

UNIVERSITA' DEGLI STUDI DI
VERONA

DIPARTIMENTO DI

NEUROSCIENZE BIOMEDICINA E MOVIMENTO

*SCUOLA DI DOTTORATO DI
SCIENZE DELLA VITA E DELLA SALUTE*

DOTTORATO DI RICERCA IN

**NEUROSCIENCE
PSYCHOLOGICAL AND PSYCHIATRIC SCIENCES**

Con il contributo di FONDAZIONE CARIVERONA

CICLO /ANNO 29°

**THE ROLE OF CLINICAL HYPNOSIS
AND SELF-HYPNOSIS
TO RELIEF PAIN AND ANXIETY
IN SEVERE CHRONIC ILLNESSES
AND IN PALLIATIVE CARE
A LONG TERM FOLLOW-UP OF TREATMENT
IN A PROSPECTIVE
OBSERVATIONAL NON-RANDOMIZED CONTROLLED
STUDY**

S.S.D. MED 06/L1 – Anestesiologia MED/41 - Anestesiologia

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The role of clinical hypnosis and self-hypnosis
to relief pain and anxiety in severe chronic illnesses and in
Palliative Care

*A long term follow-up of treatment in a prospective
observational non-randomized controlled study*

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Tesi di Dottorato
Verona, (DATA)
ISBN:

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ACKNOWLEDGMENTS

I am very grateful to Professor Enrico Polati, Director Department Anesthesiology, Intensive Care and Pain Therapy, University of Verona, Verona, Italy, for his assistance and the permission to attend, and work as pain therapist, at the Unit of Pain Therapy, Hospital GB Rossi, University of Verona, for my PhD Fellowship in Neuroscience, Psychological and Psychiatric Sciences and my PhD research.

I would like to express my special appreciation and thanks to my advisor Professor Stefano Tamburin, MD, Neurologist, Associate Professor Department Neuroscience, University of Verona, for his precious assistance in my Fellowship. I would like to thank you for encouraging my research and for allowing me to grow as a research scientist. Your advice on both research as well as on my career have been priceless.

I would also like to thank Dr. Emanuela Pasin, Psychologist, for her precious assistance with the follow-up and the assistance for the 2 groups of the patients.

My gratitude to Dr. Giancarlo Pesce, Medical Statistics, Epidemiologist, PhD in Biosciences, University of Verona, Section of Epidemiology and Medical Statistics, for his very important work on the statistical analysis.

I would especially like to thank my colleagues' physicians, the nurses, and nurse aids in the Pain Therapy Unit at University of Verona. All of you have been there to support me when I recruited patients, cured them and collected data for my Ph.D. thesis.

I would like to thank my family for all their love and encouragement. My father Dr. Angelico Brugnoli, MD, who was my first teacher of clinical hypnosis 30 years ago. He died in 2015, during my PhD fellowship, after raising me with a love of science and supporting me in all my pursuits. Thanks to my loving, supportive, encouraging, husband Andrea and my sons Luca and Alessandro, for their faithful support during the stages of this Ph.D. Lastly, but not less important, I would like to express my special appreciation and gratitude to all my patients seriously ill by severe chronic diseases and cancer, who encouraged me in this research: "You teach me the way of life." (Psalm 16:11).

ABSTRACT

Introduction: Patients with severe chronic diseases and advanced cancer in Palliative care, have a complex array of physical and psychosocial needs that can arise early in the course of illness. Palliative care therapies are well-placed to address those needs; however, referrals to the psychosocial interventions in palliative care are typically made late in the illness trajectory. We studied 2 groups of patients with severe chronic illnesses who participated in a non-randomized trial of early integration in palliative care of clinical hypnosis, versus standard pharmacological care. The purpose of the present investigation was to evaluate whether a long term intervention with clinical hypnosis and self-hypnosis as adjuvant therapy in chronic pain and anxiety, is more effective than only a therapy with medicines.

Materials and Methods: The study was performed at the comprehensive Center for Pain Therapy at the University of Verona, Italy. This is a nonrandomized trial. A total of 50 patients were studied in two groups: 25 in a group therapy with the hypnosis intervention as adjuvant therapy to medicines, 25 in a control group, who received only a pharmacological intervention. Evaluations with VAS scale for pain and HAMA Hamilton anxiety scale for anxiety were conducted for a long-term follow-up. Subjects were assessed at the first session, after one year and two years' follow-up.

Results: Fifty subjects 14 men and 36 women participated to the study. The patients suffered from 3 main types of severe chronic disease: rheumatic (n=21), neurologic (n=16) and oncologic (n=13). Sixteen of them (32%) were administered with opioids for pain control. Half of the patients (n=25) were assigned to the group administered with the self-hypnotic protocol (hypnosis group), while the remaining 25 followed the conventional pain therapies (control group). The two groups were homogeneous in the distribution of age, sex, type of disease, and use of opioids at baseline. Subjects administered with the hypnosis therapy had a greater reduction in pain and in anxiety. The VAS score at baseline was similar between the hypnosis and the control group (mean \pm standard deviation, sd: 78 ± 16 and 77 ± 14 , respectively); after 1 year and 2 years, the score decreased in both groups compared to baseline score, but it was lower in the hypnosis group compared to the control group (62 ± 15 /control; and 46 ± 14 /hypnosis, respectively). The Hamilton score in multivariate analysis, the treatment with hypnosis was

associated with a greater decrease of 7 points compared to the control group, independently from the score at baseline. The decrease in VAS and Hamilton score were studied in the two therapy groups according to the type of disease suffered by the patients: rheumatic disease, neurologic disease, or cancer. For all the 3 types of disease, the reduction in both VAS and Hamilton scores was significantly greater in the subjects who were included in the hypnosis group, after 1 and 2 years follow-up. Subjects in the hypnosis group were at lower risk of increasing the pharmacological treatment for pain control. The group 1 (hypnosis) after a long term follow-up 1 and 2 years of treatment with hypnosis as an adjuvant therapy for pain and anxiety, shows a significant statistical decrease of pain and anxiety compared with the control group.

Conclusions The themes resulting from the statistical analysis fell into 3 categories: the decrease of pain, the decrease of anxiety, and the decrease of the use of the opioids. In the hypnosis group, the focus of care in the palliative care of the severe chronic illnesses, was perceived to be disease-centered, with emphasis on controlling physical and psychological pain and anxiety.

CHAPTER 1

INTRODUCTION AND SCIENTIFIC BACKGROUND

PAIN AND ANXIETY IN SEVERE CHRONIC DISEASES AND IN PALLIATIVE CARE: RECENT ADVANCES IN THE APPLICATION OF HYPNOSIS FOR SYMPTOM MANAGEMENT.

In scientific literature, clinical hypnosis is considered as a psychological intervention and as a CAM in pain therapy and in Palliative Care (Stoelb BL, Molton IR, Jensen MP, Patterson DR., 2009; Jensen MP., 2009; Brugnoli MP, 2014; Elkins, G., 2007).

Clinical Hypnosis in cancer and in severe chronic diseases, is practiced for both chronic pain and anxiety conditions:

(1) hypnotic analgesia consistently results in greater decreases in a variety of pain outcomes compared to no treatment/standard care;

(2) hypnosis relieves anxiety-related outcomes in Palliative Care;

(3) hypnosis can reduce the use of opioids in chronic severe diseases and in palliative Care (Stoelb BL, Molton IR, Jensen MP, Patterson DR., 2009; Jensen MP., 2009; Brugnoli MP, 2014).

In severe chronic illnesses and in Palliative Care, when we cannot cure the illnesses, we can improve the well-being of the patients in the context of chronic or life-threatening illness as a patient-reported outcome consisting of growth or benefit in psychological, social, and/or spiritual dimensions representing improvement well above the patient's pre-morbid baseline.

This positive outcome often occurs despite substantial suffering during the illness, even in terminal cases.

Kearney (2000) contrasted the "treatment for pain" and "healing of suffering" perspectives in palliative care. He characterizes the "treatment for pain" perspective as seeing pain only as a

medical condition that can be assessed, treated, and in the vast majority of instances brought under control. In this perspective, relief from pain is reliant on the knowledge, skill, and intervention of a skilled practitioner. Kearney points out that many forms of suffering (such as grief) persist despite substantial efforts made by expert caregivers and by the patients themselves.

Saunders (1996) observed that the whole experience of a patient's life was reflected in that patient's dying. She advocated the concept of "total pain," a complex of physical, emotional, psychological, social, and spiritual factors. In her view, total pain can include not only physical pain but also psychological pain (e.g., anxiety, depression, and fear), social pain (e.g., concern for their family including bereavement), and/or spiritual pain (e.g., a need to find some meaning in the situation, some deeper reality in which to trust).

A large number of studies have provided evidence for the efficacy of clinical hypnosis and self-hypnosis, as a psychological intervention as an adjuvant therapy- add to therapy-, in the treatment of chronic pain, anxiety and anxiety-related symptoms in severe chronic illnesses. Hypnosis practice is increasingly being employed in Western psychology to alleviate a variety of mental and physical conditions. Scientific research into hypnosis generally falls under the umbrella of positive psychology, but hypnosis is much more. Research has been ongoing over the last twenty or thirty years, with a surge of interest over the last decade in particular.

However, the scientific literature lacks for long term follow-up (1 year and 2 year) to evaluate the efficacy of hypnosis for pain and anxiety relief in severe chronic illnesses and in Palliative Care. The purpose of this study was to investigate the efficacy of hypnosis and self-hypnosis to relief pain and anxiety, as adjuvant therapy, in severe chronic illnesses for a long-term follow up: 1 year and 2 year.

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;

- offers a support system to help the family cope during the patients illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Chronic severe diseases are the diseases that persist for a long time. A chronic disease is one lasting 3 months or more, by the definition of the U.S. National Center for Health Statistics. Chronic diseases generally cannot be prevented by vaccines or cured by medication, nor do they just disappear. Chronic diseases tend to become severe and more common with age. The leading chronic diseases in developed countries include: arthritis and severe chronic rheumatic diseases, cardiovascular diseases, neurological chronic diseases and stroke, cancer such as breast and colon cancer and other chronic diseases as diabetes, obesity, and other health problems (CDC/National Center for Health Statistics, 2015; WHO, 2002). Chronic diseases are the leading causes of death and disability worldwide.

The chronic care model (CCM) describes chronic care as “the prevention and diagnosis, management, and palliation of chronic disease” and is internationally accepted as the main strategic response to the challenges of chronic disease. The model calls for the redesign of health care to provide continuous, coordinated multi-faceted systems of health service delivery. The CCM is based on a Cochrane systematic review of chronic care interventions (Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A., 2001; Wagner EH., 1998; McKenna MT, Taylor WR, Marks JS, Koplan JP., 1998).

Pain and Suffering in severe chronic diseases and in Palliative Care

The often quoted IASP definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.

Pain and suffering are universal human experiences. Serious chronic illnesses are a major health issue in modern society. In chronic disease anxiety/depression, self-focused

attention, pain and suffering, are significant predictors of panic-fear symptoms, lower self-efficacy, and more perceived interference in wellbeing of the patient. Pain and suffering are always subjective (IASP, 2009).

Pain is a complex phenomenon involving both neurophysiologic and psychological components.

The neuromatrix theory of pain proposes that pain is a multidimensional experience produced by characteristic "neurosignature" patterns of nerve impulses generated by a widely distributed neural network-the "body-self neuromatrix"-in the brain (Melzack R., 2005). These neurosignature patterns may be triggered by sensory inputs, but they may also be generated independently of them.

The neuromatrix theory of pain provides a new conceptual framework to examine these problems. It proposes that the output patterns of the body-self neuromatrix activate perceptual, homeostatic, and behavioral programs after injury, pathology, or chronic stress. Pain, then, is produced by the output of a widely distributed neural network in the brain rather than directly by sensory input evoked by injury, inflammation, or other pathology. The neuromatrix, which is genetically determined and modified by sensory experience, is the primary mechanism that generates the neural pattern that produces pain. Its output pattern is determined by multiple influences, of which the somatic sensory input is only a part, that converge on the neuromatrix (Melzack R., 2005).

Pathophysiological mechanisms involve neural pathways, and a variety of pain-producing substances and modulating mechanisms. These include acetylcholine, serotonin, histamine, bradykinin, prostaglandins, substance P, somatostatin, cholecystokinin, vasoactive intestinal polypeptide, noradrenaline and endogenous opioid peptides. The opioid system controls pain, reward and addictive behaviors. Opioids exert their pharmacological actions through three opioid receptors, mu, delta and kappa whose genes have been cloned (Oprm, Oprd1 and Oprk1, respectively). Opioid receptors in the brain are activated by a family of endogenous peptides like enkephalins, dynorphins and endorphin, which are released by neurons (Contet CS, Kieffer BL, Befort K, 2004).

In assessing patients with pain, it is essential to evaluate the cause of the pain, its severity, type, location, duration, quality, and response to therapies, among other factors (Lasagna L., 1986). It is the perception of pain and the individual's physical and emotional reaction to the pain perception that give us the opportunity to create treatment approaches that can provide relief.

Complex psychological factors play an important role in the variability of perceived pain (Aoki J, Ikeda K, Murayama O, Yoshihara E, Ogai Y, Iwahashi K., 2010).

The patient with pain in chronic diseases and in Palliative Care, should be reassured; it is understood that the patient is suffering, and an appropriate cause for this suffering and the most effective treatment will be sought. The physicians can offer a useful service in the diagnosis and treatment of pain in many complex cases.

In 1994, responding to the need for a more useful system for describing chronic pain, the International Association for the Study of Pain (IASP) classified pain according to specific characteristics: (1) region of the body involved (e.g. abdomen, lower limbs), (2) system whose dysfunction may be causing the pain (e.g., nervous, gastrointestinal), (3) duration and pattern of occurrence, (4) intensity and time since onset, and (5) etiology.

There are two basic types of pain: acute and chronic.

Acute pain occurs for brief periods of time and is associated with temporary disorders. However, it is always an alarm signal that something may be wrong.

Chronic pain is continuous and recurrent. It is associated with chronic diseases and is one of their symptoms.

Pain intensity not only depends on the type of stimulus that caused it, but also on the subjective perception of the pain.

Difficulty in maintaining the balance between adequate pain relief and acceptable tolerability, particularly with strong opioids, can lead to the establishment of a “vicious circle” that alternates between lack of efficacy and unpleasant side effects, prompting discontinuation of treatment.

Pain management in patients due to aged heterogeneity, multimorbidity, and polypharmacy; selection of treatment in an effort to maximize patients' functional abilities in addition to relieving their pain (Schmader KE, Baron R, Haanpää ML, Mayer J, O'Connor AB, Rice AS, Stacey B., 2010).

The interplay between pain and therapy is very complex, in that pain may be a target for treatment, but can also have negative effects on therapy procedures. Moreover, side effects of drugs, which are currently used to treat pain, may negatively influence the therapy and rehabilitation outcomes in severe chronic illnesses and in Palliative Care.

Because of the lack of guidelines or consensus, the Italian Consensus Conference on Pain in Neurorehabilitation (ICCPN) was aimed to answer some open questions on the treatment of pain in this setting. To this aim, they collected evidence on the pharmacological and non-pharmacological strategies and their role in the integrated approach to pain (Tamburin S, Lacerenza MR, Castelnovo G, Agostini M, Paolucci S, Bartolo et Al, M, Bonazza S, Federico A, Formaglio F, Giusti

EM, Manzoni; Italian Consensus Conference on Pain in Neurorehabilitation, ICCPN, 2016)

Anesthesiological procedures can be helpful in diagnosis (Polati E, Luzzani A, Schweiger V, Finco G, Ischia S., 2008; Ischia S, Polati E, Finco G, Gottin L. 2002; Ambrosio F, Paoletti F, Savoia G, Amantea B, Arcuri E, Avogaro F, Barbati A, Beltrutti D, Branca L, Camaioni D, De Conno F, De Luca A, Di Massa A, Evangelista M, Finco G, Ischia S, Mattia C, Mascaro A, Mercadante S, Orlandini G, Palomba R, Pasetto A, Polati E, Raffaelli W, Varrassi G, Visentin M, Zucco E; SIAARTI., 2003; Verlato G, Polati E, Speranza G, Finco G, Gottin L, Ischia S., 2001).

The patient can appreciate that there may not be always a technological or invasive solution to the pain problem, such as the use of a nerve block, or a pill, so the patient must be willing to undergo psychological and behavioral evaluation.

Many factors may contribute to the symptoms. Concomitant depression, impaired cortical function and chronic anxiety, may all be conditions, in which the patients use the language and behavior of pain, to communicate their distress and suffering.

Sometimes, during acute pain, growth hormone levels significantly increased within minutes, and beta endorphin and prolactin were elevated proportionately with severity of injury. Cortisol was inversely correlated with injury severity, possibly reflecting impaired release from the adrenal cortex after very severe injury (Hetz, W., Kamp, H. D., Zimmermann, U., Von Bohlen, A., Wildt, L., and Schuettler, J. 1996).

In the final analysis, pain is communicated as a behavior, for it is only by word, grimacing, posturing and other behavioral signals that we know another individual is in pain.

Patients may acquire behavioral aspects of their pain problems in chronic diseases and in Palliative Care, and along with psychological and tissue-damaging problems.

Thus, such patients are unlikely to respond to therapy directed primarily at the tissue-damaging aspects, but may well need the combined efforts of conventional therapy aimed at the degenerative disease, psychological support, pharmacological treatment, and some behavior modification in an attempt to restore normal function.

Acute pain signals pass through the thalamus, and then on to the No aspect of our mental life is more important to the quality and meaning of our existence than emotions. In view of the proliferation of increasingly fruitful exchanges between researches of different stripes, it is no longer useful to speak of the philosophy of emotion in isolation from the approaches of other disciplines, particularly psychology and neurology (De Sousa, 1987).

Emotions make certain features of situations or arguments more prominent, giving them a weight in our experience that they would have lacked in the absence of emotion (De Sousa, 1987; Roberts, 1988).

Pain is considered to be chronic if it has remained essentially unrelieved for 6 months or longer. Chronic pain can be of many types and locations, and may or may not have specific tissue damage associated with it.

Chronic pain travels through the hypothalamus, which is connected to the limbic system where emotional functioning (emotions or problems, such as anxiety or depression) seems to originate. In chronic pain there is a relationship between emotions, psychological state and the intensity of the pain experience. A variety of methods are available to help the Acute and Chronic Pain patient manage their depression, anxiety and stress level, including relaxation techniques and hypnosis. Usually, some combinations of these with therapies are applied for the best results.

Knowing factors that aggravate or relieve pain helps clinicians to design a pain treatment plan in severe chronic illnesses. The initial pain assessment should elicit information about changes in activities of daily living, including work and recreational activities, sleep patterns, mobility, appetite, sexual functioning, and mood.

A psychosocial assessment should emphasize the effect of pain on patients and their families, as well as patients' preferences among pain management methods. Patients who are able to answer should be asked about the effectiveness of past and present pain treatments, such as antineoplastic therapy or specific pharmacologic and nonpharmacologic therapies. Pain can be verified objectively, and interpretation of nervous system aberrations reveals individual differences in severe chronic diseases and in Palliative Care. If the feeling of objective existence is interpreted as a negative emotion, this phenomenon can lead to the formation of somatic symptoms. However, we must organize an accurate diagnosis to verify the nature of the pain in severe chronic diseases: if it is only physical or there is a psychosomatic amount.

The number of people in their last years of life with advanced chronic conditions, palliative care needs and limited life prognosis due to different causes including multi-morbidity, organ failure, frailty and cancer is rising.

The response to their needs is usually late and largely based around institutional palliative care focused on cancer. There is a great need to identify these patients, and integrate an early palliative psychosocial approach according to their individual needs in all settings, as suggested by the World Health Organization (WHO) (Gómez-Batiste X, Murray

S, Thomas K, Blay C, Boyd K, Moine S, Gignon M, den Eynden BV, Leysen B, Wens J, Engels Y, Dees M, Costantini M., 2016).

To calm fears and anxiety in chronic pain, additional medicines – “adjuvants” – should be used; to calm fears and anxiety, additional non-pharmacological therapies and psychological therapies – “adjuvants” – should be used.

In such cases, a variety of strategies can be implemented to improve the pain control and balance between analgesia and side effects (Vielhaber and Portenoy 2002).

In 2002, NIH (National Institutes of Health) institutes, centers, and offices plus the Agency for Healthcare Research and Quality asked the Institute of Medicine to convene a study committee to explore scientific, policy, and practice questions that arise from the significant and increasing use of CAM (complementary and alternative medicine) therapies in severe chronic illnesses.

Descriptive definitions of CAM include one by Ernst et al. (1995), who write that CAM is a “diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, satisfying a demand not met by orthodox, or diversifying the conceptual framework of medicine.”

One of the most widely used classification structures, developed by NCCAM (2000), divides CAM modalities into five categories:

- 1) Alternative medical systems,
- 2) Mind-body interventions,
- 3) Biologically based treatments,
- 4) Manipulative and body-based methods, and
- 5) Energy therapies.

Anxiety and psychosomatic disorders in severe chronic diseases and in palliative care

In cancer and severe chronic illnesses, we can have pain related to stress, anxiety and psychosomatic symptoms.

Psychosomatic disorder is a condition in which psychological stresses adversely affect physiological (somatic) functioning to the point of distress. It is a condition of dysfunction or structural damage in bodily organs through inappropriate activation of the involuntary nervous system and the biochemical response (Levenson, JL., 2006, Sarno, J., 2006).

In this context, this review will consider anxiety disorders from the perspective of the psychobiological mechanisms of vulnerability to extreme stress in severe chronic illnesses.

Psychosomatic medicine is a field of behavioral medicine and a part of the practice of consultation-liaison psychiatry.

Psychosomatic medicine in palliative care, integrates interdisciplinary evaluation and management involving diverse clinical specialties including psychosocial oncology, psychiatry, psychology, neurology, internal medicine, surgery, allergy, dermatology and psychoneuroimmunology.

Clinical conditions where mental processes act as a major factor affecting medical outcomes are areas where psychosomatic medicine has competence (Levenson, JL., 2006; Sarno, J., 2006).

Thus, the psychosomatic symptom emerges as a physiological concomitant of an emotional state. In a state of rage or fear, for example, the stressed person's blood pressure is likely to be elevated and his pulse and respiratory rate to be increased. When the fear passes, the heightened physiologic processes usually subside. If the person has a persistent inhibited fear (chronic anxiety), however, which he is unable to express overtly, the emotional state remains unchanged, though unexpressed in the overt behavior, and the physiological symptoms associated with the anxiety state persist. With time, such a person becomes aware of the physiological dysfunction (Sarno, J., 2006; Fink, G., 2011).

Clinical neurobiological research pertaining to these anxiety disorders has been dominated by investigations directed toward identifying dysfunctional neural circuits and neurochemical systems, vulnerability genes, and psychopharmacology. Very often, he develops concern over the resulting physical signs and symptoms, but he denies or is unaware of the emotions that have evoked the symptoms ((Levenson, JL., 2006; Sarno, J., 2006; Fink, G., 2011).

Some physical symptoms in severe chronic diseases are believed to have a psychological component derived from the stresses and strains of everyday living. This has been suggested, for example, of muscular pain, tension type headache or high blood pressure, which some researchers have suggested may be related to stresses in everyday life (Sarno, J., 2006).

However, within a psychosomatic framework, mental and emotional states are seen as capable of significantly influencing the course of any physical illness. Psychiatry traditionally distinguishes between psychosomatic disorders, disorders in which mental factors play a significant role in the development, expression, or resolution of a physical illness, and somatoform disorders, disorders in which mental factors are the sole cause of a physical illness.

It is difficult to establish whether an illness has a psychosomatic component. A psychosomatic component is often inferred when there are some aspects of the patient's presentation that are unaccounted for by biological factors, or some cases where there is no biological explanation at all. For instance, *Helicobacter*

pylori causes 80% of peptic ulcers. However, most people living with *Helicobacter pylori* do not develop ulcers, and 20% of patients with ulcers have no *H. pylori* infection. Therefore, in these cases, psychological factors could still play some role (Fink, G., 2011). Similarly, in irritable bowel syndrome, there are abnormalities in the behavior of the gut. However, there are no actual structural changes in the gut, so stress and emotions might still play a role (Melmed, Raphael N., 2001).

The strongest perspective on psychosomatic disorders is that attempting to distinguish between purely physical and mixed psychosomatic disorders is increasingly obsolete as almost all-physical illness have mental factors that determine their onset, presentation, maintenance, susceptibility to treatment, and resolution (Charney DS., Barlow DH., Botteron K., et al., 2002; McNally RJ., 2002).

According to this view, even the course of serious illnesses, such as chronic severe diseases and cancer, can potentially be influenced by a person's thoughts, feelings, emotions and general states of mental suffering and physical symptoms. Addressing such factors is the concern of the applied field of behavioral medicine. In modern society, psychosomatic aspects of illness are often attributed to stress (Treasaden, IH., Basant K. Puri, Laking PJ., 2002), making the cure of stress one important factor in the development, treatment, and prevention of psychosomatic illness.

In the field of psychosomatic medicine, the phrase "psychosomatic illness" is used more narrowly than it is within the general population. In contrast, in contemporary psychosomatic medicine, the term is normally restricted to those illnesses that do have a clear physical basis, but where it is believed that psychological and mental factors also play a role. Some researchers within the field believe that this overly broad interpretation of the term may have caused the discipline to fall into disrepute clinically (Greco, M., 1998).

For this reason, among others, the field of behavioral medicine has taken over much of the remit of psychosomatic medicine in practice and there exist large areas of overlap in the scientific researches (Fawzy FI, Fawzy NW, Hyun CS, Elashoff R, Guthrie D, Fahey JL, Morton DL.1993; Spiegel, D, Bloom, JR, Kraemer, HC, Gottheil, E., 1989; Coyne JC, Stefanek M, Palmer SC, 2007; Wise, Thomas N., 2008;).

The anxiety disorders in severe chronic illnesses, including panic disorder, generalized anxiety disorder, social anxiety disorder, psychosomatic symptoms and posttraumatic stress disorder, are among the disabling psychological disorders in palliative care (Brugnoli MP., Brugnoli A., Norsa A., 2006; Brugnoli MP., 2014a, 2014b; Asaad, Ghazi, 1996; Erwin, E, 2002)

These disorders are currently diagnosed using standardized diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders [DSM-5] (American Psychiatric Association, 2013) and International Classification of Diseases [ICD-10]) (ICD-10-WHO Version for 2016), which are almost exclusively based upon phenomenology, and not genetics, etiology, or pathophysiology.

Anxiety disorders and mood disorders commonly produce physical symptoms. Clinicians need to rule out somatic symptoms due another primary psychiatric condition before considering a somatic symptom disorder diagnosis. Somatic symptoms can dramatically improve with successful treatment of the anxiety or mood disorder.

The DSM-5 includes 5 specific diagnoses in the Somatic Symptom Disorder and Other Related Disorder category (American Psychiatric Association, 2013). Specific Somatic Symptom Disorders diagnoses include:

- (1) Somatic symptom disorder;
- (2) Conversion disorder;
- (3) Psychological factors affecting a medical condition;
- (4) Factitious disorder;
- (5) Other specific and nonspecific somatic symptom disorders (Yates WR., Dunayevich, E., 2016).

Some evidence exists that somatization disorder is associated with increased risk for suicide attempts (Treasaden, IH., Basant K. Puri, Laking PJ., 2002). Patients with somatic symptom disorders may be misdiagnosed (Yates WR., Dunayevich, E., 2016; Chioqueta AP, Stiles TC., 2004).

Somatic symptom disorders in severe chronic illnesses may existing in childhood, adolescence, early adulthood or older adults. New onset of unexplained somatic symptom disorders, in chronic illnesses, should evidence of major depression and anxiety associated with somatization (Brugnoli MP., Brugnoli A., Norsa A., 2006; Yates WR., Dunayevich, E., 2016).

Most neuro-biochemical changes associated with pain and stress are a result of stimulation of the sympathetic nervous system, specifically the fight-or-flight response: in acute stress, this response triggers the release of substances: catecholamines, which include epinephrine, norepinephrine and cortisol, from the adrenal glands. These substances prepare the body to react to immediate danger by increasing heart rate, increasing oxygen delivery to the brain, dilating blood vessels in skeletal muscles, and increasing blood glucose levels (Charney DS., 2003; Rapee RM., 2000; Prior M., Smart D., Sanson A., Oberklaid F., 2000; Vasey MW., Dadds MR., 2001; Kagan J., Snidman N., 1999; Krizanova O, Babula P, Pacak K., 2016).

Chronic stress is characterized by the persistent presence of sources of frustration or anxiety that a person encounters every day in the severe chronic diseases.

Psychosomatic disorders resulting from chronic stress may include pain, anxiety, hypertension, respiratory failure, gastrointestinal disturbances, migraine and tension headaches, dermatitis, fibromyalgia and ulcers (Krizanova O, Babula P, Pacak K., 2016).

Pain and anxiety are the most frequent stress-response' problems in palliative care.

The patient's pain and anxiety should be acknowledged as a real physiological existent problem with biochemical changes for the patient. Attempts to differentiate between "real" and "unreal" pain, "organic" and "psychosomatic" are usually fruitless and only succeed in challenging such patients to attempt to prove further the "reality" of their suffering. The patient can appreciate that there may not be just a technological or pharmacological solution to his problem, such as the use of a nerve blocks, or medicines, so the patient must be willing to undergo psychological and behavioral evaluation. Many factors may contribute to the symptoms. Trauma, serious illnesses, concomitant depression, impaired cortical function and chronic anxiety, may all be conditions in which the patients use the language and behavior of pain to communicate their distress. In chronic stress, continuous stimulation of the fight-or-flight response leads to constant production and secretion of catecholamines. This has a variety of physiological concerns, including hyperglycemia, which can lead to type II diabetes mellitus, and hypertension, which can lead to cardiovascular diseases. Because some catecholamines such as norepinephrine act as neurotransmitters in the brain, these substances can modify cognition and other mental processes, leading to poor concentration, mood swings, agitation, depression, and anxiety (Steckler T, Holsboer F., 1999; Strome EM, Wheler GH, Higley JD, Loriaux DL, Suomi SJ, Doudet DJ., 2002; Antonijevic IA, Murck H, Bohlhalter S, Frieboes RM, Holsboer F, Steiger A., 2000; Bale TL, Vale WW., 2003).

In addition, long-term stress-induced cortisol secretion from the adrenal glands can reduce immune function, leading to increased risk of illness (Charney DS., 2003; Krizanova O, Babula P, Pacak K., 2016).

How the motor, cognitive, and affective areas of the cerebral cortex influence the adrenal medulla in severe chronic diseases? How and where does the "mind" (brain) influence the "body" (internal organs and their functions)?

Recent studies identified key areas in the primate cerebral cortex that are linked through multisynaptic connections to the adrenal medulla. The most substantial influence originates from a broad

network of motor areas that are involved in all aspects of skeletomotor control from response selection to motor preparation and movement execution (Allen YS, Adrian TE, Allen JM, Tatemoto K, Crow TJ, Bloom SR, Polak JM., 1983; Heisler L., Chu HM., Brennan T., et al., 1998; Parks C., Robinson P. ibille E, Shenk T, Toth M., 1998; Gross C., Zhuang X., Stark K., et al., 2002; Drevets WC., Frank JC., Kupfer DJ., et al., 1999; Gingrich JA., 2002; Holmes A., Yang RJ., Murphy DL., Crawley JN., 2002; Caspi A., Sugden K., Moffit TE., et al., 2003).

Thus, cortical areas involved in the control of movement, cognition, and affect are potential sources of central commands to influence sympathetic arousal. These results provide an anatomical basis for psychosomatic illness in chronic pain and anxiety, where mental states can alter the organ functions (Dum RP, Levinthal DJ, Strick PL., 2016).

These studies and results have a number of important functional implications. First, they emphasize the importance of the cortical motor areas in the top-down influence over the adrenal medulla during stress and psychosomatic disorders. Normal limb and body movements are accompanied by coordinated changes in sympathetic output that are proportional to the metabolic demands of the task (Dum RP, Levinthal DJ, Strick PL., 2016). An important component of the sympathetic activity is thought to be due to a “central command” that can precede any change in muscle activity, and we can have fibromyalgic syndromes in severe chronic illnesses (Dum RP, Levinthal DJ, Strick PL., 2016; Cechetto DF, Saper CB., 1990; Williamson JW, Fadel PJ, Mitchell JH., 2006; Shoemaker JK, Wong SW, Cechetto DF., 2012).

This command is a “predictive” response because it prepares the body to meet the anticipated metabolic needs of activities like exercise, emotional states, and fight or flight. Scientific researchers suggest that the central commands to prepare for and generate visceromotor output originate from the same cortical areas that are involved in the preparation and generation of skeletomotor output (Dum RP, Levinthal DJ, Strick PL., 2016; Shoemaker JK, Wong SW, Cechetto DF., 2012; Hatanaka N, Nambu A, Yamashita A, Takada M, Tokuno H., 2001; Strack AM, Sawyer WB, Platt KB, Loewy AD., 1989).

Second, they found that the top-down influence over the adrenal medulla by M1 originates largely from its trunk representation. This region of M1 projects to thoracic segments of the spinal cord (Dum RP, Levinthal DJ, Strick PL., 2016; Shoemaker JK, Wong SW, Cechetto DF., 2012; Hatanaka N, Nambu A, Yamashita A, Takada M, Tokuno H., 2001).

These observations suggest that there is a link between the descending control of “core muscles” and the regulation of

sympathetic output in chronic pain and anxiety (Innes KE, Bourguignon C, Taylor AG., 2005; Varga K, Kekecs Z., 2014; Astin JA, Shapiro SL, Eisenberg DM, Forsys KL., 2003; Searle, J., 1990; Tononi G, Koch C., 2008; Tononi G, Koch C., 2015). In many patients with anxiety disorders, especially those with severe chronic illnesses fear conditioning causes vivid recall of memories of traumatic events and autonomic hyperactive arousal (Dum RP, Levinthal DJ, Strick PL., 2016)

Fear conditioning is conceptualized as a form of associative learning in which subjects come to express fear responses to neutral conditioned stimuli (CS), which are paired with aversive unconditioned stimuli (US) (Dum RP, Levinthal DJ, Strick PL., 2016). Because of this pairing, the CS acquire the ability to elicit a spectrum of behavioral, autonomic, and endocrine responses that normally would only occur in the context of danger. Fear conditioning can be adaptive and enable efficient behavior in situations like severe chronic diseases.

The long loop pathway indicates that sensory information relayed to the amygdala undergoes substantial higher level processing, thereby enabling assignment of significance, based upon prior experience of anxiety, to complex stimuli (Dum RP, Levinthal DJ, Strick PL. 2016; Blair HT, Schafe GE, Bauer EP, Rodrigues SM, LeDoux JE., 2001; Walker DL, Davis M., 2000; Grillon C., 2002; Bauer EP, Schafe GE, LeDoux JE., 2002).

This link could provide a neural substrate for the control of stress and psychosomatic disorders through “core” and mind-body therapies and exercises, such as relaxation, verbal suggestions and visual imagery, yoga, acupuncture, mindfulness, autogenic training, hypnosis and self-hypnosis (Brugnoli MP, 2014a; Barber TX., Spanos NP., Chaves JF., 1974; Frischholz EJ., 2013; Gansler T., Kaw C., Crammer C., Smith T., 2008; Gelfman LP., Meier DE., Morrison RS., 2008; Grinder J., Bandler R., 1976; Hammond DC., 2010; Kleinbub JR, Palmieri A, Broggio A, Pagnini F, Benelli E, Sambin M, Sorarù G., 2015; Lankton S. , 2013; Lazar S.W., Bush G., Gollub R. L., Fricchione G. L., Khalsa G., Benson H. , 2000; Lotfi-Jam K., Carey M., Jefford M., Schofield P., Charleson C., Aranda S., 2008; Marchioro G., Azzarello G., Viviani F., Barbato F., Pavanetto M., Rosetti F., Pappagallo GL., Vinante O., 2000; Perez-De-Albeniz A., Holmes J., 2000; Plaskota M., Lucas C., Evans R., Cook K., Pizzoferro K., Saini T., 2012; Raz A., 2011; Richardson J., Smith JE., McCall G., Richardson A., Pilkington K., Kirsch I., 2007; Robertson D., 2012; Sepúlveda C., Marlin A., Yoshida T., Ullrich A., 2002; Shiber JR., Santana J. , 2006; Temel J.S., et al., 2010; Udo I., Gash A. , 2012; Untas A., Chauveau P., Dupré-Goudable C., Kolko A., Lakdja F., Cazenave N., 2013; Yapko MD., 2013; Wonderling, D., 2006;

Zitman FG, van Dyck R, Spinhoven P, Linssen AC., 1992; Kekecs Z, Varga K., 2013; Ronel J, Mehilli J, Ladwig KH, Blättler H, Oversohl N, Byrne RA, Bauer A, Schneider S, Linde K, Henningsen P, Lahmann C, Noll-Hussong M, Meissner K., 2011; Häuser W, Hagl M, Schmierer A, Hansen E., 2016; Lauche R, Cramer H, Häuser W, Dobos G, Langhorst J., 2015; Anbar RD., 2008; Anbar RD., Linden JH., 2010).

In addition, the sympathetic system innervates structures of the head (eye, salivary glands, mucus membranes of the nasal cavity), thoracic viscera (heart, lungs) and viscera of the abdominal and pelvic cavities (eg, stomach, intestines, pancreas, spleen, adrenal medulla, urinary bladder) (McCorry LK., 2007; Fox SI., 2006; Guyton AC, Hall JE., 2006; Hoffman BB., 2001; Hoffman BB, 2001a; Iversen S, Iversen L, Saper C., 2000).

The parasympathetic system predominates during quiet, resting conditions and it can be overstimulated during chronic stress and anxiety. The preganglionic neurons that arise from the brainstem exit the CNS through the cranial nerves.

Therefore, the effects of the parasympathetic system tend to be more discrete and localized, with only specific tissues being stimulated at any given moment, compared to the sympathetic system where a more diffuse discharge is possible (McCorry LK., 2007; Fox SI., 2006; Guyton AC, Hall JE., 2006; Hoffman BB., 2001; Hoffman BB., 2001a; Iversen S, Iversen L, Saper C., 2000; Dosenbach NUF, Fair DA, Cohen AL, Schlaggar BL, Petersen SE., 2008).

During acute and chronic pain, stress and anxiety, the loss of homeostasis between sympathetic and parasympathetic system, generates the psychosomatic symptoms and disorders.

Somatization is defined as the tendency to experience psychological distress in the form of physical symptoms.

The psychosomatic symptoms are described and classify in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10-WHO Version for 2016, Chapter V).

In severe chronic illnesses, anxiety and psychosomatic symptoms are usually of two types, neither of which indicates a physical disorder of the organ or system concerned. First, there are complaints based upon objective signs of autonomic arousal, such as palpitations, sweating, flushing, tremor, and expression of fear and distress about the possibility of a physical disorder. Second, there are subjective complaints of a nonspecific or changing nature such as fleeting aches and pains, sensations of burning, heaviness, tightness, and feelings of being bloated or distended, which are referred by the patient to a specific organ or system:

- Cardiac neurosis
- Gastric neurosis

- Neurocirculatory asthenia

Psychogenic forms of:

- aerophagy
- cough
- diarrhoea
- dyspepsia
- dysuria
- flatulence
- hiccough
- hyperventilation
- increased frequency of micturition
- irritable bowel syndrome
- pylorospasm
- backache
- headache
- Somatoform pain disorder
- Nonorganic sleep disorders
- *Undifferentiated somatoform disorder*
- *Somatization disorder*
- *Unspecified somatoform disorder*
- *Conversion disorder*
- *Hypochondriasis*
- *Body dysmorphic disorder*
- *Pain disorder*

The symptoms included here are the presence of an excruciating pain in one or more various parts of the body. Psychosomatic chronic symptoms in palliative care, pain and anxiety behaviors are cognitively impaired; they are communicated by:

(a) Facial expression:

- Slight frown, frightened face
- Rapid blinking

(b) Verbalizations, vocalizations:

- Verbally abusive
- Calling out, chanting, grunting

(c) Body movements:

- Rigid, tense
- Fidgeting
- Increased pacing, rocking

(d) Changes in interpersonal interactions:

- Aggressive, combative, resisting care
- Decreased cultural interaction
- Socially inappropriate, disruptive

(e) Changes in activity patterns or routines:

- Refusing food
- Increased rest periods

iii. Sleep pattern changes

(f) Mental status changes:

i. Crying, tears

ii. Increased confusion

iii. Irritable

In Palliative Care, is important to pay attention to evaluate always these signs and indicators to better relief anxiety and suffering (Brugnoli MP, 2014a, 2014b; Krizanova O, Babula P, Pacak K., 2016; Vasey MW., Dadds MR., 2001).

It is essential understanding if we have anxiety and psychosomatic symptoms associated to the severe chronic illness.

The psychosomatic symptoms cause one or more psychological and bodily-related symptoms, including pain. Even if the patient has a concomitant severe chronic disease, the symptoms may or may not be associated to the physical illness. However, regardless, they cause excessive and disproportionate levels of distress and a problematic quality of life. All symptoms are, by definition, subjective, and all disease occurs in, and is influenced by, a psychosocial context.

The chronic anxiety and psychosomatic symptoms, in palliative care, can involve and increase one or more different symptoms in organs and body systems, such as:

- Pain
- Anxiety
- Gastrointestinal complaints
- Urogenital symptoms
- Respiratory distress
- Cardiovascular symptoms
- Fibromyalgia
- Dermatological symptoms

Many people who have psychosomatic disorders in Palliative Care, will also have anxiety disorders. The distress patients experience from pain and other problems are real, regardless of whether or not a physical explanation can be found. The distress from symptoms significantly affects daily functioning, increasing the disability associated with their severe chronic illness. When there is a medical condition causing their symptoms, they may not recognize that the amount of distress they are experiencing or displaying is excessive. Patients may also dismiss any suggestion that psychiatric factors are playing a role in their symptoms.

We need to consider as psychosomatic symptom, the medical conditions that cause vague and diffuse signs. In addition, consider somatization as part of a mood for anxiety or chronic

stress' disorder in palliative care (Levenson, James L., 2006; Melmed, Raphael N., 2001).

Psychosomatic disorders may affect almost any part of the body, though they are usually found in systems not under voluntary control (Levenson, James L., 2006; Taunton OD, Roth J, Pastan I., 1969; Kulpa M, Ziętałewicz U, Kosowicz M, Stypuła-Ciuba B, Ziółkowska P., 2016; Park S, Hong JP, Lee JK, Park YM, Park Y, Jeon J, Ahn MH, Yoon SC., 2016; Choi KH, Park SM., 2016).

Commonly, we have to consider that the physical psychosomatic symptoms to threat:

- are correlates of stress and anxiety,
- may maintain stress and anxiety,
- are supported by an interplay of automatic (bottom-up) and controlled (goal-directed, top-down) processes.

In severe chronic illnesses with chronic anxiety and psychosomatic symptoms, we use psychological interventions as psychotherapy or clinical hypnosis (Fanmin Zeng, Xueli Sun, Bangxiang Yang, Hong Shen, Ling Liu, 2016).

The psychological treatment of pain, anxiety and related psychosomatic symptoms in severe chronic diseases and in Palliative Care

Treatment of psychosomatic symptoms in palliative care is difficult. It responds best to a psychologically oriented physician who is able and willing to take final responsibility and therapy for both physical and psychological care.

A strong doctor-patient relationship is key to getting help with psychosomatic symptoms. Seeing a single health care provider with experience managing symptoms can help cut down on unnecessary tests and treatments. The focus of treatment is on improving daily functioning, not on managing symptoms. Stress reduction is often an important part of getting better. Working in a multidisciplinary team should be the best way to cure the psychosomatic disorders in palliative care.

Cognitive symptoms can be alleviated with cognitive-behavioral therapy, and biological symptoms can be alleviated by medicines and local and systemic physical treatment.

It is worth noting that the methods intended to increase the knowledge of bodily symptoms from additional perspectives should vary from patient to patient and implement a diverse mode of thinking (Fanmin Zeng, Xueli Sun, Bangxiang Yang, Hong Shen, Ling Liu, 2016; Brown RJ., 2004; Fink P., 1966; Fava GA, Sonino N., 2000; Kroenke K, Spitzer RL, Williams JBW., 2002; Katon W, Kleinman A, Rosen G., 1982).

There have been few, if any, reported cures of this chronic condition. The therapeutic goal is to minimize unnecessary and

often deleterious medical interventions and to maximize the patient's quality of life. The patient is likely to continue to seek medical care from new providers unless enrolled in an ironclad system that prevents this behavior, and she is unlikely to accept a psychological explanation for her difficulties. It is sometimes possible to effect a successful referral to a mental health professional by emphasizing the emotional toll the disabilities are taking on the patient and the role of the mental health professional as an adjunct to the primary care provider (Filligim RB, Bruehl S, Dworkin RH, Dworkin SF, Loeser JD et Al., 2014; Kroenke K, Rosmalen JG., 2006; Kirmayer LJ, Robbins JM., 1991; IASP Classification of Chronic Pain). Understanding the pathophysiology of the psychosomatic symptoms in palliative care, aids in selection of treatment plans for correcting the negative effects of the psyche on specific body conditions. We know that the pharmacological options include standard opioids in cancer and other painkillers, psychotropic medications, alternative herbs and supplements. However, adjuvant other options include psychotherapies, biofeedback, cognitive-behavioral methods, hypnosis, meditation, progressive relaxation, acupuncture and many different types of holistic approaches (Shenefelt PD., 2010).

In addition to the pharmacological therapy used in any organ symptom and disease for other somatoform disorders, it is important to avoid addicting the patient to analgesics when it is possible, considering that in cancer very often patients need opioids for a complete pain relief. This concern should never deter physicians from providing adequate analgesia to acutely ill or patients at the end of life. There is a great deal of empirical evidence that such patients are widely denied appropriate pain relief. When in cancer the pain is improved by a psychosomatic problem, generally the single pharmacological therapy does not work, even if we use a high dosage of medicines and opioids. Pain clinics and departments, can be very useful in helping chronic pain patients to reduce the use of pharmacologic agents with adjuvant psychological and spiritual approaches that improve the quality of lives and give to the patient a better control of the pain (Bhatnagar S, Gupta M., 2016).

In palliative care, we have to consider that most cancer pain is caused by the tumor pressing on bones, nerves or other organs in the body. Sometimes pain is related to the cancer treatment: some chemotherapy drugs can cause neuropathic pain as numbness and tingling in the hands and feet or a burning sensation at the place where they are injected. Radiotherapy can cause skin redness and irritation. However, some pain may have nothing to do with the cancer.

Many patients suffering from pain and psychosomatic diseases associated to the chronic severe diseases, have a good response

to a combination of multicomponent adjuvant treatments, psychotherapies, and hypnosis. In less severe cases, patients can learn to manage stress without drugs, for example with self-hypnosis (Hök J, Tishelman C, Ploner A, Forss A, Falkenberg T., 2008; Brugnoli MP, 2014).

The Psychosocial and Psychological interventions, consist of a variety of therapies related to the very different symptoms.

Clinical Hypnosis and self-hypnosis for pain, anxiety and psychosomatic symptom relief in severe chronic diseases and in Palliative care

Specific objectives and hypotheses

Hypnosis has many useful psychosomatic applications in pain and anxiety relief in severe chronic diseases. Medical hypnotherapy involves guiding the patient into a trance state of narrowed awareness, focused attention, selective wakefulness, and heightened suggestibility for a specific purpose such as relaxation, pain reduction, or habit modification. The hypnotic trance compared with the usual waking state has objectively documented differences in regional cerebral blood flow (Rainville P, Hofbauer RK, Bushnell MC, et al., 2002) and EEG (Freeman R, Barabasz A, Barabasz M, Warner D., 2000) patterns. One way that hypnosis may make suggestions more effective is by inhibiting competing thoughts so that the focus can be solely on the suggestion (Barrios AA., 2009). Hypnosis may improve or clear numerous psychosomatic disorders (Brugnoli MP, 2014a; Shenefelt PD., 2008; Willemsen R, Vanderlinden J, Deconinck A, Roseeuw D., 2006).

Hypnosis is a therapeutic technique in which clinicians make suggestions to individuals who have undergone a procedure designed to relax them and focus their minds. Although hypnosis has been controversial, most clinicians now agree it can be a powerful, effective therapeutic technique for a wide range of conditions, including pain, anxiety and mood disorders (APA Division 30).

Clinical hypnosis in Pain Therapy and Palliative Care refers to the conscious calm awareness of cognitions, sensations, emotions and experiences.

The stages of hypnosis used in severe chronic illnesses and palliative care, are frequently achieved also through mindfulness and meditative states, which are practices that cultivate non judgmental awareness of the present moment.

Clinical hypnosis in palliative care, derives from as a mental factor it signifies presence of mind, attentiveness to the present, rather than the faculty of memory regarding the past. It has the

characteristic of not wobbling, not floating away from the object. Its function is absence of confusion or non-forgetfulness (Brugnoli MP, 2014; Montgomery et al., 2007, 2010; Lioffi C, Hatira P., 1999).

It is manifested as guardianship, or as the state of confronting an objective field. Its proximate cause is strong perception, and inner awareness.

Hypnosis is defined as an agreement between a person designated as the health-care hypnotist and a person designated as the patient to participate in a psychotherapeutic technique in which the hypnotist provides suggestions for changes in sensation, perception, cognition, affect, mood, or behavior (Montgomery et al., 2007, 2010). Hypnosis has documented efficacy in a variety of conditions such as mental health disorders, smoking cessation, obesity, pain reduction, anxiety, and nausea and vomiting (Deng et al., 2009; Elkins et al., 2004, 2008, 2010; Monti D et Al, 2006, 2007, 2008; Lang Elvira V, Berbaum Kevin S, Pauker Stephen G, Faintuch Salomao, Salazar Gloria M, Lutgendorf Susan, Laser Eleanor, Logan Henrietta, Spiegel David., 2008).

Optimal results are achieved by a trained therapist who has developed a good rapport and a strong level of trust with the patient. A comfortable environment, free of distraction, is needed, and the patient must be willing to undergo the procedure (Cassileth et al., 2007).

The neural correlates of Clinical Hypnosis

Mind-body interventions (MB), s clinical hypnosis, are practices that focus on the interactions among the brain, body, mind, and behavior, with the intent of using the mind to alter physical function and promote overall health (Elkins, Fisher, & Johnson, 2010). Mind-body approaches should be part of a multidisciplinary approach and aimed at reducing anxiety, mood disturbance, pain and improving QOL (Deng et al., 2009).

Understandably, a diagnosis of cancer can generate feelings of helplessness and hopelessness and is associated with a myriad of psychosocial difficulties. Understanding and assisting patients with appropriate MB interventions can enhance the provider-patient relationship, improve symptoms, and enable patients to assign meaning to their experience.

Hypnotic treatment in severe chronic diseases, for pain and symptoms relief, has proven efficacy as adjuvant therapy, and should be offered to any individual, who expresses an interest in this method. While some theorize hypnotizability as a changing attribute of the individual, there is a growing body of literature that indicates hypnotizability may be characterized as a constellation of potentially modifiable attitudes and skills, which

are strongly influenced by related factors, as suffering, in severe chronic diseases.

Consciousness has many aspects. These include awareness of the world, feelings of control over one's behaviour and mental state (volition), and the notion of continuing self. Focal (executive) attention is used to control details of our awareness and is thus closely related to volition.

The problem of consciousness involves many difficult and overlapping issues (Block 1995; Posner 1994). Perhaps the most frequently discussed role of consciousness involves awareness of our sensory world. Another aspect of consciousness is the fact or illusion of voluntary control. In the course of development, a central issue is the awareness of one's self, and another is the form of voluntary control involved in self-regulation. These functions develop within the dyad involving the child and the caregiver as a carrier of the culture's socialization process. It is possible, even likely, that brain mechanisms subserving these various forms of consciousness may cut across definitions in ways that defy the usual logical and philosophical distinctions. Clinical Hypnosis research binds phenomenology and neuroscience (Lifshitz M, Cusumano EP, Raz A., 2013).

Most researchers leverage bottom-up suppression to unlock the underlying mechanisms of unconscious processing. However, a top-down approach – for example via hypnotic suggestion – paves the road to experimental innovation and complementary data that afford new scientific insights concerning attention and the unconscious (Mathieu Landry, Krystèle Appourchaux, Amir Raz, 2014).

Hypnosis selectively targets and modifies perception of sensory events. For example, it can modify the perception of the colors (Kosslyn et al., 2000; Mallard and Bryant, 2001; Spiegel, 2003; McGeown et al., 2009; Kallio and Koivisto, 2013; Koivisto et al., 2013; Mathieu Landry, Krystèle Appourchaux, Amir Raz, 2014), induce compelling experiences of grapheme-color synesthesia – a condition characterized by perceptual experiences of anomalous combinations of cross-modal sensations (Cohen Kadosh et al., 2009; Anderson et al., 2014), and even temporarily abolish co-occurrences of secondary sensory experiences in synesthetes (Terhune et al., 2010).

Indicating the reliability and sustainability of these remarkable changes, hypnotically induced alteration of color perception correlates with corresponding modifications in neural response (Kosslyn et al., 2000; McGeown et al., 2012). Specifically, neuroimaging results of hypnotically induced altered perception show modulation of brain regions associated with color processing – i.e., bilateral fusiform gyrus, primary visual area

(Kosslyn et al., 2000; McGeown et al., 2012; Mathieu Landry, Krystèle Appourchaux, Amir Raz, 2014).

We can use this properties of hypnosis on perceptions, to modulate acute and chronic pain.

Hypnotic suggestions allow researchers to generate and study atypical experiential states that would otherwise prove unstable, rare, or short-lived. One fruitful approach employs hypnotic suggestions to produce “virtual patients” with transient syndromes nearly identical to genuine clinical psychopathologies in terms of experiential substrates and in some cases also neurobiological correlates (Oakley and Halligan, 2009; Woody and Szechtman, 2011; Lifshitz M, Cusumano EP, Raz A., 2013).

Clinical hypnosis offers insight into spontaneous cognition and the resting brain. Contemplative practices including hypnosis are emerging as valuable tools for investigating the default-mode—a network of brain regions that show increased activity at rest. Default-mode network (DMN) activity correlates with a wide range of internally directed cognitive processes, including mind-wandering, self-oriented thinking, moral reasoning, and episodic memory (Buckner et al., 2008); yet, it is difficult to experimentally manipulate the DMN alongside these processes because the defining feature of the DMN is that it activates spontaneously, in the absence of external task demands.

Accordingly, in the past few years, researchers have begun employing contemplative practices in concert with intrinsic connectivity imaging methods to elucidate the psychological correlates of resting-state brain networks such as the DMN (e.g., McGeown et al., 2009; Brewer et al., 2011; Pyka et al., 2011; Hasenkamp et al., 2012; Pagnoni, 2012; Taylor et al., 2013). Following this approach, a recent study reported that hypnotic induction increased subjective ratings of attentional absorption and decreased ratings of mind-wandering.

Moreover, these changes were associated with decreased DMN activity and increased activity in prefrontal attention networks (Deeley et al., 2012). Another recent account leveraged a similar neurophenomenological approach to show that subjective ratings of hypnotic depth following an induction were associated with changes in global functional connectivity in the electroencephalography signal. Furthermore, differences in subjective experiential dimensions such as “imagery,” “everyday concerns,” and “vestibular and other bodily experiences” were associated with distinct patterns of connectivity (Cardena et al., 2013).

These studies illustrate how manipulating the experiential state of the subject while collecting subjective reports can not only enrich and even guide the investigation of brain networks, but

also their psychological correlates in therapy (Lifshitz M, Cusumano EP, Raz A., 2013).

Although hypnosis typically involves suggestions emphasizing specific, and often unusual, behaviors or perceptual experiences, as visualizations for pain and anxiety relief.

The defining feature of hypnosis is the flexibility it affords for modulating aspects of consciousness, rather than one particular state of attention that it induces. Indeed, numerous cognitive and neuroimaging reports have documented the power suggestion wields over attention functions and associated brain networks (Egner et al., 2005; Raz et al., 2005; Iani et al., 2006, 2009; Priftis et al., 2011; Raz and Campbell, 2011; Terhune et al., 2011). Such potent subjective alterations could potentially be adapted to derail habitual patterns of conceptual judgment and support non-judgmental meta-awareness of the present moment. Investigators have already begun experimenting with using suggestion-based approaches to foster states of mindful meta-awareness for therapeutic psychological purposes (Lynn et al., 2006, 2010).

One might object that because hypnotic procedures generally involve deep relaxation and mental absorption (Rainville and Price, 2003).

Multiple experiments have demonstrated that attention, expectation and hypnosis may influence information processing in the human brain (Kosslyn, Thompson, Costantini-Ferrando, Alpert, & Spiegel, 2000; Raz, 2004b; Raz & Buhle, 2006; Raz, Fan, & Posner, 2005; Raz et al., 2003b; Raz, Shapiro, Fan, & Posner, 2002; Wager et al., 2004). Both endogenous, top-down control, and exogenous, bottom-up capture of attention, enhance performance by affecting relative increases in neural activity in a given sensory system (Raz & Buhle, 2006).

“Hypnosis typically involves an introduction to the procedure during which the subject is told that suggestions for imaginative experiences will be presented. The hypnotic induction is an extended initial suggestion for using one’s imagination, and may contain further elaborations of the introduction. A hypnotic procedure is used to encourage and evaluate responses to suggestions. When using hypnosis, one person (the subject) is guided by another (the hypnotist) to respond to suggestions for changes in subjective experience, alterations in perception, sensation, emotion, thought or behavior. Persons can also learn self-hypnosis, which is the act of administering hypnotic procedures on one’s own.” (APA Division 30: Green, J.P., Barabasz, A.F., Barrett, D., & Montgomery, G.H., 2005).

Hypnotherapy is a form of psychotherapy used to create unconscious change in the patient in the form of new responses, thoughts, attitudes, behaviors or feelings. It is undertaken with a subject in hypnosis.

In the 1950s, the psychiatrist Milton H. Erickson developed a radically new approach to hypnotism, which has subsequently become known as "Ericksonian hypnotherapy". Erickson made use of an informal conversational approach with many clients and complex language patterns, and therapeutic strategies (Grinder J., Bandler R., 1976).

In 1974, Theodore Barber and his colleagues published an influential review of the research which argued, following the earlier social psychology of Theodore R. Sarbin, that hypnotism was better understood not as a "special state" but as the result of normal psychological variables, such as active imagination, expectation, appropriate attitudes, and motivation (Barber, T. X., Spanos, N. P., Chaves, J. F., 1974).

Barber introduced the term "cognitive-behavioral" to describe the nonstate theory of hypnotism, and discussed its application to behavior therapy.

The Cognitive behavioural hypnotherapy (CBH) is an integrated psychological therapy employing clinical hypnosis and cognitive behavioural therapy (CBT) (Robertson D., 2012).

The use of CBT in conjunction with hypnotherapy may result in greater treatment effectiveness. A meta-analysis of eight different researches revealed "a 70% greater improvement" for patients undergoing an integrated treatment to those using CBT only (Kirsch I., Montgomery G., Sapirstein G., 1995).

In 1995, the US National Institutes of Health (NIH), established a Technology Assessment Conference that compiled an official statement entitled "Integration of Behavioral & Relaxation Approaches into the Treatment of Chronic Pain & Insomnia".

This is an extensive report that includes a statement on the existing research in relation to hypnotherapy for chronic pain. It concludes that: 'The evidence supporting the effectiveness of hypnosis in alleviating chronic pain associated with cancer seems strong. In addition, the panel was presented with other data suggesting the effectiveness of hypnosis in other chronic pain conditions, which include irritable bowel syndrome, oral mucositis (pain and swelling of the mucus membrane), temporomandibular disorders (jaw pain), and tension headaches.' (NIH, 1995).

In 2001, the Professional Affairs Board of the British Psychological Society (BPS) commissioned a working party of expert psychologists to publish a report entitled *The Nature of Hypnosis* (The British Psychological Society, 2001). Its remit was 'to provide a considered statement about hypnosis and important issues concerning its application and practice in a range of contexts, notably for clinical purposes, forensic investigation, academic research, entertainment and training.'

The report provides a concise (c. 20 pages) summary of the

current scientific research on hypnosis. It opens with the following introductory remark:

- 'Hypnosis is a valid subject for scientific study and research and a proven therapeutic medium.'

With regard to the therapeutic uses of hypnosis, the report said:

- 'Enough studies have now accumulated to suggest that the inclusion of hypnotic procedures may be beneficial in the management and treatment of a wide range of conditions and problems encountered in the practice of medicine, psychiatry and psychotherapy.'

In 2007, a meta-analysis of the efficacy of hypnotherapy was published by Flammer E. and Alladin A.: they discovered that Hypnotherapy is claimed to be effective in treatment of psychosomatic disorders. A meta-analysis was conducted with 21 randomized, controlled clinical studies to evaluate efficacy of hypnosis in psychosomatic disorders. Studies compared patients exclusively treated with hypnotherapy to untreated controls. Studies providing adjunctive standard medical care in either treatment condition were also admitted. Hypnotherapy was categorized into classic (n = 9), mixed form (n = 5), and modern (n = 3). Results showed the weighted mean effect size for 21 studies was $d (+) = .61$ ($p = .0000$). Regression of outcome on treatment dose failed to show a significant relationship.

Numerical values for correlation between suggestibility and outcome were only reported in three studies (mean $r = .31$). The meta-analysis clearly indicates hypnotherapy is highly effective in treatment of psychosomatic disorders.

Results of scientific studies demonstrate that hypnosis is an effective and efficient means of developing the resources of people suffering from serious illness (Handel DL., 2001, 2008, 2010). After an average of few hypnotherapy sessions in Palliative Care, patients are able to locate previously unexploited resources within themselves and are able to become autonomous in the use of self-hypnosis. The major benefit reported concerned a reduction in anxiety (Teike Luethi F, Currat T, Spencer B, Jayet N, Cantin B., 2012; Brugnoli M.P., 2014).

Clinical hypnosis in palliative care is indicated for patients with any serious illness and who have physical, psychological, social, or spiritual distress as a result of the treatment they are seeking or receiving (Brugnoli M.P., 2014; Handel DL., 2001).

Clinical Hypnosis in Palliative Care

Palliative care is the specialized medical care for people with serious illnesses. It focuses on providing patients with relief from the symptoms, pain, and stress of a serious illness, whatever the diagnosis.

Palliative medicine utilizes a multidisciplinary approach in patient care to relieve pain and symptoms (American Academy of Hospice and Palliative Medicine, 2013; Delgado-Guay, M. O.; Parsons, H. A.; Li, Z.; Palmer, L. J.; Bruera, E., 2009).

In the past decade, there has been a dramatic increase in the number and quality of research studies examining effects of clinical hypnosis on pain and anxiety.

Specifically, clinicians treating patients with chronic pain in Palliative Care should:

- include hypnotic suggestions that impact all of the neurophysiological processes that may underlie a patient's pain;
- include suggestions that impact other key quality of life domains (e.g., anxiety, sleep quality, relief from nausea in chemotherapy);
- train patients in the use of self-hypnosis to achieve immediate pain relief;
- provide audio recordings of treatment sessions to enhance treatment effects

We perceive pain, anxiety and suffering as separate entities.

The physical, anatomic, and neurochemical expression of pain is treated by physical therapy, medicines, nerve block, electric stimulators, and surgery.

The suffering component involves the patient's

- (1) nonacceptance,
- (2) fear of the unknown and anxiety,
- (3) pessimistic evaluation of the meaning of pain and depression,
- (4) feeling of no time limit to suffering, and
- (5) often self-destructive feelings of guilt and resentment.

These emotions and imaginings are quite amenable to good hypnotherapy. When suffering is removed, pain tends to become tolerable or may even disappear (Ewin DM., 1978, 1992, 2001).

Clinical Hypnosis provides relief from pain, anxiety and other distressing symptoms.

Several reviews and systematic research studies confirm that psychological interventions and clinical hypnosis are efficacious in the treatment of acute and chronic pain (Vannoni S., Brugnoli A., 1971; Brugnoli A. 1974a, 1974b; Ewin DM., 1978, 1992, 2001), in disability and cancer-related pain (Spiegel and Bloom,

1983; Jensen, Hanley, Engel, Romano, Barber, Cardenas et al., 2005).

For both chronic and acute pain conditions:

(1) hypnotic analgesia consistently results in greater decreases in a variety of pain outcomes compared to no treatment/standard care;

(2) hypnosis frequently out-performs non-hypnotic interventions (e.g. education, supportive therapy) in terms of reductions in pain-related outcomes; and

(3) hypnosis performs similarly to treatments that contain hypnotic elements (such as progressive muscle relaxation), but is not surpassed in efficacy by these alternative treatments (Stoelb BL, Molton IR, Jensen MP, Patterson DR., 2009; Patterson DR, Jensen MP, Wiechman SA, Sharar SR., 2010).

The brain imaging studies are demonstrating the neurophysiological changes that can and do occur as a result of hypnotic analgesia treatment. Studies using fMRI and PET scan technology have revealed that a number of brain structures involved in the perception of pain (e.g. somatosensory cortex, anterior cingulate cortex, insula) are demonstrably affected through hypnotic suggestion (Rainville, Duncan, Price, Carrier, and Bushnell, 1997; Hofbauer, Rainville, Duncan and Bushnell, 2001; Derbyshire, Whalley, Stenger and Oakley, 2004).

Many common potential problems can arise in chronic illnesses and during the last days and hours of a patient's life (Strang P., Strang S., Hultborn R., Arnér S., 2004).

Suffering from uncontrolled pain is a significant fear of those with chronic illnesses and at end of life (Agency for Healthcare Research and Quality, 2013).

We can consider clinical hypnosis as an adjuvant for pharmacological therapies, in pain therapy (Brugnoli M.P., 2014).

Pain is a serious health care problem and there is increasing evidence to support the use of hypnosis for pain management. Clinical Hypnosis is efficacious for managing chronic pain and hypnosis interventions consistently produce significant decreases in pain associated with a variety of chronic-pain problems. Also, hypnosis is generally found to be more effective than nonhypnotic interventions such as attention, physical therapy, and education. Most of the hypnosis interventions for chronic pain include instructions in self-hypnosis (Brugnoli M.P., 2014; Adachi T, Fujino H, Nakae A, Mashimo T, Sasaki J., 2014; Elkins G, Jensen MP, Patterson DR., 2007; Elkins G, Johnson A, Fisher W., 2012).

Anxiety is addressed as a special form of mind/body problem involving deep interaction between mental and physical distress in chronic illnesses.

The scientific researches suggest that for those who experience significantly impairing and/or distressing anxiety, it often goes undertreated (Otto MW, Smits JA, Reese HE., 2004).

Hypnosis and self-hypnosis training represents a rapid, cost-effective, and safe adjuvant or alternative to medication for the treatment of anxiety-related conditions (Hammond DC., 2010; Untas A, Chauveau P, Dupré-Goudable C, Kolko A, Lakdja F, Cazenave N., 2013).

Cognitive hypnotherapy, is applied to the treatment of anxiety disorders (Golden WL.,2012).

Rapid and sustained relief of severe anxiety is necessary to achieve comfort at the end of life: skilled additions of psychological therapies as clinical hypnosis with breathing exercises, and combined pharmacotherapy, led to control of anxiety (Udo I. Gash A., 2012).

The dying process is characterized by feelings of sadness and fear. It is normal for patients at the end of life to worry and grieve the loss of their health. However, when these feelings become excessive and interfere with all aspects of the patient's life, they are abnormal responses to the stress of terminal illness. Depression in chronic illnesses and in Palliative Care, is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings and sense of well-being (Salmans, S.,1997).

Depressed people feel sad, anxious, empty, hopeless, worried, helpless, worthless, guilty, irritable, hurt, or restless. They may lose interest in activities that once were pleasurable, experience loss of appetite or overeating, have problems concentrating, remembering details, or making decisions, and may contemplate, attempt, or commit suicide.

Insomnia, excessive sleeping, fatigue, loss of energy, or aches, pains, or digestive problems that are resistant to treatment may also be present (NIMH, 2012).

Screening for depression in terminally ill patients can optimize their physical comfort at the end of life and provide them the opportunity to confront and prepare for death (Braun UK, Kunik ME, Pham C., 2008).

The core issue regarding antidepressants for many clinicians is whether they perform significantly better than placebos.

However, The enhanced effects of psychotherapy utilizing hypnosis offer a means of avoiding most, if not all, of the problems associated with the use of antidepressants as a primary form of treatment (Yapko MD., 2013; Frischholz EJ., 2013; Lankton S.,2013).

Alladin A, and Alibhai A., (2007), to investigate the effectiveness of cognitive hypnotherapy (CH), hypnosis combined with cognitive-behavioral therapy (CBT), on depression, studied 84 patients with depression: they were

randomly assigned to 16 weeks of treatment of either CH or CBT alone. At the end of treatment, patients from both groups significantly improved compared to baseline scores. However, the CH group produced significantly larger changes in Beck Depression Inventory, Beck Anxiety Inventory, and Beck Hopelessness Scale. The effect size was maintained at 6-month and 12-month follow-ups. This study represents the first controlled comparison of hypnotherapy with a well-established psychotherapy for depression, meeting the APA criteria for a "probably efficacious" treatment for depression (Alladin A., Alibhai A., 2007).

Evidence-based strategies, including hypnosis, are studied in the context of cognitive hypnotherapy for depression, to illustrate how expectancy effect can be maximized in psychotherapy and clinical hypnosis (Alladin A., 2013).

During the final months of the life pain, anxiety, depression, fatigue, loss of appetite, dependency and feeling unwell are the most prevalent symptoms. Physical symptoms are more often treated than psychosocial symptoms. The number of medical disciplines involved in the patient's care decreased in the period before death, but the number of informal caregivers increased: many patients die peacefully (Georges JJ, Onwuteaka-Philipsen BD, van der Heide A, van der Wal G, van der Maas PJ., 2005). Relief of cancer-related symptoms is essential in the supportive and palliative care of cancer patients and in chronic illnesses. While apparently not painful for the patient, the association of the symptoms in severe chronic illnesses with impending death can create fear and uncertainty for those at the bedside.

Nausea is a sensation of unease and discomfort in the upper stomach with an involuntary urge to vomit. It often, but not always, precedes vomiting. A person with chronic disease can suffer nausea and/or vomiting.

Nausea is a non-specific symptom, which means that it has many possible causes. Some common causes of nausea are motion sickness, dizziness, headache, fainting, gastroenteritis (stomach infection), or the side effects of many medications including cancer chemotherapy. Nausea may also be caused by anxiety, and depression. Typically, it is controlled using cyclizine; or other anti-emetics. In addition to nausea and vomiting following chemotherapy treatment, cancer patients can experience these side effects prior to a treatment session, the so-called anticipatory nausea and vomiting.

Richardson, Smith, McCall, Richardson, Pilkington, and Kirsch (2007) systematically reviewed the research evidence on the effectiveness of hypnosis for cancer chemotherapy-induced nausea and vomiting (CINV). A comprehensive search of major biomedical databases including MEDLINE, EMBASE, CINAHL, PsycINFO and the Cochrane Library was conducted.

Specialist complementary and alternative medicine databases were searched and efforts were made to identify unpublished and ongoing research. Citations were included from the databases' inception to March 2005. Randomized controlled trials (RCTs) were appraised and meta-analysis undertaken. Clinical commentaries were obtained. Six RCTs evaluating the effectiveness of hypnosis in CINV were found. In five of these studies the participants were children. Studies report positive results including statistically significant reductions in anticipatory and CINV. Meta-analysis revealed a large effect size of hypnotic treatment when compared with treatment as usual, and the effect was at least as large as that of cognitive-behavioural therapy. Meta-analysis has demonstrated that hypnosis could be a clinically valuable intervention for anticipatory and CINV in children with cancer.

The scientific experience highlights the potential value of hypnosis in the management of anticipatory nausea and vomiting in chemotherapy; furthermore, the susceptibility to anticipatory nausea and vomiting is discussed under the psychoanalytic point of view (Marchioro G, Azzarello G, Viviani F, Barbato F, Pavanetto M, Rosetti F, Pappagallo GL, Vinante O., 2000).

Adverse effects of chemotherapy can be severe and can have a significant impact on a person's quality of life.

With chemotherapy treatment increasingly administered in the ambulatory setting, there is a need for patients to be informed about effective self-care strategies to manage treatment adverse effects. Relevant studies published in peer-reviewed journals between 1980 and August 2007 was conducted to identify self-care strategies for reducing nausea/vomiting, constipation, diarrhea, fatigue, dyspnea. They recognized reasonable quality of nonpharmacologic strategies for managing common chemotherapy adverse effects, as cognitive distraction, exercise, hypnosis, relaxation, and systematic desensitization to reduce symptoms in cancer (Lotfi-Jam K, Carey M, Jefford M, Schofield P, Charleson C, Aranda S, 2008; Syrjala KL, Cummings C, Donaldson GW., 1992).

Hypnotherapy in palliation, can be useful in the management of anxiety, discomfort, and psychosomatic symptoms, all of which may contribute to a complaint of dyspnea.

The case illustrates the strength of hypnosis for accessing resources outside of conscious awareness and use of dissociative language to both support and alter the patient's defenses (Anbar RD, Linden JH., 2010).

The focus of the hypnotherapy in Palliative Care, is to ameliorate the effects of pain and anxiety to restore a level of psychological and physical wellbeing (Marcus J, Elkins G, Mott F., 2003).

The Research aims

Hypnosis offers the possibility to create a strong therapeutic alliance between the caregiver and the patient, an alliance characterized by motivation, trust, and collaboration. Motivation is based on the desire the patient has to feel better, to reach a comfort zone, to find his/her own resources to face death; trust is reached as soon as the patient experiences the benefits of hypnotic suggestions and self-hypnosis; the collaboration with the hypnotist is a natural answer of gratitude and recognition for the physical and psychological benefits.

The specific aims of this study are:

1. to measure of hypnosis's influence and efficacy, as an adjuvant therapy, on pain in severe chronic diseases and in Palliative Care
2. to measure of hypnosis's influence and efficacy, as an adjuvant therapy, on anxiety symptoms in severe chronic diseases and in Palliative Care
3. to measure of hypnosis's influence and efficacy, as an adjuvant therapy, on the use of opioids in severe chronic diseases and in Palliative Care
4. to demonstrate reliability and validity of the effectiveness of the use of hypnosis, and self-hypnosis to relief pain and anxiety in severe chronic illnesses and in Palliative Care for a long term follow-up (1 year and 2 years).

CHAPTER 2

MATERIALS AND METHODS

Description of Study Design: Nonrandomized Clinical Trial

Type of study: Research on primary data with a long-term follow-up

This is a long term follow-up of treatment in a prospective observational non-randomized controlled study.

We have enrolled in our study the patients with these severe chronic diseases:

1. Cancer
2. Neurological severe chronic diseases
3. Rheumatologic severe chronic diseases

All the patients enrolled in our study were diagnosed by the colleagues' specialists for these particular diseases.

The patients were enrolled in 2 groups:

1. The group with the intervention of hypnosis and self-hypnosis as adjuvant therapy, added to the pharmacological therapy
2. The group with no hypnosis intervention had only the pharmacological therapy

The patients of the 2 groups, were all cured with the pharmacological therapy, and the group hypnosis with clinical hypnosis as adjuvant therapy, added to the pharmacological therapy, from the same physicians and pain therapist Dr. Maria Paola Brugnoli, Specializations in Anesthesia and Critical Care, Pain Therapy and Palliative Care, Hypnotherapist, at the Department of Anesthesia, Intensive care and Pain Therapy, University of Verona, Italy. The group Hypnosis had 2 therapist for the hypnosis interventions: Dr. Brugnoli (the principal

investigator) and Dr. Emanuela Pasin, Psychologist, Psychotherapist and Hypnotherapist, to avoid bias about administration and procedures about hypnosis and follow-up. When we enrolled the patients, we would have liked to organize a randomized study, but it was impossible to organize, because some patients asked to add clinical hypnosis to their therapies, to have a better quality of life; other patients would not use hypnosis because they have fear. This was a clinical research with very suffering people in palliative care, and not with volunteers, so we have decided that patients could choose the group.

Study Population

The setting where the patients were cured and studied was the Department of Anesthesiology, Intensive Care and Pain Therapy, at the University of Verona, Verona, Italy, Director Professor Enrico Polati.

We cured the outpatients referring to the Pain Therapy Ambulatory.

Eligibility Criteria For Participants

Inclusion criteria

- Gender: both female and male participants are being studied
- Age Limits: Minimum Age 18; maximum age no limits
- Severe chronic disease: For both the 2 groups the patients must have a severe chronic disease:
 1. Cancer (C)
 2. Chronic Neurological diseases (ND)
 3. Chronic Rheumatological diseases (CRD)
- All the patients of the 2 groups, are cured as outpatient at the Department of Anesthesia, Intensive Care and Pain Therapy, for chronic pain, only with a pharmacological therapy by the same physician: dr. Maria Paola Brugnoli.
- All the patients of the 2 groups are only partially responder to conventional pharmacological therapies, but they do not want to increase the use of medicines. They do not want use anxiolytics for different motivations (as to drive the car, or to be always perfectly aware).
- Chronic pain: where they were affected with Chronic pain and intensity VAS (0-100) = > 40
- Anxiety: where they were affected by anxiety evaluated by the Hamilton Anxiety Scale (0-30)

where they were affected with a score of 1-30, indicates mild, severe or less anxiety.

- Patients must not have diagnosed severe cognitive disorders
- Patients must not have diagnosed major psychiatric disorders, as schizophrenia
- Patients enrolled in the group of hypnosis have to attend at least the 50% of the meeting on hypnosis techniques (they had to sign their attendance)
- Patients enrolled in the 2 groups have the same type of pain: muscular pain, visceral pain and osteoarthritis pain, but not neuropathic pain (see exclusion criteria).

Exclusion criteria

- Children: age < 18 years
- Patients with cognitive disorders
- Patients with major psychiatric disorders as schizophrenia
- Patient can be enrolled in the two groups only if they use only a pharmacological therapy with Opioids, NSAIDS and/or Corticosteroids
- Patients cannot be enrolled if they use Antidepressants, Anxiolytics or Antiepileptics, because they could be bias for the study of anxiety.
- Patients cannot be enrolled if they suffer for neuropathic pain, for the use of Antidepressants or Antiepileptics, because they could be bias for the study of anxiety.
- Patient cannot be enrolled if they use other therapies than only medicines as: psychotherapy, anesthesiological blocks, acupuncture, mesotherapy (they could be bias to study pain and anxiety).
- Patients with less than 1 year expectation of life (one of the aim of the study is a long-term follow-up) (however, even if some patients were not enrolled in the study, they could have attended the hypnosis' sessions).
 - Inability to perform informed consent

Justification for the exclusion of Minors: Subjects under 18 years of age are excluded because the adjustment processes of children and adolescents are demonstrably dissimilar from those of adults, and because of these marked differences in coping and resilience patterns, psychosocial research generally does not combine work on children and adults in the same study.

The recruitment procedure

We would have organized a randomized study, but some patients would have liked to learn hypnosis, and some other would not,

because they had fear of hypnosis. Some other patients could not attend the hypnotic sessions due to their work.

We decided to organize a nonrandomized clinical trial.

This is a clinical trial in which the participants are not assigned by chance to different treatment groups. Participants may choose which group they want to be in: this is an ethical choose of the authors, considering that all patients have severe chronic illnesses and some of them are at the end of life. Although randomization is preferable because it helps to control for factors other than the intervention that may be responsible for differences in outcomes, non-randomized assignment may be necessary when randomization is not feasible or ethical.

The specific purpose of this sequential clinical trial is to continuously compare the two treatments (group with hypnosis as adjuvant therapy and group without hypnosis) as data becomes available after the follow-up (1 and 2 years).

The effect of the intervention is evaluated by comparing the group of subjects receiving a standard pharmacological intervention (control group) to the group receiving hypnosis as adjuvant therapy added to the pharmacological intervention.

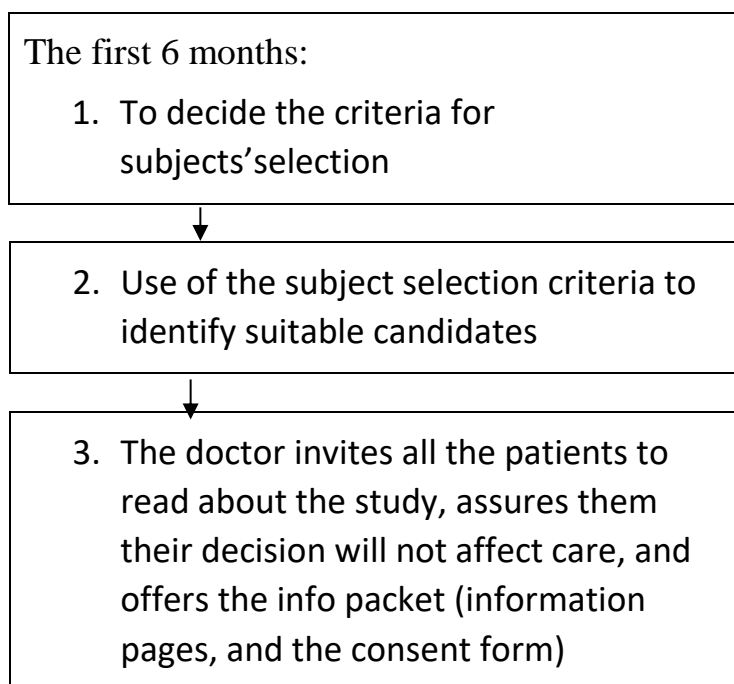
This study started on January 2014.

The first six months, we enrolled 76 patients with severe chronic illnesses and in Palliative Care.

Only 56 entered in the inclusion criteria, and 6 declined to participate to the study.

We have studied 50 patients, divided in 2 groups (hypnosis and non hypnosis- the control group)

Table 1: The Recruitment Procedure



During the Phase 1 of the research program and recruitment, potential subjects have been given a packet that contains:

- Introduction (first page of packet) and information
- Informed consent – on white paper
- Subject contact sheet (for the subject's contact information) – on white paper
- Written interview questionnaires (VAS and HAMA)
- Information on how to complete the questionnaires by section
- Where they can complete questionnaire and where to place completed packet

Steps by subject – After informed consent, instructions to subjects for maintaining confidentiality are provided. Subject consideration, recruitment, screening, and full participation in this study are without preference for race, socio-economic level, or gender.

The Informed consent

The Informed consent provides all the important information about the study, so that potential participants can decide whether to enroll (or, if enrolled, to continue participating). Ensures that potential participants understand there are no risks and potential benefits of participating in the study. Stress that enrolling in (and staying in) a clinical study is completely voluntary. Because giving consent to participate in research is not a contract, participants can leave a study at any time. The researcher and the potential participants had discussions that included answering the participant's questions about the research. Participants of the two groups (hypnosis and no hypnosis) must be aware that they are free to limit their participation in the research study, or withdraw their participation altogether at any time. If there is an item on a questionnaire that the participant does not want to answer because it makes them feel uncomfortable, they are free to skip it. If there is an aspect of the treatment that they do not feel comfortable with, they are free to sit out. Furthermore, if the research study is making them uncomfortable, they are free to quit the study.

All the important information about the study have also be given to the potential participant in a written document that is clear and easy to understand. All the patients signed the informed consent document to be enrolled in the study. This research study does not provide pharmacological intervention, added to the medicines the patients take at the time of their recruitment. Participants also had the fundamental right of privacy.

Confidentiality means that participants' responses was only be seen by researchers who are directly involved in the study. Data and safety of data will be monitored by the Principal Investigator PI (Dr. Maria Paola Brugnoli). All surveys will be de-identified and assigned a unique ID number prior to being entered into the data base. De-identified questionnaires will be retained in a locked file. A memorandum of understanding will be executed by the principal investigator.

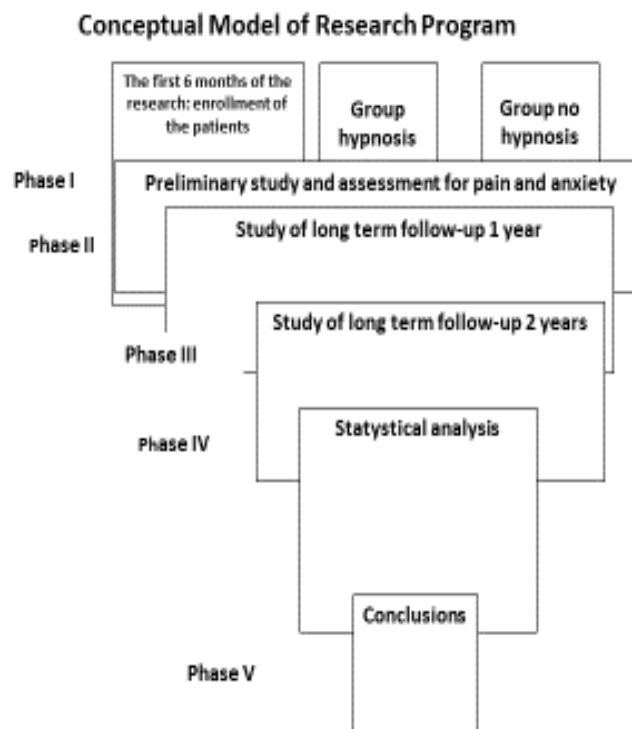


Table 2: the Conceptual model of the research program

The Study Design

We have organized 2 groups of 25 patients each, with severe chronic illnesses, evolving in pain, anxiety and anxiety-related symptoms.

All the patients of the 2 groups, were cured as outpatients afferring to the Pain Therapy Ambulatory, with conventional pharmacological therapy (FANS and/or opioids) by dr. Maria Paola Brugnoli, Anesthesiologist, Pain therapist and hypnotherapist at University of Verona, Department of

Anesthesiology, Intensive Care, and Pain Therapy, Hospital GB. Rossi, Verona, Italy.

The conventional pharmacological therapy of the group of hypnosis, was added with the hypnosis' adjuvant therapy, utilizing the group therapy with direct and indirect clinical hypnosis and self-hypnosis, by metaphors and relaxing musical video. This methodology to teach hypnosis, is conducted by Dr. Maria Paola Brugnoli (PI), with the assistance of Dr. Emanuela Pasin, Psychologist, and Dr. Maria Francesca Basile, Psychologist, that assisted dr Brugnoli during the assessment of the surveys, the follow-up and to organize the meeting to teach hypnosis to the patients.

The training for this protocol for the assistant researcher included:

- General information about the purpose and the protocol of the study. This is important so the research assistants could appropriately handle any problems that might come up in the study.
- The importance of following the directions exactly to avoid unnecessary error in the research study.
- An overview of what the instruments are measuring. Like understanding the purpose of the study, understanding the purpose of the instrument helped the research assistants answer unexpected questions during the study.
- A detailed review of the protocol.
- A demonstration of how the research procedures should be carried out.
- The research assistant had an opportunity to practice the procedures.

At the beginning of the study, all the Participants in the treatment group attended a 2 hours workshop with the Principal investigator and the research assistants, which covered the explanations for the skills and effective instructional practices. During the workshops, the principal investigator and the 2 researches, used discussion, lecture, video demonstrations, small group discussions, and practice teaching demonstrations to educate participants about clinical hypnosis.

Cluster

The statistical analyses used in most scientific studies, are based on the assumption that observed outcomes in different patients treated by the same physician or in the same center are independent. This assumption is realistic in most double-blind pharmacologic studies. However, the validity of this assumption could be doubtful in trials assessing nonpharmacologic treatments, as the success of the treatment could partly depend on health care providers' skill or expertise. Consequently, in

these trials, observations of participants treated by the same health care provider, may be correlated or “clustered.” To avoid the cluster for the clinical hypnosis treatment in our research, the patients of hypnosis group, were treated alternatively by two expert hypnotherapists: the principal investigator, Dr. Maria Paola Brugnoli and the assistant researcher, Dr. Emanuela Pasin. The 2 groups (table 3) were very homogeneous at baseline for: sex, age, diseases, use of opioids, VAS score and Hamilton score.

Table 3: Characteristics of the 2 groups of the patients at baseline (2014) the time of the recruitment.

	Control group (n=25)	Hypnosis group (n=25)	p-value
Sex (males)	8 (32%)	6 (24%)	0.529
Age	67 ± 14	61 ± 13	0.114
Disease			0.829
Rheumatic	10 (40%)	11 (44%)	
Neurologic	9 (36%)	7 (28%)	
Cancer	6 (24%)	7 (28%)	
Use of opioids	8 (32%)	8 (32%)	1.000
VAS score	78.5 ± 14.8	81.9 ± 14.6	0.827
Hamilton score	29.8 ± 11.9	32.6 ± 12.8	0.428

Data expressed in n (%) or mean ± SD

Demographic data and characteristics of the patients and of the 2 groups

Fifty subjects – 14 men and 36 women - participated to the study. The average age of the subjects was 64 years, ranging from a minimum of 33 to a maximum of 83 years. The patients suffered from 3 main types of disease:

1. Rheumatic severe chronic diseases (Rheumatoid Arthritis and Autoimmune Rheumatic Diseases) (n=21);
2. Neurologic severe chronic diseases (Multiple sclerosis; Parkinson's disease; Spinal cord injuryies - ASIA B is having some sensory function below the injury, but no motor function; ASIA C some motor function below level of injury, but half the muscles cannot move against gravity- American Spinal Injury Association classification) (n=16);

3. Oncologic (Breast cancer, Colon cancer, Leukemia and Lymphoma) (n=13).

As we can see on table n. 3, (demographic data) the two groups of patients were homogeneous for the features: age, diseases, use of opioids, VAS score at baseline, Hamilton score at baseline.

Sixteen of them (32%) were administered with opioids for pain control.

Half of the patients (n=25) were assigned to the group administered with the hypnotic protocol (hypnosis group), while the remaining 25 followed the conventional pharmacological pain therapies (control group). The two groups were homogeneous in the distribution of sex, type and subtypes of diseases, and use of opioids at baseline (Table 3)

Measuring instruments

After the workshop introductions on the first day, the pre-tests VAS and HAMA, were explained and administered. Participants were instructed to complete the questionnaire based on their own understanding of pain and anxiety. They were given 30 minutes to complete the pre-test. All participants finished within this time period.

After the last educational session about hypnosis, on the final day (after 1 year and after 2 years), participants were asked to complete the first (1 year) and the second (2 years) follow-up with the post-test questionnaires VAS and HAMA. Again, they were given 30 minutes to complete the questionnaire.

Participants in the control group did not attend the workshops of hypnosis.

The control group also completed the same pre- and post test (after 1 year and after 2 years), just as the treatment group. Participants are asked to complete 2 evaluations (VAS and HAMA) before the first lesson, and the 2 long-term follow-up were made for all the patients of the 2 groups, after 1 year (2015) and 2 years (2016) to compare the results of the 2 groups (group hypnosis and the control group).

The evaluations for pain and anxiety were performed with the test:

1. VAS the visual analogical scale for the evaluation of the pain
2. HAMA Hamilton anxiety scale for the evaluation of the anxiety

We have compared, in the statistical analysis, the increase and decrease of the use of opioids in the 2 groups.

1. VAS the visual analog scale for the evaluation of the pain.

The visual analog scale (VAS) is a validated, psychometric response scale which can be used in questionnaires. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points.

The visual analog scale (VAS) is one of the most commonly used measures of pain intensity in pain research. For pain intensity, the scale is most commonly anchored by “no pain” (score of 0) and “pain as bad as it could be” or “worst imaginable pain” (score of 100 [100-mm scale]).

Method of administration. The pain VAS is self-completed by the respondent. The respondent is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity. **Scoring.** Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the “no pain” anchor and the patient’s mark, providing a range of scores from 0–100.

Score interpretation. A higher score indicates greater pain intensity. Based on the distribution of pain VAS scores in postsurgical patients (knee replacement, hysterectomy, or laparoscopic myomectomy) who described their postoperative pain intensity as none, mild, moderate, or severe, the following cut points on the pain VAS have been recommended: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm).

(Jensen MP, Chen C, Brugger AM., 2003).

2. HAMA Hamilton anxiety scale: The Hamilton Anxiety Rating Scale

It is a validated, clinician-rated evaluation whose purpose is to analyze the severity of anxiety. The scale consists of 14 items designed to assess the severity of a patient’s anxiety. Each of the 14 items contains a number of symptoms (anxiety related symptoms) and each group of symptoms is rated on a scale of zero to four, with four being the most severe.

The Hamilton Anxiety Rating Scale is composed of fourteen items. On the scale, each item is presented in a specific format. The items, correspond to the psychosomatic disorders related to anxiety, that are generally existing in severe chronic illnesses. Following the item number, the item itself is listed along with a brief description of the criterion. This description is in the form of a short phrase that elaborates on the item and provides specificity to the clinician regarding the appropriate evaluation.

Adjacent to each item is a five-point scale, displaying the numerals 0 to 4 outlined by a square. To learn more about the specific scoring regarding the Hamilton Anxiety Rating Scale, please proceed to the Scoring section. Each criterion on the scale is an independent feeling that is related to anxiety. The collaboration of each of these independently rated criteria are meant to evaluate a patient's anxiety severity. Below are the verbatim criteria and their brief definitions (as described above) as presented in the Hamilton Anxiety Rating Scale.

We have chosen the Hamilton anxiety scale, because it is strongly related with the psychosomatic suffering of the patients. The items are:

1. Anxious mood: Worries, anticipation of the worst, fearful anticipation, irritability.
2. Tension: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.
3. Fears: Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.
4. Insomnia: Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.
5. Intellectual: Difficulty in concentration, poor memory.
6. Depressed mood: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.
7. Somatic (muscular): Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.
8. Somatic (sensory): Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.
9. Cardiovascular symptoms: Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.
10. Respiratory symptoms: Pressure or constriction in chest, choking feelings, sighing, dyspnea.
11. Gastrointestinal symptoms: Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.
12. Genitourinary symptoms: Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.
13. Autonomic symptoms: Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.
14. Behavior at interview: Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc."

The Hamilton Anxiety Rating Scale is a validated, clinician-rated scale that is intended to provide an analysis of the severity of anxiety in adults, adolescents, and children. It is scored based upon the composite rating of fourteen individually evaluated criteria.

The evaluator is instructed to assess the extent to which the patient displays the given criterion. Each item is scored independently based on a five-point, ratio scale. A rating of 0 indicates that the feeling is not present in the patient. A rating of 1 indicates mild prevalence of the feeling in the patient. A rating of 2 indicates moderate prevalence of the feeling in the patient. A rating of 3 indicates severe prevalence of the feeling in the patient. A rating of 4 indicates a very severe prevalence of the feeling in the patient. To implement the Hamilton Anxiety Rating Scale, the acting clinician proceeds through the fourteen items, evaluating each criterion independently in form of the five-point scale described above.

Upon the completion of the evaluation, the clinician compiles a total, composite score based upon the summation of each of the 14 individually rated items. This calculation will yield a comprehensive score in the range of 0 to 56. It has been predetermined that the results of the evaluation can be interpreted as follows. A score of 17 or less indicates mild anxiety severity. A score from 18 to 24 indicates mild to moderate anxiety severity. Lastly, a score of 25 to 30 indicates a moderate to severe anxiety severity (McDowell, I., Newell, C., & McDowell, I., 2006; Maier W, Buller R, Philipp M, Heuser I., 1998; Hamilton M., 1959).

In this study, HAMA enlightens the anxiety, the pain –related symptoms and the psychosomatic symptoms related to anxiety. All of these scores are used to compute an overarching score that indicates a person’s anxiety severity.

We have chosen the Hamilton Anxiety Scale, because the items are related to the psychosomatic symptoms in severe chronic diseases and in palliative care.

Hypnotizability and hypnotic induction profile

Hypnotizability, which is the capacity to experience a transition into a hypnotic state and to perform hypnotic tasks, has a wide range of degrees, from difficult being hypnotizable at all to being able to respond with intriguing and even surprising intensity to hypnotic instructions.

The history of hypnosis has been strongly influenced by the observation of highly hypnotizable subjects and their unusual abilities, such as hypnotic analgesia.

In past decades, much effort has been devoted to rating most subjective phenomena in psychology and psychiatry, such as

psychiatric symptoms and disorders, pain, general anesthesia, consciousness, and coma. A wealth of scales and tests have been published so far, with a threefold role: (a) quantifying the intensity and severity of symptoms and their changes following treatment; (b) providing information on prognosis; and (c) enabling comparison between treatments.

As a result, the concept of depth of anesthesia has been elusive, and no gold standard has emerged so far, despite the vast number of published studies analyzing the effectiveness of both clinical and neurophysiological parameters. Likewise, the problem of vegetative and minimally responsive states has no solution yet: a substantial controversy about the terminology, diagnosis, prognosis, perception of pain, and conscious awareness persists in the literature, despite a wealth of studies published in the past 40 years (Celesia, 2013). As a result, a mistaken diagnosis is still present in up to 43% of cases (Celesia, 2013; Schnakers et al., 2009; Facco E, Testoni I, Ronconi, Casiglia E, Zanette G. & David Spiegel, 2017).

Hypnosis can be considered at the same time a procedure and its product (Barnier & Nash, 2008). The contradictory issue of hypnosis as an ASC (altered state of consciousness) has been debated in the literature (Kirsch, 2011; Mazzoni, Venneri, McGeown, & Kirsch, 2013; Pekala et al., 2010a, 2010b). A recent definition from Division 30 of the American Psychological Association emphasizes that hypnosis does involve an altered state of consciousness including absorption, dissociation, and enhanced capacity for response to suggestions (Elkins, Barabasz, Council, & Spiegel, 2015).

The psychological features of hypnotizability are still ill defined, despite the availability of a wealth of data on the relationship between hypnotizability and personality, including the assessment of hypnoticlike experiences, personality traits (e.g., Minnesota Multiphasic Personality Inventory [MMPI]), cognitive control, suggestibility, imaginative involvement, absorption, dissociation, ego receptivity, and insight (H. Spiegel & Spiegel, 2004, pp.137–149). Some relationships between hypnotizability and absorption, dissociative experiences, proneness to fantasy, reaction time in a Go/No-Go Task, proneness to trust, and empathy have been established (Balthazard & Woody, 1992; Council & Green, 2004; Dienes et al., 2009; Frankel, 1990; Green, 1997; Green & Council, 2004; Green & Green, 2010; Wickramasekera & Szlyk, 2010; Zachariae, Jorgensen, & Christensen, 2000; Facco E, Testoni I, Ronconi, Casiglia E, Zanette G. & David Spiegel, 2017). Ian E. Wickramasekera and Janet P. Szlyk (2010) examined whether trait empathy is related to hypnotic ability and absorption. Sixty-four graduate students and mental health professionals completed the Harvard Group Scale of Hypnotic

Susceptibility, Form A; the Davis Interpersonal Reactivity Index; and the Tellegen Absorption Scale as measures of hypnotic ability, empathy, and absorption. Correlation analysis determined that statistically significant relationships exist between empathy and hypnotic ability ($r = .41$); empathy and absorption ($r = .43$); and absorption and hypnotic ability ($r = .31$). The results also indicate that empathy and absorption are both predictors of hypnotic ability, although absorption does not appear to contribute a statistically significant amount of the explained variance in hypnotizability that is independent of empathy. It may be that the conceptual ground shared by both empathy and absorption is what predicts hypnotic ability (Wickramasekera, I. E., & Szlyk, J. P., 2010).

Previous studies using the Minnesota Multiphasic Personality Inventory and other similar personality tests have failed to show any correlation with the available scales of hypnotizability (Laurence, Beaulieu-Prévost, & du Chéné, 2008). Focused attention and absorption are essential features of hypnosis, allowing the subject to dissociate from competing stimuli and thoughts (Spiegel H., 1977; D. Spiegel, 2013; H. Spiegel & Spiegel, 2004). Absorption is defined as total attention that fully engages one's representational resources, leading to imperviousness to distracting events; it also involves an openness to absorbing and self-altering experiences (Tellegen & Atkinson, 1974).

However, absorption might be more strongly related to difficult hypnotic performances than to easy ones (Balthazard & Woody, 1992), while the correlation may also be influenced by contextual factors such as acquiescence (or "yeasaying") and motivation consistency (Council & Green, 2004). Furthermore, some authors (Laurence et al., 2008) consider absorption more a cognitive pattern of response than a steady personality trait, related to motivation, attention, and capability of processing its objects.

Dissociation, which is considered a relevant component of hypnosis, is a term with a wide range of psychological and psychiatric meanings (Brown, 2006; Frankel, 1990), ranging from psychological detachment (essential for fairness, serenity, wisdom, and judgment) to Bleuler's psychiatric concept of *Spaltung* (division, split) to a failure of normal integration of identity, memory, consciousness, and perception (American Psychiatric Association, 2013; D. Spiegel et al., 2013).

This calls for a better definition of what is meant by dissociation in the context of hypnosis in order to avoid harmful misinterpretations. In short, hypnotizability is a complex phenomenon, which cannot be ascribed to a single personality trait or psychological attitude. Absorption and dissociation play a relevant but, perhaps, context sensitive role; also, other

features, like expectation, imagery, empathy, trust, capability to automatize, and ability to manage attentional resources may be involved as well and are worthy of further study (Kirenskaya, Novototsky-Vlasov, Chistyakov, & Zvonikov, 2011; Laurence et al., 2008; Muller, Bacht, Prochnow, Schramm, & Seitz, 2012; Rossi & Rossi, 2006).

The scientific data imply some criticism of the available scales, which were introduced some 50 years ago and were constructed upon a definition of hypnosis mainly based on suggestibility. Furthermore, if hypnotizability is a stable capability, it should be theoretically possible to test it even outside of hypnotic induction (Hilgard, 1991). There is recent evidence of functional resting state brain subregion connectivity differences between high and low hypnotizable subjects undergoing functional magnetic resonance imaging (fMRI) scanning while not hypnotized (Hoeft et al., 2012). This difference involves greater functional connectivity between the left dorsolateral prefrontal cortex and the dorsal anterior cingulate gyrus among high compared to low hypnotizable individuals as measured using the Hypnotic Induction Profile. However, in a practical sense, hypnotizability can be assessed only with a formal induction of hypnosis including standardized tasks, which allow for scoring different hypnotic abilities.

Clinical hypnosis is likely to function as a relaxation technique, decreasing sympathetic tone or increasing parasympathetic tone, or both, and, therefore, modulating anxiety and stress reactions. This also confirms the psychosomatic implications of hypnosis, allowing a subject to enhance control even over hemodynamic reactions to strongly stressful events, like surgery and chronic pain in severe chronic diseases (Facco, Pasquali, Zanette, & Casiglia, 2013; Lang et al., 2000; Facco E, Testoni I, Ronconi, Casiglia E, Zanette G. & David Spiegel, 2017) Thus making hypnosis a powerful tool for patient's empowerment in facing both stressful physical and psychological events.

Despite the continuous evolution of psychology and neuropsychology and the availability of a large number of studies, the process of developing a definition of hypnosis and hypnotizability is not yet concluded. Suggestibility, which played a central role in the past, is still uncertain and still defined and does not appear to be specific to hypnosis (Tasso & Perez, 2008). Furthermore, it is not clear whether hypnotic capacity is related to suggestibility or, rather, to the subject's trust, motivation, and cognitive flexibility, since they may lead one to effectively follow the same hypnotic instructions for very different reasons (Lifshitz, M., Howells, C., & Raz, A., 2012).

To summarize, there is a need to reappraise the concepts of hypnosis, hypnotizability, and its scales after some half century since their introduction. This might lead to a better definition of

hypnosis, more congruent with a neurophysiological perspective (Facco E, Testoni I, Ronconi, Casiglia E, Zanette G. & David Spiegel, 2017).

Today, hypnotizability and the hypnotic induction profile are used in experimental neurophysiological studies with volunteers.

Not always, they are used in clinical studies with patients.

Indeed, to study the hypnotic induction profile, we must induce in hypnosis the patients, and sometimes they avoid the experiment, because they have fear of hypnosis.

Medical studies must consider, individual ethics (protection of the individual), the respect of the patient and collective ethics (benefit for society) (Palmer CR., 1993).

In our study, we could have not to organize and to study the hypnotic induction profile, because 11/25 patients of the control group (no-hypnosis), avoided the test (every hypnotical test is made under hypnosis) because they had fear of hypnosis.

We have decided, as other authors have done in clinical studies of hypnosis, for respecting the patients, not use any hypnotic induction profile.

Treatment procedures

- The overall goal of the treatment was to teach clinical hypnosis and self-hypnosis to the patients, as added therapy to the pharmacological therapy, to relief pain and anxiety
- The treatment lasted two years.
- The participants at the hypnosis group met for the treatment: two hours once per week, every week for two years
- They had to attend the 50% of the lessons in one year
- Each treatment meeting lasted: two hours.
- The treatment meetings held at the Department of Anesthesia, Intensive Care and Pain Therapy, at the University of Verona, Italy, in the meeting room: the participants could have been induced in hypnosis, while sitting in their chairs.
- The typical format of each meeting was a workshop teorical-practical: the first hour the explanation of the techniques and the feedback for the previous techniques explained (if they had difficulties to do by themselves at home); the second hour to try with the first or the second investigator a practical techniques all together in group.
- A series of workshops of 2 hours, every week, for 2 years, are conducted on chronic pain assessment and management of anxiety and related symptoms, teaching directly to the patients of the hypnosis group, how to use the hypnosis and the self-hypnotic techniques.
- The lessons are theoretical and practical.
- The detailed descriptions of the techniques of clinical hypnosis used in this research, are in the chapter N.5

The hypnotherapy group is a group therapy, where the people context and group process is explicitly utilized with clinical hypnosis as a mechanism of change by developing the manifestations of conscious energy, exploring and examining interpersonal relationships within the group, to discover the benefits of pain and anxiety relief in chronic illnesses and cancer.

At the same time, all the patients of the two groups were cured with a pharmacological therapy for pain therapy, by the principal investigator, Dr. Maria Paola Brugnoli.

The control group (no hypnosis) was cured only with the conventional pharmacological therapy.

Clinical hypnosis can be considered in this research, a nonpharmacological intervention as “adjuvant” in pain therapy. Nonpharmacologic approaches and hypnosis, are intended to supplement, not substitute for, the pharmacologic or invasive techniques described.

Nonpharmacologic interventions as clinical hypnosis, are appropriate in chronic diseases, in cancer patients and in Palliative Care, for the patient who:

- 1) finds such interventions appealing;
- 2) expresses anxiety or fear, as long as the anxiety is not incapacitating or due to a medical or psychiatric condition that has a –non specific treatment;
- 3) may benefit from avoiding or reducing drug therapy (e.g., history of adverse reactions, fear of or physiological reason to avoid oversedation);
- 4) is likely to experience and need to cope with a prolonged interval of postoperative pain, particularly if punctuated by recurrent episodes of intense treatment, or procedure–related pain;
- 5) has incomplete pain relief following appropriate pharmacologic interventions. Cognitive–behavioral approaches include preparatory information, simple relaxation, imagery and hypnosis. Physical therapeutic agents and modalities include application of superficial heat or cold, massage, exercise, immobility, and electroanalgesia such as TENS therapy or electroacupuncture;
- 6) for physical and psychological suffering relief, and in Palliative Care at the end of life.

The cognitive–behavioral strategies, require greater professional involvement; these include complex imagery, hypnosis, biofeedback, mindfulness and combined therapies. Such strategies can be commonly applied when patients have acute or chronic pain.

The techniques of clinical hypnosis for pain and anxiety relief in severe chronic illnesses and in palliative care

Following are described the details of the techniques of clinical hypnosis used in this research in 2 years of hypnotic training for the hypnosis' group.

In the two years of hypnotical training with the patients, I have explained them several different techniques, because using hypnosis and self-hypnosis in severe chronic illnesses and in palliative care, the patients must be choose from different techniques, which are the best practice for themselves.

Self-hypnosis is the way to use hypnosis alone, without the therapist.

Self-hypnosis is a naturally occurring state of mind which can be defined as a heightened state of focused concentration. With it, you can change your thinking, kick bad habits, and take control of the person you are, along with relaxation and destressing from everyday life. It's similar to meditation and results in a better you.

Self-hypnosis is used extensively in modern hypnotherapy. It can take the form of hypnosis carried out by means of a learned routine. Hypnosis may help pain management, anxiety, depression, sleep disorders, asthma, and skin conditions. When this practice is mastered, it can improve concentration, recall, enhance problem solving, alleviate headaches and even improve one's control of emotions.

Steps commonly used for self-hypnosis:

Self-Hypnosis requires four distinct steps.

Step 1: Motivation. Without proper motivation, an individual can find very difficult to practice self-hypnosis

Step 2: Relaxation of the body and mind: The individual must be thoroughly relaxed and must set aside time to perform this act. Additionally, distractions should be eliminated as full attention is needed.

Step 3: Concentration: the individual needs to concentrate completely as energy is generated each time the mind focuses on a single image.

Step 4: Directing: This is an option used only when the individual wants to work on a specific goal. The individual must direct their concentration on visualizing the desired result (Adi Da Samraj, 2005; Austin, J. H.,1999).

We have added other important steps:

Step 5: Resilience: Resilience is that ineffable quality that allows some people to be knocked down by life and come back stronger than ever. Rather than letting failure overcome them and drain their resolve, they find a way to rise from the suffering.

Step 6: Self-Communication: Mastering communication with ourselves determines our quality of life as it determines our ability to experience life as we would like.

Step 7: Empathy: Empathy is the capacity to understand or feel what another person is experiencing from within the other person's frame of reference, i.e., the capacity to place oneself in another's position. There are many definitions for empathy that encompass a broad range of emotional states. Types of empathy include cognitive empathy, emotional empathy, and somatic empathy. Self – hypnosis can help the patients to improve these skills.

Step 8: Compassion: Compassion and self-compassion motivates people to go out of their way to help the physical, spiritual, or emotional hurts and pains of another.

The Technique of the different interpretation of the symptoms

When a state of a lighter or deeper relaxation is achieved through different techniques, the patient is trained as to how to interpret the feeling of chronic pain coming from a specific place in the body and to transform it slowly from a feeling of pain to a feeling of different nature, for example, light or medium tension, moderate pressure, beneficial warmth or cold sensation of anesthetizing nature.

Example of anesthesia to one hand

“... While in a state of relaxation, you can imagine immersing your hand in a container of melting ice cubes and from the wrist up to the tip of your fingers the ice acts on your hand like a very powerful anesthesia ... making it feel more and more insensitive. You will feel your hand becoming increasingly insensitive ... and the anesthesia will increase. You will also know that the anesthesia will last until you repeat to yourself for three times “ Everything is normal ”.

Exercise “warm hands”

Duration: 5 or also only 3 minutes.

During this exercise you will repeat to yourselves:

“ MY HANDS ARE WARM”

During the period of “deep relaxation “ you will imagine to keep your hand in front of the flames of an open oven, or under a solar lamp (UVB lamp), or immersed in hot water or any other thought of this kind that might come easy to you.

We can help the patient teaching him to visualize himself in a beautiful place that help him with these new sensations instead of the pain.

The Technique of the transferred symptoms

After achieving relatively strong analgesia in a certain part of the body with the techniques described above, you aim to mentally transfer the analgesia to another part of the body (for instance, instance from the hands to the abdomen or to the back) obtaining this way a gradual and progressive reduction of the global suffering.in a state of well-being...

The Technique of the transport of the symptom

When the patient has achieved a medium or better a deeper state of relaxation, you do an intense analgesia on one hand, preferably the one that is most used.

You then proceed by moving the analogized hand on to the painful side of the body, or wherever you want to direct the analgesia.

In this way with repeated procedures, you can obtain a good decrease of the suffering part of the body, especially if this pain has not been there for a very long time.in a state of well-being...

The Technique of the positive visualizations

(for pain or anxiety relief)

When the patient is always in a state of relaxation or in medium hypnosis status, you introduce particular visualizations that will cause after a certain time, major feeling visualization, which is capable of modify the painful information in the central nervous system, and therefore, reduce the pain to the patient.

Let's have an example of a complete hypnosis induction:

The technique for the desensitization of the pain

During the deep hypnotic status, the patient does not seem to react to the surrounding environment and usually seems to have a reduced sensitivity to painful stimulation, this happens even if you can have some or all the reflexive or vegetative signs of the painful stimulation.

The best use, therefore, for this technique is to induce deep relaxation up until the unconscious can register and activate through hypnotic suggestion a minor sensitivity to pain for a longer time even in a state of normal awakening,

The use of this technique is to diminish the anxiety connected with pain, in the case of headaches where besides the body pain, a great emotional dysfunction arises, also in the case of the phantom arm or leg after the amputation of an arm or leg or in the chronic pain of cancer patients.

The methods most used during the state of deep relaxation or hypnosis are:

- Direct instructions for the reduction of pain.
- The use of metaphors.
- The transportation of the painful symptom.
- The detachment of pain through imagination.

The Technique of the partial or total hypnotic amnesia

(for pain or anxiety relief)

Furthermore, for this technique, you need the patient to be in a medium or deep hypnotic state. It 's possible to achieve a better result by following this procedure:

Taking the patient back to the well-being and healthy status before the illness started through specific questions.

In this way, the patient will eventually forget the memories of the bad experiences, which are related to his pain and in some cases also forget the memories of the anxiety, which is related to the pain in chronic diseases.

The Technique of the activation of a type of conditioned reflex

This technique called the "non painful pain" uses the same methods that Pavlov applied to dogs. He created a typical conditioned reflex on dogs by showing them the food together with or soon after a painful stimulation. After a certain number of tests depending also from the breed and the sex of the dog the painful stimulation was not felt thanks to the gratification of the food.

Almost the same happens with the human beings' thanks to a mechanism of emotional restructuring in the perception of the painful stimulation at the level of the brain areas.

During a deep status of relaxation, it is possible to activate a conditioned reflex through images and music preferred by the patient so that the pain is reduced:

The Technique of the switching of attention

(for pain or anxiety relief)

This method used by Kroger can be very useful for chronic pain, by training the patient to move his attention to those parts of the body, which are not affected by pain.

Using gratifying visualization you train the patient to move his attention to another pleasant sensation of his body, which are past or present. This method is also useful in chronic pain when it is not too strong, but it is understood that the patient must participate actively to the visualization.

Sometimes this is also easier than the previous systems, especially by suggesting gratifying visualization.

If the patient cannot do the self training you can use the following method:

Method of the CD

This consists of simply record the desired suggestion on a CD, and then listen to it when you are relaxing. This will be very effective for people that have difficulty in visualizing.

Hypnosis technique of the self-training of Shultz

(for pain or anxiety relief)

Autogenic training is a desensitization-relaxation technique developed by the German psychiatrist Johannes Heinrich Schultz and first published in 1932. The technique involves the daily practice of sessions that last around 15 minutes. During each session, the practitioner repeats a set of visualisations that induce a state of relaxation. Each session can be practiced in a position chosen amongst a set of recommended postures (for example, lying down, sitting meditation, sitting like a rag doll). The technique can be used to alleviate many stress-induced psychosomatic disorders (Luthe, W. & Schultz, JH., 2001)

We can use these exercises as techniques for self-hypnosis. When the patient has been well trained to practice the basic easier exercises of the self-training of Shultz, we can use these exercises during the hypnotic state, to obtain a good relief of pain. The simple exercises of the self-training of Shultz are:

- Exercise of feeling heavy (for pain relief)
- Exercise of the heat (for pain relief)

- Exercise of the heart (for anxiety relief)
- Exercise of the breath (for anxiety relief)
- Exercise of the abdomen (for pain relief)
- Exercise of the cool forehead (for pain relief)

All of the above exercises are suitable to the pain therapy, but we will consider here only a few examples

Exercise of the cool forehead

“My forehead is pleasantly cool”

This can be another exercise also used for the pain-relief therapy depending on the patient’s personality and character. This is also a very important exercise used to control the chronic headache and as well used for different types of cancer. This is how to carry out the technique of the cool forehead:

Concentrating on your forehead please repeat.....

My head is light all the muscles of my face are rested

....

I am calm.... Calm.... Perfectly calm.. in a state of great wellbeing.....

My forehead is cool... pleasantly cool..... Even more pleasantly cool.....

The coolness is all around me and gives me wellbeing

Wellbeing of the body and wellbeing of the mind.....

Repeat this formula between 5 and 10 times.

Technique of the self- hypnosis for pain relief

This is one of the most efficient techniques and is carried out in three phases:

1. You are living a pleasant feeling in deep relaxation.
2. You connect this feeling mentally to your symptoms.
3. You are using it mentally to cancel your symptoms.

The most efficient way to achieve this feeling is to repeat this technique until you achieve your goal and sometimes this will take quite a while.

Let’s imagine that we are going to use this technique of post-hypnotic state, to achieve the following goal: “I can hear a very soft music that helps my pain.”

Phase 1 – You are living this moment in a status of relaxation.

You relax for five minutes and concentrate on remembering the last time you could hear a soft music.

You can hear the harmony of this music, and of all the other times that you heard soft music in your past.

You imagine hearing this music in the ears of your mind; after you have recaptured that moment, you go to phase 2.

Phase 2 – you make the connection with the hypnosis. Yet again in a state of relaxation, you can see yourself in the different circumstances use the key words: “ Let me hear the soft sound of the music” and at that point, you will be hear.

Phase 3 – you use this system to eliminate the pain: Try to examine the result of your experiment and if necessary repeat the whole procedure again.

The body relaxation with hypnosis for the treatment of the acute pain in severe chronic illnesses

With this exercise, you will be under hypnosis for different lengths of time, measured in minutes or seconds (acute pain in emergency and in critical care).

ALWAYS THINK BEFORE YOU COUNT DOWN FROM 20 TO 1:

“Now I will sleep for X minutes meanwhile my pain will decrease.”

THEN begin to count down from 20, to 1.

While you are practicing this experiment, you must use the following suggestion:

EVERY TIME FASTER AND DEEPER...

This means of course that every time you will go to sleep with your eyes will close faster, and you will sleep more deeply.

Try this exercise for different length of time.

Try to do self-inductions that last 10, 15, 20 seconds.

This technique can be used in the acute pain relief.

The techniques for deep states of hypnosis used for pain and suffering relief in palliative care

Deepening hypnosis Suggestions:

The deepening suggestions that are easiest to use in this situation are suggestions that relate to breathing, escalators, elevators and counting. Here are some examples.

- Breathing

"And every single deep and natural breath you take allows you to deepen your relaxation."

- *Counting*

"In a moment, I'm going to count from 10 down to 1...
And in allowing each number to help your body grow more relaxed...

your mind go more relaxed...
so that certain thoughts just fade away...
like sand slipping through your fingers...
You can find that easy relaxation of mind and body...
because of these words... just happens now...

.....
10easily relaxing all over again.....
9then...
8 deeper still....
.... feeling great
7.... 6..... 5.....
mind and body relaxed....
4... relaxing more...
... 3 then2...
your deepening grew at
1.... derful deep levels
going deeper ...
.....That's right...

- *Elevators & Escalators*

In a moment, I'm going to ask you to imagine yourself at the top of an escalator. I'm going to count down from 10 to 1, as I say the number 10 in your imagination, step onto the escalator.

.....Allow yourself to go deeper into relaxation with each number I say.
.....When I reach the number 1, step off the escalator into a state of relaxation deeper than you've ever felt before.
10steps on the escalator and go much deeper...
9..... relaxing more and more with each number...
8allowing yourself to go deeper and deeper with each number...
7each number and each easy, natural breath you take helps you relax more fully...
6...
5... doing deeper into relaxation...
4... feeling relaxation flow and every area of your body...
3...
2... allowing your body to feel a wonderful... at the relaxation...
1... now more deeply relaxed than ever before...

After the hypnosis induction slowly...we return to being awake...
now let's take a deep breath...

and slowly...return to being awake...
I regain my normal waking state.
I can start my first movements of my feet and hands,
calm....without rushing...slowly...
I can start to slowly open my eyes.....slowly.....
and regain.....always slowly.....my normal waking state,
moving my arms and my legs.....
I move again.....good. I am awake.

Statistical analyses

Data were summarized with means \pm standard deviation (SD) or number (percentage), as appropriate. Comparisons of variables between groups were performed using the Person's chi-squared, the Student's T, or the Wilcoxon's rank-sum tests, accordingly to the nature and the distribution of each variable.

The associations of each variable with 1 year variations in VAS score, Hamilton's score, and in pharmacological therapy were evaluated by linear, quantile, and binomial regression models, respectively. Multivariate models were performed using a stepwise backward approach, with a significance level for removal from the model of 0.20.

Longitudinal scores of VAS and Hamilton were analysed using repeated measures ANOVA, in order to test the effectiveness of the hypnotic treatment and its potential interaction with the type of chronic disease.

A significance level of 0.05 was adopted for the statistical tests. The analyses were all performed using STATA 14.1.

CHAPTER 3

RESULTS

The Figure 1 shows The Flow diagram of the progress through the phases of the parallel non-randomized trial of the two groups (that is enrolment, intervention, follow-up at 1 year and 2 years). We assessed all patients who were studied (intention-to-treat principle). The first 6 months of the study, we enrolled 76 patients with severe chronic diseases, but only 55 were eligible for the inclusion criteria. 5 patients declined to participate to the research. We enrolled 50 patients divided in 2 groups of 25 each for a non randomized controlled trial. At the first long term follow-up at 1 year we do not had drop-out. At the second long term follow-up at 2 years we had 7 drop-out in the hypnosis group and 6 drop-out in non-hypnosis group.

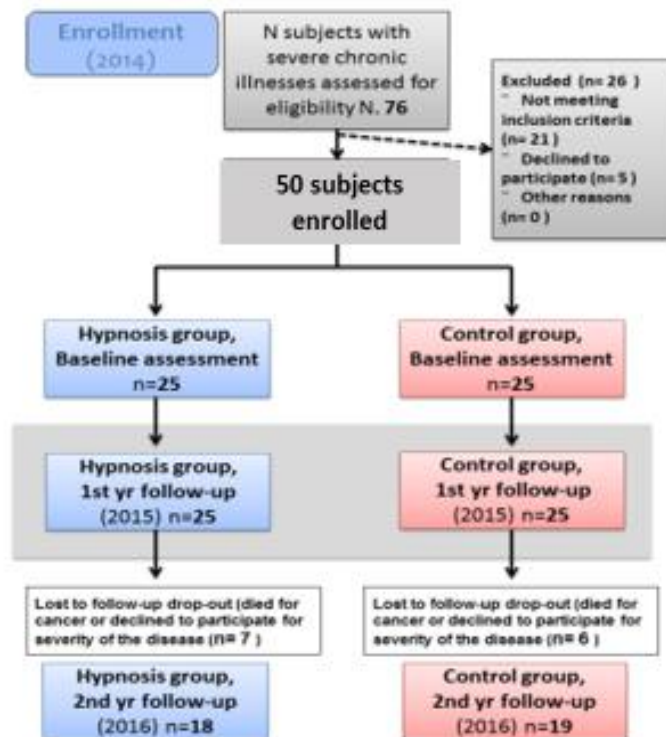


Figure 1: The Flow diagram of the progress through the phases of the parallel trial of the two groups

Characteristics of the subjects and of the groups:

Fifty subjects – 14 men and 36 women - participated to the study. The average age of the subjects was 64 years, ranging from a minimum of 33 to a maximum of 83 years. The patients suffered from 3 main types of disease: rheumatic (n=21), neurologic (n=16), or oncologic (n=13). Sixteen of them (32%) were administered with opioids for pain control.

Half of the patients (n=25) were assigned to the group administered with the auto-hypnotic protocol (hypnosis group), while the remaining 25 followed the conventional pain therapies (control group). The two groups were homogeneous in the distribution of sex, type of disease, and use of opioids at baseline.

Subjects administered with the hypnosis therapy had a greater reduction in pain and in anxiety. The VAS score at baseline was similar between the hypnosis and the control group (mean \pm standard deviation, sd: 78 ± 16 and 77 ± 14 , respectively); after 1 year and 2 years, the score decreased in both groups compared to baseline score, and it was lower in the hypnosis compared to the control group (62 ± 15 and 46 ± 14 , respectively).

The Hamilton score in multivariate analysis, the treatment with hypnosis was associated with a greater decrease of 7 points compared to the control group, independently from the score at baseline. The decrease in VAS and Hamilton score were studied in the two therapy groups according to the type of disease suffered by the patients: rheumatic disease, neurologic disease, or cancer. For all the 3 types of disease, the reduction in both VAS and Hamilton scores was significantly greater in the subjects who were included in the hypnosis group, after 1 and 2 years follow-up. Subjects in the hypnosis group were at lower risk of increasing the pharmacological treatment for pain control. Only 16% of the subjects included in the hypnosis group had to increase the pharmacological treatment for pain control after 1 year, compared to 52% of the subjects in the control group (p-value for difference = 0.007). On the other hand, 56% of the subjects who were administered with opioids at baseline had to increase the pharmacological therapy, compared to 24% of the subjects who were not administered with opioids.(p-value = 0.023).

The statistical analysis of the patients of the group 1 (hypnosis) after a long term follow-up 1 and 2 years of treatment with hypnosis as an adjuvant therapy for pain and anxiety, shows a significant statistical decrease of pain and anxiety compared with the control group, and have a less risk to have to increase the pharmacological treatment with opioids for pain relief.

The specific aims of this study were:

1. to measure of hypnosis's influence and efficacy, as an adjuvant therapy, on pain in severe chronic diseases and in Palliative Care
2. to measure of hypnosis's influence and efficacy, as an adjuvant therapy, on anxiety symptoms in severe chronic diseases and in Palliative Care
3. to measure of hypnosis's influence and efficacy, as an adjuvant therapy, on the use of opioids in severe chronic diseases and in Palliative Care
4. to demonstrate reliability and validity of the effectiveness of the use of hypnosis, and self-hypnosis to relief pain and anxiety in severe chronic illnesses and in Palliative Care for a long term follow-up (1 year and 2 years).

The first long-term follow-up at 1 year

One of the aim of this research was to demonstrate reliability and validity of the effectiveness of the use of hypnosis, and self-hypnosis to relief pain and anxiety in severe chronic illnesses and in Palliative Care for a long term follow-up (1 year and 2 years). In fact, the scientific literature about clinical hypnosis in pain therapy and palliative care, lack about long term follow-ups about the efficacy during the time.

The figures from 2 to 5 show the measure of the pain, anxiety and the use of the opioids in the group treated with clinical hypnosis, after the Primary long-term follow-up: one-year. We can observe the hypnosis's influence and efficacy, as an adjuvant therapy, on pain in the group treated with clinical hypnosis as adjuvant therapy added to the pharmacological therapy (figure 2 and 3).

In Figure 3 we observe the group n. 1 treated with hypnosis as an adjuvant therapy, and his statistical significant decrease of VAS pain' score, after 1 year follow up in each of the 3 different types of diseases: cancer, neurological diseases ND, and reumathic diseases CRD: the efficacy of the therapy is homogenous in the different diseases.

We obtained a significant decrease on anxiety symptoms in the group treated with clinical hypnosis as adjuvant therapy added to the pharmacological therapy (figure 4, 5 and 6).

In Figure 5 we observe the group n. 1 treated with hypnosis as an adjuvant therapy, and his statistical significant decrease of Hamilton anxiety score, after 1 year follow up in each of the 3 different types of diseases: cancer, ND and CRD: the efficacy of the therapy is homogenous in the different diseases.

We obtained a significant decrease on the use of opioids in severe

chronic diseases and in Palliative Care (figure 7).

In the Primary long-term one-year follow-up, we have decided to study also one item of the HAMA scale, the muscle contracture, because we observed that the patients with very severe diseases, at the end of life, in the 2 groups, presented an important muscular pain. We decided to study this item to observe if with the hypnosis intervention the hypnosis' group could have muscular pain and contracture relieved (figure 6). The group n. 1 treated with hypnosis as an adjuvant therapy, had a statistical significant decrease of muscle contracture after 1 year follow up.

The figure 7 shows the significant statistical decrease of the use of opioids (pain-control medicines at 1 year follow-up in the group-hypnosis. The most of the patients asked to doctor Brugnoli (the principal investigator) the permission to decrease the opioids they were using, because they obtained a good pain relief.

Table 1 shows the characteristics of the 2 groups at the baseline and after 1-year follow-up we did not have drop-out.

The Scores of pain, anxiety, and muscle contracture across the 2 groups at baseline and at 1-year follow up. The score of VAS and Hamilton are homogeneous at the baseline in the 2 groups. We observe a significative decrease of pain, anxiety and muscle contracture in the group-hypnosis compared to the control-group (table 2a and 2b).

The coefficients from the linear regression models: the hypnotic therapy and the VAS score at baselines have a significant and independent association with the decrease of the VAS score after 1 year. In particular, the persons who had the hypnotic treatment had also a decrease of 16 points in the VAS score compared to the group that had not the hypnotic treatment (table 3).

The coefficients from the quantile regression models: the hypnotic therapy and the Hamilton anxiety score at baselines have a significant and independent association with the decrease of the Hamilton anxiety score after 1 year. In particular, the group who had the hypnotic treatment had also a decrease of 7 points in the Hamilton anxiety score compared to the group that had not the hypnotic treatment (table 4).

Table n. 5 shows that only the 16% of the patients treated with hypnosis had to increase the pharmacological therapy, but the 52% of the control group, had to increase the pharmacological therapy after 1 year. The use of opioids is less in people who practice hypnosis. Who practice hypnosis has a less risk of 60% to have to increase the pharmacological therapy, compared with the control group.

Data were summarized with means \pm standard deviation (SD) or number (percentage), as appropriate. Comparisons of variables between groups were performed using the Person's chi-squared, the Student's T, or the Wilcoxon's rank-sum tests, accordingly to the nature and the distribution of each variable. The associations of each variable with 1 year variations in VAS score, Hamilton's score, and in pharmacological therapy were evaluated by linear, quantile, and binomial regression models, respectively.

Follow-up after 1 year:

- drop-out: none
- GROUP N.1 = 25 patients treated with hypnosis
- and comparison with GROUP N. 2 = 25 patients of the control group (no hypnosis)

The following figures show the measure of the pain, anxiety and the use of the opioids in the group treated with clinical hypnosis, after the Primary long-term outcome: one-year follow-up.

We can see:

- the hypnosis's influence and efficacy, as an adjuvant therapy, on pain in the group treated with clinical hypnosis as adjuvant therapy added to the pharmacological therapy (figure 2 and 3)
- the hypnosis's influence and efficacy, as an adjuvant therapy, on anxiety symptoms in the group treated with clinical hypnosis as adjuvant therapy added to the pharmacological therapy (figure 4, 5 and 6)
- the hypnosis's influence and efficacy, as an adjuvant therapy, on the use of opioids in severe chronic diseases and in Palliative Care (figure 7)
- In the Primary long-term outcome: one-year follow-up, we have decided to study also one item of the HAMA scale, the muscle contracture, because we observed that the patients with very severe diseases, at the end of life, in the 2 groups, presented an important muscular pain. We decided to study this item to observe if with the hypnosis intervention the hypnosis' group could have muscular pain and contracture relieved.

The statistical analysis and correlations between group 1 (hypnosis and self-hypnosis) and group 2 (no hypnosis) at the long-term follow up of 1 year.

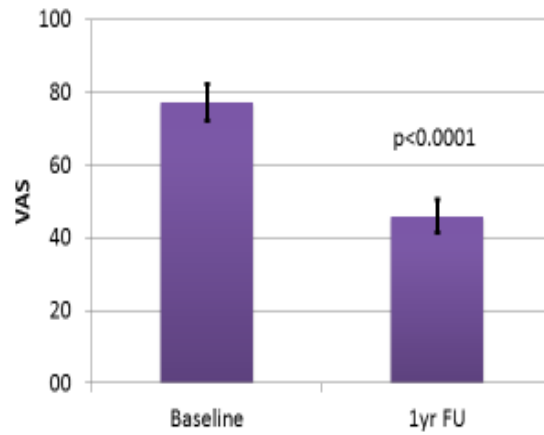
Table 1 shows the Characteristics of the 2 groups at the baseline and after 1-year follow-up (no drop-out)
Data are expressed in n (%) or mean \pm SD.

	Control group (n=25)	Hypnosis group (n=25)	p-value
Sex (males)	8 (32%)	6 (24%)	0.529
Age	67 \pm 14	61 \pm 13	0.114
Disease			0.829
Rheumatic	10 (40%)	11 (44%)	
Neurologic	9 (36%)	7 (28%)	
Cancer	6 (24%)	7 (28%)	

At the first 1 –year long term follow-up we did not had any drop-out.

The study of the 2 groups of 25 patients each (total 50 patients studied after 1 year follow-up), were homogeneous for the sex, age and the types of the severe chronic diseases, the same of the baseline.

Pain



VAS	Obs	mean \pm SD	[min-max]
Baseline	25	77.1 \pm 14.5	[51-97]
1year Follow-up	25	45.9 \pm 13.8	[23-78]

Figure 2: the group n. 1 treated with hypnosis as an adjuvant therapy, and his statistical significant decrease of VAS pain' score, after 1 year follow up.

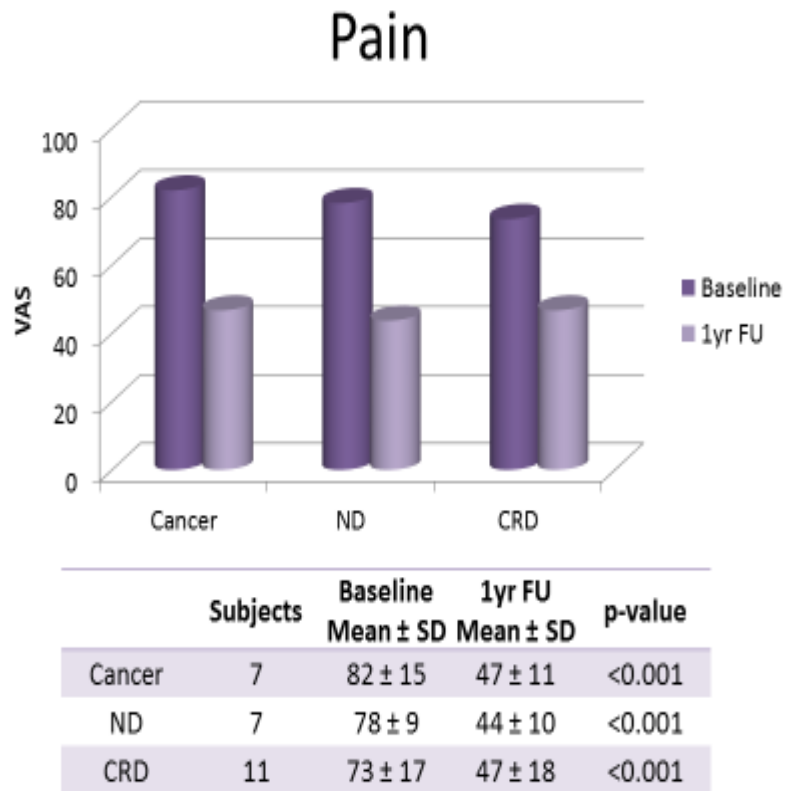


Figure 3: the group n. 1 treated with hypnosis as an adjuvant therapy, and his statistical significant decrease of VAS pain' score, after 1year follow up in each of the 3 different types of diseases: cancer, neurological diseases ND, and reumathic diseases CRD: the efficacy of the therapy is homogeneous in the different diseases.

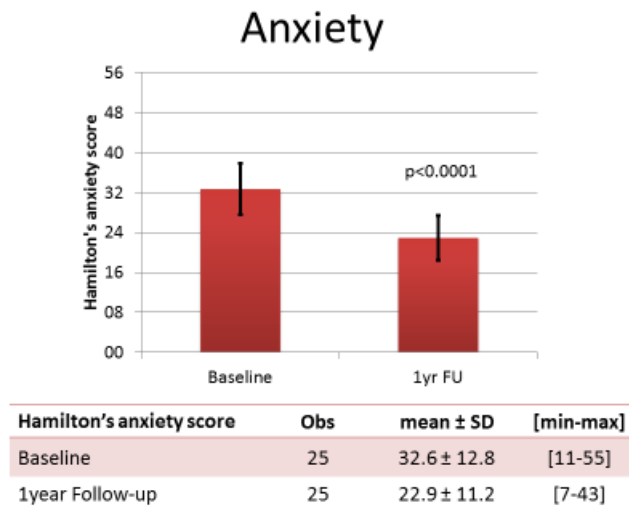


Figure 4: the group n. 1 treated with hypnosis as an adjuvant therapy, and his statistical significant decrease of Hamilton anxiety score, after 1 year follow up.

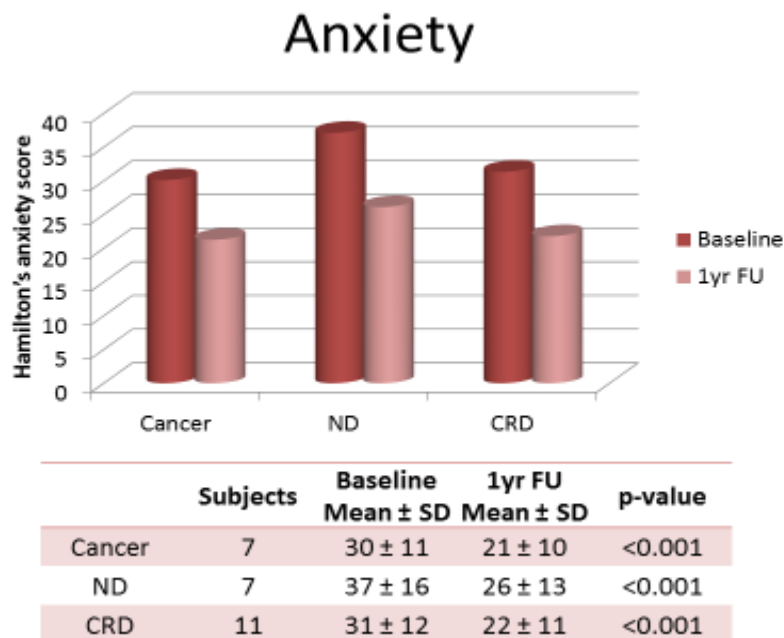


Figure 5: the group n. 1 treated with hypnosis as an adjuvant therapy, and his statistical significant decrease of Hamilton anxiety score, after 1 year follow up in each of the 3 different types of diseases: cancer, ND and CRD: the efficacy of the therapy is homogeneous in the different diseases.

Anxiety and muscular contracture:

Figure 6: at the first follow-up (1 year) we have studied the item of the HAMA about the muscle contracture, because the patients with the most severe diseases (the advanced illnesses), presented a fibromyalgia syndrome associated to the chronic diseases. The group n. 1 treated with hypnosis as an adjuvant therapy, had a statistical significant decrease of muscle contracture after 1 year follow up.

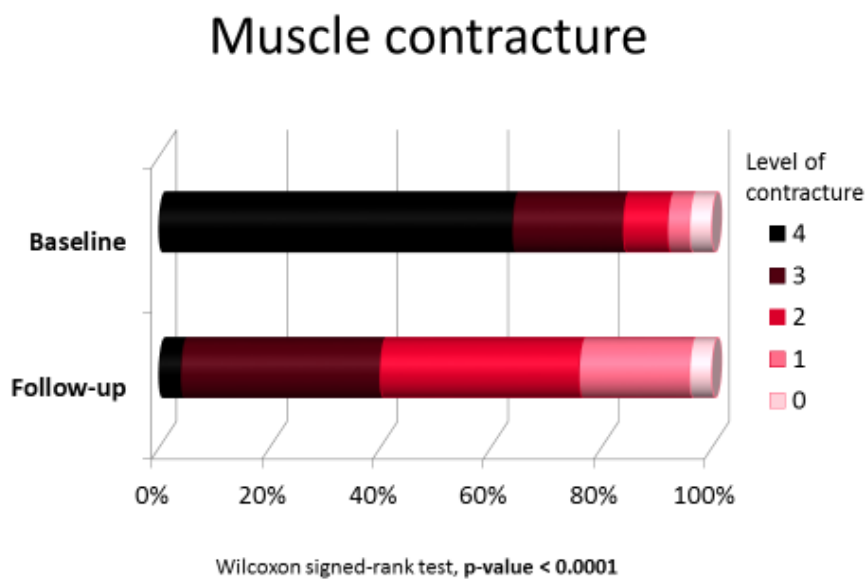


Figure 7: USE OF OPIOIDS

The figure shows the significant statistical decrease of the use of opioids (pain-control medicines at 1 year follow-up in the group-hypnosis. The most of the patients asked to doctor Brugnoli (the principal investigator) the permission to decrease the opioids they were using, because they obtained a good pain relief.

Use of pain-control medicines at FU

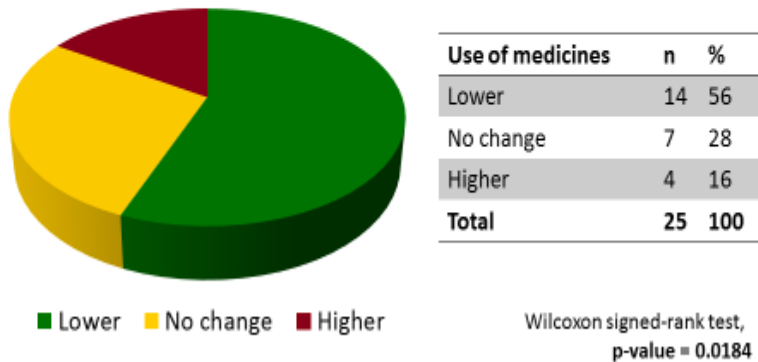


Table 2 a and b shows the Scores of pain, anxiety, and muscle contracture across the 2 groups at baseline and at 1-year follow up. The score of VAS and Hamilton are homogeneous at the baseline in the 2 groups. We observe a significative decrease of pain, anxiety and muscle contracture in the group-hypnosis compared to the control-group.

Table 2a: Data expressed in mean \pm SD; p-values from t test

	Hypnosis group	Control group	p-value
VAS score (pain)			
Baseline	77 \pm 15	78 \pm 16	0.827
1year fu	46 \pm 14	77 \pm 14	<0.001
Hamilton score (anxiety)			
Baseline	33 \pm 13	30 \pm 12	0.427
1year fu	23 \pm 11	26 \pm 13	0.348
Muscle contracture			
Baseline	3.4 \pm 1.1	3.4 \pm 0.9	1.000
1year fu	2.2 \pm 0.9	3.0 \pm 1.0	0.004

Table 2b : Scores of pain, anxiety, and muscle contracture across the 2 groups at baseline and at 1-year follow up. The score of VAS and Hamilton are homogeneous at the baseline in the 2 groups. We observe a significant decrease of pain, anxiety and muscle contracture in the group-hypnosis compared to the control-group.

Data expressed in median (1st;3rd quartile); p-values from Mann-Whitney test

	Hypnosis group	Control group	p-value
VAS pain score			
Baseline	81 (68;85)	82 (72;90)	0.553
1year fu	45 (38;56)	63 (54;68)	<0.001
Hamilton's anxiety score			
Baseline	32 (24;38)	27 (21;36)	0.351
1year fu	21 (14;23)	27 (18;33)	0.281
Muscle contracture			
Baseline	4 (3;4)	4 (3;4)	0.797
1year fu	2 (2;3)	3 (2;4)	0.005

Table 3 shows the Variables associated with variations in VAS pain score. Coefficients from the linear regression models Table 3 shows coefficients from the linear regression models: the hypnotic therapy and the VAS score at baselines have a significant and independent association with the decrease of the VAS score after 1 year. In particular, the persons who had the hypnotic treatment had also a decrease of 16 points in the VAS score compared to the group that had not the hypnotic treatment.

Table 3: Variables associated with variations in VAS pain score. Coefficients from the linear regression models

	Univar			Multivar		
	Coef	(95%CI)	p-value	Coef	(95%CI)	p-value
Hypnosis	-15.3	(-23.1;-7.4)	<0.001	-16.2	(-23.1;-9.3)	<0.001
Baseline VAS score	-.43	(-.70;-.16)	0.002	-.41	(-.66;-.18)	0.001
Sex (male)	-6.8	(-16.7;3.0)	0.171	-.38	(-8.99;8.24)	.930
Age	-.01	(-.34;32)	0.949			
Disease (vs. Rheumatologic)						
Neurological disease	-8.0	(-18.4;2.4)	0.126	-8.6	(-17.5;39)	0.060
Cancer	-6.5	(-17.6;4.5)	0.242	-3.4	(-13.2;6.4)	0.486
Use of opioids	-6.6	(-16.0;2.9)	0.170	-1.8	(-10.7;7.1)	0.687

Table 4 shows coefficients from the quantile regression models: the hypnotic therapy and the Hamilton anxiety score at baselines have a significant and independent association with the decrease of the Hamilton anxiety score after 1 year. In particular, the group who had the hypnotic treatment had also a decrease of 7 points in the Hamilton anxiety score compared to the group that had not the hypnotic treatment.

Table 4: Variables associated with variations in Hamilton’s anxiety score. Coefficients from the quantile regression models

	Univar*			Multivar*		
	Coef	(95%CI)	p-value	Coef	(95%CI)	p-value
Hypnosis	-9	(-13.0;-5.0)	<0.001	-6.9	(-9.8;-4.0)	<0.001
Baseline Hamilton’s score	-.21	(-.42;.01)	0.060	-.14	(-.25;-.02)	0.024
Sex (male)	-4	(-10.4;2.4)	0.217			
Age	.14	(-.06;.34)	0.178	-.01	(-.11;.10)	0.909
Disease (vs. Rheumatologic)						
Neurologic	-4	(-11.0;3.0)	0.259			
Cancer	0	(-7.5;7.5)	1.000			
Use of opioids	-3	(-9.2;3.2)	0.333			

Table 5 shows the Variables associated with increase in pharmacological therapy (opioids). Adjusted risk ratios from the binomial.

Table n. 5 shows that only the 16% of the patients treated with hypnosis had to increase the pharmacological therapy, but the 52% of the control group, had to increase the pharmacological therapy after 1 year. The use of opioids is less in people who practice hypnosis. Who practice hypnosis has a less risk of 60% to have to increase the pharmacological therapy, compared with the control group.

Table 5: Variables associated with increase in pharmacological therapy (opioids). Adjusted risk ratios from the binomial.

	n/N	%	p-value	aRR	(95%CI)	p-value
Hypnosis			0.007			
No	13/25	52%				
Yes	4/25	16%		0.36	(.14;.90)	0.029
Sex			0.837			
Female	12/36	33%				
Male	5/14	36%				
Age			0.930			
≤60	5/16	31%				
61-70	6/16	38%				
>70	6/18	33%				
Disease			0.487			
Rheumatologic	7/21	33%				
Neurologic	4/16	25%				
Cancer	6/13	46%				
Use of opioids			0.023			
No	8/34	24%				
Yes	9/16	56%		1.91	(.94;3.81)	0.063
TOTAL	17/50	34%				

2 years long term follow-up

Table 6 shows the Characteristics of eligible subjects who completed and didn't complete (drop-out) the 2yr follow-up study.

After 2 years, we have a total of 13 drop-out in the 2 groups:

- 7 drop-out in the hypnosis group
- 6 drop-out in the control group.

The patients affected by cancer, enrolled at baseline in the 2 groups = 13

6 patients in control group: 3 Breast cancer with multiple metastasis, 1 Colon cancer with multiple metastasis, 1 Leukemia, 1 Lymphoma;

7 patients in hypnosis group: 4 Breast cancer with multiple metastasis, 2 Leukemia, 1 Lymphoma.

DROP OUT:

CANCER

n. 6 cancer patients, died for the cancer:

Control group: 1 died for Breast cancer, 1 died for colon cancer.

Group hypnosis: 2 died for Breast Cancer, 2 died for Leukemia.

NEUROLOGICAL DISEASES

n. 3 patients with the neurological diseases (multiple sclerosis) had an increase of the severity of the diseases and could not to come to the hospital anymore. They could not attend the hypnosis group and the control group could not to come to the hospital for pain therapy with the medicines and the follow-up. 2 patients with multiple sclerosis dropped out from the control group and 1 from hypnosis group.

REUMATIC DISEASES

n. 4 patients with the rheumatic diseases: 2 had an increase of the severity of the diseases and could not to come to the hospital anymore: they were patients of the hypnosis group.

1 patient of the control group would like to use anxiolitics and entered in the exclusion criteria; 1 patient of the control group avoided to do the follow-up at the second year (she avoided to come to the hospital to be cured).

The second year we have studied the relationship of hypnosis on:

- Pain relief
- Anxiety relief
- Use of opioids

These 3 are the aims of the research.

In the secondary long-term outcome: two-years follow-up, we have decided do not study anymore the item of the HAMA scale, the muscle contracture, because we observed that the patients with the very severe diseases, at the end of life, that had in the first follow-up the muscular contracture, were the patients dropped out. This added study to the other 3 main aims of the research, at this point, would not have been important, because at the follow-up of 2 years, most of the patients of both the 2 groups, remained in the study, was not suffering of contractures and fibromyalgia syndrome.

Table 6 shows the characteristics of eligible subjects who completed and didn't complete (drop-out) the 2yr follow-up study. The Data are expressed in n (%) or mean \pm SD

In the secondary long-term outcome: two-years follow-up, we have decided do not study anymore the item of the HAMA scale, the muscle contracture, because we observed that the patients with the very severe diseases, at the end of life, that had in the first follow-up the muscular contracture, were the patients dropped out. This added study to the other 3 main aims of the research, at this point, would not have been important, because at the follow-up of 2 years, most of the patients of both the 2 groups, remained in the study, was not suffering of contractures and fibromyalgia syndrome.

The decrease of the pain (VAS) was most important with the patient of the group hypnosis than in the control group ($p=0.0001$). We must remember that both the two groups of the patients were cured with a pharmacological therapy and hypnosis was an adjuvant therapy, added in the hypnosis group. The Hamilton score is decreased from 32.6 at baseline to 22.9 and 17.1 at the first and second follow-up in the hypnosis group. In the control group it is the same at baseline (29.8), after 1 year (26.1) and after 2 years (28.5).

In both the measures of VAS and HAMA, we do not have differences between the different diseases: cancer, neurological diseases and rheumatic diseases, because the hypnosis intervention has the same therapeutic effect in the different diseases: the patients could have the same pain and anxiety relief in all the different diseases.

Table 6: Characteristics of eligible subjects who completed and did not complete (drop-out) the 2yr follow-up study.
Data expressed in n (%) or mean \pm SD

	Non drop-out (n=37)	Drop-out (n=13)	p-value
Group			.747
Hypnosis	18 (72%)	7 (28%)	
Control	19 (76%)	6 (24%)	
Sex			.646
Males	11 (79%)	3 (21%)	
Females	26 (72%)	10 (28%)	
Age	66.9 \pm 12.7	57.5 \pm 15.2	.036
Disease			.157
Rheumatic	17 (81%)	4 (19%)	
Neurologic	13 (81%)	3 (19%)	
Cancer	7 (54%)	6 (46%)	
Use of opioids			.203
No	27 (79%)	7 (21%)	
Yes	10 (63%)	6 (38%)	
VAS score	76.8 \pm 16.0	79.8 \pm 13.5	.558
Hamilton score	30.9 \pm 12.0	32.3 \pm 13.8	.720

The statistical analysis shows that the decrease of the pain (VAS) was most important with the patient of the group hypnosis than in the control group ($p=0.0001$). We must remember that both the two groups of the patients were cured with a pharmacological therapy and hypnosis was an adjuvant therapy, added in the hypnosis group. The Hamilton score is decreased from 32.6 at baseline to 22.9 and 17.1 at the first and second follow-up in the hypnosis group. In the control group it is the same at baseline (29.8), after 1 year (26.1) and after 2 years (28.5).

ANOVA shows that the difference between the two groups is statistically significant ($p<0.0001$). In both the measures of VAS and HAMA, we do not have differences between the different diseases: cancer, neurological diseases and rheumatic diseases, because the hypnosis intervention has the same therapeutic effect in the different diseases.

Table 7 : Assessment of subjects at baseline, 1-yr, and 2-yr follow-up: Data expressed in mean \pm SD (n)

	Baseline	1yr follow-up	2 yr follow-up
VAS score			
Control	78.5 \pm 14.8	62.1 \pm 15.4	57.1 \pm 15.9
Hypnosis	81.9 \pm 14.6	45.9 \pm 13.8	38.9 \pm 12.4
p.value	.827	<.001	<.001
Hamilton score			
Control	29.8 \pm 11.9	26.1 \pm 12.6	28.5 \pm 6.6
Hypnosis	32.6 \pm 12.8	22.9 \pm 11.2	17.1 \pm 5.3
p.value	.428	.348	<.001

Table 7 shows the Assessment of subjects at baseline, 1-yr, and 2-yr follow-up. The 2 groups were homogeneous.

The p-value show in the table the relationship between the 2 groups at 1 and 2 years follow-up. The 2 groups have very different score of VAS the first year and HAMA very different the second years.

The statistical analysis with ANOVA underlines that the decreases for VAS is most important in the hypnosis group than in the control group ($p=0.0001$).

The score of HAMA for anxiety decreases from da 32.6 at baseline to 22.9 and 17.1 at the follow-up of 1 year and 2 year in the hypnosis group, while it is the same in the control group (29.8, 26.1, e 28.5 at baseline, 1 and 2 years).

ANOVA underlines that the difference between the 2 groups is statistically significant ($p<0.0001$).

Figure 7: the VAS scores for Control and Hypnosis groups at baseline, year 1 and year 2, according to the type of disease suffered by subjects.

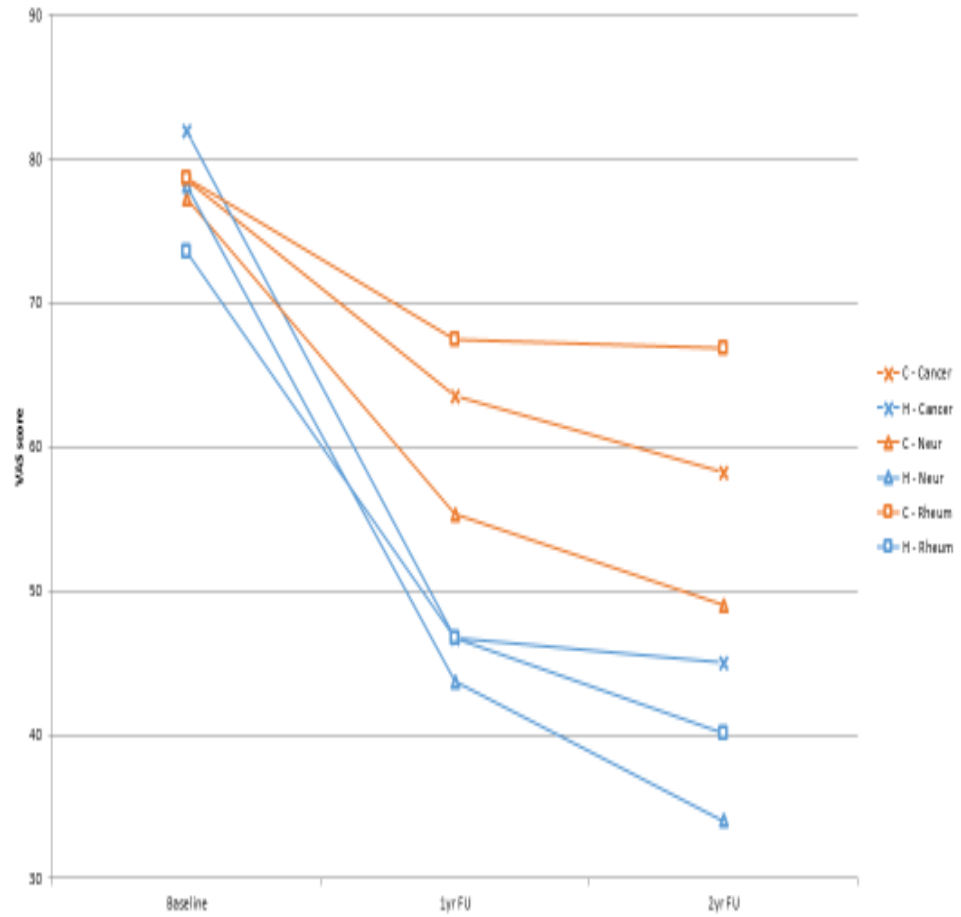


Table 8 and Figure 7 show the VAS scores for Control and Hypnosis groups at baseline, year 1 and year 2, according to the type of disease suffered by subjects.

Table 8: VAS scores for Control and Hypnosis groups at baseline, year1 and year2, according to the type of disease suffered by subjects (mean \pm sd) Data expressed in mean \pm SD (n)

	Baseline	1yr follow-up	2 yr follow-up
Cancer			
Control	78.5 \pm 14.8 (6)	63.5 \pm 15.9 (6)	58.2 \pm 14.7 (5)
Hypnosis	81.9 \pm 14.6 (7)	46.7 \pm 10.8 (7)	45.0 \pm 7.1 (2)
Neurologic disease			
Control	77.2 \pm 22.3 (9)	55.3 \pm 20.2 (9)	49.0 \pm 17.7 (8)
Hypnosis	78.1 \pm 9.1 (7)	43.7 \pm 10.0 (7)	34.0 \pm 16.7 (5)
Rheumatic disease			
Control	78.6 \pm 12.1 (10)	67.4 \pm 7.2 (10)	66.8 \pm 8.7 (6)
Hypnosis	73.5 \pm 17.3 (11)	46.7 \pm 18.0 (11)	40.1 \pm 11.2 (11)

Figure 8 and 9 and Table 9 show the Hamilton scores (mean \pm sd) for Control and Hypnosis groups at baseline, year1 and year2, according to the type of disease suffered by subjects: in all the severe diseases there is an important decrease for the the pain much more in the hypnosis group.

Figure 8: Hamilton scores for Control and Hypnosis groups at baseline, year1 and year2, according to the type of disease suffered by subjects

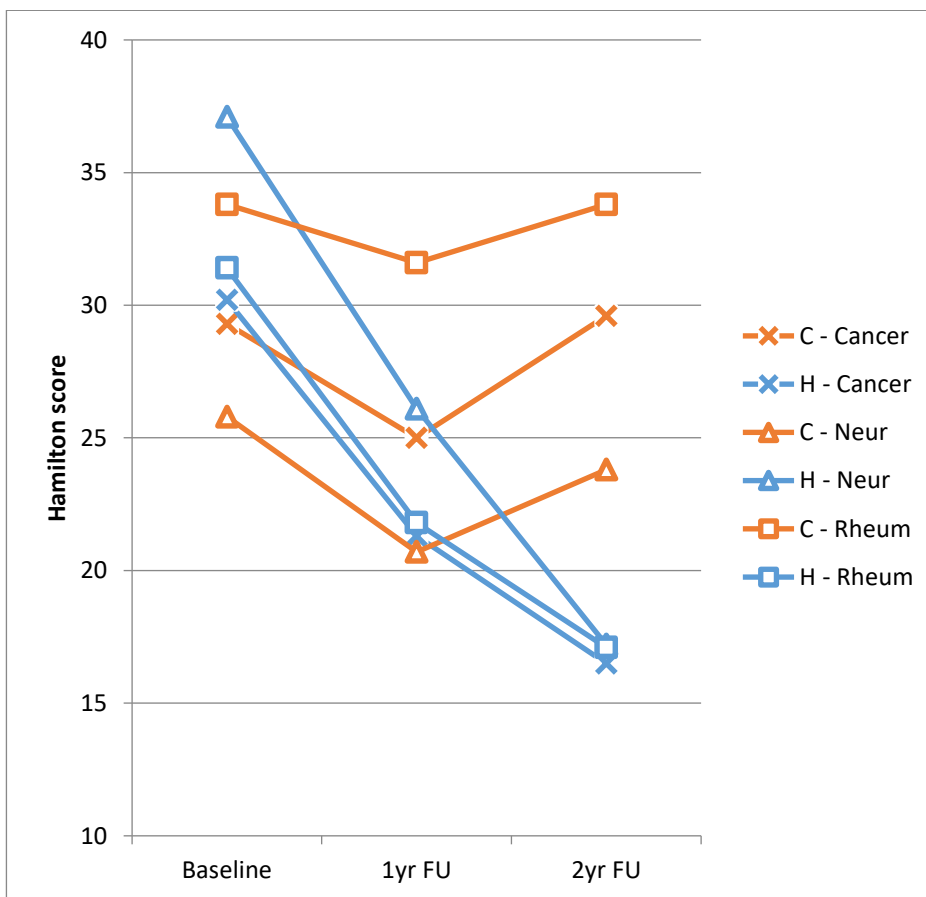


Table 9 shows the Hamilton scores (mean \pm sd) for Control and Hypnosis groups at baseline, year1 and year2, according to the type of disease suffered by subjects *Data expressed in mean \pm SD (n)*

	Baseline	1yr follow-up	2 yr follow-up
Cancer			
Control	29.3 \pm 10.0 (6)	25.0 \pm 13.5 (6)	29.6 \pm 2.4 (5)
Hypnosis	30.2 \pm 11.1 (7)	21.3 \pm 10.1 (7)	16.5 \pm 2.1 (2)
Neurologic disease			
Control	25.8 \pm 10.4 (9)	20.7 \pm 9.4 (9)	23.8 \pm 5.4 (8)
Hypnosis	37.1 \pm 15.7 (7)	26.1 \pm 13.2 (7)	17.2 \pm 4.9 (5)
Rheumatic disease			
Control	33.8 \pm 13.9 (10)	31.6 \pm 13.5 (10)	33.8 \pm 6.4 (6)
Hypnosis	31.4 \pm 12.4 (11)	21.8 \pm 11.1 (11)	17.1 \pm 6.1 (11)

Table 9 and figure 8, shows the Hamilton scores (mean \pm sd) for Control and Hypnosis groups at baseline, year1 and year2, according to the type of disease suffered by subjects: in all the severe diseases there is an important decrease for the the anxiety only in the hypnosis group.

Figure 9

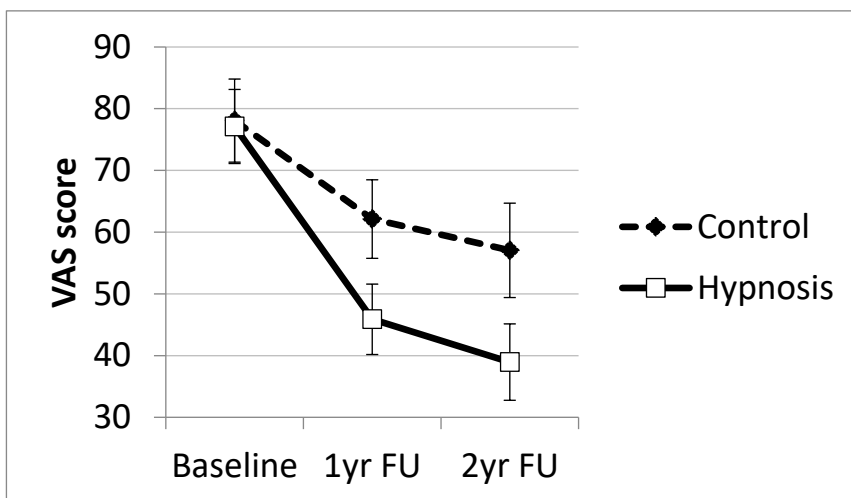


Figure 9 and 10: Change in VAS and Hamilton score across treatment groups.

Figure 10

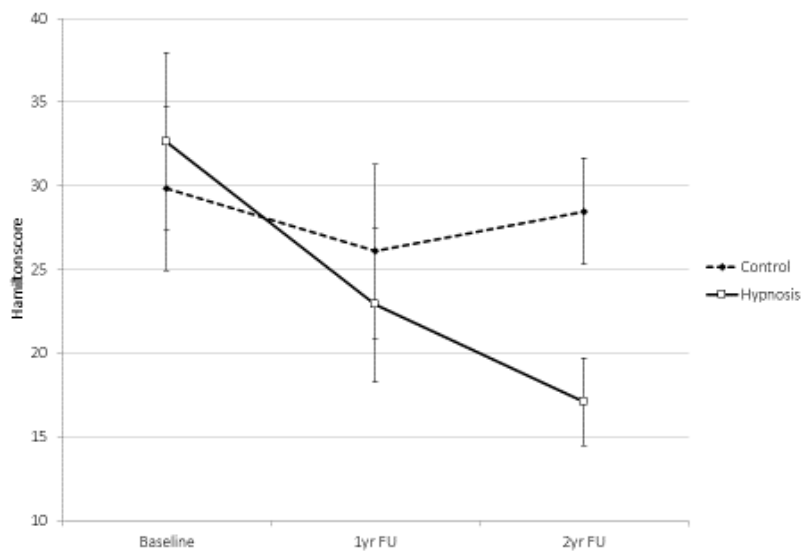


Figure 11: Hamilton scores for Control and Hypnosis groups at baseline, year1 and year2, according to the type of disease suffered by subjects.

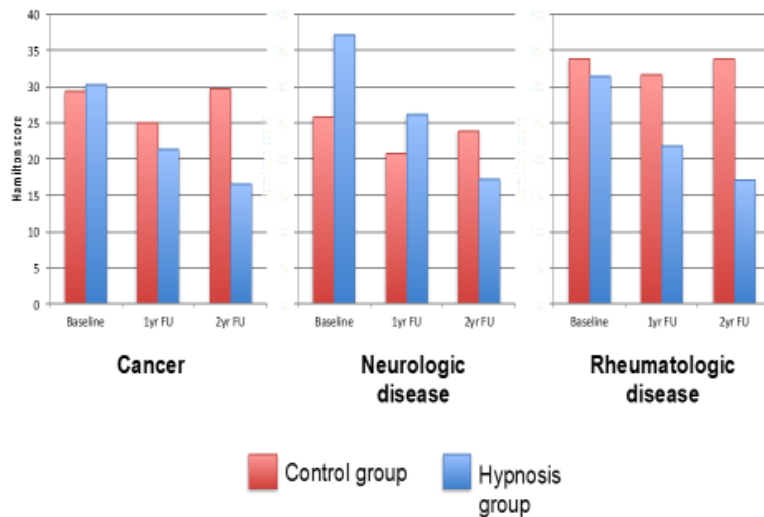
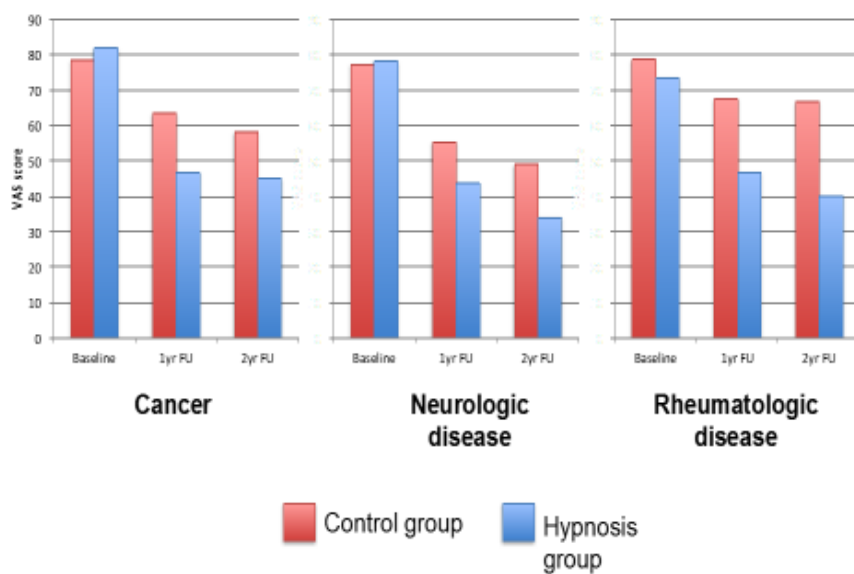


Figure 12: VAS scores for Control and Hypnosis groups at baseline, year1 and year2, according to the type of disease suffered by subjects.



CHAPTER 4

DISCUSSION AND CONCLUSIONS

Discussion

When a distressful injury or pathology is resistant to treatment and persists, when pain persists after the injury, or pathology has healed, and when medical science cannot identify the cause of pain, the task of medicine is to relieve suffering.

We have observed the patients who performed hypnosis and self-hypnosis, not only had a significant decrease of pain, anxiety and the reduction of the use of opioids, but are more likely to adopt a positive lifestyle.

The VAS scores for Control and Hypnosis groups at baseline, year1 and year2, according to the type of disease suffered by subjects, shows that in all the severe diseases there is an important decrease for the the pain much more in the hypnosis group.

This is relevant, given that all patients in this study had received a pharmacological therapy for pain relief.

The Hamilton scores (mean \pm sd) for Control and Hypnosis groups at baseline, year1 and year2, according to the type of disease suffered by subjects shows in all the severe diseases there is an important decrease for the the anxiety only in the hypnosis group.

For all the 3 types of disease, the reduction in both VAS and Hamilton scores was significantly greater in the subjects who were included in the hypnosis group, after 1 and 2 years follow-up. Subjects in the hypnosis group were at lower risk of increasing the pharmacological treatment for pain control.

Only 16% of the subjects included in the hypnosis group had to increase the pharmacological treatment for pain control after 1 year, compared to 52% of the subjects in the control group. the patients of the group 1 (hypnosis) after a long term follow-up 1 and 2 years of treatment with hypnosis as an adjuvant therapy for pain and anxiety, shows a significant statistical decrease of pain and anxiety compared with the control group,

and have a less risk to have to increase the pharmacological treatment with opioids for pain relief.

In our clinical reflection of the results, we observe that many of them had a decrease of psychosomatic symptoms associated to pain and anxiety like insomnia, muscular contracture and depression.

Many chronic pain patients often have reversed diurnal rhythms whereby they catnap during the day, reclining on couches and spent the night awake and restless.

Hypnosis can often be quite successful in reestablishing a normal sleep pattern in such patients, often resulting in an improved sense of well-being and pain relief.

Clinical hypnosis is a valid help for the patients with severe chronic diseases to enhance a sense of control, and improve pain and suffering relief, which is often lacking when someone has a chronic illness.

Pain management with clinical hypnosis distills down to a very simple endpoint, patients' relief and comfort. If the patient feels better, feels comforted, feels less stressed and more functional in life, and their practice pose no health risk, then supporting complementary and alternative therapies, creates a true holistic partnership in health care.

Hypnotic phenomena comprise numerous brain systems, depending on the content of the hypnotic suggestion and the targeted function. Therefore hypnotic suggestions act through various means: while certain suggestions engage suppression mechanisms and yield subliminal processing, other suggestions interfere with the deployment of top-down amplification and elicit preconscious processing. During hypnotically induced subliminal and preconscious processing, hypnotic responses recruit frontal networks implicated in top-down attentional regulation, control and monitoring processes (Rainville et al., 1999; Casale et al., 2012; Kihlstrom, 2013; Oakley and Halligan, 2013). As mentioned previously, these brain regions associate with the implementation of cognitive strategies to successfully comply with hypnotic suggestions. Subsequent neural effects putatively reflect the targeted function of the hypnotic suggestion (Oakley, 2008). For example, alterations of colour perception correspond with significant changes in the visual areas (Kosslyn et al., 2000; McGeown et al., 2012) and oscillatory modulations of posterior brain activity 70 to 120 milliseconds post stimulus onset (Koivisto et al., 2013). These results suggest the presence of an early mechanism that supplants the actual representation of sensory events with the suggestion-related stored representation, subsequently producing alteration of perception and suppressing sensory input. In addition, because hypnosis supposedly elicits modifications of monitoring processes, perceptual alterations could also involve

modifications of reality monitoring – i.e., the cognitive ability to assess the authenticity of changes in perception (Bryant and Mallard, 2003, 2005; Landry M, Appourchaux K, Raz A., 2014; Landry M, Lifshitz M, Raz A., 2017).

Clinical hypnosis can be considered a nonpharmacological intervention as “adjuvant” in pain therapy.

In my profession, pain, suffering and death are always very close, and when I started to experiment on the process of clinical hypnosis in its deepest way, I discovered not only pain and anxiety relief, but also the awakening of the inner self with the acceptance of the death, at the end of life and in palliative care.

Because the mechanisms of pain in cancer, chronic diseases and in Palliative Care, may be complex, involving several causes, such patients often have difficulty obtaining an adequate therapy (Baker TA, Krok-Schoen JL, McMillan SC., 2016; Brugnoli MP, Brugnoli A, Norsa A., 2006).

In our clinical observation for 2 years of treatment with clinical hypnosis, we perceived from a clinical point of view, in patient treated with hypnosis other several benefits like:

- have a good muscle relaxation of the body
- have a good muscle relaxation of the mind (anxiety relief)
- reduce anxiety in palliative care and at the end of life
- reduce the ‘Total suffering’
- have a good acute and chronic pain relief
- altered perception of pain.
- facilitate new patterns of thoughts, feelings and consciousness
- reduce depression
- reduce sleep disturbances
- reduce pre-operative anxiety (in cancer patients)
- reframe or redefine a problem or situation with resilience
- bypass normal ego defenses
- suggest solutions and new options
- increase communication with family and other people
- improve mind-body relationship, as a psychotherapy
- lighten up the "spiritual" dimension in dying patients
- accept death and dying.

The hypnosis' techniques, allow the patients' mind to settle inward beyond thought to experience the source of thought, inner resilience to relief pain and anxiety in severe chronic illnesses.

In this state of restful alertness, your brain functions with significantly greater coherence and your body gains deep rest (Austin, J. H.,1999).

The aim of clinical hypnosis and self-hypnosis is to bring an inner state of well-being within ourselves and the world, in a positive mental and (at the end of life) spiritual way. This research has shown clinical hypnosis to be helpful not only for acute and chronic pain, but also to accept serenely the end of life. We did not measure this topic in our patients, but clinically we noted a very great difference between the patients of the 2 groups.

A hypnotherapist can teach to the patients the self-regulation skills. For instance, someone with arthritis or cancer pain, may learn to turn down pain like the volume on a radio.

Hypnotherapy can be used to help manage chronic illness.

Self-hypnosis can enhance a sense of control, and improve pain and suffering relief, which is often lacking when someone has a chronic illness.

This research shows that hypnotherapy reduces pain, anxiety, and discomfort, and reduces the use of opioids.

Pain is the major problem in the treatment of patients with chronic diseases and cancer. During prolonged illnesses, the best way that we can create that change our suffering, is to modify our thoughts, from being negative about positive.

The positive discovery about clinical hypnosis, is that we are focusing within ourselves, and becoming free of negativity.

Clinical hypnosis improves psychological resilience. It is an individual's tendency to cope with stress and adversity. This coping may result in the individual "bouncing back" to a previous state of normal functioning, or simply not showing negative effects. In all these instances, resilience is best understood as a process. It is often assumed to be a trait of the individual, an idea more typically referred to as "resiliency."

Most research now, shows that resilience is the result of individuals being able to interact with their environments, and the processes that either promotes well-being or protects them against the overwhelming influence of risk factors.

These processes can be individual coping with strategies, or may be helped by clinical hypnosis (Casula C., 2001).

Clinical hypnosis' techniques, simply involve a process of transforming ourselves, our thoughts, and recognizing the negative thoughts, and changing them into beneficial and peaceful thoughts, not only psychologically, but also with a physical pain relief. (Erickson, M.H., 1959; De Sousa, R.,1987;

Brugnoli, M.P., Brugnoli, A., Norsa, A., 2006; Brugnoli, A., 2005; Linden JH., 1999; Casula C., 2001).

The best attitude towards hypnosis, is to be very patient, as the mind does not always want to focus. Having a sense of expectation towards positive results, can create uncomfortable pressure and thus take away the enjoyment of the experience. By practicing hypnosis regularly, the person gains a wonderful sense of the suffering relief.

Self-hypnosis is a self-healing process: any form of pain is a sign of our negative thinking and distress within our mind. If we don't attend to distress in the mind, we may find that chronic suffering can lead to disease of the body (Fourie, D.P., 1997; Handel, DL., 2001; Patterson, D.R., 2010).

This is that we have been proven by this scientific research. Nonpharmacologic approaches as hypnosis, are intended to supplement, not substitute for, the pharmacologic or invasive techniques described.

Nonpharmacologic interventions are appropriate in chronic diseases, in cancer patients and in Palliative Care, for the patient who:

- 1) finds such interventions appealing;
- 2) expresses anxiety or fear, as long as the anxiety is not incapacitating or due to a medical or psychiatric condition that has a non-specific treatment;
- 3) may benefit from avoiding or reducing drug therapy for pain and anxiety (e.g., history of adverse reactions, fear of or physiological reason to avoid oversedation);
- 4) is likely to experience and need to cope with a prolonged interval of postoperative pain, particularly if punctuated by recurrent episodes of intense treatment, or procedure-related pain.
- 5) has incomplete pain relief following appropriate pharmacologic interventions.

During my research as pain therapist and palliative care physician, I was always very touched by the suffering and the death of my patients with cancer and severe chronic diseases, but I understood that clinical hypnosis could be an important empathetic and compassionate approach for the total suffering, as an adjuvant therapy.

The suffering of these patients is not only physical but also psychological and spiritual, and clinical hypnosis can really help the patients with chronic diseases, in a state of 'total pain' at the end of life.

Palliative care was perceived in the hypnosis group, to be more holistic and person-focused, even if it was a group therapy, with an emphasis on symptoms' management. The group therapies with clinical hypnosis, were seen as following an empathetic and compassionate model, in contrast to the simply pharmacological

model experienced in the palliative care of the control group. An important statistical differences on the score of pain and anxiety were found after one year and two years of follow-up between participants in the hypnotical intervention and the control group.

Limitations and recommendations for future researches

The limitations of the current research preclude our ability to draw strong conclusions to inform clinical practice or public policy regarding optimal use of the hypnosis and self-hypnosis therapies for severe chronic diseases and in palliative care.

The following limitations are evidence point to numerous opportunities to improve future research. Questions remain about the efficacy, comparative effectiveness, and differential response among subgroup populations.

We would have compare a third group of patients studied with alternative/complementary medicine, or psychotherapy, but we did not have enough patients to enroll that could met the inclusion criteria.

One of the most pertinent questions regarding clinical hypnosis therapies for pain and anxiety is: What effects might one expect of a given intervention relative to no intervention? This clinically relevant question is best addressed by a randomized clinical trial. However, for an ethical choose, we decided to respect the enthusiasm of patients with severe chronic diseases, to add self-hypnosis to the pharmacological therapy: expectations and motivations could be also a bias. But we could observe that the patient of hypnosis group, died for cancer, developed better resilience and self growth at the end of life, respect to the patients of control group.

Although this therapeutic approach has not been used widely, such strategies merit consideration as an alternative to increase medicines.

Another pertinent inquiry is: to what extent might placebo, or nonspecific effects account for observed clinical outcomes? This question can be hard to answer for CAM therapies, like hypnosis, for which it may be difficult to design a sham procedure that is both truly inert and that appears sufficiently similar to the active intervention to isolate the specific effect of the intervention. The fields of psychotherapy research have long grappled with similar issues. Strong recommendations and methodological guidelines now exist to guide these efforts (Schnurr PP., 2007).

Although more costly and challenging to conduct, comparative effectiveness designs also may be indicated to give patients and clinicians the most direct evidence about competing treatment options.

We must also consider that is difficult compare the exat interaction of the many different chemotherapies on pain relief.

All our cancer patients was in a stage of severe disease and all of them had almost a cycle of chemotherapy in the 2 years of the follow-up. However, we must consider also that they were shared equitably in the two groups: 28% in the hypnosis group and 24% in the control group.

Conclusions

Several studies are needed to improve the knowledge of clinical hypnosis in Palliative Care. Advances in health information and studies are enabling a transformation in health research that could facilitate studies that were not feasible in the past, and thus lead to new insights regarding health and disease.

The greatest limit to its use in today's palliation is the lack of education by hospital personnel in its use, and their resulting failure to recommend its use for patients. There are also too few hypnotherapists with specific training and experience in this field.

Clinical Hypnosis in Palliative care offers patients in pain not a measurable quantity of days, but quality of life, with pain and anxiety relief, and ready to accept the natural dying process characterized by the failing of the body.

Key Messages

Hypnosis offers the opportunity to relief :

- Physical pain relief (Patterson, D.R., 2010; Patterson, D.R., Jensen, M.P., 2005; Landry M, Lifshitz M, Raz A., 2017).
- Psychological anxiety and spiritual suffering relief (Perez-De-Albeniz, A., Jeremy H., 2000; Linden JH, Bhardwaj A, Anbar RD., 2006).
- the reduction of the use of the opioids (Berger MM, Davadant M, Marin C, Wasserfallen JB, Pinget C, Maravic P, Koch N, Raffoul W, Chiolo RL., 2010).
- Clinical hypnosis is a valid therapy for a long treatment (we have a follow-up of 2 years)
- clinical hypnosis is an interdisciplinary therapy and is centered around the quality of life of the patients.

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