single physician functioning within a complex health care institution which offers appropriate consultative and therapeutic services could qualify as a pain clinic, if chronic pain patients were suitably assessed and managed. The absence of interdisciplinary assessment and management distinguishes this type of facility from a multidisciplinary pain center or clinic. Pain clinics can, and should be encouraged to, carry out research, but it is not a required characteristic of this type of facility.

5. Modality-oriented clinic:
This is a health care facility which offers a specific type of treatment and does not provide comprehensive assessment or management. Examples include nerve block clinic, transcutaneous nerve stimulation clinic, acupuncture clinic, biofeedback clinic, etc. Such a facility may have one or more health care providers with different professional training; because of its limited treatment options and the lack of an integrated, comprehensive approach, it does not qualify for the term multidisciplinary.

Desirable Characteristics of Multidisciplinary Pain Centers

1. A multidisciplinary pain center (MPC) should have on its staff a variety of health care providers capable of assessing and treating physical, psychosocial, medical, vocational and social aspects of chronic pain. These can include physicians, nurses, psychologists, physical therapists, occupational therapists, vocational counselors, social workers and any other type of health care professional who can make a contribution to patient diagnosis or treatment.

2. At least three medical specialties should be represented on the staff of a multidisciplinary pain center. If one of the physicians is not a psychiatrist, physicians from two specialties and a clinical psychologist are the minimum required. A multidisciplinary pain center must be able to assess and treat both the physical and the psychosocial aspects of a patient’s complaints. The need for other types of health care providers should be determined on the basis of the population served by the MPC.
3. The health care professionals should communicate with each other on a regular basis both about individual patients and the programs which are offered in the pain treatment facility.

4. There should be a Director or Coordinator of the MPC. He or she needs not be a physician, but if not, there should be a Director of Medical Services who will be responsible for monitoring of the medical services provided.

5. The MPC should offer diagnostic and therapeutic services which include medication management, referral for appropriate medical consultation, review of prior medical records and diagnostic tests, physical examination, psychological assessment and treatment, physical therapy, vocational assessment and counseling and other facilities as appropriate.

6. The MPC should have a designated space for its activities. The MPC should include facilities for inpatient services and outpatient services.

7. The MPC should maintain records on its patients so as to be able to assess individual treatment outcomes and to evaluate overall program effectiveness.

8. The MPC should have adequate support staff to carry out its activities.

9. Health care providers active in a MPC should have appropriate knowledge of both the basic sciences and clinical practices relevant to chronic pain patients.

10. The MPC should have a medically trained professional available to deal with patient referrals and emergencies.

11. All health care providers in an MPC should be appropriately licensed in the country or state in which they practice.

12. The MPC should be able to deal with a wide variety of chronic pain patients, including those with pain due to cancer and pain due to other diseases.

13. An MPC should establish protocols for patient management and assess their efficacy periodically.

14. An MPC should see an adequate number and variety of patients for its professional staff to maintain their skills in diagnosis and treatment.

15. Members of a MPC should be carrying out research on chronic pain. This does not mean that everyone should be doing both research and patient care. Some will only function in one arena, but the institution should have ongoing research activities.

16. The MPC should be active in educational programs for a wide variety of health care providers, including undergraduate, graduate and postdoctoral levels.

17. The MPC should be part of or closely affiliated with a major health sciences educational or research institution.

Desirable Characteristics for a Multidisciplinary Pain Clinic

The distinction between a Multidisciplinary Pain Center and a Multidisciplinary Pain Clinic is that the former has research and teaching components that need not be present in the latter. Hence, items #15, 16 and 17 above are not required for a Multidisciplinary Pain Clinic. All of the other items should be present.

Desirable Characteristics for a Pain Clinic

1. A Pain Clinic should have access to and regular interaction with at least three types of medical specialties or health care providers. If one of the physicians is not a psychiatrist, a clinical psychologist is essential.

2. The health care providers should communicate with each other on a regular basis both about individual patients and programs offered in the pain treatment facility.

3. There should be a Director or Coordinator of the Pain Clinic. If he or she is not a physician, there should be a Director of Medical Services who is responsible for the monitoring of medical services which are provided to the patients.

4. The Pain Clinic should offer both diagnostic and therapeutic services.

5. The Pain Clinic should have designated space for its activities.

6. The Pain Clinic should maintain records on its patients so as to be able to assess individual treatment outcomes and to evaluate overall program effectiveness.

7. The Pain Clinic should have adequate support staff to carry out its activities.

8. Health care providers working in a Pain Clinic should have appropriate knowledge of both the basic sciences and clinical practices relevant to pain patients.

9. The Pain Clinic should have a trained health care professional available to deal with patient referrals and emergencies.

10. All health care providers in a Pain Clinic should be appropriately licensed in the country and state in which they practice.

Discussion

The Task Force is strongly committed to the idea that a multidisciplinary approach to diagnosis and treatment is the preferred method of delivering health care to patients with chronic pain of any etiology. Not every patient referred to a pain treatment facility is in need of multidisciplinary diagnosis or treatment, but the facility should have those resources available when they are appropriate. Although the Task Force recognizes that health care resources are not uniformly distributed throughout any country or the world and that compromises will be necessary, all health care providers should strive to attain the standards set forth in this document for the care of patients with chronic pain. Health care providers in pain treatment facilities should be encouraged and expected to be members of IASP and its national chapters in order to facilitate exchange of information and research activities.

The primary goal for a pain treatment facility is to provide effective, humane care for those who suffer from chronic
pain. The complexities of the chronic pain patient must be recognized to accomplish these goals. In the modern era, however, the issue of cost effectiveness must also be considered and we cannot erect standards for chronic pain treatment which are above and beyond the standards for patients with other types of complaints. Moreover, health care delivery systems are rapidly changing and standards that prevent innovation and progress should not be proposed.

All patients with chronic pain should be appropriately evaluated before treatment is implemented. Facilities that offer only one type of treatment or have limited access to professionals in various disciplines must demonstrate appropriate patient selection prior to the initiation of therapy. Patients who attend such a health care facility should have been fully evaluated elsewhere before such a referral is made. For example, if a “pain clinic” specializes in headache patients and offers only biofeedback therapy, the patients referred to such a facility must have an appropriate medical evaluation prior to embarking on this treatment program. Pain treatment facilities must go beyond this stereotypic approach and determine what services the patient needs prior to embarking upon one or another type of treatment. If what the patient needs is not available, the patient should be referred elsewhere.

Resources and patient demands vary throughout the world, and there is no single guideline that can be made which will apply to every location. In developing nations, pain treatment facilities may appropriately consist of a small number of health care professionals with limited resources. Such groups may mainly see chronic pain due to cancer or to nervous system injuries; the problems of chronic pain as seen in the industrialized nations may have not yet arrived. Treatments may be limited to nerve blocks and drugs if economic conditions preclude more expensive treatment strategies. It is unlikely that research activities will be carried out in such an environment, but the mission of teaching other health care providers should never be overlooked.

In the developed nations of the world, there would seem to be no reason to allow an isolated practitioner to call himself a pain clinic. The diagnosis and management of patients with chronic pain has become so complex that multiple skills and knowledge are required. There are many possible combinations, but such a facility must have at least one physician who assumes responsibility for obtaining a complete history and performing a screening physical examination. Old records must also be reviewed. The specialty of the physician performing this review is not particularly relevant, but clearly someone with expertise in the type of disease process responsible for the patient’s chronic pain should be either the referring physician or part of the pain treatment facility’s assessment team. At least two other medical specialties as well as other types of health care providers should be represented to justify the term, multidisciplinary pain clinic. There is some question as to whether any pain management facilities which are not multidisciplinary should exist in a developed nation.

Other types of health care professionals are of great value in a pain treatment facility. These include psychologists, nurses, physical therapists, occupational therapists, social workers, vocational counselors and others. The variety and number will be determined by the types of patients seen and the number of visits per year to the facility. We should remember that the etiologies of chronic pain are not well understood; medical treatments have already failed many of these patients and effective evaluation and treatment may be administered by other health care professionals.

In summary, the developed nations should require that any facility calling itself a pain clinic or pain center offer a multidisciplinary array of diagnostic and treatment facilities. Single modality therapy programs should be identified by the modality they utilize; e.g. “Biofeedback Clinic” rather than the term, “Pain Clinic.” Neurosurgeons who perform pain-relieving procedures do not call themselves a “Pain Clinic,” nor should any other solitary specialist. Health care facilities which specialize in one region of the body should be identified by that region in their title; e.g. “Headache Clinic,” rather than “Pain Clinic.” A Multidisciplinary Pain Clinic or Center should provide comprehensive, integrated approaches to both assessment and treatment.

In developing nations, it may not be immediately possible to amass the professional and physical resources to establish a multidisciplinary pain clinic. A single health care provider may initiate a health care facility with the goals of adding other personnel as the institution evolves. This should be encouraged by IASP even though the health care facility at its inception may not meet the desired standards.

Pain Clinics and Pain Centers require not only physical resources but also specially trained health care providers. There is no specific training program in pain management at this time, so all health care providers have entered this area from existing specialties. Fellowships in pain management are beginning to develop, and those individuals who wish to specialize in pain management should be encouraged to obtain such a period of training. Others become reasonably skilled through their work with pain patients, but the field should move toward the establishment of specific training programs in pain management and the development of a method of evaluation and certification of individual health care providers by responsible leaders.

All pain clinics should work toward the use of a single method of coding diagnoses and treatments. Although the ICD-9 system is utilized in many countries, it is not particularly good for illnesses in which pain is the major complaint. The IASP Taxonomy system is a step in the right direction, but it will need further refinement before it becomes clinically acceptable. Nonetheless, excellence in pain management will require a standardized reporting system which can be used by all types of treatment facilities throughout the world.

Finally, excellence is dependent upon education of young health care providers who may wish to enter this field. Pain Centers need to establish educational programs on all levels to accomplish this goal. These programs should attempt to incorporate with degree granting institutions in all the health sciences as well as post-graduate educational programs.

This document has been prepared by a Task Force appointed by the President of IASP, Dr. Michael J. Cousins, and chaired by the Secretary of IASP, Dr. John D. Loeser.
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INTRODUCTION TO PSYCHONEUROIMMUNOLOGY

Dr Mariske Pienaar
Clinical Psychologist

INTRODUCTION

A connection between psyche and body was postulated, e.g. Galen who in 131-201 AD proposed that a balance of the ‘passions’ was essential for physical health. These beliefs persisted throughout the medieval period and the early Renaissance and are best reflected in the Anatomy of Melancholy by Robert Burton (1621/1693): ‘...the mind most effectually works upon the body, producing by his passions and perturbations miraculous alterations...cruel diseases and sometimes death itself’. Until recent all these beliefs were intuitive, speculative. Science has for the first time succeeded in starting to support these hunches about the human condition (Kiecolt-Glaser et al., 2002).

In the 17th century, René Descartes proposed a dualistic view of humans that said that soul (mind) and body were separate entities. This was a great step forward because the Catholic Church accepted his concept as well as its logical conclusion that the human body could be studied without negatively affecting the soul!

The term Psychoneuroimmunology (PNI) was introduced by Dr Robert Ader in 1981 via a conference and a published book. The idea however started in the 50’s with George Solomon who wrote about psychoimmunology (the extent to which personality influences disease). In 1975 Ader and Cohen discovered that immunosuppression could be achieved by behavioural conditioning (Kaye et al., 2000). Candice Pert presented her first paper on PNI in 1984 in Rome. As it turned out, two other presenters synchronistically referred to the same triad in their slides. It was the beginning of a threateningly interdisciplinary era in understanding health and disease! The first meeting of the Psychoneuroimmunology Research Society was held in Miami in 1995 and the 15th meeting in 2008 (Goodkin et al., 1995; Pert, 1999).

PNI is the study of the bi-directional interrelations between the mind/psyche (the functioning of the brain), the endocrine system, the nervous system, and the immune system, and constitutes a meeting ground for medicine, biochemistry, genetics, psychology and human etiology. PNI suggests a network rather than a hierarchical structure, in which all locations are equal and information can enter at any point and quickly get to another point. Increasingly there is more science and less speculation about this interconnectedness. It is also noteworthy that during ontogeny, the neuroendocrine system and the immune system develop in mutual interconnections between nerve cells of the brain … Stated simply, the regulation of gene expression by social factors makes all bodily functions, including all functions of the brain, susceptible to social influences. (Kandal, 1998, p.461)

NEUROENDOCRINE SYSTEM

Since the 50’s there have been an ongoing discovery of a wide variety of protein molecules embedded in cell membranes, called receptors. They do not import or export material, but take in information that dramatically alters the internal activities of the cell and its functional relationship to the rest of the body. They sense like ‘tiny ears, eyes or taste buds’ (Pert, 1999).

It was previously believed that the only messengers (ligands) in the body that link with these receptors were:

- **neurotransmitters** working in an ‘on/off’ fashion at synapses of neurons (e.g. dopamine, serotonin, epinephrine etc.);
- **steroids** secreted by glands/gonads into the blood stream (e.g. cortisol, oestrogen, progesterone, testosterone etc.).

However, the largest category of ligands (up to 95%) are the:

- **neuropeptides**. Up to a 100 or more peptides have now been discovered e.g. cytokines, lymphokines, chemokines and interleukins. Their binding receptors can be found anywhere on a nerve’s membrane. A single nerve may have millions of receptors at any given moment. They are not transferred across synaptic clefts, but circulate freely in the blood stream and all other bodily fluids. Our bodies are capable of making more peptides, perfectly produced in a purified state, in one night’s sleep than all the peptide chemists who have ever lived since 1953. More surprisingly, neuropeptides are not produced and received only by neurons, but by

*For easy reference, all neurotransmitters in text coloured green, all steroids red, all neuropeptides blue, all immune cells pink.*
many of the body’s tissues, including the gut tube, the muscles, the glands, the lungs and various kinds of cells in the immune system (Pert, 1999).

One of the most fascinating, and significant, things about neuropeptides is that above and beyond the local responses found in particular cells and tissues, they are in a more general way mood specific. They are therefore also called molecules of emotion by some researchers. The binding of specific peptides to particular cells sets off the experience of a particular feeling state, which in turn releases a particular neuropeptide to bind with receptors on specific cells. Since emotional expression is always tied to a definite flow of peptides in the body, the persistent suppression of emotions results in a massive disturbance of the psychosomatic network. The solution is to allow the natural flow of emotions. Core limbic brain structures, such as the amygdalae, hippocampi and limbic cortex, believed by neuroscientists to be involved in emotional behaviour, contains 85 to 95% of the various neuropeptide receptors, confirming their important role in emotions. It is remarkable that the sensations and motor reverberations that occur in response to sensing are emotions. These emotions consist of organic changes in the body, muscular and visceral and are not a directly aroused primary feeling, but a secondary one, indirectly aroused by the body’s activities (Pert, 1999).

It is also fascinating that all mammals and many other creatures, even those who do not have nervous systems, have exactly the same peptide and binding molecules. It appears that evolution has carefully preserved this basic communication system throughout the development of species.

The neuropeptides, it seems, are the informational ‘connective tissue’ that unite and co-ordinate all cells and systems, weaving them into a single web that reacts to both internal and external environmental changes with complex and subtly orchestrated responses.

Peptides are the sheet music containing the notes, phrases, and rhythms that allow the orchestra - your body - to play as an integrated entity. And the music that results is the tone or feeling that you experience subjectively as your emotions (Pert, 1999, p. 148).

Peptides form part of the so-called paracrine system (rather than endocrine), because of the shorter effective range of communication. This distinction, however, is blurred and not readily used (Evans et al., 2000).

**IMMUNE SYSTEM**

The role of the immune system (IS) is to distinguish between the body and its invaders and to attack and to protect the body from anything that is ‘foreign’ e.g. viruses, bacteria, fungi and parasites (*antigens*). If the IS overreacts, it leads to allergies. If it mistakes the body itself for an invader, it can lead to *autoimmune* disorders (e.g. multiple sclerosis, rheumatoid arthritis (RA), insulin-dependent diabetes, lupus, Graves disease, inflammatory bowel disease). When the system is working well, the term *immunocompetence* is used. If the system is failing in some way, the term immunocompromise is used. Acute inflammation (triggered by infection and trauma) is critical to resolving infections and repairing tissue damage. However, chronic inflammation is associated with the development of periodontal disease, urinary tract infections, chronic obstructive pulmonary disease, chronic renal disease, cardiovascular disease (CVD), osteoporosis, arthritis, type 2 diabetes, certain cancers (e.g. multiple myeloma, non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia), and Alzheimer’s disease (Cohen & Herbert, 1996; Ogden, 2004).

There are roughly 4 ways to measure immunity (each with its own restrictions) (Ogden, 2004):

a) tumour growth
b) wound healing
c) secretory immunoglobulin (sIgA) found in saliva
d) natural killer cell cytotoxicity (NKCC), T cells found in the blood

The main organs of the IS are the lymphoid organs (bone marrow, lymph nodes and vessels, spleen, adenoids, thymus, appendix, tonsils and Peyer’s patches – clumps of immune tissue in the small intestines). They produce a range of ‘white blood’ cells or leukocytes that identify and disable antigens (Cohen & Herbert, 1996; McGregor, 1992).

There are 3 levels of IS activity (Azar, 2001; Cohen & Herbert, 1996; Evans et al., 2000; Kaye et al., 2000; Kiecolt-Glaser et al., 2002; Ogden, 2004):

1) **Non specific immunity** – Phagocytes. They attack any kind of antigen non-specifically. Monocytes transform into macrophages when they leave the bloodstream and enter the tissues to perform phagocytosis.

2) **Cell mediated immunity** – T cells (lymphocytes) that defend against viruses within the cells of the body and are made within the thymus. They consist of killer T cells (CD8) that defend by cytotoxic/cell-destroying mechanisms, memory T cells, delayed hypersensitivity T cells, helper T cells (CD4) and suppressor T cells. They produce a wide variety of cytokines (proinflammatory interleukin-1 [IL-1], IL-6 – especially in CVD, depression and anxiety - and anti-inflammatory IL-10, IL-13), and cell-surface polypeptides. They also stimulate corticotropin-releasing factor (CRF).

3) **Humoral mediated immunity** – B cells (lymphocytes) and antibodies that bind to antigens from extracellular organisms and clear them from the body. They operate in the body’s fluids before the antigens have entered any cells. B cells originate in the bone marrow and proliferate and differentiate into memory B cells and plasma cells. The B cells have antibodies or immunoglobulins (IgG, IgM, IgA, IgD, IgE) on their surface (unlike T cells) that act as receptors for antigens. The plasma cells also produce antibodies or immunoglobulins that appear in body fluids and bind to antigens. Hyperactive Ig’s lead to bone marrow and organ cancers, autoimmune diseases and chronic infections. Hypoactive Ig’s are associated with cancers,
The immune response usually looks like this (Kaye et al., 2000; Ogden, 2004):

- Antigens enter the body
- Macrophages (transformed monocytes) seize some antigens and display them on their membranes’ surfaces
- Some helper T cells (CD4) ‘read’ and bind to these antigens on the macrophages, becoming activated
- Once activated the CD4 cells begin to multiply and stimulate killer T cells (CD8) - immunosuppressive - and B cells
- The CD8 cells sacrifice already infected cells by chemically puncturing their membranes and letting the contents spill out
- The B cells will start producing antibodies that bind to the antigen’s surface and prevent them from attacking other cells
- As the invaders are contained, suppressor T cells halt all the immune responses to keep them from spiralling out of control
- Memory T and B cells are then left in the blood and lymphatic system should the antigens attack again
- Natural Killer cells (NK) (CD16) then kill virus-infected cells and neoplastic cells by secreting cytotoxins (NK cells are active without any prior exposure to the invader and have no specificity, they kill without antibodies, though antibodies enhance their effectiveness; they can detect and kill some cancerous cells!)
- Lymphokines and interleukin aid the killing of invaders by NK cells and other immune cells by enhancing communication between them. (Interleukin-2 activated NK cells are being used for the treatment of certain cancers)

Every neuropeptide receptor found in the brain, is also found on the surface of the human monocyte e.g. opiates, phencyclidine (PCP) and bombesin. Peptides therefore control the routing and migration of monocytes, and the overall health of a person. Peptides like cytokines, lymphokines, chemokines and interleukins also communicate with lymphocytes (T and B cells) and induce an antiviral state in other cells (Pert, 1999). Interleukin-1 also binds to receptors on the paraganglia, which send neurotransmitters to activate the vagus nerve, which sends a signal to the brain. This signal triggers the brain to make its own interleukin-1 which sets off the sickness response and sends signals back to the immune system, further activating immune cells – a complete immune-to-brain circuit. Stress and infection activate overlapping neural circuits that critically involve interleukin-1 as a mediator (Azar, 2001).

The immune cells travel through the blood and bodily fluids, ‘sense’ peptides and ‘chemotax’ (crawls to it), fixing the peptide to the receptor on the membrane of the immune cells. Therefore, one can conclude that immune cells are in fact, wandering neurons, information gatherers and receptors that float freely out of every nook and cranny of the body. This greatly extends the sensitivity of the nervous system, making it responsive to microscopic elements in the body that are too fine to be picked up by the nerve ends. In addition the immune cells communicate with other peptide-active cells and tissues, making them active information links. On top of all this, immune cells also make, store and secrete peptides (Pert, 1999).

Neurokinins are a newly identified neurotransmitter system composed of 3 related peptides, the most well known is substance P (found in the peripheral and central NS, most commonly with serotonin). Neurokinins interact directly with immune cells and play an active role in the regulation of pain, asthma, inflammatory bowel disease, psoriasis, migraine, emesis, schizophrenia, depression and anxiety. Norepinephrine (NE) also works directly on the immune cells (Caine, 2003).

The blood-brain barrier usually restricts communication with the brain. However, peptides like cytokines, chemokines, lymphokines and interleukins can breach the barrier by binding with receptors on the surface of the brain affecting the permeability of the membrane. They then propagate signals that are picked up by other peptides and receptors deep within the brain. Therefore the brain (neuro) and the IS are linked by information carriers – neuropeptides (Cohen & Herbert, 1996).

Factors that affect the immune system directly, are ageing, sleep deprivation, chronic inflammation, cancer and anticipation of a cancer diagnosis, surgery, malnutrition, overtraining in athletes, noise, smoke, pollution, alcohol, emotional distress, loss, unemployment, disruption of social support, caring for a loved one with chronic disease, and chronic negative emotions (Hodo, 2001).

THE CENTRAL NERVOUS SYSTEM (CNS) AND STRESS

The reaction of the CNS to stress is quite likely a multilayered response. Perhaps as a function of evolutionary development, the organism functions in such a way that homeostasis and survival can be maintained through numerous back-up systems.

There are 4 key subsystems within the CNS that play a role in the modulation of psychological stressors and the promotion of homeostasis and survival of the organism (Fox et al., 1999; Kaye et al., 2000; Ogden, 2004):

1. The autonomic nervous system (ANS) functions by way of motor neurons and chemical messengers that regulate the activities of the viscera, involuntary smooth muscles, cardiac muscle and glands.

2. The limbic system is a group of subcortical nuclei and fibre tracts that form a border around the brainstem – it is not a gross anatomical structure. The limbic system has 40 times more neuropeptide receptors than other parts of the brain, thereby containing the biochemical connection for emotional and cognitive modulation of the immune system. It comprises of the:
- hypothalamus (regulates physiological drives such as appetite, libido, thirst, sleep and initiates the hypothalamic-pituitary-adrenal (HPA) axis by secreting corticotropin-releasing factor (CRF))

- hippocampus (regulates recent memory; central emotive processes originate in hippocampus and are transmitted to the thalamus and cingulate gyrus – the receptive cortical region for emotional impulses)

- amygdala (integrates autonomic and visceral functions via connections with hypothalamus and brainstem; involved in complex cognitive functions that influence emotion and behaviour; might be involved in emotional learning and memory storage)

3. The basal ganglia play a significant role in modulating and processing information related to the limbic lobe, neocortical association areas or prefrontal and temporal areas. The process of perceiving psychological stressor occurs through a series of loop circuits that connect certain cortical areas with the basal ganglia. These loops might play a role in planning, programming and executing behavioural, autonomic and somatic motor responses related to emotions, affect and problem solving. Almost 80% of all dopamine in the CNS is found in the basal ganglia.

4. Two specific extrathalamic cortical modulatory systems also influence PNI:

- The locus ceruleus (LC) that communicates via an estimated 40,000 neurons to all levels of the CNS. The LC is located bilaterally in the dorsal pons near the floor of the fourth ventricle. It is the (a) main source of catecholamines especially norepinephrine (NE), (b) influences dopamine, acetylcholine and serotonin, (c) affects hormones via the hypothalamus. Thus LC links the limbic system (emotions), the hypothalamus (hormones) and frontal cortex (affect and abstract thinking), and forms a bi-directional communication network through the limbic system to affect the immune system and vice versa.

- The raphe nuclei, located in the pons and the medulla have widely distributed serotonergic neurons connecting to the hippocampus, basal ganglia, hypothalamus, cerebral cortex and brainstem. Serotonin inhibits aggressive or impulsive behaviour patterns.

Incoming stimuli may be perceived within the CNS as a stressor via instinct, conditioning or higher levels of cognitive analyses and may take two psychobiological pathways (Caine, 2003; Fox et al., 1999; Kaye et al., 2000; Starkweather et al., 2005; Stoppler, 2005):

- Hypothalamic-Pituitary-Adrenal axis (HPA)

- At the instinctual level the amygdala picks up on the stimulus, perceives it as a stressor and then triggers the extrathalamic modulatory systems.

- The brain is now more vigilant to incoming stimuli.

- The amygdala then triggers the hypothalamus, which under normal circumstances has an ANS-controlled
diurnal release of corticosteroids, but then becomes driven by signals from the hippocampus.

- Stimuli produced by stressful thoughts and emotions reach the hypothalamus via the amygdala-hippocampal formation.
- Within minutes the hypothalamus secretes CRF.
- CRF stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH).
- ACTH stimulates the adrenal cortex to secrete cortisol (glucocorticoids).

Cortisol is a catabolic (destructive) steroid made from cholesterol, which converts into pregnenolone, which converts to progesterone, which converts to cortisol. It has been described as low-grade adrenaline. Cortisol is absolutely required for the body’s metabolism to function, particularly energy metabolism, cardiac maintenance, muscle function, and suppressing inflammations. Cortisol levels are affected by the circadian rhythm ('sleep-wake' cycle). Cortisol secretion increases in response to any stress in the body, whether physical (such as illness, trauma, surgery, or temperature extremes) or psychological. When cortisol is secreted, it causes a breakdown of muscle protein, leading to a release of amino acids (the ‘building blocks’ of protein) into the bloodstream. These amino acids are then used by the liver to synthesize glucose for energy, in a process called gluconeogenesis. This process raises the blood sugar level so the brain will have more glucose for energy. At the same time the other tissues of the body decrease their use of glucose as fuel. Cortisol also leads to the release of so-called fatty acids, an energy source from fat cells, for use by the muscles. Taken together, these energy-directing processes prepare the individual to deal with stressors and ensure that the brain receives adequate energy sources. If cortisol is secreted, it causes a breakdown of muscle protein, leading to a release of amino acids (the ‘building blocks’ of protein) into the bloodstream. These amino acids are then used by the liver to synthesize glucose for energy, in a process called gluconeogenesis. This process raises the blood sugar level so the brain will have more glucose for energy. At the same time the other tissues of the body decrease their use of glucose as fuel. Cortisol also leads to the release of so-called fatty acids, an energy source from fat cells, for use by the muscles. Taken together, these energy-directing processes prepare the individual to deal with stressors and ensure that the brain receives adequate energy sources. If released chronically, ‘disarming’ the regulating feedback-loop (HPA axis), it has diverse suppressive effects on the immune system. It alters the circulating population of white blood cells, causing an overall decrease in T and B cells. The phagocyte system as well as macrophage differentiation is affected. It also inhibits the production of lymphokines, NK cell activity and gamma interferon (a cytokine). Prolonged secretion of cortisol initiates, perpetuates and aggravates syndromal depression, anxiety, high blood pressure, unstable blood glucose levels, hormonal imbalances (especially sex hormones), elevated cholesterol levels, obesity, osteoporosis, menstrual disorders, hypothyroidism, insomnia, Cushing’s Syndrome and poor memory. Prolonged production can result in damage to neurons in the hippocampus affecting memory and learning. If ongoing, the adrenals can become ‘exhausted’ (‘adrenal fatigue’) and levels drop below normal. This is often the case in ‘chronic fatigue syndromes’ and Addison’s disease.
- Furthermore, emotion-affecting neuropeptides (e.g. encephalins and beta-endorphins) released by the hypothalamus, pituitary gland and adrenal gland control the migration of monocytes.

- **CNS activation**
  - Stress stimulates neurons in the hypothalamus to secrete CRF.
Depression is strongly associated with elevated stress and illness and the amygdala-hippocampal complex. Involve interactions between higher-level cortical centres (limbic system, hypothalamus, frontal cortex).

This leads to depressed mood and distorted thinking.

The flood of catecholamines (NE, dopamine, epinephrine) lower immune function by altering T cells (stimulate immunosuppressive CD8 cells and reduce immuno-enhancing CD4 cells). (According to Ogden (2004) the prolonged production of these hormones can also result in blood clot formation, increased blood pressure, increased heart rate, irregular heart beats, fat deposits in cells and plaque formation in the arteries.)

They might induce secretion of cytokines or beta-endorphins (modulators of cellular immunity).

- The medulla oblongata and pons also contain NE neurons.
- Their cell bodies are serotonergic (in many regions serotonergic and noradrenergic projections overlap, explaining the new NE-serotonin reuptake inhibitors (NSRI) – they block the uptake of serotonin and NE).

Now the body is on ‘full alert’ to the perceived stressor. As the cortical neurons are more attuned to the stressor, previously conditioned responses are retrieved from memory via the amygdala-hippocampal connection to create an additional level of responsiveness. Further triggering of the hypothalamus continues from the amygdala.

A third pathway may exist in which higher level cognitive processing perceives a stimulus to be a stressor in the absence of instinct or conditioning. This scenario would involve interactions between higher-level cortical centres and the amygdala-hippocampal complex.

**STRESS AND ILLNESS**

Depression is strongly associated with elevated cortisol levels, which results from state-dependent influences involving stress, neurotransmitter dysregulation and associated effects on the HPA axis activity. Depression is also associated with lowered activity of hypothalamic-growth hormone (GH), secreted by the anterior pituitary gland and modulated by dopamine, NE and serotonin. A reduction in NK cell activity has also been seen (Kaye et al., 2000; Kiecolt-Glaser et al., 2002).

Research by Sherwood et al. (2007) and Dickens et al. (2007) have also shown that depression significantly increases the risk of major health problems, hospitalisation and even death in elderly people with chronic heart failure.

Research (Caine, 2003) show that depressed and anxious mood states are associated with decreases in lymphocyte proliferation and NK cells activity, and with changes in the quantity of white blood cells and antibodies circulating in the blood. The longer the stress and the greater the degree of pessimism, the greater is the decrease in lymphocytes.

Stress / allostatic load are physically measured by a broad battery: blood pressure, overnight urinary cortisol and catecholamine secretions, waist to hip ratio, glycosylated haemoglobin, ratio of serum high-density lipoprotein, total serum cholesterol concentration, Dehydroepiandrosterone (DHEA) sulphate. DHEA is an endogenous hormone (made in the human body), and secreted by the adrenal glands. DHEA serves as a precursor to male and female sex hormones (androgens and estrogens). There is sufficient evidence supporting the use of DHEA in the treatment of adrenal insufficiency, depression, induction of labor, and systemic lupus erythematosus. (Kiecolt-Glaser et al., 2002)

Chronic stress is significantly correlated with illness frequency and severity. Illnesses activated or worsened by stress include tuberculosis, malignant diseases such as certain cancers, cardiac disorders, dyspnea, respiratory diseases, osteoporosis, Alzheimer’s disease, periodontal disease, tachycardia, auto-immune diseases, hypertension, and hypotension (Caine, 2003; Kiecolt-Glaser et al., 2002). Research suggests that the immune system does not always adapt and that perhaps some irreversible damage to the immune system occurs in the presence of chronic uncontrollable psychological stressors. No human body has infinite capacity for handling stress – when the capacity is exhausted, the body can no longer fight off the effects of stress and dies (Fox et al., 1999).

**PNI HOMEOSTASIS STRATEGIES**

Factors that have been clinically shown to impact on stress (and the PNI network), are listed below (Bennett et al., 2003; Caine, 2003; Cardinai, 2001; Cohen et al., 1996; Evans et al., 2000; Goodkin et al., 1995; Heesin et al., 2000; Jessop, 1998; Jozuka et al., 2003; Kiecolt-Glaser et al., 2002; Kodama et al., 2007; Kolb & Whishaw, 1990; Lustman et al., 2007; McGregor, 1992; Miller & Thoresen, 2003; Ogden, 2004; Paquette, 2004; Ray, 2004; Segerstrom, 2005; Segerstrom & Miller, 2004; Sprague et al., 2007; Thompson et al., 2007; Vollrath, 2006; Yates, 2004):

Foster **hope and optimism**

This is linked to the experience of meaning; positive appraisal of stressful life events; the development of positive illusions; and the realisation of life’s possibilities.

Both experimental and naturalistic studies show that optimism is negatively related to measures of cellular immunity when stressors are difficult (e.g., complex, persistent, and uncontrollable) but positively related when stressors are easy (e.g., straightforward, brief, and controllable). Although the negative relationship between optimism and immunity has been attributed to the violation of optimists' positive expectancies and subsequent disappointment, empirical evidence suggests that it is more likely to be a consequence of optimists’ greater engagement during difficult stressors. For example, negative mood does not account for the effect, but conscientiousness, a personality facet related to engagement, does. The mixed immunological correlates of optimism may explain why it does not consistently predict better disease outcomes.
**Inner resources and knowledge**

This refers to a set of beliefs, assumptions and predictions that adaptively alter inner or outer reality in order to minimise distress. Knowledge about oneself, the illness and the surrounding world.

**Promote a sense of autonomy**

This implies advocating a person’s personal decision making and choices, or sharing decision making.

**Incorporate strategies that promote sleep**

Deep sleep (especially phase 3 & 4) stimulates growth hormones that enhance immune function and energy, and serotonin that enhances mood.

Partial sleep loss one evening results in elevated cortisol levels the next evening. A cortisol rhythm disrupted by chronic stress, both mentally and physically, can impair the ability to fall asleep or stay asleep. Cortisol is also sometimes referred to as the ‘anti-sleep’ hormone.

Benzodiazepines can be used with caution.

**Promote a supportive social setting**

This refers to esteem support, informational support, social companionship, and physical support.

The positive influence of supportive interpersonal relationships is one of the most robust findings in PNI. They increase NK cell number and activity, and the number of lymphocytes, and decrease T-helper cells.

Loneliness lowers NK cell activity.

**Alleviate pain**

Examples of strategies used are relaxation, cognitive coping strategies, and the self-monitoring of stressors.

**Promote healthy eating habits**

Regular meals maintain steady blood glucose levels and mood. Skipping meals can also lead to cortisol release.

Neurotransmitters and other chemicals are dependent on healthy eating habits (acetylcholine is made in part of choline, which is obtained from the diet; dopamine and NE are synthesised from the dietary amino acid tyrosine; serotonin is derived from the dietary amino acid tryptophan in bananas; etc).

Controlling depression may help control glucose levels, weight loss and diabetes self-control.

Recommend the use of vitamins and minerals, especially vitamin C, B complex and D; also magnesium.

**Promote physical exercise** (endurance, strength, flexibility)

High IL-6 and C-reactive protein (CRP), risk factors for CVD, are associated with low levels of exercise.

Exercise increases the number of lymphocytes, endorphins, NK cell number and activity, and T cells.

Exercise may boost ‘good’ cholesterol levels (HDL) – 120 minutes a week or 900 calories burnt per week. Exercise duration, not frequency or intensity is associated with HDL cholesterol changes.

Exercise may reduce risk of breast cancer.

Exercise should fit the person’s lifestyle and abilities. Habitual moderate exercise has been shown to lower cortisol levels and reduce the risks in CHD events for most people; vigorous exercise tend to increase cortisol and might be a risk for sudden cardiac death and acute myocardial infarction in patients with hypertropic cardiomyopathy and anomalous coronary arteries or those patients who are least habitually active. Vigorous physical activity may cause coronary thrombosis by worsening mild plaque fissure.

Determine the need for psychotropic medications

Examples are anti-depressants, anxiolytics and sedatives/hypnotics.

**Promote the appropriate release of emotions**

Repression of emotions, rejection sensitivity, attributional style and sociability are associated with a deregulated immune function.

**Limit chronic negative emotions**

Chronic negative emotions can directly stimulate the production of proinflammatory cytokines that enhance further negative emotions, lethargy, fatigue, shivering, loss of appetite etc.

**Try to maintain a normal body mass index**

IL-6 and CRP levels are higher in higher body mass indexes.

**Recommend healthy habits**

Smoking increases IL-6 and CRP levels.

Alcohol and drugs have a variety of influences.

Stimulants (e.g. caffeine) tend to raise cortisol levels.

**Religion or spirituality**

Belief, religious behaviour, the use of religion in coping, spirituality, faith etc. have an influence on PNI homeostasis.

**Focus on limiting chronic hostility/anger**

Research is ambiguous about the link between Type A behaviour and illness, but more clear on the link between hostility/anger and illness.

**Use different coping strategies** that (1) reduce the intensity and duration of the stressor itself and (2) reduce the likelihood that stress will lead to illness (negative outcomes):

- Try to avoid or manage short-term less-supportive atmospheres;
- Approach longer-term stressors by confronting the problem, gathering information and taking direct action;
- Use problem focused coping in work situations and perceived controllable problems. This involves taking
action to reduce the demands of the stressor or increasing the resources available to manage the stressor; using problem solving, and cultivating acceptance styles;

• Use emotion focused coping when emotions are evoked by stress and the problem is perceived to be uncontrollable. This includes talking to friends, reframing the situation more positively and trying to find meaning.

Psychotherapy

Psychotherapy focussing on cognitions and behaviour, imagery, visualisation, biofeedback, and wellness seems to benefit patients.

Relaxation involving changing breathing

Change the rate and depth of breathing as this leads to increased T cell effectiveness; increased NK cell activity; and decreased blood levels of stress hormones.

Mirthful laughing and humour

This leads to increased immunoglobulin A; and increased lymphocyte count and activity.

Consider the use of music

Especially wavy, relaxing music have been proved helpful. Cortisol levels tend to lower and DHEA levels tend to be raised.

Aromatherapy

Mindfulness

This refers to the skill of being in the here and now, appreciating experiences, doing one thing at a time, and contemplating the most effective behaviour/thought pattern at a specific point in time.

Perceived unpredictable or uncontrollable stress (feel more hopeless, lack of control, tension, unhappiness, anxiety, depression) leads to central catecholamine depletion, decreased GABA release, HPA axis increase, release of corticosteroids and inhibits lymphocyte metabolism (especially CD4). These changes are not observed after identical amounts of perceived controllable stress. Exposure to chronic stress therefore does not necessarily result in immunosuppression but may lead to adaptation (Evans et al, 2000; Kaye et al, 2000; Hodo, 2001).

Higher levels of control (predictability, responsibility, choices, boundaries etc.) relates to a reduction in stress. A combination of high workload, low satisfaction and low control are the best predictors of coronary heart disease. Accepting uncontrollability (perception of helplessness) may be less stressful than attempting to control an uncontrollable situation (Ogden, 2004).

The ability to ‘unwind’ after stressful encounters, i.e. quicker return to one’s neuroendocrine baseline, influences the total burden that stressor s place on an individual (Kiecolt-Glaser et al., 2002).

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Pain among the oldest old in community and institutional settings

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Abstract

The relationship between pain and increasing age was investigated using data from two different care settings collected on a province-wide basis in Ontario. Home care clients (HC) and complex continuing care patients (CCC) are assessed using the Resident Assessment Instrument – Home Care and Resident Assessment Instrument 2.0 instruments, respectively, as part of normal clinical practice. For this study, the sample was restricted to those aged 65 years and older and totaled 193,158 individuals. Centenarians (those 100 years of age or older) made up 0.41% (n = 788) of the sample. Pain was assessed according to a previously validated pain scale embedded in both assessments that uses items on frequency and intensity. Based on 5-year age groups beginning at 65, the mean reported pain score was lower with each increment in age for men and women. Multiple logistic regression models were constructed and the odds ratios for pain in both HC and CCC groups decreased consistently in higher age groups after adjusting for disease diagnoses, cognition, functional status and health indicators. A model that included categories of analgesic medications coded based on the WHO pain ladder showed the relationship persisted after controlling for analgesia. In clinical settings, the oldest old appear to have lower levels of pain compared with the young old after adjusting for a variety of potential confounding variables.

Keywords: InterRAI; Assessment; Home care; Centenarian

I. Introduction

The experience of pain is a major public health problem. Pain – a subjective symptom not directly verifiable by clinicians – is an important factor in motivating patients to seek medical attention (Lim et al., 2006). The increased incidence of chronic diseases with aging means that the elderly have an elevated risk for experiencing both acute and chronic pain (Scudds and Østbye, 2001). At present, there is still only limited knowledge regarding the effects of normal or pathological aging on pain (Jakobsson et al., 2003), and there is a particular dearth of knowledge regarding pain in the oldest old (e.g., centenarians – those 100 years of age or older) (Gibson and Helme, 2001). Various studies have reported contradictory results which show that the rates of pain increase (Elliott et al., 1999; Edwards et al., 2003; Jakobsson et al., 2003), decrease (Mobily et al., 1994; Brattberg et al., 1996; Li et al., 2001; Gagliese and Katz, 2003) or do not change (Thomas et al., 2004) with age. Few studies consider the oldest part of the population (Zarit et al., 2004), and there do not appear to be any studies of pain in which sufficient numbers of centenarians are available to examine them as a separate subgroup. Individuals who survive to very advanced ages may represent a positive model of aging in terms of lifelong beneficial health behaviours that reduce the risk of
premature mortality, but they may also be a distinct subpopulation of survivors with a differential level of risk for lethal chronic diseases, compared with the general population (Cicconetti et al., 2002; Evert et al., 2003; Perls and Terry, 2003). The number of centenarians is increasing rapidly in North America, Europe and Japan, where the number of years needed to double the number of centenarians in a population (centenarian doubling time) is currently 10 years or less (Robine and Paccaud, 2005). In the 2001 Canadian Census, 1380 people aged 100 and over were enumerated in Ontario, which represents a 21.6% increase from 1996 (Office of Economic Policy, 2003).

The aim of this work is to analyze the prevalence and correlates of assessed pain among the Canadian elderly in home care and institutional settings, with a particular focus on the patterns of pain in individuals of advanced age. Specifically, census-level data from the Resident Assessment Instrument 2.0 (RAI 2.0) (Fries et al., 1997) used in Ontario Complex Continuing Care Hospitals/Units and from the Resident Assessment Instrument – Home Care (RAI-HC) (Morris et al., 1997) used in Ontario Community Care Access Centres are examined in order to compare age differences in the experience of and factors associated with pain.

2. Methods

Since 2002, the RAI-HC has been the mandatory assessment system used by Ontario case managers in all 42 Community Care Access Centres (CCACs) with all home care clients who are expected to be on service for 60 days or more. CCACs are single-point entry agencies with the responsibility of determining the need for home care or facility placement and for contracting community-based services. In addition, the RAI 2.0 has been the mandatory assessment instrument for all 134 Complex Continuing Care (CCC) hospitals/units in Ontario since 1996. CCC hospitals/units account for about 10–15% of beds in institutional settings for the elderly. They are comparable to skilled nursing facilities in the United States in that they provide care to older persons with complex medical needs, functional disabilities, and cognitive impairments. They are distinct from long term care homes in that they target a post-acute population with unstable health conditions. Almost 90% of CCC admissions come from hospital settings, compared with about 60% in long term care homes (Canadian Institute for Health Information, 2006). About 76% of CCC patients are discharged within one year, compared to about 22% of long term care home residents.

The assessments in CCAC and CCC settings are completed by trained professionals (usually nurses) as part of normal clinical practice. These assessments address a wide range of domains, including physical and cognitive functions, continence, mood, medical diagnoses, pain, activity patterns, and medications. The RAI-HC and the RAI 2.0 are the main data sources for the Canadian Institute for Health Information’s (CIHI) national Home Care Reporting System and Continuing Care Reporting System (www.cihi.ca), respectively. The reliability and validity of these instruments have been established through numerous international studies (Hawes et al., 1995; Morris et al., 1997; Mor et al., 2003).

For the present study, elderly people were selected from two different care settings with census-level data in Ontario: (a) the Home Care (HC) group consisted of all long-stay clients (expected to receive home care services for more than two months) aged 65 years and older who were assessed between February 2003 and September 2004 (n = 114,499); and (b) the Complex Continuing Care (CCC) group consisted of all patients aged 65 years and older in CCC hospitals/units (n = 78,659). The only exclusion criteria were age (under 65 were excluded) and end-of-life status (palliative care clients/patients were excluded); however, there were no exclusions based on disease diagnoses.

Although the RAI 2.0 is currently being implemented in long term care homes in Ontario, data are only available for the first 20 of 650 homes to implement the system. The present analyses exclude those homes because one cannot be certain that the 20 homes are fully representative of all long term care homes, and the sample size (about 2300) cases are too small to provide adequate numbers of very old residents. The main consequence of the sample selection is that results are not reported for the elderly in settings with residents who tend to have moderate to severe cognitive and functional deficits but relatively stable medical conditions. There are also no data available for the general population of older persons in Ontario who are not receiving any community or facility based services. Consequently, the results reported here should be considered representative of the elderly in two major service settings, but they do not necessarily reflect distributions in the entire elderly population. Based on evidence from other studies, such bias is likely to affect the accuracy of estimates of prevalence, but detection of associations is less likely to be affected (e.g., Heilbrun et al., 1982; Hirdes and Forbes, 1989; Eagan et al., 2002).

In order to obtain a sufficiently large sample size to examine individuals of advanced age in CCC, the entire July 1996 to March 2004 CCC dataset was used. In total, there were 193,158 records in the combined database. In order to avoid duplicate observations on the same person, the most recent RAI 2.0 and RAI-HC assessments were used for CCC and CCACs, respectively. An alternative strategy would have been to use the first assessment, but this approach did not yield substantively different findings. There is a small possibility that there are some duplicates of individuals who received care from both CCC and CCACs in the study period; however, based on discharges from CCC to home care (Canadian Institute for Health Information, 2004), this is estimated to be about 1.5% of the annual home care clientele receiving the RAI-HC. There is no direct way to estimate overlap between the two sectors, because personal identifiers in the datasets are either deleted or encrypted for privacy reasons. Also, the analyses are stratified by care setting, so there would still be no duplication of individuals within strata.

Pain was assessed according to a pain scale that is embedded in the RAI-HC and RAI 2.0 (Fries et al., 2001). The scale uses items on pain frequency and pain intensity to create a four-point scale that ranges from no pain (0) to daily horrible or excruciating pain (3). This pain scale has been used in numerous international studies including, for example, an
Pain is a significant issue in nursing homes, with a 11-country study of pain and depression among home care clients in the European Union (Onder et al., 2005); a US study of the adequacy of pain management in nursing home residents with cancer (Bernabei et al., 1998); a Hong Kong study of pain and depression in stroke patients (Fung et al., 2005); and a US initiative to measure nursing home quality (Wu et al., 2005a).

Pain was documented if it had occurred in the seven days before the assessment in the CCC group, or within the last three days in the HC group. This difference in observation period may slightly reduce the detection of less than daily pain in the RAI-HC; however, it would only affect less than daily pain that occurs in cycles of four days or more. Assessors were directed to not only ask about pain, but also to look for overt signs, such as wincing, verbalizations, and indications of discomfort. They then used their clinical judgement to record the most appropriate response considering all sources of information available to them. Consequently, it was possible for assessors to rate pain in all populations, including those with cognitive impairment. The pain scale has been validated against the Visual Analogue Scale (Fries et al., 2001) in nursing homes, and it has been shown to be associated with pain-causing conditions in cognitively intact and cognitively impaired CCC patients (Proctor and Hirdes, 2001). However, even with the use of multiple sources of information including verbal and nonverbal indicators, pain is likely to be underestimated in persons with cognitive impairment (et al., 2005; and a Wu et al., 2005b). In a study of 3736 nursing home residents Wu et al. (2005b) reported good inter-rater reliability for the pain items used here with κ values above 0.5 and polychoric correlations greater than 0.7. Doran et al. (2006) used the RAI 2.0 pain items and self-reported measures of pain severity and frequency to study nursing-sensitive outcomes in acute and long term care settings. They reported that the RAI 2.0 pain items showed a similar response pattern to the self-reported measures in terms of direction and effect size.

The mental status of each participant was assessed using the Cognitive Performance Scale (CPS), which has been validated against the Mini-Mental State Examination in nursing home and home care settings (Morris et al., 1994; Landi et al., 2000). Scores on this scale range from cognitively intact (CPS = 0) to severe cognitive impairment (CPS = 6). The Activities of Daily Living (ADL) Hierarchy score was used as a measure of physical function (Morris et al., 1999) and includes items on personal hygiene, toilet use, locomotion, and eating. The scale identifies the level of disablement, ranging from a score of 0 (independent) to 6 (totally dependent in late-loss ADLs).

Depression was measured by the Depression Rating Scale (DRS), which has been validated against the Hamilton and Cornell scales for depression and psychiatrists’ ratings (Burr et al., 2000). The DRS is based on a sum of frequency scores for seven mood items and yields scores that range from 0 to 14. Conventionally, a scale score of 3 or greater is considered to indicate the possibility of major or minor depression.

The CHESS scale (Changes in Health, End-stage disease, and Signs and Symptoms) identifies individuals at risk of mortality or serious decline in health using scores ranging from 0 to 5 to depict the level of instability in health (Hirdes et al., 2003). A count of the following health symptoms is taken into consideration: vomiting, dehydration, leaving food uneaten, weight loss, shortness of breath, and oedema. The sum of these symptoms contributes 0 points (no symptoms), 1 point (at least one symptom present) or 2 points (2 or more symptoms present) to the CHESS score. Also, one point is added to the CHESS score for each of the following three conditions: end-stage disease, decline in cognition, and decline in ADL. Higher CHESS scores are associated with reduced survival rates in CCC and CCACs.

Disease diagnoses were coded according to The International Classification of Disease, 9th Revision – Clinical Modification (ICD-9-CM, 1989). Information on disease status was generally obtained from the individuals’ medical records.

Reporting of drug-specific medication data is only compulsory for the HC population, therefore, detailed drug data are not available for the CCC sample. For HC clients, analgesics were classified into three categories, according to the WHO pain ladder (Levy, 1996; Bernabei et al., 1998): Level 1 – salicylates, acetaminophen, and nonsteroidal anti-inflammatory drugs; Level 2 – codeine phosphate or codeine sulfate, oxycodone hydrochloride, hydrocodone bitartrate, propoxyphene hydrochloride, or propoxyphene napsylate, meperidine hydrochloride, pentazocine hydrochloride, pentazocine lactate, butorphanol tartrate and any combination of these compounds with WHO level-1 drugs; and Level 3 – morphone sulfate, hydromorphone hydrochloride, oxymorphone hydrochloride, methadone hydrochloride, and fentanyl citrate. In 2002, the Canadian Institute for Health Information (CIHI) added a general item on use of any analgesics in the last seven days to the Canadian version of the RAI 2.0, but it is not possible to calculate the WHO pain ladder from that item.

All analyses were based on prevalence samples comprised of the most recent assessment done for each individual in the HC or CCC datasets described above. Bivariate analyses were based mainly on frequency tables stratified by 5-year age groups, beginning at age 65. All individuals aged 100 years or more were grouped together in order to preserve adequate cell sizes for centenarians. To identify factors associated with pain, odds ratios (adjusted for age and sex) were calculated for variables that were expected to be clinically important, or that had been shown to be associated with pain in previous studies. Variables that were significant at the bivariate level were then considered as candidates for multivariate logistic regression models, with pain collapsed as a binary variable (no pain vs any pain). The final model was comprised of variables that were significant at the .05 level in either of the two clinical populations. In order to avoid order-of-entry/deletion effects, stepwise methods were not used to reduce the models (see Leigh, 1988 for a discussion of problems associated with stepwise models). Instead, a variety of alternative logistic regression models that considered different sets of independent variables were examined before a final model was specified.

3. Results

3.1. Sample characteristics

Table 1 summarizes the sample characteristics. In both care settings, the majority were female and the
Table 1
Characteristics of Home Care clients and Complex Continuing Care patients in study sample

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Home Care n = 114,499</th>
<th>Complex Continuing Care n = 78,659</th>
</tr>
</thead>
<tbody>
<tr>
<td>65–69 % (n)</td>
<td>12.3 (14134)</td>
<td>14.3 (11272)</td>
</tr>
<tr>
<td>70–74 % (n)</td>
<td>26.2 (29956)</td>
<td>21.1 (16610)</td>
</tr>
<tr>
<td>75–79 % (n)</td>
<td>20.3 (23254)</td>
<td>23.5 (18551)</td>
</tr>
<tr>
<td>80–84 % (n)</td>
<td>11.1 (12717)</td>
<td>19.4 (15217)</td>
</tr>
<tr>
<td>85–89 % (n)</td>
<td>2.7 (3079)</td>
<td>10.0 (7838)</td>
</tr>
<tr>
<td>90–94 % (n)</td>
<td>0.4 (483)</td>
<td>2.7 (2150)</td>
</tr>
<tr>
<td>95–99 % (n)</td>
<td>79.3 (383)</td>
<td>51.4 (248)</td>
</tr>
</tbody>
</table>

**Female**

| All HC subgroups | 60.4 (4071) | 55.2 (5875) |

**Diagnosis**

| All CCC subgroups | 12.3 (14134) | 17.3 (1546) |

**Summary Measures**

| Pain Scale | 1.41 (0.38–1.43) | 1.37 (1.35–1.39) |
| Cognitive Performance Scale | 0.87 (0.84–0.90) | 0.86 (0.84–0.89) |
| ADL Hierarchy Scale | 1.12 (1.09–1.16) | 1.17 (1.15–1.19) |
| Depression Rating Scale | 1.05 (1.01–1.08) | 0.98 (0.96–1.00) |

| All CCC subgroups | 49.7 (3351) | 55.2 (5875) |

**Diagnosis**

| All CCC subgroups | 12.3 (14134) | 17.3 (1546) |

**Summary Measures**

| Pain Scale | 1.41 (0.38–1.43) | 1.37 (1.35–1.39) |
| Cognitive Performance Scale | 0.87 (0.84–0.90) | 0.86 (0.84–0.89) |
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| Depression Rating Scale | 1.05 (1.01–1.08) | 0.98 (0.96–1.00) |
First aid pain relief for those sensitive to codeine!

Fight pain, fever and inflammation!

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Ibuprofen
Paracetamol

For further information refer to package insert.
percentage of females increased with each age category from 60.4% (65–70 years old) to 79.3% (100–115 years old) in the HC group and from 49.7% to 83.3% in the CCC group. There was a significant decrease in the mean pain scale scores from 1.41 in the youngest age category to just under 1.00 in the oldest category for both HC and CCC groups. Also, the percentage of people reporting no pain generally increased with age in both groups, while the percentage reporting severe pain decreased among higher age groups. Among centenarians, almost 50% of the individuals reported no pain, in both HC and CCC settings.

With respect to other scales, CPS scores were higher (indicating greater cognitive impairment) among older age groups in both settings; however, CPS scores were much lower in the community (0.9–1.8) than in institutions (2.3–3.9). Mean ADL Hierarchy scores in both groups were relatively consistent until age 90, when they increased sharply. Mean CHESS scores were similar across all age categories in both groups. The Depression Rating Scale score was lower among older age categories in home care, but was relatively consistent across age groups in institutions.

There were also notable differences in disease profile between across age groups in the two care settings. The most common diagnoses in individuals under 75 years were arthritis, diabetes, stroke and cancer in HC, and cancer, diabetes, stroke and psychiatric diseases in CCC. However, among centenarians in both settings, arthritis was the most frequent diagnosis, and it was found in over half of the HC population. The next most frequent diagnoses were osteoporosis and dementia among the oldest individuals. In both settings, there was a clear trend of lower rates of psychiatric, diabetes and cancer diagnoses among the higher age categories.

Fig. 1 shows that men generally reported less pain than women; however, this gender difference appeared to be smaller with higher CPS scores. In the HC population, those with a higher CPS score (3 or more) reported less pain overall than those who were less cognitively impaired. However, given that the level of pain reported decreased with increasing age category among those who are cognitively intact (CPS = 0), it is unlikely that the age differences in pain are simply a function of changes in cognition with age.

Fig. 1. Mean pain score stratified by Cognitive Performance Scale and gender (HC and CCC). The lines represent the mean pain score (out of 3) across the age categories. Diamonds represent CPS = 0 (cognitively intact), Squares represent CPS = 1, 2 (mildly impaired), and triangles represent CPS = 3 (impaired cognition). Solid symbols with dashed lines represent women, hollow symbols with solid lines represent men.

Similar trends were evident in the CCC population: the mean pain scale score in all CPS levels was higher than that in the HC population, and differences between genders and CPS levels were much less pronounced than in the HC group. Nevertheless, the cognitively intact group showed a decrease in mean pain score with increasing age category, and males with a CPS score of 0 in the 90–95 and 95–100 age categories reported less pain than those in any other CPS level. Centenarians in CCC do not seem to follow these trends; however, this is probably a function of small cell sizes for centenarians with CPS = 0 in CCC (females n = 18, males n = 7).

As one would expect, Fig. 2 shows that certain disease diagnoses are associated with higher pain scale scores. In home care, arthritis and osteoporosis are related to the highest levels of pain. As age increases, the pain scale score associated with these diagnoses decreases. The level of pain reported by those with a diagnosis of dementia remained fairly stable across the age categories and was lower than that associated with other diagnoses. In the centenarian group, the trends tended to continue, except for cancer, which was associated with the same level of pain as arthritis.

In the CCC population, cancer was associated with the highest pain scores. The level of pain decreased as age category increased; however, even in the centenarian group, cancer (along with psychiatric diagnoses and osteoporosis) was still associated with the most pain.

Table 2 provides the final multiple logistic regression models for the presence of pain by age after adjusting for disease diagnoses and various scale scores for each care setting. In both HC and CCC, the odds ratios for pain declined consistently among higher age groups after adjusting for other risk factors (e.g., cognitive impairment). Compared with 65- to 69-year-olds, the odds ratio for pain in centenarians was 0.42 (CL: 0.35–0.51) and 0.56 (CL: 0.40–0.79) in HC and CCC,
was developed; however, because drug data were not available for the CCC cases, this could only be done for the HC group. This model is comparable to the previously reported logistic regression that yielded similar odds ratios as were noted for the common independent variables. In particular, advanced age continued to be consistently associated with a lower likelihood of pain after adjusting for analgesia. The higher values of the \( c \) statistic indicated that the addition of the WHO pain ladders improved the predictive power of the model, compared with that reported in Table 2.

4. Discussion

The findings reported here agree with results obtained by others who considered younger samples of the elderly (Mobily et al., 1994; Brattberg et al., 1996; Li et al., 2001; Gagliese and Katz, 2003). On the other hand, the decrease of reported pain with age seems to contradict some other papers in the literature (Elliott et al., 1999; Edwards et al., 2003). This apparent contradiction might be due to differences in the age groups analyzed. For instance, Elliott et al. (1999) showed that the prevalence of chronic pain increases with age; however, their youngest group consisted of people aged 25–35, and the oldest group included people older than 75.

The present study is distinct from much of the published literature because it considered the prevalence and risk factors for pain in large samples of the oldest old in two different care settings. For example, while most studies of centenarians are restricted to small samples, the present study examined the experience of pain in almost 800 centenarians. The large sample sizes, combined with the broad range of covariates that might be confounding variables, provided an opportunity to gain unique insights into the relationships between advanced age and pain. Moreover, the availability of directly comparable measures between CCC hospitals/units and community health care settings addressed the potential problem of a bias caused by the movement of frail persons of advanced age out of community samples into institutional settings. That is, the present results do not support the argument that the apparent reduction of pain levels among the oldest old can be explained by the selective admission of those who are in pain in those age groups to long term care settings. The finding of greatest interest in this research is the consistently lowered pain level evident with every age-group increment in home care and institutional settings. This finding persists after controlling for a variety of risk factors, such as diagnosis, cognition, disability, medical complexity, depression, and analgesia. Although these results reflect age differences rather than age changes that can be detected with longitudinal data, they raise some intriguing questions about the nature of the aging process with respect to pain. One must ask if there are other potential confounding variables not available in the

---

Fig. 2. Mean pain score stratified by disease state (HC and CCC). The lines represent the mean pain score (out of 3) across the age categories. The solid diamond represents dementia, the ‘x’ represents stroke, the hollow diamond represents diabetes, the plus sign represents cancer, the solid square represents any psychiatric diagnosis, the solid triangle represents a diagnosis of osteoporosis or hip fracture, and the hollow square represents arthritis respectively, after adjusting for diagnosis, cognition, ADL, depression, and health instability. In both settings, the probability of pain was higher with arthritis, diabetes, osteoporosis or hip fracture, cancer, more severe ADL impairment, DRS score of 3 or more, and CHESS score of 2 or more. The odds ratios for pain were below 1.0 for stroke and CPS scores of 2 or more. The presence of a psychiatric diagnosis was only significantly related to a greater probability of pain in CCC Table 3.

Fig. 3 considers the use of analgesics (categorized using the WHO pain ladder) among those in home care who report severe pain. There is a consistent decline in the percentage of individuals receiving analgesia at levels 2 and 3 (codeine and morphine) among the higher age groups. In the centenarian category, more than 20% of those who reported severe pain were not receiving any analgesia, and only about 30% were receiving level 2 or 3 analgesia compared with about 50% of the 65- to 69-year-olds.

In order to take into account the possibility that analgesia may have affected pain ratings, another logistic regression model that included the WHO pain ladder was developed; however, because drug data were not
RAI-HC or RAI 2.0 that could have fully accounted for the decline in the probability of pain presence that the other independent variables did not adjust for. Perhaps this relationship may have been weakened somewhat by more detailed measures of the domains considered (e.g., cancer stage vs. cancer diagnosis as a binary variable). There is also the possibility that the exclusion of: (a) healthy individuals from the general elderly population that do not receive any formal care services (e.g., home care) and (b) long term care home residents left important gaps in the populations considered. The absence of data on the former population is probably a more important confound than the lack of data on long term care residents. Healthy 65-year-olds who receive no formal services probably have lower levels of pain than 65-year-olds receiving home care, which means the home care data would probably overestimate the prevalence of pain in the overall population of community-based 65-year-olds.

There are at least three other potential explanations for the age differences noted here. First, survival biases may result in populations comprised of increasing proportions of robust individuals at advanced ages because the weaker members of their cohort have died. The relative absence of pain in these individuals may reflect the fact that they represent a “healthier elite” subset of the population. Second, the oldest old may report less pain – especially chronic pain – because they have partly accepted it and become accustomed to the pain. In other words, the oldest elderly may report less pain due to increased stoicism (Brattberg et al., 1997; Gibson and Helme, 2001; Yong et al., 2001) or because they adapt to pain by modifying their activities to reduce the likelihood of experiencing pain. Third, these results may also point to a change related to aging that has not been sufficiently considered in the current literature (Gibson and Helme, 2001). That is, more research must be done on individuals of advanced age to determine whether biological changes associated with aging reduce the likelihood of experiencing pain at advanced ages. There has been some research which suggests that persons with dementia may have reduced pain sensitivity due to neurodegenerative diseases. The biology of aging may affect pain pathways and thresholds as well, since degenerative changes occur in the central and the autonomic nervous systems with loss of quality of nerve cell processes (Scherder et al., 2003; Scherder et al., 2005). There is also evidence that parts of the inflammatory cascade are impaired in older adults and inflammation is typically reduced (Grove, 1989).

This study also demonstrated relatively consistent gender differences in pain across age groups, with men reporting less pain than women, as has been shown in other studies (Keogh and Arendt-Nielsen, 2004; Leveille

### Table 2
Logistic regression model for presence of pain in home care and complex continuing care

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Home Care odds ratio (95% CL)</th>
<th>Complex Continuing Care odds ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>1.29 (1.25–1.32)</td>
<td>1.39 (1.34–1.45)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–74</td>
<td>0.76 (0.73–0.80)</td>
<td>0.89 (0.83–0.95)</td>
</tr>
<tr>
<td>75–79</td>
<td>0.70 (0.67–0.72)</td>
<td>0.83 (0.79–0.89)</td>
</tr>
<tr>
<td>80–84</td>
<td>0.64 (0.62–0.67)</td>
<td>0.78 (0.73–0.82)</td>
</tr>
<tr>
<td>85–89</td>
<td>0.58 (0.56–0.61)</td>
<td>0.72 (0.68–0.77)</td>
</tr>
<tr>
<td>90–94</td>
<td>0.54 (0.51–0.56)</td>
<td>0.71 (0.66–0.77)</td>
</tr>
<tr>
<td>95–99</td>
<td>0.46 (0.43–0.50)</td>
<td>0.61 (0.54–0.69)</td>
</tr>
<tr>
<td>100–115</td>
<td>0.42 (0.35–0.51)</td>
<td>0.56 (0.40–0.79)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>3.55 (3.46–3.64)</td>
<td>2.18 (2.07–2.30)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.14 (1.10–1.17)</td>
<td>1.08 (1.03–1.13)</td>
</tr>
<tr>
<td>Osteoporosis/hip fracture</td>
<td>1.66 (1.61–1.71)</td>
<td>2.64 (2.50–2.79)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1.04 (1.00–1.08)</td>
<td>1.11 (1.06–1.17)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.11 (1.07–1.15)</td>
<td>2.23 (2.12–2.34)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.89 (0.86–0.92)</td>
<td>0.76 (0.73–0.80)</td>
</tr>
<tr>
<td>Cognitive Performance Scale &gt;2</td>
<td>0.47 (0.45–0.48)</td>
<td>0.57 (0.55–0.60)</td>
</tr>
<tr>
<td>ADL Hierarchy Scale &gt;2</td>
<td>1.05 (1.02–1.08)</td>
<td>1.61 (1.53–1.69)</td>
</tr>
<tr>
<td>Depression Rating Scale &gt;3</td>
<td>1.74 (1.67–1.81)</td>
<td>1.78 (1.69–1.87)</td>
</tr>
<tr>
<td>CHESS Scale &gt;2</td>
<td>1.55 (1.51–1.59)</td>
<td>1.84 (1.77–1.92)</td>
</tr>
<tr>
<td>c statistic</td>
<td>0.73</td>
<td>0.72</td>
</tr>
</tbody>
</table>

*Abbreviations: ADL, activities of daily living; CHESS, changes in health, end stage disease and signs and symptoms.*
As many authors have noted, pain is probably best understood with a biopsychosocial approach that takes into account not only objective evidence of pathology but also individual, social and cultural differences that may affect the perception of and response to pain (Turk and Okifuji, 1999; Turk and Okifuji, 2002; Wool and Mor, 2005). In our study, gender was significant in both settings (HC and CCC) after controlling for numerous health conditions and diagnoses. While these may be the product, at least in part, of biological differences (e.g., influence of gonadal hormones, cytokines) (Craft et al., 2004; Aloisi et al., 2005), they may also reflect cultural norms related to the expression of feelings of pain, or gender differences in coping methods.

With respect to analgesia, the present results are consistent with Bernabei et al. (1998) who reported that the use of level 2 and 3 analgesics decreased with age among elderly cancer patients in US nursing homes. Perhaps this reflects the reluctance of physicians to use higher-level analgesics in persons who have survived to advanced ages, or a lower likelihood of cancer being treated with strong analgesics among the oldest old. That being said, it was surprising to see that about 20% of home care clients in severe pain received no analgesia, and this difference persisted in all age groups, including centenarians. Since detailed medication data are not available in the CCC population, it is difficult to rule out the possibility that the quality of pain management improves with increasing patient age of the patient in this setting. However, the study of cancer pain management in US nursing homes by Bernabei et al. (1998) reported the opposite trend – adequate pain management was less likely among older nursing home residents with cancer.

The present study showed that, although the mean pain scores by age group were comparable in community and institutional settings, there was notably greater variance in pain levels within age groups in the community. This may be due to the fact that the CCC group is more homogeneous because of standardized admission criteria.

An important limitation of this study is the lack of information about the type of pain, its location and its cause. For example, if one specific type of pain (e.g., visceral pain) declines with age, global ratings of pain may imply an overall reduction of pain even if other types of pain do not change or increase in frequency and severity.

5. Conclusions

Advanced age is an independent factor that predicts lower levels of pain in persons in community and institutional settings. This study shows that this relationship is independent of disease diagnoses, cognitive impairment, various health conditions, and analgesia use. However, among persons in severe pain, the likelihood of non-treatment with analgesia is substantial (about 20%) and consistent among different age groups. Moreover, those of advanced age are significantly more

Table 3
Logistic regression model for presence of pain in home care only, including analgesia level according to WHO pain ladder

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Odds ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Male</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>1.28 (1.24-1.31)</td>
</tr>
<tr>
<td>Age group</td>
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<tr>
<td>65-69</td>
<td>Reference</td>
</tr>
<tr>
<td>70-74</td>
<td>0.80 (0.76-0.84)</td>
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<td>75-79</td>
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</tr>
<tr>
<td>Osteoporosis/hip fracture</td>
<td>1.54 (1.49-1.60)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1.04 (0.99-1.08)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.91 (0.88-0.95)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.89 (0.87-0.92)</td>
</tr>
<tr>
<td>Cognitive Performance Scale &gt;2</td>
<td>0.52 (0.51-0.54)</td>
</tr>
<tr>
<td>ADL Hierarchy Scale &gt;2</td>
<td>1.03 (1.00-1.06)</td>
</tr>
<tr>
<td>Depression Rating Scale &gt;2</td>
<td>1.73 (1.66-1.80)</td>
</tr>
<tr>
<td>CHESS Scale &gt;2</td>
<td>1.44 (1.40-1.48)</td>
</tr>
<tr>
<td>Analgesia</td>
<td></td>
</tr>
<tr>
<td>WHO level 1</td>
<td>2.09 (2.03-2.14)</td>
</tr>
<tr>
<td>WHO level 2</td>
<td>9.13 (8.65-9.65)</td>
</tr>
<tr>
<td>WHO level 3</td>
<td>13.46 (12.27-14.78)</td>
</tr>
</tbody>
</table>

\[ c \text{ statistic} = 0.78 \]

Abbreviations: ADL, Activities of Daily Living; CHESS, Changes in Health, End stage disease and Signs and Symptoms; WHO, World Health Organization.

Fig. 3. Analgesic use in those who report severe pain. The levels in the bars represent the percentage of people receiving each WHO pain ladder level of analgesia in those Home Care clients who reported the highest pain scores. From lowest to highest on each bar, they are: No Analgesia (solid black), Level 1 (diagonal stripes), Level 2 (dots), Level 3 (solid white).
likely to receive less-potent medications than younger home care clients. Further research is required to determine whether the less frequent reporting of pain among the oldest old is indeed equivalent to a lack of suffering and perceived pain or whether some alternative explanations account for these differences.

Acknowledgements

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The incidence of complex regional pain syndrome:
A population-based study

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Abstract

The complex regional pain syndrome (CRPS) is a painful disorder that can occur in an extremity after any type of injury, or even spontaneously. Data on the incidence of CRPS are scarce and mostly hospital based. Therefore the size of the problem and its burden on health care and society are unknown. The objective of the present study was to estimate the incidence of CRPS in the general population. A retrospective cohort study was conducted during 1996–2005 in the Integrated Primary Care Information (IPCI) project, a general practice research database with electronic patient record data from 600,000 patients throughout the Netherlands. Potential CRPS cases were identified by a sensitive search algorithm including synonyms and abbreviations for CRPS. Subsequently, cases were validated by electronic record review, supplemented with original specialist letters and information from an enquiry of general practitioners. The estimated overall incidence rate of CRPS was 26.2 per 100,000 person years (95% CI: 23.0–29.7). Females were affected at least three times more often than males (ratio: 3.4). The highest incidence occurred in females in the age category of 61–70 years. The upper extremity was affected more frequently than the lower extremity and a fracture was the most common precipitating event (44%). The observed incidence rate of CRPS is more as four times higher than the incidence rate observed in the only other population-based study, performed in Olmsted County, USA. Postmenopausal woman appeared to be at the highest risk for the development of CRPS.

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Keywords: Complex regional pain syndrome; Dystrophy; Incidence; Epidemiology

1. Introduction

Complex regional pain syndrome (CRPS), formerly known as Sudecks dystrophy or reflex sympathetic dystrophy, is a painful disease with clinical features that include pain, sensory, sudomotor and vasomotor disturbances, trophic changes and impaired motor function (Bruehl et al., 2002). The disease course varies from relatively mild and self-limiting to chronic disease with a high impact on daily functioning and quality of life (Galer et al., 2000). Usually, symptoms appear in one extremity after even a relatively mild trauma, for example a fracture, contusion or surgery, but symptoms have also been described after varicella zoster infection and myocardial infarction (Merritt, 2005). The diagnosis is based on the findings during the history and physical examination, for which several diagnostic criteria sets have been developed. The most well known are the IASP (International Association for the Study of Pain) criteria, that were...
established during a consensus meeting of experts in 1994 (Stanton-Hicks et al., 1995). The pathogenesis and etiology may involve both neurological and inflammatory disorders, but remain to be completely unraveled (Janig and Baron, 2004; Birkinley, 2005).

Due to its complexity and broad spectrum of symptoms, CRPS patients are treated by physicians from different clinical backgrounds, including anesthesiologists, (orthopedic) surgeons, neurologists, rheumatologists and rehabilitation doctors. The incidence of CRPS has been studied retrospectively and prospectively in clinical settings after a certain precipitating event, most frequently after a distal radius fracture (Atkins et al., 1990; Veldman et al., 1993; Field and Atkins, 1997; Zollinger et al., 1999; Dijkstra et al., 2003). Sandroni and colleagues have been the only ones so far to assess the incidence of CRPS in the general population (Olmsted County, USA) and they reported an incidence rate of 5.46/100,000 person years (Sandroni et al., 2003).

In our study, the objective was to assess the incidence of CRPS in the general population in the Netherlands. Moreover, we classified cases according to different diagnostic criteria and described the precipitating events of CRPS.

2. Patients and methods

2.1. Setting

The Integrated Primary Care Information Project (IPCI) is a longitudinal observational database including electronic patient’s records of more than 600,000 patients from more than 150 general practitioners (GPs). The patient population is representative of the Dutch population regarding age and sex (Lamberts et al., 1992; van der Lei et al., 1993).

In the Dutch Health Care System, all persons need to be registered with a GP who acts as a gatekeeper for further medical care. The electronic records store information on demographics, signs and symptoms (using the International Classification for Primary Care (ICPC) codes (a classification system for primary care (de Lusignan, 2005)) and narratives), diagnoses (using ICPC and narratives), clinical findings, specialist referrals, laboratory findings, hospitalizations, and drug prescriptions. Summaries of the hospital discharge letters and information and letters from specialists are entered in a free text format and hard copies of original letters can be provided upon request. To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The system complies with the European Union guidelines on the use of medical data for medical research and has been proven valid for (pharmaco)-epidemiological studies (Vlug et al., 1999). The Scientific and Ethical Advisory Group of the IPCI project approved the study (Project No. 04/70).

2.2. Source population

The source population comprised all persons of all ages, with at least 1 year of valid history in the IPCI database during the study period (January 1996–June 2003). This meant that the practice had been contributing data to the IPCI database for at least 1 year and that the patient had been registered with the GP for at least 1 year. This 1-year period was required to have sufficient background information on all subjects. Follow-up started at the beginning of the study period or on the date that 1 year of valid history was available, whichever date was latest. Follow-up was terminated when the person transferred out of the practice, on the date of last data supply by the GP, death, diagnosis of CRPS or at the end of the study period, whichever came first.

Since additional data collection was required for validation of CRPS, the source population was restricted to all practices that were still active in the IPCI database in 2006 and provided additional information. For clarification of the data collection procedures see also Fig. 1.

2.3. Case definition

Potential cases of CRPS were identified in the IPCI database using an extensive string search including an exhaustive list of synonyms and abbreviations for CRPS (for example complex regional pain syndrome, RSD, PTD, etc.), plus prescriptions of dimethyl sulfoxide (DMSO). In the Netherlands, DMSO is exclusively prescribed for CRPS. In a first validation step, performed by a medical doctor with clinical experience in CRPS, all potential cases were manually evaluated by reading the patient records in order to eliminate obvious non-cases and to classify possible cases as incident or prevalent. A possible case was defined as each patient for whom CRPS was suggested or diagnosed in the patient record. A possible case was considered incident when the first occurrence fell within the follow-up time of that person.

To further validate the diagnosis of CRPS in the incident possible cases, a short questionnaire was mailed to the GPs. The questionnaire was used to confirm whether the person, according to the GP’s judgment, indeed suffered from CRPS and whether the patient had been seen and diagnosed by a specialist. Copies of all specialist letters were requested. Specialist letters usually provide information about history and physical examination of the patient. That information was used to verify the fulfillment of diagnostic criteria for CRPS according to the IASP criteria (Stanton-Hicks et al., 1995), the Bruehl criteria (Bruehl et al., 1999; Harden et al., 1999), and the Veldman criteria (Veldman et al., 1993) (see the legend of Table 1b for a description of the criteria sets). The choice for these sets of criteria was based on international acceptance of the IASP criteria, high specificity of the Bruehl criteria, and national acceptance of the Veldman criteria. These criteria sets differ from each other in the types and the number of symptoms and signs that have to be present in order to establish the diagnosis CRPS. The IASP criteria are regarded as very sensitive, whereas the Bruehl criteria have lower sensitivity, but are highly specific. The Veldman criteria are the only ones that theoretically allow a diagnosis of CRPS in the absence of pain.
The fulfillment of the diagnosis according to the different criteria sets was judged independently by two physicians who are familiar with CRPS. In case of discrepancies between their judgments, consensus was reached by discussion. Where pain and an increase of the symptoms after use of the affected limb (an obligatory feature according to the Veldman criteria) were not mentioned in the letters, it was reasonable to assume that they were present in most of the cases. Therefore, the criteria were first applied both in a strict sense, and subsequently without taking into account the presence of pain and increase after use of the affected limb. Information on precipitating events and referrals were derived from the electronic medical records and the specialist letters.

2.4. Analysis

The incidence rate of CRPS was calculated by dividing the number of incident cases (as established by reconfirmation of the diagnosis) (numerator), by the total number of accrued person years in the population (denominator). Incidence rates (IR) were calculated per calendar year, sex, and age category. Calculations were stratified for CRPS following a fracture and CRPS following other precipitating events. 95% Confidence intervals were constructed around the rates based on the Poisson distribution.

In addition to the incidence rate based on the reconfirmed diagnoses, we also calculated an incidence rate based on cases that fulfilled the IASP criteria. However, the IASP criteria could only be applied in a subset of the specialist-diagnosed cases (for whom specialist letters with diagnostic information were available). Therefore, the percentage of fulfillment was extrapolated only within the specialist-diagnosed case group. Cases that were diagnosed by the GP alone were excluded from this analysis.

In order to be able to compare our results with the incidence found by Sandroni and colleagues, we calculated standardized morbidity ratios (SMR), using the method of indirect standardization on age and gender, as described by Rothman (Rothman, 1986).

Standard descriptive statistics were used to compare categorical variables ($\chi^2$ test, univariate logistic regression), or means (Student’s t-test). $\kappa$ statistics were calculated to judge interrater agreement for the diagnostic criteria. The Statistical Package for Social Sciences (SPSS) 12.0 for Windows was used for all statistical tests.

3. Results

In the initial source population of 217,653 persons registered with at least 1 year of valid history at one
of the 52 active practices in the IPCI database, 238 incident cases of CRPS could be identified after finalization of the validation process (Fig. 1). The response rate for the short questionnaires amongst GPs was 88%. Only the populations from the practices that responded were included in the source population for calculations of the IR. This source population comprised 190,902 persons from 46 practices, and concerned the mentioned 238 cases.

For 95 (54%) of the 177 cases that were diagnosed by a specialist, letters with information on anamnesis and physical examination were available. Structured extraction of data (Table 1a) allowed for classification of the cases according to different CRPS criteria sets (Table 1b). Eighty-six percentage of these specialist-diagnosed cases fulfilled the strictly applied IASP criteria for CRPS. If pain and an increase in pain after use of the body part were assumed to be present (even if not mentioned in the letter), 93% of the cases fulfilled the IASP criteria, 47% the Bruehl criteria and 58% the Veldman criteria (Table 1b). The interrater agreement varied between the different criteria sets, with the lowest $\kappa = 0.43$ (moderate) for the IASP criteria with pain assumed to be present, and the highest $\kappa = 0.78$ (good) for the Veldman criteria. In the available specialist letters the presence or absence of vaso- and sudomotor and motor-trophic signs and symptoms was reported more frequently than the presence or absence of sensory and neurological signs and symptoms.

Characteristics of the cases are displayed in Table 2. The mean age at CRPS diagnosis was $52.7 \pm 2.20$ (range 7–90) years in the total group. The mean age for males was $51.1 \pm 4.2$ years and for females $53.0 \pm 2.6$ years. The age at diagnosis did not differ between males and females ($p = 0.404$). The most common precipitating event for CRPS was a fracture, followed by a contusion/sprain. In more than ten percent of the cases no precipitating event was reported or could be identified in the medical record. Upper extremities were more often affected than lower extremities ($59.2\%$ versus $39.1\%$, $p < 0.001$), whereas the right side and left side of the body were affected with the same frequency ($p = 0.464$). Patients who were diagnosed only by GPs were significantly older than patients who were also

### Table 1a

<table>
<thead>
<tr>
<th>Symptom/sign ($N = 95$)</th>
<th>Anamnesis ($n$, %)</th>
<th>Physical examination ($n$, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous pain</td>
<td>81 (85.3)</td>
<td>14 (14.7)</td>
</tr>
<tr>
<td>Hyperesthesia</td>
<td>4 (4.2)</td>
<td>91 (95.8)</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>95 (100)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Allodynia</td>
<td>9 (9.5)</td>
<td>86 (90.5)</td>
</tr>
<tr>
<td>Hyperpathy</td>
<td>2 (2.1)</td>
<td>93 (97.9)</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>9 (9.5)</td>
<td>86 (90.5)</td>
</tr>
<tr>
<td>Vasomotor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature asymmetry</td>
<td>56 (58.9)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Color asymmetry</td>
<td>51 (52.6)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Sudomotor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling/edema</td>
<td>53 (55.8)</td>
<td>42 (44.2)</td>
</tr>
<tr>
<td>Sweating asymmetry</td>
<td>23 (24.2)</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Motor-trophic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited range of motion</td>
<td>20 (21.1)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Paresis</td>
<td>7 (7.4)</td>
<td>88 (92.6)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>4 (4.2)</td>
<td>91 (95.8)</td>
</tr>
<tr>
<td>Altered hair growth</td>
<td>2 (2.1)</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Altered nail growth</td>
<td>4 (4.4)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Skin atrophy</td>
<td>95 (100)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disturbed coordination</td>
<td>2 (2.1)</td>
<td>93 (97.9)</td>
</tr>
<tr>
<td>Tremor</td>
<td>95 (100)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Involuntary movements</td>
<td>1 (1.1)</td>
<td>94 (98.9)</td>
</tr>
<tr>
<td>Paralysis</td>
<td>95 (100)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>95 (100)</td>
<td>7 (7.4)</td>
</tr>
<tr>
<td>Various</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase of complaints after use</td>
<td>26 (27.4)</td>
<td>69 (72.6)</td>
</tr>
<tr>
<td>Alternative diagnosis</td>
<td>6 (6.3)</td>
<td>89 (93.7)</td>
</tr>
</tbody>
</table>
### Table 1b

Classification of cases by different diagnostic criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Strict n (%)</th>
<th>When the presence of pain was not taken into account n (%)</th>
<th>When the presence of increase of pain after use was not taken into account n (%)</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>IASP⁵ (Stanton-Hicks et al., 1995)</td>
<td>82 (86.3)</td>
<td>88 (92.6)</td>
<td>Not applicable</td>
<td>0.43–0.66 (moderate-good)</td>
</tr>
<tr>
<td>Bruehl⁵ (Bruehl et al., 1999; Harden et al., 1999)</td>
<td>41 (43.2)</td>
<td>45 (47.4)</td>
<td>Not applicable</td>
<td>0.66–0.69 (good)</td>
</tr>
<tr>
<td>Veldman⁵ (Veldman et al., 1993)</td>
<td>17 (17.8)</td>
<td>17 (17.8)</td>
<td>55 (57.9)</td>
<td>0.63–0.78 (good)</td>
</tr>
</tbody>
</table>

a IASP criteria: 1. Develops after an initiating noxious event (type I) or after a nerve injury (type II). 2. Spontaneous pain or allodynia/hyperalgesia that is not limited to the territory of a single peripheral nerve and is disproportionate to the inciting event. 3. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event. 4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

b Bruehl criteria: 1. Continuing pain which is disproportionate to any inciting event. 2. Must report at least one symptom (history) in each of the following categories. Sensory: hyperesthesia, hyperalgesia (to pinprick) and/or allodynia (to light touch). Vasomotor: temperature asymmetry and/or skin color changes and/or skin color asymmetry. Sudomotor/edema: edema and/or sweating changes and/or sweating asymmetry. Motor/trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

c Veldman criteria: 1. Four or five of: unexplained diffuse pain; difference in skin color relative to other limb; diffuse edema; difference in skin temperature relative to other limb; limited active range of motion. 2. Occurrence or increase of above signs and symptoms after use. 3. Above signs are present in an area larger than the area of primary injury or operation and including the area distal to the primary injury.

### Table 2

Characteristics of CRPS patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total N (238)</th>
<th>By GP only N (61)</th>
<th>By specialist N (177)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at onset (SD)</td>
<td>52.7 (17.31)</td>
<td>56.6 (19.63)</td>
<td>51.3 (16.27)</td>
<td>0.039</td>
</tr>
<tr>
<td>Female</td>
<td>184</td>
<td>77.3</td>
<td>52</td>
<td>85.2</td>
</tr>
<tr>
<td>CRPS II</td>
<td>7</td>
<td>2.9</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Precipitating event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25</td>
<td>10.8</td>
<td>8</td>
<td>13.1</td>
</tr>
<tr>
<td>Fracture</td>
<td>105</td>
<td>44.1</td>
<td>28</td>
<td>45.9</td>
</tr>
<tr>
<td>Sprain</td>
<td>42</td>
<td>17.6</td>
<td>13</td>
<td>21.3</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>29</td>
<td>12.2</td>
<td>5</td>
<td>8.2</td>
</tr>
<tr>
<td>CTS</td>
<td>8</td>
<td>3.4</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Dupuytren</td>
<td>6</td>
<td>2.5</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Tendon injury</td>
<td>13</td>
<td>5.5</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Others</td>
<td>21</td>
<td>8.8</td>
<td>4</td>
<td>6.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>1.3</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Localization at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right side of the body</td>
<td>114</td>
<td>47.9</td>
<td>31</td>
<td>50.8</td>
</tr>
<tr>
<td>Left side of the body</td>
<td>115</td>
<td>48.3</td>
<td>26</td>
<td>42.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td>3.8</td>
<td>4</td>
<td>6.6</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>141</td>
<td>59.2</td>
<td>40</td>
<td>65.6</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>93</td>
<td>39.1</td>
<td>19</td>
<td>32.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>1.7</td>
<td>2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Type of specialist to whom patient is referred (more than one possible)

- Anesthesiologist | 87 | 47.7 |
- Rehabilitation doctor | 52 | 29.4 |
- Orthopedic surgeon | 49 | 27.7 |
- Surgeon | 45 | 25.4 |
- Neurologist | 19 | 10.7 |
- Rheumatologist | 8 | 4.5 |
- Plastic surgeon | 5 | 2.8 |
- Other | 6 | 3.4 |

Number of specialists seen

| 1 | 105 | 59.3 |
| 2 | 54 | 30.5 |
| 3 | 14 | 7.9 |
| 4 | 4 | 2.3 |

* p-values are given for differences in characteristics between patients diagnosed by GPs alone and patients confirmed by a specialist.
- Indicated for the treatment of mild to moderate post-operative pain
- Fast onset of action – pain relief as early as 5 minutes
- Analgesic effect comparable to morphine 10 mg IM and ketorolac 30 mg IV
- Proven opioid-sparing effect
- Recognised safety profile of paracetamol
- Ready to use in patients with an IV line

*IV paracetamol 1 g (Perfalgan®) is therapeutically equivalent to IV paracetamol 2 g

Release the true potential of paracetamol

References:
referred to and diagnosed by a specialist \((p = 0.039)\). Anesthesiologists were the most frequently involved specialists and usually one type of specialist was seen by the patient.

The incidence rate of CRPS in the Netherlands was 26.2 per 100,000 person years \((95\% \text{ CI: } 23.0–29.7)\) (Table 3). The standardized morbidity ratio \((\text{SMR})\) was calculated as 4.2, meaning that, after standardization for age and gender to the source population of Sandroni and colleagues, we found a 4.2 times higher incidence rate than described in their study. If only specialist confirmed cases were considered, the incidence rate was 19.5 per 100,000 person years \((95\% \text{ CI: } 16.8–22.5)\). The incidence rate based on specialist-diagnosed cases that fulfilled the IASP criteria was 16.8 per 100,000 person years \((95\% \text{ CI: } 14.7–19.2)\). The SMR compared to the results of Sandroni was 2.7.

Gender-specific incidence rates, based on the reconfirmed diagnoses, for females and males were 40.4 \((95\% \text{ CI: } 34.8–46.8)\) and 11.9 \((95\% \text{ CI: } 9.0–15.4)\) per 100,000 person years, respectively. The incidence of CRPS was more than threefold higher in females than in males \((\text{RR: } 3.4, 95\% \text{ CI: } 2.9–3.9)\). The incidence rate of CRPS did not change significantly over time between 1996 and 2005 (Fig. 2). The confidence intervals in 1996 and 2005 were relatively wide due to the low number of person-years by left censoring in 1996 (early stage of the IPCI database) and a high degree of right censoring in 2005 (data available only until June). The incidence varied profoundly with age, the highest incidence rate was observed in the group 61–70 years of age (Fig.3). The age and sex distribution pattern was similar in a subgroup including only the cases with another precipitating event than a fracture.

### 4. Discussion

In this study, we demonstrated that the population-based incidence of CRPS in the Netherlands is 26.2 per 100,000 person-years, with a peak incidence at 61–70 years of age. Fracture was the most common precipitating event accounting for 44% of the CRPS cases. The upper extremities were more often affected than the lower extremities with no preference for either left or right side. A wide variety of specialists was involved in the diagnosis and treatment of CRPS patients.

The incidence rate in this study is more than four times higher than the population-based incidence rate that was reported by Sandroni and colleagues in Olmsted County \((\text{Sandroni et al., 2003})\). The difference sustained even after standardization \((\text{IR: } 22.8 \text{ per } 100,000 \text{ person-years})\) and when we included only specialist-diagnosed cases in our calculations \((\text{IR: } 19.0 \text{ per } 100,000 \text{ person-years})\). Possibly, differences in population characteristics such as ethnicity, socio-economic factors and incidence of fractures can explain the observed difference. More likely, however, it is secondary to the difference in case definitions and validation.

### Table 3

| Age group | Males | | | | | Females | | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | PY at risk | IR per 100,000 PY | | Cases | PY at risk | IR per 100,000 PY | | Cases | PY at risk | IR per 100,000 PY |
| Year | | | | | | | | | | | | | |
| 1996 | 2 | 11,674 | 16.8 | 8 | 12,484 | 64.1 | 10 | 24,158 | 41.1 |
| 1997 | 0 | 19,800 | 0.0 | 9 | 20,663 | 43.6 | 9 | 40,464 | 22.2 |
| 1998 | 1 | 30,296 | 3.3 | 8 | 31,231 | 25.6 | 9 | 61,528 | 14.6 |
| 1999 | 2 | 50,098 | 3.9 | 16 | 50,335 | 31.8 | 18 | 100,433 | 17.9 |
| 2000 | 12 | 60,441 | 19.9 | 24 | 60,619 | 39.6 | 36 | 121,060 | 29.7 |
| 2001 | 8 | 61,394 | 13.0 | 29 | 61,529 | 47.1 | 37 | 122,923 | 30.1 |
| 2002 | 12 | 66,799 | 18.0 | 28 | 66,888 | 41.9 | 40 | 133,687 | 29.9 |
| 2003 | 10 | 70,710 | 14.1 | 23 | 70,679 | 32.6 | 33 | 141,390 | 23.3 |
| 2004 | 6 | 64,790 | 9.3 | 31 | 64,524 | 48.0 | 37 | 129,314 | 28.6 |
| 2005 | 1 | 17,220 | 5.8 | 8 | 17,063 | 46.9 | 9 | 34,283 | 26.3 |
| Age group | | | | | | | | | | | | | |
| <10 | 1 | 51,252 | 2.0 | 1 | 49,182 | 2.0 | 2 | 100,434 | 2.0 |
| 10–19 | 1 | 56,063 | 1.8 | 8 | 53,639 | 14.9 | 9 | 109,702 | 8.2 |
| 20–29 | 4 | 64,319 | 6.2 | 17 | 60,723 | 28.0 | 21 | 125,042 | 16.8 |
| 30–39 | 7 | 77,401 | 9.0 | 20 | 72,058 | 27.7 | 27 | 149,459 | 18.1 |
| 40–49 | 11 | 70,805 | 15.5 | 19 | 69,640 | 27.2 | 30 | 140,445 | 21.4 |
| 50–59 | 15 | 61,482 | 24.4 | 43 | 59,597 | 72.1 | 58 | 77,760 | 47.9 |
| 60–69 | 12 | 38,206 | 31.4 | 48 | 39,554 | 121.3 | 60 | 75,777 | 77.2 |
| 70–79 | 3 | 24,582 | 12.2 | 19 | 32,695 | 58.1 | 22 | 57,277 | 38.4 |
| >80 | 0 | 9,313 | 0.0 | 9 | 18,931 | 47.5 | 9 | 28,245 | 31.9 |
| Total | 54 | 453,425 | 11.9 (9.0–15.4) | 184 | 456,018 | 40.4 (34.8–46.8) | 238 | 909,443 | 26.2 (23.0–29.7) |
The study of Sandroni and colleagues used the IASP criteria, which were applied retrospectively to information from electronic medical records. We also used a retrospective approach and used both electronic medical records as well as information from GP questionnaires and specialist letters for the diagnosis. In contrast to Sandroni we did not require that all cases should fulfill diagnostic criteria; we retained all cases on the basis of a reconfirmed diagnosis of CRPS by the GP or specialist.

Criteria sets were also applied on a subset for which detailed diagnostic data were available, but were used merely to see differences in criteria sets. However, an incidence rate based on the strictly applied IASP criteria (IR: 16.8 per 100,000 person years), as done in the Sandroni study, was calculated and was still almost three times higher in our study as the incidence rate found in Olmsted County (SMR = 2.7). Remarkable is, that in our subset of specialist-diagnosed cases 86% fulfilled the IASP criteria, compared to 19% of the cases in the Sandroni study. The supposedly high rate of incorrectness of the CRPS diagnosis (81%) in the Sandroni study has been questioned by others before (Bennett and Harden, 2003), and suggests that the retrospective application of the IASP criteria to information on electronic charts might have been overly strict. The IASP criteria are considered highly sensitive and incidence rates based on this should be comparable with incidence rates based on specialist’s diagnoses.

The highest incidence rate in our study was observed in the age group of 61–70 years and the mean age at diagnosis was 52.7 years. This age peak is higher than is generally expected and observed in some non-population-based investigations (Veldman et al., 1993). However, other clinical studies show high average ages of the

![Fig. 2. Incidence rates of CRPS in the Netherlands according to calendar year, with upper and lower 95% confidence lines.](image)

![Fig. 3. Incidence rates of CRPS in the Netherlands according to age group and by level of confirmation (diagnosed only by specialist or all diagnosed).](image)
included CRPS patients, in line with our observation (Atkins et al., 1990; Field and Atkins, 1997; Zollinger et al., 1999). It could be suggested that the increasing incidence of CRPS with age is due to a higher occurrence of fractures at older age. However, the same age distribution pattern was observed in the group of patients with another precipitating event than a fracture. From our findings, it can be concluded that the majority of the CRPS cases in females occur in the postmenopausal stage of life. This was noted before by Zollinger and colleagues (Zollinger et al., 1999). The age and sex distribution pattern suggests that hormonal etiological factors may be involved in the pathogenesis of CRPS.

Noteworthy is that less than half of the CRPS cases have a fracture as precipitating event, similar to the observations of Sandroni and colleagues. Fracture is often regarded as the primary precipitating event and the incidence of CRPS after a fracture has been studied prospectively (Veldman et al., 1993; Dijkstra et al., 2003). Hence, other precipitating events, such as surgery and tendon rupture, may be worthwhile including in prospective research. Additional findings of interest were the fact that patients who were diagnosed only by the GP without referral to a specialist tended to be older.

Limitations in our study are related to the absence of a gold standard for the diagnosis of CRPS. As observed in the specialist letters, physicians focused on vaso- and sudomotor and motor-trophic signs, whereas the presence or absence of sensory and neurological symptoms was not frequently reported. van de Beek and colleagues have stated that general dissatisfaction with the available criteria has resulted in the use of personally favoured criteria (van de Beek et al., 2002). As a consequence of this, descriptions of the patients differ and lack detail, which has complicated uniform classification of the cases in our study. However, if detailed information for the application of diagnostic criteria would have been available as in a prospective study, the choice for one specific criteria set for validation of the diagnosis above the others would also have been disputable, since none of them is definitely superior (van de Beek et al., 2002). For this reason we decided that the most reliable incidence rate calculations would be based on reconfirmed clinical diagnoses. However, the problems regarding case definition that were encountered during our study emphasize again the need for validated and well-documented diagnostic criteria, that can be applied more in primary and secondary care and in prospective and retrospective studies.

Despite the above described, we do not believe that the inability to uniformly classify all patients has resulted in an overestimation of the incidence rate. We sought reconfirmation of all cases and allowed GPs to reconsider whether an initial diagnosis actually was correct. In addition, almost three-quarters of the patients were referred to a medical specialist who reconfirmed the diagnosis as well, after exclusion of alternative diagnoses. The actual incidence rates varied with the choice to base the validation of the CRPS diagnosis on GP or specialist confirmed cases. However, the pattern of the incidence rate (sex and age distribution) was similar for both groups. On the contrary, we consider it more likely that our incidence rates are an underestimation of the reality. Although we have used a sensitive search algorithm for identification of the CRPS cases, we might have missed cases that had symptoms but were not diagnosed as such in the medical record because of unfamiliarity of the GP with the syndrome and its nomenclature. Mainly the relative mild and self-limiting cases of CRPS might not always have been recorded as such in the medical journal and were therefore not included in our calculations.

In conclusion, we estimated an incidence of CRPS in the general population of the Netherlands of 26.2 per 100,000 person-years, which is much higher than previously described. Postmenopausal women appeared to be at an increased risk for the development of the disease. Uniform use of more generally accepted diagnostic criteria would improve the quality of epidemiological and clinical studies concerning CRPS in the future.

Acknowledgements

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References

Unfortunately no data is available for South Africa. There is no reason to believe that the local incidence should differ from that of other international data. It is clear that this condition is associated with orthopaedic injuries and procedures. Reuben (Anesthesiology. 2004;101:1215-1224) published the incidence of CRPS following orthopaedic surgery.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthroscopic knee surgery</td>
<td>2.3%-4%</td>
</tr>
<tr>
<td>Carpal tunnel release</td>
<td>2.1%-5%</td>
</tr>
<tr>
<td>Ankle surgery</td>
<td>13.6%</td>
</tr>
<tr>
<td>TKA</td>
<td>0.8%-13%</td>
</tr>
<tr>
<td>Wrist fractures</td>
<td>7%-37%</td>
</tr>
<tr>
<td>Dupuytren's contracture</td>
<td>4.5%-40%</td>
</tr>
</tbody>
</table>

Other data does indicate that only 16.4% of CRPS cases resulted from surgery and a large percentage followed minor sprains and strains. I was not able to confirm the authors findings from South African data. What is clear is that this condition occurs more frequently than previously noted.

The take home message is that when a patient presents with pain that is way above the expected level following surgery or a minor orthopaedic injury that we should consider CRPS as a possible diagnosis. If any of the typical signs are present such as hair loss on the affected extremity, a difference in extremity temperatures, nail changes, or oedema of the affected part then we should intervene appropriately with physiotherapy and should it become necessary, either medical or surgical means.

The Editor
Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain

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Abstract

A central question in prescribing opioids for chronic non-cancer pain (CNCP) is how to best balance the risk of opioid abuse and dependence with the benefits of pain relief. To achieve this balance, clinicians need an understanding of the risk factors for opioid abuse, an issue that is only partially understood. We conducted a secondary data analysis of regional VA longitudinal administrative data (years 2000–2005) for chronic users of opioids for CNCP (n = 15,160) to investigate risk factors for the development of clinically recognized (i.e., diagnosed) opioid abuse or dependence among these individuals. We analyzed four broad groups of possible risk factors: (i) non-opioid substance abuse disorders, (ii) painful physical health disorders, (iii) mental health disorders, and (iv) socio-demographic factors. In adjusted models, a diagnosis of non-opioid substance abuse was the strongest predictor of opioid abuse/dependence (OR = 2.34, p < 0.001). Mental health disorders were moderately strong predictors (OR = 1.46, p = 0.005) of opioid abuse/dependence. However, the prevalence of mental health disorders was much higher than the prevalence of non-opioid substance abuse disorders (45.3% vs. 7.6%) among users of opioids for CNCP, suggesting that mental health disorders account for more of the population attributable risk for opioid abuse than does non-opioid substance abuse. Males, younger adults, and individuals with greater days supply of prescription opioids dispensed in 2002 were more likely to develop opioid abuse/dependence. Clinicians need to carefully screen for substance abuse and mental health disorders in candidates for opioid therapy and facilitate appropriate treatment of these disorders.

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Keywords: Mental health; Pain; Opioids; Opioid abuse; Substance abuse

1. Introduction

Chronic non-cancer pain (CNCP) significantly affects approximately 20% of the population. (Gureje et al., 1998; Verhaak et al., 1998). Opioid use for CNCP has increased substantially (Caudill-Slosberg et al., 2004; Gilson et al., 2004). While some pain specialists view increasing use as evidence of better attention to unrelieved pain, others express concern that “safety and effectiveness of long-term opioid therapy” in CNCP remains unproven (Von Korff and Deyo, 2004). Further, abuse of prescribed opioids is a serious public health concern (Zacny et al., 2003). A central
question in prescribing opioids for CNCP is how to best balance the risk of opioid abuse with the benefit of pain relief.

To achieve this balance, clinicians need to understand the risk factors for opioid abuse, which are only partially understood (Chabal et al., 1997; Reid et al., 2002; Cowan et al., 2003; Michna et al., 2004; Chełminksi et al., 2005; Schieffer et al., 2005). In studies of small clinical samples, current or past substance abuse is the factor most commonly linked with abuse of prescribed opioids (Reid et al., 2002; Michna et al., 2004; Schieffer et al., 2005). Prescribing guidelines stress substance abuse as a risk factor for opioid abuse (American Academy of Pain Medicine, 1997; Veterans Health Administration/Department of Defense (VA/DOD), 2003; The Pain Society, 2004; National Pharmaceutical Council, 2001), while recognizing that other factors remain to be identified.

An important question is whether mental disorders are risk factors for opioid abuse, as these disorders are common among individuals receiving opioids for CNCP (Sullivan et al., 2006) and are potentially modifiable with treatment. The relationship between mental disorders and opioid outcomes is not well understood, partly because mental disorders have been exclusion criteria in most controlled trials of opioids for CNCP (Kalso et al., 2004). Reasons to suspect an increased risk of opioid abuse in those with mental disorders include high levels of mental and substance abuse disorder comorbidity (Kessler et al., 1996; Grant et al., 2004), and self-medication of mental health symptoms (Harris and Edlund, 2005). Studies in specialty pain clinics found an association between mental disorders and opioid abuse (Michna et al., 2004; Schieffer et al., 2005), as did a study using community survey data (Edlund et al., 2007).

Opioid prescribing guidelines vary in their recommendations concerning mental disorders. VA guidelines note that a “comprehensive assessment of the patient,” including a psychiatric history, should be done before initiating opioids, as psychiatric disorders “can complicate treatment” (VA/DOD, 2003); however, the guidelines do not explicate the complications. Other guidelines are less detailed.

We utilized longitudinal data from a “real world” sample of patients in the VHA health care system to investigate risk factors associated with clinically recognized (i.e., diagnosed) opioid abuse among those using chronic opioids for CNCP. This sample is large enough to identify risk factors independently associated with opioid abuse. Controlling for non-opioid substance abuse, the best understood risk factor, we investigated three groups of possible risk factors: painful physical conditions; mental disorders; and socio-demographic factors.

2. Methods

2.1. Data

All of the data used in this study were obtained from an extract of the South Central Veterans Affairs (VA) Health Care Network (VISN16) data warehouse after approval by the Institutional Review Board of the University of Arkansas for Medical Sciences and the VA Research and Development Committee at the Central Arkansas Veterans Healthcare System. The South Central VA Network encompasses the states of Arkansas, Louisiana, Mississippi, Oklahoma, and portions of Alabama, Florida, Missouri, Tennessee, and Texas. It is one of the largest regions in the Veterans Health Administration serving 1.9 million veterans, 442,234 of whom received care during 2005, with 10 medical centers, 33 community-based outpatient clinics, and 7 nursing homes (VISN 16 South Central VA Healthcare Network, 2006). VA patients have high rates of CNCP (Kerns et al., 2003). Veterans with at least one prescription for an opioid between January 1, 2002 and December 30, 2002 were identified in the data warehouse and their demographic, diagnostic and pharmacy records were extracted for years 2000–2005. To strengthen causal inference we utilized independent variables from 2002 to predict a new diagnosis of opioid abuse or dependence in 2003, 2004, or 2005.

The presence of the various medical and psychiatric conditions analyzed in this study was determined by the International Classification of Diseases, Clinical Modification, Ninth Revision (ICD-9-CM) codes associated with every outpatient visit and inpatient stay made by the veteran during 2002. Each visit or stay can have up to 10 diagnosis codes. An individual was considered to have the condition in question if he or she had at least one visit or inpatient stay with the associated ICD-9-CM code.

2.2. Analytical sample

We used the VA drug class of “opioid analgesics” to identify each veteran with at least one opioid prescription in 2002. Total days supply dispensed was summed across all opioid prescriptions received in 2002 by these veterans. There were 60,446 veterans with any opioid use in VISN16 in 2002, and the majority had less than 91 total days supplied (68%).

The cutoff of 91 days or more was chosen to indicate chronic use of opioids and represents the third of opioid users with the highest total days supplied. We believe that 91 or more days of opioid use during a 12-month period enjoys good face validity as a measure of chronic opioid use and provides the proper balance between sensitivity and specificity. First, it is unlikely that an individual would receive more than 90 days supply of opioids for an acute condition, such as post-operative or post-injury pain. In many health care systems, it would require 4 prescriptions to obtain 91 or more days supply of opioids, although opioid prescriptions in our VA Healthcare Network can be written for greater than 30 days supply. Second, we believe that a cutoff point of 91 or more days corresponds to an important point in the treatment process, where clinicians will be concerned about the possibility of opioid misuse with continuing therapy.
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A total of 19,335 veterans met our definition of chronic opioid use. We then excluded individuals with any cancer diagnosis (ICD-9-CM codes between 140.0 and 208.9; n = 3248) to isolate non-cancer pain, then excluded anyone with an opioid substance abuse disorder in years 2000, 2001, or 2002 (ICD-9-CM codes 304.0x, 304.7x, 305.5x, 965.0x, and E850.0–E850.2; n = 372) to ensure that predictors preceded the outcome. For this analysis of substance abuse, individuals with prescriptions for methadone in 2001 or 2002 were excluded (N = 555) to avoid confounding the relationship between prescribed opioid use and opioid misuse, since methadone maintenance is an accepted treatment for opioid dependence. Our final analysis sample contains 15,160 veterans.

2.3. Dependent variable: opioid-involved substance abuse or dependence

The dependent variable for this study is the presence of the diagnosis of abuse or dependence of opioids within the individual’s outpatient and inpatient records for 2003–2005. Specifically, this was ICD-9-CM codes of 304.00–304.03 (opioid dependence), 304.70–304.73 (dependence; combinations of opioid type drug with any other), and 305.50–305.53 (opioid abuse).

2.4. Independent variables

The primary independent variables of interest were the presence of mental disorders and non-opioid substance abuse disorders in 2002. These categories were defined by classes of ICD-9-CM diagnoses from outpatient visits and inpatient stays. Non-opioid substance abuse includes both abuse (305.00–305.93, excluding 305.50–305.53) and dependence (303.00–304.93, excluding 304.00–304.03 and 304.70–304.73) for alcohol and other drugs. Mental health diagnoses included the major disorders (293.0–302.9), excludes the substance disorders, 306.0–316) and personal history of mental disorder (V11.0, V11.1, V11.2, V11.8, and V11.9). An individual with any of the mental health diagnoses in their outpatient visit or inpatient hospitalization records was considered to have a mental health diagnosis.

We also created indicators for the diagnoses of common painful conditions in 2002. Back pain was defined as ICD-9-CM codes 720.0 through 724.9 and arthritis was defined as 710.0 through 739.9, excluding the back pain codes. Headache included migraines (346.0 through 346.9), tension headaches (307.81), and headache symptom (784.0). As a proxy for overall level of health, we included the number of unique days the individual attended outpatient appointments at any medical clinic within the network with corresponding ICD-9-CM for physical health conditions (i.e., not the codes described above for mental health and substance use) in 2002. While some veterans may have more than one clinic visit in a single day, we believe this measure of health services use captures intensity of use sufficiently for this study. We included this in the model as a series of indicator variables, with cutoffs defined by the quartiles of the distribution. We also included an indicator variable for whether the individual had an overnight hospital stay in 2002 for physical health reasons.

An additional reason for controlling for number of health care visits is that an individual who seeks health care more frequently may be more likely to be diagnosed with a mental disorder (or non-opioid substance use disorder) and also more likely to have his or her opioid abuse recognized, because the clinician knows the patient better, and/or the patient is being evaluated by multiple clinicians. Such a situation could produce a spurious association between mental disorders and clinically recognized opioid abuse, but controlling for the number of health care visits provides some protection against such bias.

We included a measure of the number of days of opioids prescribed (91–150 days, 151–220 days, 221+ days) to investigate whether there is a relationship between the number of days supplied and opioid abuse/dependence. We also included a measure of whether or not the individual was a new user of chronic opioids (i.e., had or had not received at least 91 days of opioids in the previous year).

The remaining variables in the analysis are standard demographic characteristics including age, which we grouped into under forty, forties, fifties, and sixty or older. Marital status indicators included currently married, divorced, single (never married), separated, and widowed. Race was categorized into white, African-American, other, or unknown. As is often seen with data from the VA medical records (VA Information Resource Center, 2004), race was not specified for a substantial portion of the sample, in this case 15.6%. Lastly, an indicator was included for being female, though women comprised only 5.8% of the sample.

2.5. Analyses

Demographic and clinical characteristics (from 2002) for chronic users of opioids with and without diagnosed opioid abuse/dependence during the years 2003–2005 were compared using Z2 analysis. Using multiple logistic regression, we then regressed opioid abuse/dependence on the relevant covariates. All analyses were conducted using STATA version 8.2 (College Station, TX) with the Huber–White estimates of standard errors (Huber, 1967; White, 1982).

3. Results

Our analytical sample included 15,160 chronic users of opioids (other than methadone) in 2002. The characteristics of the analytical sample (chronic opioid use, no cancer diagnosis, and no opioid abuse or dependence in 2000–2002) are shown in Table 1. Slightly less than half of the total sample of chronic opioid users had a mental health diagnosis (45.3%) in 2002, while 7.6% had a non-opioid substance abuse diagnosis. Sixty-eight percent had a diagnosis of arthritis (musculoskeletal disorders not related to the back/spine), 53.6% had a back pain diagnosis, while headaches (migraines, tension, and other headaches) were much less common at 8.4%.

The rate of a new clinically recognized opioid abuse or dependence diagnosis (years 2003–2005) among users of chronic opioids with no opioid abuse/dependence diagnosis in 2000–2002 was 2.0%. Unadjusted rates of
clinically recognized opioid abuse and dependence, by sociodemographic characteristics, are shown in Table 2. In multiple logistic regression models with our sample of chronic users of opioids, non-opioid substance abuse was a strong predictor of opioid abuse/dependence (OR = 2.34, 95% CI = 1.75, 3.14, p < 0.001) (Table 3). Mental disorders were also significantly associated with opioid abuse/dependence (OR = 1.46, 95% CI = 1.12, 1.91, p = 0.005). Age was a strong predictor of opioid abuse/dependence, with the risk of opioid abuse decreasing monotonically with increasing age. Individuals with more health care visits had significantly higher rates of opioid abuse/dependence, while Blacks had significantly lower rates of opioid abuse/dependence. Men were more likely to develop opioid abuse or dependence, as were individuals who were divorced, single, or separated. Finally, individuals who received at least 211 days supply of prescribed opioids were more likely to develop opioid abuse or dependence than those who received 91–120 days. Whether or not the individual used opioids chronically in the prior year (i.e., continuing vs. new users of chronic opioids) did not significantly affect the odds of developing clinically recognized opioid abuse or dependence.

4. Discussion

To our knowledge this is the largest prospective investigation of risk factors for diagnosis of opioid abuse or dependence among “real world” users of chronic opioids for CNCP. In adjusted models we found that patients with a diagnosis of non-opioid substance
abuse in 2002 were more likely to develop diagnosed opioid abuse/dependence in 2003–2005 (OR = 2.34). A mental health diagnosis was a moderately strong (OR = 1.46) predictor of opioid abuse/dependence in 2003–2005. While the odds ratio is smaller for mental disorders than non-opioid substance abuse, their prevalence was much higher than the prevalence of non-opioid substance abuse disorders in this population (45.3% vs 7.6%). These prevalence estimates mirror our previous work with Healthcare for Communities (HCC), a nationally representative household survey, where we also found that mental disorders were much more common than substance abuse disorders in individuals using opioids for CNCP (Sullivan et al., 2006).

It is interesting to assess our results in terms of the population-attributable risk for opioid abuse/dependence (that is, the proportion of opioid abuse/dependence among users of opioids for CNCP that can be attributed to various factors), which is a function of both the strength and the prevalence of the risk factor.
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**References:**
The OR for non-opioid substance abuse was 1.6 times as large as the OR for mental disorders, while the prevalence of mental disorders was over five times greater than that of non-opioid substance abuse/dependence. Thus, among veterans with chronic opioid therapy, the population-attributable risk for opioid abuse/dependence from mental disorders may actually be as great or greater than the population-attributable risk from substance disorders, approximately 14% versus 4%, respectively.

Interestingly, in our previous research using data from HCC, we found that substance disorders and mental disorders were prospectively associated with receipt of chronic opioids for CNCP in the general population (Sullivan et al., 2006), although the causal pathways are not well understood and may be reciprocal. Thus, our results suggest that those populations who are the most likely to receive chronic opioids for CNCP also have the greatest vulnerability to opioid abuse/dependence.

What are the clinical implications of these results? Our findings could justify simply withholding opioids from individuals with CNCP and comorbid mental disorders. However, only 3% of the group with comorbid mental disorders had clinically recognized opioid abuse or dependence. Blanket withholding of opioids from this group seems too severe a strategy. It is well documented that individuals with mental disorders receive lower quality physical health care (Druss et al., 2001), and we feel that a blanket prohibition would only exacerbate this situation. Rather, we believe that if mental disorders are important risk factors for opioid abuse, then clinicians need to carefully screen for these disorders in candidates for opioid therapy and facilitate appropriate mental health treatment as part of chronic pain treatment. The ultimate goal should be to decrease the risk of opioid abuse/dependence through detection and appropriate treatment of mental disorders in candidates for chronic opioid therapy. This may also facilitate adequate pain relief, since there is evidence that appropriate treatment of mental disorders helps with pain management (Lin et al., 2003).

We also found evidence for a “dose-response” relationship between number of days that opioids were prescribed in 2002 and subsequent development of clinically recognized opioid abuse/dependence, with individuals receiving 211 or more days about 1.8 times as likely to develop opioid abuse as those who received 91–120 days. This may mean that risks of opioid abuse increase with increasing duration of opioid therapy. But it may also mean that opioid abuse is more likely diagnosed in those who are still taking daily opioids in 2003–2005.

Our results should be viewed within the context of several important limitations that are common to analysis of administrative databases. First, we utilized physician diagnoses of opioid abuse/dependence. While physician diagnoses are often viewed as the “gold standard,” they are also subject to under-detection and under-reporting, although those with the greatest severity are the most likely to be detected (Cleary et al., 1988; Wells et al., 1989; Buchsbaum et al., 1992; Callahan et al., 1994; Mathias et al., 1994; Simon and Von Korff, 1995; Spitzer et al., 1999; Lefevre et al., 1999; Borowsky et al., 2000).

To increase our chances of identifying opioid use disorders, we utilized data over several years, rather than just one year, as suggested by measurement experts (O’Malley et al., 2005). Our rate of opioid abuse/dependence was 2.0%; while the comparable rate from Health Care for Communities ranged from 3.5% to 7.3%, depending on the strictness of criteria (even the most stringent definition of problem opioid use in HCC is less strict than DSM-IV criteria). Thus our rate may represent a lower bound, given that physicians frequently do not detect disorders, and given that we excluded individuals with an opioid abuse/dependence diagnosis in 2000–2002 and those on methadone. Further, while this rate may seem like a low rate from a clinical perspective, it represents a significant public health concern, given that millions of individuals receive chronic opioid therapy for CNCP. Under-detection is problematic when estimating rates of opioid abuse from diagnoses, as estimates of abuse/dependence rates are likely biased downwards (poor sensitivity). On the other hand, it is likely that individuals with opioid abuse/dependence diagnoses do actually have opioid abuse/dependence (good specificity). In this situation, with under-detection of disorders, odds ratios indicating increased risk may be biased towards 1.00 (Bound et al., 1994). Therefore, our estimates of the effects of non-opioid substance abuse, mental disorders, and other covariates are likely conservative.

While we utilized a broad range of measures of physical health, mental health, substance abuse, health care utilization, and sociodemographic factors, it is possible that our models do not include all relevant risk factors, given the limited literature on risk factors for opioid abuse/dependence to guide variable selection. Our analyses included measures of painful diagnostic conditions, but no measure of pain severity or activity interference. We utilized the number of days with a health care visit for physical conditions as a proxy for health status. While there are comorbidity measures for use with administrative data, such as Elixhauser and Charlson/Deyo methods (Deyo et al., 1992; Elixhauser et al., 1998; Southern et al., 2004), a major motivation for the development of these methods was to risk adjust for outcomes associated with hospitalization, such as mortality or hospital length of stay, and they have been validated for these outcomes. Obviously our outcome is much different. In any event, we found that the number of days with a physical health care visit is a strong pre-
dicator of opioid abuse diagnosis. Of course, this may represent the greater likelihood of detection when one is seen by a clinician more often, rather than underlying physical health conditions, although we do control for the number of health care visits. Given our dataset, we focused exclusively on patient characteristics. However, the receipt of prescriptions for opioids is also dependent on the physician. Clinicians may be more vigilant in monitoring for opioid abuse or dependence in those patients with a history of non-opioid substance abuse or mental disorder.

Our data come from VA patients living in the South Central U.S., both populations with high rates of opioid use (Luo et al., 2004), and may not be applicable to other populations. All of these limitations suggest a need for future studies that utilize nationally representative, longitudinal data that include appropriate measures of pain, mental disorders, and substance abuse disorders.

In conclusion, we found that non-opioid substance abuse is by far the strongest risk factor for opioid abuse, but is relatively uncommon. On the other hand, mental disorders are significant risk factors with a smaller magnitude than non-opioid substance misuse but are much more common among patients utilizing chronic opioids. Clinicians need to carefully screen for these disorders in candidates for opioid therapy and facilitate appropriate mental health and substance abuse treatment.

Acknowledgements

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Understanding Neuropathic Pain – Clinical presentation

“The worst pain one can possibly imagine” is how many people who suffer from neuropathies describe their pain. Neuropathic pain is a significant problem affecting millions of people worldwide and can result in substantial reductions in patients’ health-related quality of life. In addition, comorbid conditions, such as depression, are common complications of chronic pain, and further contribute to increased impairment and disability in patients’ daily activities. Pain may be the most common reason patients seek treatment from physicians. When persistent and unrelieved, pain can frustrate both the person suffering with this condition and the physician trying to alleviate it.

The International Association for the Study of Pain defines neuropathic pain as “Pain initiated or caused by a primary lesion or dysfunction in the nervous system.” Neuropathic pain has many different causes, including peripheral causes such as diabetic peripheral neuropathy, postherpetic neuralgia, HIV sensory neuropathy, phantom limb pain and trigeminal neuralgia as well as radiculopathy and posttraumatic nerve injury. Central causes include poststroke pain, pain from multiple sclerosis and spinal cord injury pain.

Pain manifests with positive and negative sensory symptoms. Positive symptoms include pain, paraesthesia (abnormal sensation either evoked or spontaneous), dysesthesia (unpleasant abnormal sensation either evoked or spontaneous), hyperalgesia (increased response to a normally painful stimulus) and allodynia (painful response to a non-noxious stimulus).

Negative sensory symptoms include hypoesthesia (loss of sensitivity to stimulation in general) and hypoalgesia (loss of sensitivity to painful stimuli).

From a patient perspective, the most common adjectives they use to describe neuropathic pain are electric shocks, burning and tingling. Others include a cold, prickling or itching sensation. All of these terms should suggest a neuropathic aetiology for the pain.

A particular challenge is to differentiate neuropathic pain from nociceptive pain. This is difficult as both result in persistent pain and utilise the same pain pathways. However, with nociceptive pain there is usually an acute identifiable cause. Therefore, pain signals an “alarm” that subsequently leads to a protective response.

In patients with neuropathic pain it is often difficult to identify an acute cause and the pain, which signals no imminent danger, represents a delayed, ongoing response to damage that is no longer acute but which continues to be expressed as painful sensations.

References.

Study of Novartis’ Prexige highlights favourable results on blood pressure by Daniel Beaulieu

New study data showed that Novartis’ COX-2 inhibitor Prexige (lumiracoxib) affected blood pressure significantly less than ibuprofen in patients with osteoarthritis and controlled hypertension. The findings were presented at EULAR.

As part of the trial, 741 patients with osteoarthritis and treated hypertension received Prexige once-daily, or ibuprofen three times daily. Findings showed that after four weeks, patients who received Prexige had a small decrease in average daily blood pressure, compared to a slight increase in those who received ibuprofen. Prexige and ibuprofen had similar efficacy and a comparable incidence of adverse events, the results indicated.

Analyst Karl-Heinz Koch of Vontobel commented that the data support Prexige’s safety profile, and suggested that the findings give the drug a better chance of garnering US approval than Merck & Co’s COX-2 inhibitor, Arcoxia (etoricoxib), which was issued a non-approvable letter by the FDA in April over concerns about cardiovascular safety risks. Koch indicated that Prexige could have annual sales of $1 billion, if approved, not including US sales.

The drug, which has been approved in the EU, Canada and other countries to treat osteoarthritis pain of the knee and hip in certain patients, is currently under review by the FDA to treat the symptoms of osteoarthritis.
Persistent and has no biological benefit, representing a maladaptive response to nerve damage.

Inflammatory soup" sensitization or damage to the nociceptive system.

Noradrenergic neurons mediate the descending inhibitory influences.

Analgesics, have been used to treat neuropathic pain, each targeting a different mechanism.

Substances act on the primary afferent nociceptors causing pain by sensitizing it to painful and non-noxious stimuli – producing hyperalgesia and allodynia. Peripheral sensitization may be an important component of the pain associated with post-herpetic neuralgia.

Afferent input of pain signals to higher centers in the brain is modulated by descending inhibitory neurons. These benefit a person by alerting them to potential or actual tissue damage and enabling a fight or flight response, even in the presence of significant tissue damage. However, in neuropathic pain, pain is persistent and has no biological benefit, representing a maladaptive response to nerve damage.

There are several mechanisms in the pain pathway whereby neuronal injury is thought to bring about neuropathic pain. One of these is termed peripheral sensitization or damage to the nociceptive system. Peripheral injury causes the release of inflammatory mediators and other tissue products, "the inflammatory soup". These substances act on the primary afferent nociceptors causing pain by sensitizing it to painful and non-noxious stimuli – producing hyperalgesia and allodynia. Peripheral sensitization may be an important component of the pain associated with post-herpetic neuralgia.

A second mechanism is known as ectopic activity (ectopic neuronal discharges). There is dysregulation of voltage-gated sodium channels at the neuroma site, tips of injured axons and at the dorsal nerve root ganglia. These may produce foci of hyperexcitability and ectopic action potential discharge in the axon and cell body of injured neurons, which may result in pain which is independent of a stimulus.

Central sensitization is a third mechanism, and occurs as a result of repetitive C fiber firing, leading to alterations in gene regulation and gene expression in central neurons. Manifestations of this include reduction in the sensory threshold for pain evocation (allodynia), and increased responsiveness of the dorsal horn neurons to a suprathreshold stimulus (hyperalgesia).

A fourth mechanism termed, disinhibition and attenuation of inhibition, may be an important component of neuropathic pain. The inhibitory neurotransmitters such as GABA and glycine, mediate this process, and there is evidence of loss of GABAergic inhibition after peripheral nerve injury. Serotonergic and noradrenergic neurons mediate the descending inhibitory influences.

Due to the complex mechanisms generating neuropathic pain it comes as no surprise that a variety of diverse pharmacological classes, the so-called adjuvant analgesics, have been used to treat neuropathic pain, each targeting a different mechanism.

Local therapies such as topical lidocaine patches and capsaicin cream work on the peripheral sensitization mechanism.

All the anticonvulsants that work on sodium channels in the dorsal horn may mediate their effects via the ectopic activity mechanism.

The process of central sensitization may be modified by modulation of the activity of the presynaptic central neuron. Among the drugs that may have this effect are gabapentin and pregabalin, which bind to the \( \alpha \)-subunit of the calcium channel, and the opioids. Central sensitization in the postsynaptic neuron may be modulated by NMDA receptor antagonists, protein kinase inhibitors, and glycine antagonists.

Finally disinhibition, where serotonin and noradrenaline are involved, may be targeted by use of TCA and SNRI antidepressants to enhance the inhibitory mechanisms.

Despite a significant increase in our understanding of neuropathic pain syndromes over recent years, the clinical management of this condition remains challenging. Symptoms vary considerably among patients and are largely resistant to treatment with commonly prescribed analgesics. Many patients are not receiving optimal therapy, with very few patients achieving complete pain relief.

In order to provide optimal pain relief for patients, current treatment strategies need to address the multifactorial nature of this condition and the presence of comorbid conditions.

This requires a methodical and mechanistic approach to diagnosis and a patient, flexible, interdisciplinary approach to treatment.

References.


3M Pharmaceuticals becomes iNova Pharmaceuticals

3M Pharmaceuticals has announced it has changed its name to iNova Pharmaceuticals (Pty) Ltd.

The new company was formed following the agreement in November 2006 between Australian investors and 3M to acquire 3M Pharmaceuticals Asia Pacific and Africa.

Based in Sydney, iNova Pharmaceuticals develops and supplies a range of prescription and over-the-counter medicines including drugs to treat skin cancer, heart conditions, weight loss, asthma, coughs, sore throats and sport injuries. Brands well-known to the South African market include Aldara, Andolex, Pholtex, Migril, Duromine, Norflex and Metrogel V.

June 15, 2007 marked the official opening of the South African head office situated in Elandsfontein.

Chief executive Tony Martin said that iNova Pharmaceuticals would focus on geographical expansion and expanding the company brand.

"iNova Pharmaceuticals is ideally positioned with its diverse product portfolio and high growth outlook to expand into new and existing markets," Mr Martin said.

"We intend to grow the business throughout South Africa, and continue to build on product innovation."

iNova Pharmaceuticals has manufacturing and laboratory facilities in Thornleigh, Australia and distributes products to South Africa and throughout the Asia-Pacific region including Australia, New Zealand, Malaysia, the Philippines, Thailand, Singapore, Japan, South Korea, China, Taiwan and Hong Kong. The local company also manufactures part of their range in South Africa.

For further information, please contact iNova Pharmaceuticals on (011) 821 0124.
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Another useful service offered on the PFIZER website is the CELEBREX® reimbursement guideline. This gives a summary of all the medical aids that will cover the costs of treatment with CELEBREX®. If you need to motivate for a patient to receive CELEBREX® on their chronic medicines benefit, PFIZER also offers one-on-one assistance via their ACCESS representatives. Just call 0860 PFIZER or 0860 734 937 and ask to see the PFIZER ACCESS representative in your area.

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Reference:
1. TPM June 2007.


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