Prevalence of Depression among Patients with Chronic Low Back Pain

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Presented By

Huda Hossam Eldin Abd Elhafez

(M.B.B.ch.)

Faculty of Medicine-Benha University

Supervised By

Prof. Rizk Mohamed Khodair

Professor of Neurology

Faculty of Medicine - Benha University

Prof. Hussein El-Olemy Elsheikh

Professor of Psychaitry

Faculty of Medicine - Benha University

Dr. Ibrahim Ahmed Abd-Elrassoul

Lecturer of Neurology

Faculty of Medicine - Benha University

Faculty of Medicine - Benha University

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Huda Hossam Eldin Abd Elhafez

Contents

List of Abbreviation

1H-MRS	Proton MRS.
95% CI	95% confidence interval.
ANOVA	Analysis of covariance.
BA	Bronchial asthma.
BMI	Body mass index.
BP	Blood Pressure.
CBC	Complete blood count.
CBT	Cognitive behavioral therapy.
CDD	*Chronic Depressive Disorder*.
Cho	Choline.
CIDI	*WHO Composite International Diagnostic Interview*.
CLBP	Chronic low back pain.
CNS	Central nervous system.
COPD	Chronic obstructive pulmonary disease.
Cr	Phosphocreatine complex.
CRH	Corticotrophin-releasing hormone.
CRP	C-reactive protein.
CT	Computed tomography.
CTA	*Epidemiologic Catchment Area Survey*.
DALY	Disability adjusted life years.
DBI	Depression Beck Inventory.
DM	Diabetes mellitus.
DM	Diabetes Mellitus.
DSM	Diagnostic and Statistical Manual of Mental Disorders.
ECT	Electroconvulsive therapy.
EEG	Electroencephalography.
ESR	Erythrocyte sedimentation rate.
FDA	Food and Drug Administration.
GABA	Gamma-aminobutyric acid.
GR	Glucocorticoid.
HDL	High Density Lipoprotein.
HPA	Hypothalamic-pituitary-adrenal axis.
HRQoL	Health-related quality of life.

ICD-10	*International Classification for Diseases and Related Disorders.*
IL	Interleukin.
INR	International Normalized Ratio.
LBP	Low back pain.
LDL-C	Low Density Lipoprotein Cholesterol.
Lp (a)	Lipoprotein (a).
MDD	Major Depressive Disorder.
MR	Mineralocorticoid.
MRA	Magnetic Resonance Angiography.
MRI	Magnetic resonance imaging.
NAA	N-acetylaspartate.
NAC	Nucleus accumbens.
NCS	*National Comorbidity Survey.*
NCS-R	National Comorbidity Survey-Replication.
NMDA	N-methyl-D-aspartate.
NSAIDs	Non-steroid anti-inflammatory drugs.
ODIN	Outcome of Depression International Network.
PET	Positron emission tomography.
PVD	Peripheral vascular disease.
RA	Rheumatoid arthritis.
REM	Rapid eye movement.
rTMS	Repetitive transcranial magnetic stimulation.
SD	Standard deviation.
SPSS	Statistical Package for Social Science.
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants.
VBM	Voxel-based morphometry.
VTA	Ventral tegmental area.
WHO	*World Health Organizations'.*

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Introduction

Back pain is common and is considered a major health concern with lifetime prevalence estimated at over 70% in industrialized nations ***(Borenstein et al., 2004).*** The recent burden of disease findings showed that back pain is the leading cause of disability-adjusted life years in Western Europe and Australia, and is ranked sixth of the top 25 diseases for disability burden globally ***(Murray et al., 2012).***

Disability associated with back pain can have widespread effects on both the economy, because of extensive health care costs and absence from work, as well as on the individuals and their family. Similar evidence on low back pain prevalence, disease burden, and associated risk factors have also been reported in populations in Iran ***(Biglarian et al., 2012).***

Chronic low back pain (CLBP), lasting more than 3 months, accounts for no more than 10% of cases but is one of the greatest health problems in industrialized societies, with costs of US$100–$200 billion a year ***(Dagenais et al., 2008).***

Pain has consistently been shown in prospective epidemiological studies to be a risk factor for the development of depression, with people reporting disabling spinal pain having over double the risk for developing depression. Evidence indicates that psychological factors such as depression can represent a significant barrier to recovery, and psychological interventions are now part of biopsychosocial treatment strategies for chronic pain conditions such as back pain ***(Linton and Shaw, 2011; Magni et al., 1994)***.

Previous reports found that between 43% and 66% of individuals who meet the criteria for depression also report painful symptoms in contrast to 16% of the general population. According to **Lepine and Briley (2004**), probably even more than 75% of patients with depression experience chronic or recurring pain. Likewise, patients with chronic pain show high rates of depression, from 11% to 100% ***(Lépine and Briley, 2004).***

Therefore, a reduction in the development of depression would be an important outcome for those who experience back pain. To date, there is no previous study which reported the prevalence of depression among Egyptian patients with CLPB. Therefore, we conducted this study to assess the prevalence of depression among Egyptian patients with CLPB.

Aim of the Work

To assess the prevalence of depression in patients with CLPB, using a psychiatric diagnostic interview.

Chapter I: Chronic Low Back Pain

Low-back pain is one of the most common painful conditions experienced by human beings throughout their life. Lifetime prevalence has been reported to be as high as 84% depending on the case definition used, and no age group is spared, even children ***(Manchikanti et al., 2009).***

Low-back pain is also an occupational disorder and, probably, the most common among occupational disorders worldwide *(**Manchikanti et al., 2009**)*.

Although low-back pain is not a lethal condition, it was estimated at the third rank among all diseases by disability-adjusted life-years in 2010 in the USA, after ischemic heart disease and chronic obstructive pulmonary disease, and at the first rank by years lived with disability. It also ranked high globally for the same year, in disability-adjusted life-years*(**Murray et al., 2013**)*.

This chapter will provide an overview of modern concepts of chronic low-back pain (CLBP).

A-<u>Definition and Epidemiology of CLBP:</u>

Low back pain is defined as "pain, muscle tension or stiffness localized below the costal margin and above the inferior gluteal folds, with or without referred leg pain". With respect to pain etiology, clinical guidelines usually call for distinguishing two main categories of low back pain*(**Waddell and Burton, 2001**):*

- Nonspecific low-back pain, which is defined as a condition attributable to no recognizable known specific pathology (including low-back pain deemed to be of mechanical origin)
- Specific low-back pain, which is defined as a condition attributable to a recognizable known specific pathology (e.g., infection, tumor, fracture, inflammatory process, radicular syndrome).
- Nonspecific low-back pain accounts for the vast majority (85%) of cases of this condition; most of these cases will recover spontaneously within a couple of weeks.

However, in some cases pain and disability have a longer duration, so low-back pain is currently classified, with regard to duration of symptoms, as*(**van Tulder et al., 2006**):*

- ***Acute:*** an episode of low-back pain lasting less than 6 weeks.
- ***Subacute:*** duration between 6 and 12 weeks.
- ***Chronic:*** duration more than 12 weeks.

The precise incidence and prevalence of low back pain are difficult to characterize due to significant heterogeneity in the epidemiologic studies. In a survey of ***Saskatchewan adults***, 84% of participants reported experiencing at least one episode of back pain in their lifetime ***(Côté et al., 1998)***.

A 2002 US National Health Interview Study found that 26.4% of the 30,000 participants had experienced at least one full day of back pain in the past 3 months. A 2010 review article reported 1-year incidences of first time, any time, and recurrent low back pain episodes as ranging from 1.5% to 80%, and the 1-year prevalence of low back pain ranging from 0.8% to 82.5% ***(Deyo et al., 2006)***.

Overall, the annual prevalence of CLBP has been reported to range from 15% to 45%, with a point prevalence of 30%. Studies evaluating CLBP have estimated that the average age-related prevalence of persistent low back pain is approximately 15% in adults and 27% in the elderly*(**Manchikanti et al., 2009**)*.

Contrary to the popular belief that the prevalence of low back pain is steady or declining, studies have shown an increasing prevalence of low back pain. ***Freburger et al.*** reported the rising prevalence of CLPB following an evaluation of North Carolina households conducted in 1992 and repeated in 2006. The results showed an increase in the prevalence of chronic impairing low back pain over a 14-year interval, from 3.9% (95% confidence interval [CI], 3.4–4.4%) in 1992 to 10.2% (95% CI, 9.3–11.0%) in 2006 ***(Freburger et al., 2009).***

Increases were seen for all adult age strata, in men and women, and in whites and African Americans. The overall prevalence of low back pain increased by 162% with increases of 226% in non-Hispanic blacks and 219% in the 45- to 54-year-old age group. While the overall prevalence of CLBP increased 162%, among women aged 21 to 34 it increased 320% and among men aged 45 to 54 it increased 293%. Furthermore, the authors also found that episodes of acute low back pain defined as pain that limited usual activities for at least one day, but less than three months, or less than 25 episodes of low back pain that limited activities in the past year, increased from 7.3% to 10.5% *(**Freburger et al., 2009**)*.

B- Pathophysiology of CLBP:

1- Anatomy:

There are 5 lumbar vertebrae, each of which is composed of a vertebral body, 2 pedicles, 2 lamina, 4 articular facets, and a spinous process. Between each pair of vertebrae are the foramina, openings through which pass the spinal nerves, radicular blood vessels, and sinuvertebral nerves. The spinal canal is formed anteriorly by the posterior surface of the vertebral bodies, intervertebral discs, and posterior longitudinal ligament, laterally by the pedicles, and posteriorly by the ligamentum flavum and lamina ***(Delitto et al., 2012)***.

In the normal spine, the anterior structures including the vertebral bodies and intervertebral discs perform weight-bearing and shock-absorbing functions. The posterolateral structures, including the vertebral arches, lamina, transverse, and spinous processes, provide protection for the spinal cord and nerve roots. Balance, flexibility, and stability are provided by the facet joints and paraspinous muscles and ligaments ***(Delitto et al., 2012)***.

2- Physiology

Low back pain is often characterized in terms of radiologic findings (spondylosis, spondylolisthesis, and spondylolysis) and clinical and neurologic findings (lordosis, kyphosis, radiculopathy, sciatica). Experimental studies indicate that mechanical low back pain can originate in one or more of the many structures of the spine, including ligaments, facet joints, intervertebral discs, paravertebral musculature and fascia, and spinal nerve roots ***(Delitto et al., 2012).***

3- The development of CLBP

- ***CLBP - a biopsychosocial condition***

CLBP affects the back from below the costal margin to the gluteal fold. It is a significantly disabling condition that is responsible for long periods of absence from work and often early retirement. Current thinking is that CLBP is a biopsychosocial illness. This means that even if an initial anatomical injury can be identified, the patient's pain experience and disability are determined by a wide range of psychosocial factors ***(Morlion, 2013).***

Some of these – e.g. previous pain experiences, general and psychological health, anxiety and fear-avoidance – are directly related to the patient's CLBP. Others such as social wellbeing, job satisfaction, economic status, level of education and compensation claims, have little or no connection ***(Goffaux et al., 2011)***.

- ***Central sensitization***

It is unclear why acute pain progresses to chronic pain in some patients but not others. A number of patient-related risk factors have been identified, but these can only provide an approximate probability of chronic pain developing. Pain signals from the initial peripheral injury to central pain pathways definitely play a role. High levels of peripheral input increase synaptic efficacy and reduce inhibition in the CNS, producing central sensitization ***(Paulson et al., 1998; Woolf, 1983)***.

The modulated signals are then transmitted via ascending pathways to the brain. This maladaptive neuroplasticity enhances the pain response to noxious stimuli in amplitude, duration and spatial extent, i.e. inducing hyperalgesia. Also, subliminal signals from non-noxious stimuli that are normally too weak to generate pain are now above the lowered threshold and activate the pain circuit, causing allodynia ***(Pergolizzi et al., 2014)***.

In addition, central sensitization appears to affect the descending modulatory pathways that influence the clinical pain experience. Inhibitory pathways which suppress diffuse noxious stimuli are attenuated and facilitatory pathways are amplified, producing a net increase in pain signal transmission ***(Staud et al., 2007)***.

- ***The 'neuromatrix'***

The transition from acute to chronic pain may also alter the way that pain signals are processed by the so-called 'neuromatrix' in the brain, which integrates multiple inputs to produce the output pattern that evokes pain. When pain becomes chronic, the efficacy of the neuromatrix is strengthened such that less input, both nociceptive and non-nociceptive, is required to produce pain. The characteristic changes seen in central sensitization are increased activity in areas of the brain involved in processing acute pain signals (e.g. insula, prefrontal cortex), and concurrent activity in other areas not known to be involved in acute pain processing, such as brainstem nuclei and the dorsolateral frontal cortex ***(Melzack, 1999; Moseley, 2003)***.

The forebrain can influence brainstem nuclei, including those associated with descending pathways, and this offers a potential route for cognitive thought and emotions to affect pain levels. Furthermore, there is evidence that brain activity related to acute or subacute back pain is limited to networks associated with acute pain, whereas in chronic back pain the networks engage more with emotion-related circuitry ***(Seifert and Maihöfner, 2009)***.

C-Risk Factors of CLBP:

Low back pain is a multifactorial disorder with many possible etiologies. Consequently, to analyze the various risk factors of low back pain and dissect this 20th-century health-care enigma, many epidemiologic studies have focused on risk factors for low back pain, attempting to analyze occupational, non-occupational, and psychosocial factors. **Cohen et al**. concluded that the risk factors for progression to chronic back pain are predominantly psychosocial and occupational ***(Cohen et al., 2008)***.

1- Comorbid Factors

In an evaluation of the association of comorbidities, utilization, and costs for patients identified with low back pain, **Ritzwoller et al**. showed that diabetes, rheumatoid arthritis, anxiety, psychiatric illness, and depression were associated with significant incremental increases in back pain disability and costs. The prevalence of risk comorbidity was highest for anxiety, followed by depression in fifth place, and psychosis in 12th place out of 14 comorbid categories. Bronchial asthma, chronic obstructive pulmonary disease, and cardio/peripheral vascular disease occupied categories 2 to 4 ***(Ritzwoller et al., 2006)***.

2- Psychological Factors

The role of psychological distress in the development of low back pain has been highlighted by a number of authors. Factors such as anxiety and depression, catastrophizing, kinesophobia (fear of movement), and somatization (the expression of distress as physical symptoms or their persistence) have been suggested as risk factors for low back pain in

prospective studies in adults and children ***(Croft et al., 1995; Larson et al., 2004)***.

3- Occupational Factors

Employment and workplace factors, both physical and psychological, have been associated with low back pain. Heavy lifting, pushing, pulling, and prolonged walking or standing were found to be predictors of future back pain, as well as similar associations with heavy lifting, physical workload, job demands and control, stressful and monotonous work, and dissatisfaction with work ***(Sitthipornvorakul et al., 2011)***.

Vehicular driving had been associated with a higher incidence of back symptoms and degenerative changes, and was attributed to the effects of whole-body vibration on the intervertebral disc ***(Battié et al., 2009; Palmer et al., 2008)***.

However, in an extensive review by the Swedish National Institute for Work and Life, it was cautioned that though most studies revealed significantly higher frequencies of back symptoms and degenerative changes in the vertebrae and intervertebral discs of drivers, "uncontrolled confounding factors may have affected the results in all studies, and the conclusions about the causal role of whole-body vibration for observed injuries and/or disorders, therefore, becomes uncertain." ***(Wikström et al., 1994)***

4- Lifestyle and Social Demographic Factors

A number of lifestyle and social demographic factors have been linked with low back pain in a variety of studies. Body mass index has been linked to low back pain with obese people in particular at increased

risk. ***Leboeuf-Yde***, in a systematic review of epidemiologic literature to establish whether body weight is truly associated with low back pain and whether the link may be causal, showed that of the 65 studies reviewed, 32% reported a statistically significant positive weak association between body weight and low back pain. However, one study found this to be true only among women ***(Leboeuf-Yde, 2000)***.

In a study of the impact of body mass index on the prevalence of low back pain in a large population, the results showed that in both sexes, a high body mass index was significantly associated with an increased prevalence of low back pain. While additional adjustments for education, smoking status, leisure time physical activity, employment status, and activity at work hardly affected these associations, there were no interactions found with most other factors. The authors concluded that this large population-based study indicates that obesity is associated with a high prevalence of low back pain ***(Heuch et al., 2010).***

Leboeuf-Yde conducted a systematic review of the literature on smoking and low back pain in 47 epidemiologic studies. This analysis showed consistent evidence in favor of a causal link between smoking and low back pain ***(Leboeuf-Yde, 1999).***

Furthermore, ***Leboeuf-Yde et al.,*** in a cross-sectional postal survey of 29,424 persons aged 12 to 41 years, showed a positive association between smoking and low back pain that increased with the duration of low back pain. They concluded that there was a definite link between smoking and low back pain that increased with the duration and frequency of the low back pain problem, but that the link was unlikely to be causal ***(Leboeuf-Yde et al., 1998)***.

In chronic pain settings, current cigarette smokers reported significantly greater pain intensity and pain interference with functioning. Symptoms were more pronounced in smokers with more severe nicotine dependence. Smokers also are more likely to use analgesic medications than people who have never smoked. Cigarette smokers enrolled in a national spine network database have shown to have more severe back pain and lower functional status than nonsmokers***(John et al., 2006).***

A study by ***Du and Leigh*** assessed the incidence of workers' compensation indemnity claims across sociodemographic and job characteristics. They looked at data spanning from 1997 through 2005 and found that the odds ratio for men and African Americans were relatively large and strongly significant predictors of claims; significance for Hispanics was moderate and confounded by education. Odds ratios for variables measuring education were the largest for all statistically significant covariates; however, neither low wages nor employer-provided health insurance was a consistent predictor. In addition, due to confounding from the “not salaried” variable, overtime was not a consistently significant predictor(Du and Leigh, 2011).

Leigh et al. evaluated lifestyle risk factors to predict health-care costs in an aging cohort. They compared annual survey data from 1986 through 1994 for lifestyle factors and health utilization from 1994 through 1998. Health-care costs in nine categories were ascertained from validated utilization. The results showed that fewer cigarette-pack years and lower body mass index were the most significant predictors of lower total costs in 1998. Daily walking, measured at baseline, also predicted lower costs for hospitalizations and diagnostic testing. They concluded that seniors who are leaner, smoked fewer cigarettes over a lifetime, reduced their smoking, or walked farther had significant subsequent cost

savings compared with those with less-healthy lifestyle-related habits*(**Leigh et al., 2005**)*.

Associations between low back pain and social class, low levels of education, and low income also have been reported. Social problems, such as sexual and physical abuse or deterioration in social life, have been suggested as risk factors for low back pain*(**Webb et al., 2003**)*.

A study evaluating the role of overindebtedness and its association with the prevalence of back pain showed that the point prevalence of back pain was 80% in the over indebted compared with 20% in the general population. Being over indebted was identified as an independent modifier and was associated with an 11 times increased probability to suffer from back pain*(**Ochsmann et al., 2009**)*.

5- Role of Age and Degenerative Disease

Many degenerative conditions, including degenerative disc, facet, sacroiliac joint, and other pathologies that result in low back pain, have been viewed as a result of aging and "wear and tear" from mechanical trauma and injuries. However, some of them are now viewed as being determined in great part by genetic influences. ***Battié et al. (1995)*** in a review of contributions to a changing view of disc degeneration, concluded that disc degeneration is now considered a condition that is primarily genetically determined, although elusive environmental factors also play an important role.

Moreover, most of the specific environmental factors once thought to be the primary risk factors for disc degeneration appear to have very modest effects, if any. Other work on disc degeneration in twins established the substantial role of heredity and disc degeneration through

the identification of high degrees of familial aggregation, suggesting a substantial genetic influence. However, the investigation of genetic influences on disc degeneration is still in its infancy***(Battié et al., 2009)***.

Increasing age has been associated with an increase in musculoskeletal symptoms. A US national survey of physician visits among patients aged 75 or older revealed that back pain is the third most frequently reported symptom in general and the most commonly reported in the musculoskeletal system***(Hsiao et al., 2010).***

A Canadian epidemiological report ranked back problems as the third leading cause of chronic health problems in the 65-years-and-older age category for women and the fourth leading cause of such problems for men in the same age category***(Hsiao et al., 2010).***

Estimates of the prevalence of back pain in the USA showed higher rates for the elderly (over the age of 65), with at least one day of back pain in the past three months and a lifetime prevalence of low back pain lasting at least two weeks. The prevalence of low back pain was higher in 2005 and 2006 for elderly over the age of 65. It has been stated that low back pain usually begins early on in life, with the highest frequency of symptoms occurring in the age range of 35 to 55, and that sickness, absence, and symptom duration increase with age.*(**Blackwell et al., 2014**)*.

6- Role of Gender

Low back pain has been reported consistently in a higher proportion of females than males. Back pain appears to be a significant problem during pregnancy and often continues after delivery. In a recent multicenter study conducted in the Spanish National Health Service, the

four-week prevalence of low back pain and leg pain was 71.3% and 46.2%, respectively. The main factors associated with a higher likelihood of reporting low back pain were a history of low back pain, pain both related and unrelated to previous pregnancy and postpartum, pain augmented by time spent in bed, and anxiety. In contrast, the factors associated with a higher likelihood of reporting leg pain were reporting low back pain, a lower education level, younger age, depression, a lower number of hours of sleep per day, and a higher body mass index ***(Hoy et al., 2012; Kristiansson et al., 1996; Olsson et al., 2012)***. **(Table 1)**

Table 1 shows some of the risk factors for development of low back pain (Manchikanti et al., 2014).

Physical Factors	***Comorbid Factors***	***Psychological Factors***	***Occupational Factors***	***Lifestyle and Social Factors***
1- Older age ***2- Female gender***	*1- DM* *2- RA* *3- COPD* *4- BA* *5- PVD*	*1- Depression* *2- Anxiety* *3- Somatization disorder*	*1- Physically or psychologically strenuous work* *2- Sedentary work* *3- Whole body vibration* *4- Low social support in the workplace* *5- Job dissatisfaction* *6- Workers compensation insurance*	*1- Obesity* *2- Smoking* *3- Low educational achievement* *4- Low income*

D- Differential Diagnosis of CLBP:

One approach to organizing the differential diagnosis of low back pain is to consider it in terms of nonspecific "mechanical" low back pain versus back pain with lower extremity symptoms versus systemic and visceral diseases***(Deyo and Weinstein, 2001),*** as shown in **Table 2.**

By far the most common causes of low back pain are mechanical, representing about 97% of patients. In clinical practice, it is often difficult to determine the precise source of a patient's mechanical back pain. ***Deyo***

and Weinstein have reported that a definitive diagnosis cannot be made in up to 85% of patients due to the weak association between symptoms, pathologic changes, and findings on imaging. The inability to make precise diagnoses results in the frequent use of nonspecific diagnostic terms, such as sprain, strain, spasm, and degenerative changes***(Deyo and Weinstein, 2001).***

There are also non-mechanical causes of low back pain, including neoplasms, infections, and inflammatory conditions. Non-mechanical causes of back pain are usually accompanied by systemic signs and symptoms or a severe, rapidly progressing course. Visceral organ pain, including bowel, kidney, and pelvic organ pain, can also be referred to the spine. Overall, non-mechanical spine conditions and referred visceral organ pain are much less common causes of low back pain than mechanical causes***(Andersson, 1999).***

Table 2 Differential diagnosis of low back pain(Manchikanti et al., 2014)

Nonspecific "Mechanical" Low Back Pain	***Back Pain with Lower Extremity Symptoms***	***Systemic and Visceral Diseases***
1- Idiopathic musculoligamentous strain/ sprain ***2- Disc/facet degeneration*** ***3- Osteoporotic compression fracture*** ***4- Spondylolisthesis*** ***5- Severe scoliosis, kyphosis, asymmetric***	*1- Disc herniation* *2- Spinal stenosis*	*1- Neoplasia (Multiple myeloma, Metastatic carcinoma, Lymphoma/leukemia, Spinal cord tumors, Retroperitoneal tumors)* *2- Infection (Osteomyelitis, Septic discitis, Paraspinous abscess, Epidural abscess, Shingles)* *3- Inflammatory disease* *4- Visceral disease* *5- Other (Osteochondrosis, Paget's*

transitional vertebrae	*disease)*
6- Traumatic fracture	

E- Evaluation of CLBP Patients:

The initial evaluation, including a history and physical examination, of patients with CLBP should attempt to place patients into one of the following categories: (1) non-specific low back pain; (2) back pain associated with radiculopathy or spinal stenosis; (3) back pain referred from a non-spinal source; or (4) back pain associated with another specific spinal cause . For patients who have back pain associated with radiculopathy, spinal stenosis, or another specific spinal cause, magnetic resonance imaging (MRI) or computed tomography (CT) may establish the diagnosis and guide management ***(Haldeman and Dagenais, 2008).***

The medical history should include questions about osteoporosis, osteoarthritis, and cancer, and a review of any prior imaging studies. Review of systems should focus on unexplained fevers, weight loss, morning stiffness, gynecologic symptoms, and urinary and gastrointestinal problems*(**Chou et al., 2007**).*

The physical examination should include the straight leg raise and a focused neuromuscular examination. A positive straight leg raise test (pain with the leg fully extended at the knee and flexed at the hip between 30 and 70 degrees) can suggest lumbar disk herniation, with ipsilateral pain being more sensitive (i.e., better at ruling out disk herniation if negative) and contralateral pain being more specific (i.e., better at ruling in herniation if positive). Testing deep tendon reflexes, strength, and sensation can help identify which nerve roots are involved ***(Chou et al., 2007; Devillé et al., 2000)***.

Laboratory assessment, including erythrocyte sedimentation rate, complete blood count, and C-reactive protein level, should be considered when red flags indicating the possibility of a serious underlying condition

are present (**Table.3**). Urinalysis may be useful when urinary tract infections are suspected, and alkaline phosphatase and calcium levels can help identify conditions, such as Paget disease of bone, that affect bone metabolism; however, these tests are not needed in all patients with chronic low back pain ***(Kinkade, 2007).***

Imaging has limited utility because most patients with chronic low back pain have nonspecific findings on imaging studies, and asymptomatic patients often have abnormal findings. Initial imaging with MRI, which is the preferred study, or CT is only recommended for patients with red flags for serious or rapidly progressive disease or radicular symptoms that do not spontaneously resolve after six weeks. Because evidence of improved outcomes is lacking, imaging, such as lumbar spine radiography, should be delayed at least one to two months in patients with nonspecific pain without red flags for serious disease ***(Kinkade, 2007).***

Psychosocial issues play an important role in guiding the treatment of patients with chronic low back pain. One study found that patients with chronic low back pain who have a reduced sense of life control, disturbed mood, negative self-efficacy, high anxiety levels, and mental health disorders, and who engage in catastrophizing tend to not respond well to treatments such as epidural steroid injections. “Yellow flags” are psychosocial risk factors for long-term disability (**Table.4**). Evaluation of psychosocial problems and “yellow flags” are useful in identifying patients with a poor prognosis ***(van Wijk et al., 2008)***

Table 3: Red Flags Indicating Serious Causes of Chronic Low Back Pain and Evaluation Strategies ***(Last and Hulbert, 2009)***

Finding	Diagnosis of concern				Evaluation strategy		
	Cauda equine syndrome	Fracture	Cancer	Infection	Cbc/esr/crp level	Plain radiography	Mri
Age older than 50 years		X	X		1*	1	2
Fever; chills; recent urinary tract or skin infection; penetrating wound near spine				X	1	1	1
Significant trauma		X				1	2
Unrelenting night pain or pain at rest			X	X	1*	1	2
Progressive motor or sensory deficit	X		X				1E
Saddle anesthesia; bilateral sciatica or leg weakness; difficulty urinating; fecal incontinence	X						1E
Unexplained weight loss			X		1*	1	2
History of cancer or strong suspicion for current cancer			X		1*	1	2
History of osteoporosis		X				1	2
Immunosuppression				X	1	1	2
Chronic oral steroid use		X		X	1	1	2
Intravenous drug use		X		X	1	1	2
Substance abuse		X		X	1	1	2
Failure to improve after six weeks of conservative therapy			X	X	1*	1	2 (or unnecessary)

NOTE: Red flags indicate the possibility of a serious underlying condition.

1 = first-line evaluation in most situations; 2 = follow-up evaluation; CBC = complete blood count; CRP = C-reactive protein; E = emergent evaluation required; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging.

*— Prostate-specific antigen testing may be indicated in men in whom cancer is suspected.

Table 4 Psychosocial "Yellow Flags" Predicting Long-Term Disability in Patients with Chronic Low Back Pain(**Kendall, 1999**)

Affect
Anxiety; depression; feeling of uselessness; irritability
Behavior
Adverse coping strategies; impaired sleep because of pain; passive attitude about treatment; withdrawal from activities
Beliefs
Thinks "the worst" or that pain is harmful or uncontrollable, or that it needs to be eliminated (before returning to activities or work)
Social
History of sexual abuse, physical abuse, or substance abuse; lack of support; older age; overprotective family
Work
Expectation that pain will increase with work and activity; pending litigation; problems with worker's compensation or claims; poor job satisfaction; unsupportive work environment

F- Management of CLBP Patients:

If low back pain persists for more than 12 weeks and serious conditions have been ruled out, the focus of care should shift from pain-resolution to pain-management strategies that control pain while maximizing function and quality of life and preventing disability ***(Borenstein et al., 2004).***

Treatment of chronic low back pain is often multidisciplinary, involving a combination of self-care, analgesics, spinal manipulation, physical therapy with or without cognitive behavioral therapy, massage, acupuncture, yoga, and in some cases, invasive interventions such as glucocorticoid injections and surgical procedures ***(Morlion, 2013). (Figure.1)***

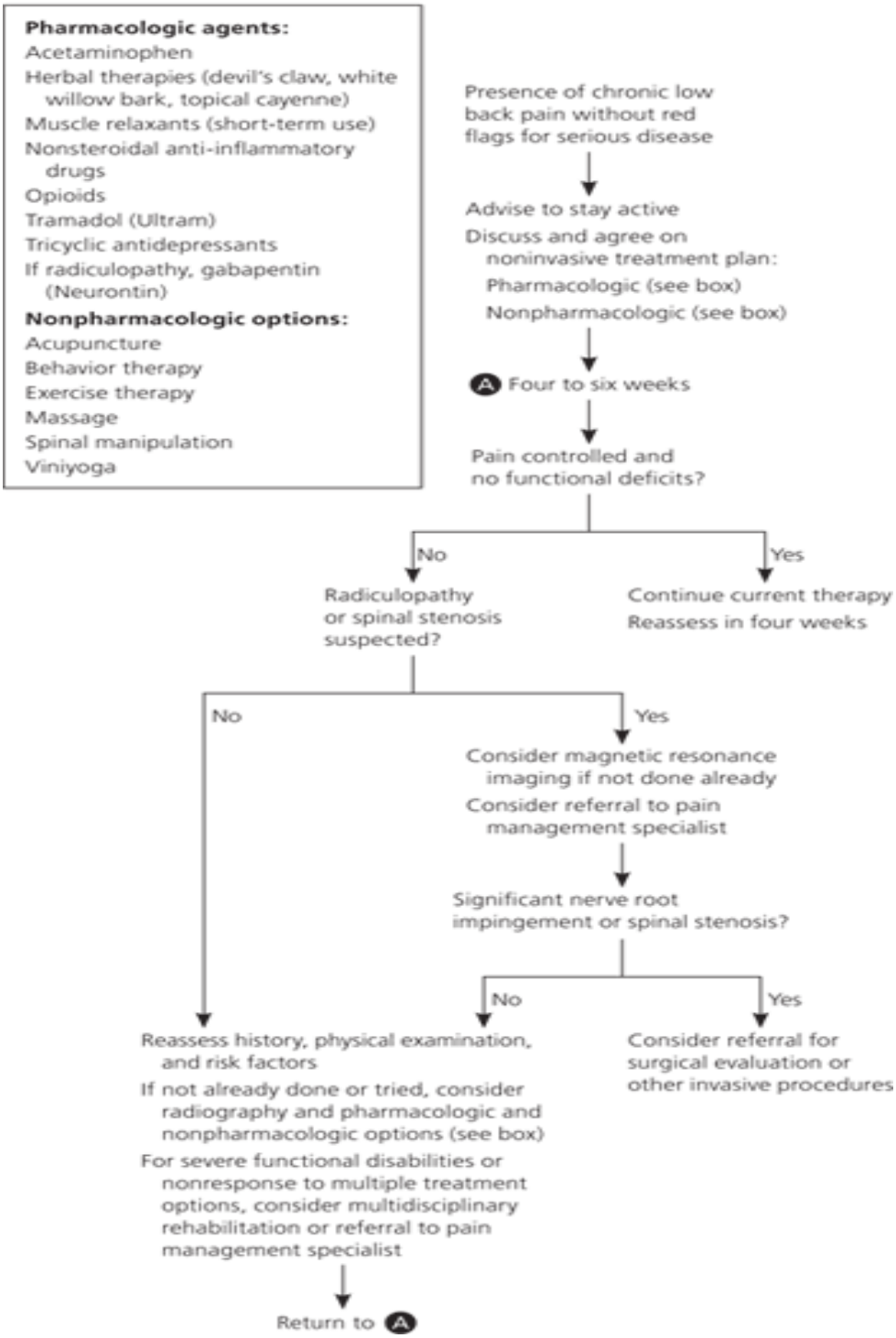

Figure 1: Treatment algorithm for patients with chronic low back pain ***(Chou et al., 2007)***

1- Analgesics

Regarding analgesics, most of the evidence for their benefit comes from short-term trials; therefore, the efficacy and safety for long-term use is unproven. Short-term courses of acetaminophen or NSAIDs are typically recommended for acute exacerbations of chronic low back pain if the side-effect profiles are acceptable for the patient. The long-term use of NSAIDs is limited by their potential gastric, renal, and cardiac toxicity ***(Koes et al., 2010)***.

Opioids have been increasingly used for chronic low back pain; however, evidence to support their use is minimal. A 2013 Cochrane Review found low- to moderate quality evidence for short-term efficacy for pain and function when opioids were compared with placebo, but none of the trials persisted beyond 12 weeks. In addition, the meta-analysis found that there is no high-quality evidence that long-term use of opiates is superior to other medications (NSAIDs, antidepressants) for pain relief and function. Furthermore, patients who use chronic opiates, especially in high doses, have a significant risk of adverse effects, including dependence, misuse, and overdose ***(van Wijk et al., 2008)***.

Therefore, the long-term use of opioids for chronic low back pain should be restricted to patients who demonstrate a functional improvement with opioid use, are at low risk for misuse, and can be monitored closely for adverse effects ***(van Wijk et al., 2008)***.

Antiepileptics and tricyclic antidepressants (TCAs) are frequently used to treat patients with radicular low back pain or spinal stenosis. However, a 2008 systematic review concluded there is not compelling evidence that antidepressants are superior to placebo in the treatment of nonspecific low back pain ***(Urquhart et al., 2008)***.

Similarly, a 2012 systematic review concluded there is only low-quality evidence for the use of antiepileptics given scarcity and poor methodology of existing trials. Furthermore, the use of these medications is often limited by side effects, including somnolence, dizziness (antiepileptics and TCAs), and anticholinergic effects (TCAs) ***(Ammendolia et al., 2012).***

2- Non-pharmacologic Noninvasive Treatments

Non-pharmacologic noninvasive evidence-based treatments for chronic low back pain include physical therapy, spinal manipulation, acupuncture, massage, yoga, and cognitive behavioral therapy. These treatments have B-grade evidence, meaning there is fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens***(Standaert et al., 2011).***

All patients with chronic low back pain should be advised to remain active. Beyond that, use of the other non-pharmacologic treatments can be pursued based on provider and patient preferences and treatment availability ***(Standaert et al., 2011).***

3- Invasive Nonsurgical Treatments

Invasive nonsurgical treatments for chronic low back pain include epidural steroid injections, intradisc steroid injections, facet joint injections, medial branch blocks, and radiofrequency denervation. Of these, there is moderate-quality evidence only for epidural steroid injections in patients with sciatica or radiculopathy, and the benefit is short term (less than 6 weeks) ***(Chou et al., 2009).***

4- Surgical Referrals

Urgent surgical evaluation is recommended for patients with severe or progressive motor weakness or evidence of cauda equina syndrome. In the absence of severe progressive neurologic deficits, surgery may be considered an elective treatment of patients with radiculopathy and spinal stenosis who have chronic disabling symptoms and have not responded to appropriate trials of nonsurgical treatments. In general, surgical outcomes may be superior to nonsurgical management in the short term, but the difference does not persist after longer-term follow-up(**Szpalski *et al.*, 2010**).

Chapter II: Depression

Depression is one of the most commonly diagnosed mental disorders among adults. Our understanding of the course and nature of depression has changed significantly in the last 20 years. From being seen as an acute and self-limiting illness, to a growing clarity that for many depression is now considered a chronic, lifelong illness*(**Dyrbye et al., 2006**)*.

Prevalence of depression is of concern, as the cost that depression exacts is considerable. It is not only economically detrimental, but also engenders significant personal and interpersonal suffering alongside its societal impact*(**Dyrbye et al., 2006**)*.

This chapter is reviewing the recent advances in the literature regarding the epidemiology and pathophysiology of Major Depression.

A- Historical Development:

Historically, mood disorders have been conceived as either "organic" or "reactive," as found in the Diagnostic and Statistical Manual of Mental Disorders—First Edition (DSM-I). The second edition of the manual (DSM-II) continues this basic distinction using the terms "psychotic" and "neurotic." Mood disorders were understood as either a disease of the brain and organic, or neurotic and therefore a disease of the mind*(**American Psychiatric Association., 1968**)*.

Disorders of a neurotic or reactive variety could be cured once the cause was removed. Those of a psychotic or organic nature were viewed as having a less favorable outcome. Considered chronic, their fate was institutionalization combined with somatic treatment. The prevailing understanding left no room outside of the categories curable or chronic*(**Boland and Keller, 2009**)*.

The Diagnostic and Statistical Manual of Mental Disorders—Third Edition (DSM-III) favored a descriptive approach, whereby individuals were diagnosed with a mood disorder based on whether or not they met clear diagnostic criteria, which was based on a constellation of symptoms and specific duration. The goal of treatment was symptom reduction or extinction if possible. However, treatment outcomes including continued relapse and recurrence posed challenges to developing adequate treatments. It became clear that the effectiveness of interventions was reduced without the context of natural course informing them*(**American Psychiatric Association, 1987**)*.

From the 1980's onwards, long-term studies on the course of depression and outcomes in patients began to be reported.

B- Classification:

The Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV-TR) describes a Major Depressive Disorder (MDD) diagnosis based on the presence of a specified number of symptoms with a precise duration. Primarily symptoms of either depressed mood or loss of interest or pleasure are present. Additionally the criteria of at least five items from the DSM-IV-TR list need to be present for a duration of 2 weeks and as such, represents a change from previous functioning. It includes depressive mood and loss of interest in most activities, appetite and sleep disturbance, feelings of worthlessness and guilt, suicidal thoughts and ideation***(Bell, 1994)***.

The DSM-IV-TR describes Dysthymic Disorder as chronic and symptoms should not be as severe as that for MDD, but present for at least 2 years. It includes symptoms of depressed mood for most of the day, and at least two of the following: poor appetite, insomnia, low energy, poor self-esteem, lack of concentration, and feelings of hopelessness. If an individual is symptom-free for 2 months or more, then it is not diagnosable. Double depression is dysthymia with MDD ***(American Psychiatric Association (APA), 2000)*.**

The DSM-5, like the DSM-IV-TR, continues the diagnostic distinctions of MDD and dysthymic disorder. However, the latter is renamed as Chronic Depressive Disorder (CDD). For DSM-5 the criteria for diagnosis of these disorders remain the same as DSM-IV-TR. The DSM-5 proposes additional diagnostic categories such as mixed

Anxiety/Depression and also integrates childhood and adolescent psychiatric disorders into relevant chapters*(**Andrews et al., 1999**)*.

The World Health Organizations'(WHO) International Classification for Diseases and Related Disorders (ICD-10) describes the criteria for a depressive episode, where at least four items, such as loss of interest in activities, lack of emotional reactions, sleep disturbance, loss of appetite, motor retardation, weight loss, loss of libido, and decreased energy are present for a duration of 2 weeks*(**Andrews et al., 1999**)*.

Dysthymia is described as "a period of at least 2 years of constant and constantly recurring depressed mood". Symptoms are not as severe or persistent as recurrent depression, but intervening periods of normal mood rarely last for longer than a few weeks. At least three symptom items from the list above are present during these periods, including items such as, often in tears, difficulty concentrating, loss of confidence and feelings of inadequacy and hopelessness, inability to cope, and despair about the future ***(World Health Organization, 1993).***

The difference that exists between the two classification systems described is associated with the lower threshold of symptom requirements for ICD-10 compared to DSM-IV-TR. However, high concordance has been demonstrated between both classifications systems for depressive episode and dysthymia. The definitions could be made identical as the differences do not produce significant numbers of discrepant diagnoses(**Andrews *et al.*, 1999**).

C- <u>Epidemiology of Depression:</u>

Several major epidemiological studies have been carried out to determine the prevalence of depressive disorder in the general population.

Two such large-scale surveys from the U.S. are the Baltimore Epidemiologic Catchment Area Survey (ECA) and the National Comorbidity Survey (NCS), initially conducted in 1991 and replicated in 2001. Using the Diagnostic Interview Schedule (DIS) based on the DSM-III, the ECA surveyed 18,571 households and 2290 institutional residents aged eighteen years and older. In general terms the data from this survey reveals that in any 6-month period, 19.5% of the adult U.S. population, or 1 in every 5 persons eighteen years and above, suffers with a diagnosable mental health disorder ***(Eaton et al., 1989)***.

The National Comorbidity Survey (NCS) epidemiologic investigation was designed to study prevalence of Diagnostic and Statistical Manual of Mental Disorders-Third Edition Revised (DSM-III-R) disorders and associated use of health and mental health services. The survey administered the WHO Composite International Diagnostic Interview (CIDI) to a sample of over 8000 respondents. The NCS report a 12-month prevalence of 8.6% and a lifetime prevalence of 14.9% of depressive disorder in the population ***(Robins and Regier, 1991)***.

Like the earlier ECA study, they also report on the early age onset of depression. These figures are higher than those reported by the earlier ECA survey. However, the NCS did lower the age range to fifteen as opposed to eighteen years and given that they noted the early age onset, perhaps the extension allowed for this to be recorded with more accuracy ***(Bell, 1994)***.

The high prevalence estimates found in both the ECA and NCS surveys was a cause of concern. A National Comorbidity Survey-Replication (NCS-R) was administered, using the CIDI. The prevalence

reported for depressive disorder in the population was 16.2% for lifetime and 6.6% for 12-month prevalence ***(Robins et al., 1988)***.

A plausible explanation might be that the increasing prevalence reflects a finding first noted in the 1980's related to the increased incidence of depression among younger age cohorts. Other plausible explanations are an increased willingness to report and a general increase in accurate reporting, aided by methodological advances in data interview schedules developed in stem-branch format. Stem-branch format allows a question to be asked and then follow-up questions to support and add detail to the initial answer given collection instruments and add detail to the initial answer given ***(Robins et al., 1988)***.

Outside of the U.S., the World Health Organization (WHO) has demonstrated that depressive disorders are one of the leading causes of disease worldwide. The reported prevalence throughout the world of depressive episodes is 16 per 100,000 per year for males and 25 per 100,000 per year for females. Their results show depression as the fourth leading cause of disease burden in the world accounting for 4.4% of total disability adjusted life years (DALY)***(Ustun, 2004)***.

The WHO highlights the occurrence of depression in younger age groups (20–25 years). Based on data from the NCS-R, half of all lifetime cases of mood disorders start at 14 years and three-fourths by 24 years***(Kessler et al., 2003)***. One review of the literature posits the peak years for onset to be between 15 and 29 years of age. Epidemiological surveys have highlighted the shift for early age onset combined with increased prevalence in younger age periods. Analysis of the data from the ECA demonstrates a gradual shift to increased rates for major depression between the ages of 15 and 19 years***(Burke et al., 1991)***.

Zisook et al. report that earlier age onset of major depression affects the course and is associated with greater illness burden across a wide range of indicators compared to those with later ages at onset. These indicators include: never being married, social and occupational impairment, poorer quality of life, greater comorbidity both medical and psychiatric, a more negative outlook, a greater number of depressive episodes alongside increased symptom severity, and increased suicidal ideation and attempted suicide*(**Zisook et al., 2007**)*.

Consequently, depression is a major health problem for which it is important to develop treatments and the occurrence in younger age groups highlights the need for early intervention. The WHO report that in Europe, the prevalence of depressive episodes for males is 16 per 100,000 per year and for females is 27 per 100,000 per year. This data includes information collected from fourteen European countries. A recent report estimates that depression accounts for 6% of DALY*(**Sobocki et al., 2006**)*.

A cross-sectional community study by the European Outcome of Depression International Network (ODIN) included urban and rural areas within Ireland, Spain, the U.K., Norway, and Finland. The survey reports a 12-month prevalence of depressive disorders of 8.56%. Similar to the WHO survey, depressive disorder was defined in two ways based on both the ICD-10 and the DSM-IV*(**Bebbington et al., 1998**)*.

The global sample comprising the five countries returns a weighted mean 12 month prevalence of 6.6% (CI: 5.4–8.4) for depressive episode as assessed by the ICD, and as assessed by the DSM-IV, a weighted mean 12-month prevalence of 6.7% (CI: 5.4 8.2). Given the concordance

between these classification systems, it is not surprising that they return similar percentages*(**Andrews et al., 1999**)*.

In the ODIN study, the 12-month prevalence rate of 8.56% is the same as the 12-month reported prevalence in the initial NCS study (8.6%), but higher than what is reported in the 12-month prevalence NCS-R survey (6.3%). The survey confirms the prevalence of greater burden of depression in women (10.05%) than men (6.61%) and demonstrates that depressive disorders are highly prevalent among adults in Europe*(**Bebbington et al., 1998**)*.

Another European study reports on prevalence of depression in subjects aged 65 and older. This survey complements the earlier ODIN survey whose age range included 18– 64 years. The 12-month prevalence reported across the European centers was 12.3%. The survey further supports the gender divide literature, giving overall prevalence of depression of 14.1% for women and 8.6% for men*(**Copeland et al., 2004**)*.

Epidemiological studies highlight magnitude of the problem and also uncover the extent of co-morbidity. The U.S. epidemiological studies (ECA and NCS) found that up to 75% of cases display at least one of the other DSM (APA, 1980, 1987, 1994) classified disorders. Patients with a diagnosis of major depression and a coexisting DSM classified disorder, report significantly poorer psychosocial functioning and poorer recovery rates over 12 months compared with patients who have a single diagnosis of depression. The strongest comorbidity is with the anxiety disorders of one form or other. Comorbid anxiety disorders are present in 50% of subjects with major depression*(**Fava et al., 1997**)*.

A similar level of comorbid anxiety with major depression is also found in nonclinical samples. Comorbidity is associated with greater severity of depressive symptoms, and lower treatment response rates, alongside greater social and occupational impairment***(Wittchen et al., 2011)***.

The association with depression is particularly strong for post-traumatic stress disorder, generalized anxiety disorder, obsessive–compulsive disorder, and social phobia. The Zurich study notes higher prevalence of depression and panic disorder reporting that 12% of their sample displayed comorbidity***(Volirath and Angst, 1989)***.

D- <u>Pathophysiology of Depression:</u>

MDD is a common and costly disorder, which is usually associated with severe and persistent symptoms leading to important social role impairment and increased mortality. This part is aimed at summarizing the solid evidence on the etiology and pathophysiology of MDD that is likely relevant for clinical psychiatry.

❖ Genes and Psychological stress

Family, twin, and adoption studies provide very solid and consistent evidence that MDD is a familial disorder and that this familiality is mostly or entirely due to genetic factors. This important finding suggests that parental social behavior and other familial environmental risk factors are not as important in the pathogenesis of MDD as previously assumed and should not be the major focus of the treatment of the disorder ***(Sullivan et al., 2000)***.

The previous studies consistently show that the influence of genetic factors is around 30-40%. Non-genetic factors, explaining the remaining

60-70% of the variance in susceptibility to MDD, are individual-specific environmental effects (including measurement error effects and gene-environment interactions). These effects are mostly adverse events in childhood and ongoing or recent stress due to interpersonal adversities, including childhood sexual abuse, other lifetime trauma, low social support, marital problems, and divorce ***(Kendler et al., 2006).***

These results suggest that there is a huge potential in the prevention of MDD by means of psychosocial interventions (e.g., in schools, at workplace). In addition, these results mirror the clinical practice of empirically validated psychotherapies to treat depression, including interpersonal, psychodynamic and cognitive behavioral psychotherapies and cognitive behavioural analysis system of psychotherapy, which all focus directly or indirectly on interpersonal difficulties and skills. This does not exclude the fact that unidentified non-genetic, non-psychosocial risk factors may also play important roles in some patients (e.g., climatic change, medical conditions) ***(Meyer et al., 2002).***

Stress sensitivity in depression is partly gender-specific. While men and women are, in general, equally sensitive to the depressogenic effects of stressful life events, their responses vary depending upon the type of stressor. Specifically, men are more likely to have depressive episodes following divorce, separation, and work difficulties, whereas women are more sensitive to events in their proximal social network, such as difficulty getting along with an individual, serious illness, or death. These findings point to the importance of gender-sensitive psychosocial approaches in the prevention and treatment of MDD ***(Kendler et al., 2001).***

In contrast to the very solid evidence from epidemiological studies on broad risk factor domains, there is no solid evidence for specific genes and specific gene-by-environment interactions in the pathogenesis of MDD. Genome-wide association studies have indicated that many genes with small effects are involved in complex diseases, increasing the difficulty in identifying such genes. While there has been progress in the search for risk genes for several complex diseases despite this methodological problem, psychiatric conditions have turned out to be very resistant to robust gene identification ***(Donnelly, 2008).***

For example, based on a community-based prospective study, it has been proposed that a specific genetic variation in the promoter region of the serotonin transporter (a target of antidepressant drugs) interacts with stressful life events in the pathogenesis of depression***(Donnelly, 2008).***

Although there is high clinical and neurobiological plausibility of this interaction, a recent meta-analysis yielded no evidence that the serotonin transporter gene alone or in interaction with psychological stress was associated with the risk of depression***(Risch et al., 2009).***

❖ Stress Hormones and Cytokines

Corticotrophin-releasing hormone (CRH) is released from the hypothalamus in response to the perception of psychological stress by cortical brain regions. This hormone induces the secretion of pituitary corticotrophin, which stimulates the adrenal gland to release cortisol into the plasma. The physiologic response to stress is partly gender-specific: women show generally greater stress responsiveness than men, which is consistent with the greater incidence of major depression in women. Moreover, men show greater cortisol responses to achievement

challenges, whereas women show greater cortisol responses to social rejection challenges*(**Stroud et al., 2002**)*.

Although MDD is considered as a stress disorder, most subjects treated for MDD have no evidence of dysfunctions of the hypothalamic-pituitary-adrenal axis (HPA). However, some subjects with MDD do show abnormalities of that axis and of the extra-hypothalamic CRH system. Altered stress hormone secretion appeared to be most prominent in depressed subjects with a history of childhood trauma. Elevated cortisol may act as a mediator between major depression and its physical long-term consequences such as coronary heart disease, type II diabetes, and osteoporosis*(**Gold and Chrousos, 1999**; **Heim et al., 2008**)*.

The importance of HPA axis dysfunction for the efficacy of antidepressants is a matter of debate. This axis is regulated through a dual system of mineralocorticoid (MR) and glucocorticoid (GR) receptors. Decreased limbic GR receptor function and increased functional activity of the MR system suggest an imbalance in the MR/GR ratio in stress-related conditions such as MDD. Epigenetic regulation of the glucocorticoid receptors has been associated with childhood abuse. Such environmental programming of gene expression may represent one possible mechanism that links early life stress to abnormal HPA axis function and increased risk of MDD in adults ***(McGowan et al., 2009; Mizoguchi et al., 2003).***

There is convergent evidence for CRH to play a major role in the pathogenesis of certain types of depression. Levels of CRH in the cerebrospinal fluid are elevated in some depressed subjects. Post-mortem studies reported an increased number of CRH secreting neurons in limbic brain regions in depression, likely reflecting a compensatory response to

increased CRH concentrations. In addition, CRH produces a number of physiological and behavioral alterations that resemble the symptoms of major depression, including decreased appetite, disrupted sleep, decreased libido, and psychomotor alterations. There is also preliminary evidence that CRH1 receptor antagonists reduce symptoms of depression and anxiety***(Nemeroff et al., 1984; Raadsheer et al., 2008).***

Clinical data suggest that cytokines may play a role in the pathophysiology of a subgroup of depressed subjects, particularly those with comorbid physical conditions. The antidepressant enhancing effect of acetylsalicylic acid points to the possible clinical relevance of psychoneuroimmunology in clinical depression research***(Mendlewicz et al., 2006).***

Taken together, the laboratory tests with the highest potential to be clinically useful in the care of depressed individuals are based on abnormalities of the neuroendocrine and neuroimmune systems. Despite the large amount of basic science data suggesting that the HPA axis is importantly involved in the pathophysiology of depression, the effect of pharmacological modulation of this neuroendocrine system as antidepressant therapy has been disappointing. The link between childhood trauma and a permanently altered physiologic stress system points to the use of specific psychotherapies in the treatment of depressed patients with a history of early life trauma***(Nemeroff et al., 2003).***

❖ The mediating role of monoamines

Most of the serotonergic, noradrenergic and dopaminergic neurons are located in midbrain and brainstem nuclei and project to large areas of the entire brain. This anatomy suggests that monoaminergic systems are involved in the regulation of a broad range of brain functions, including

mood, attention, reward processing, sleep, appetite, and cognition. Almost every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant. Inhibiting the enzyme monoamine oxidase, which induces an increased availability of monoamines in presynaptic neurons, also has antidepressant effects. These observations led to the pharmacologically most relevant theory of depression, referred to as the monoamine-deficiency hypothesis ***(Belmaker and Agam, 2008).***

The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system***(Belmaker and Agam, 2008).***

Serotonin is the most extensively studied neurotransmitter in depression. The most direct evidence for an abnormally reduced function of central serotonergic system comes from studies using tryptophan depletion, which reduces central serotonin synthesis. Such a reduction leads to the development of depressive symptoms in subjects at increased risk of depression (subjects with MDD in full remission, healthy subjects with a family history of depression), possibly mediated by increased brain metabolism in the ventromedial prefrontal cortex and subcortical brain regions***(Neumeister et al., 2002).***

Experimentally reduced central serotonin has been associated with mood congruent memory bias, altered reward-related behaviors, and disruption of inhibitory affective processing, all of which add to the clinical plausibility of the serotonin deficiency hypothesis. There is also evidence for abnormalities of serotonin receptors in depression, with the

most solid evidence pointing to the serotonin-1A receptor, which regulates serotonin function. Decreased availability of this receptor has been found in multiple brain areas of patients with MDD, although this abnormality is not highly specific for MDD and has been found in patients with panic disorder and temporal lobe epilepsy, possibly contributing to the considerable comorbidity among these conditions***(Hasler et al., 2007; Neumeister, 2004).***

However, there is no explanation for the mechanism of serotonin loss in depressed patients, and studies of serotonin metabolites in plasma, urine and cerebrospinal fluid, as well as post-mortem research on the serotonergic system in depression, have yielded inconsistent results. There is preliminary evidence that an increased availability of the brain monoamine oxidase, which metabolizes serotonin, may cause serotonin deficiency. In addition, loss-of-function mutations in the gene coding for the brain-specific enzyme tryptophan hydroxylase-2 may explain the loss of serotonin production as a rare risk factor for depression ***(Meyer et al., 2006).***

Dysfunction of the central noradrenergic system has been hypothesized to play a role in the pathophysiology of MDD, based upon evidence of decreased norepinephrine metabolism, increased activity of tyrosine hydroxylase, and decreased density of norepinephrine transporter in the locus coeruleus in depressed patients. In addition, decreased neuronal counts in the locus coeruleus, increased alpha-2 adrenergic receptor density, and decreased alpha-1 adrenergic receptor density have been found in the brains of depressed suicide victims' post-mortem. Since there is no method to selectively deplete central norepinephrine and no imaging tool to study the central norepinephrine system, solid evidence

for abnormalities of this system in depression is lacking ***(Charney and Manji, 2004).***

While the classical theories of the neurobiology of depression mainly focused on serotonin and norepinephrine, there is increasing interest in the role of dopamine. Dopamine reuptake inhibitors (e.g., nomifensine) and dopamine receptor agonists (e.g., pramipexole) had antidepressant effects in placebo-controlled studies of MDD 51. In the cerebrospinal fluid and jugular vein plasma, levels of dopamine metabolites were consistently reduced in depression, suggesting decreased dopamine turnover. Striatal dopamine transporter binding and dopamine uptake were reduced in MDD, consistent with a reduction in dopamine neurotransmission ***(Nutt, 2006).***

Degeneration of dopamine projections to the striatum in Parkinson's disease was associated with a major depressive syndrome in about one half of cases, which usually preceded the appearance of motor signs. Experimentally reduced dopaminergic transmission into the accumbens has been associated with anhedonic symptoms and performance deficits on a reward processing task in subjects at increased risk of depression ***(Santamaria et al., 1986).***

These findings are consistent with the clinical observation that depressed patients have a blunted reaction to positive re-inforcers and an abnormal response to negative feedback ***(Murphy et al., 2003).***

Almost all established antidepressants target the monoamine systems. However, full and partial resistance to these drugs and their delayed onset of action suggest that dysfunctions of monoaminergic neurotransmitter systems found in MDD represent the downstream effects of other, more primary abnormalities. Despite this limitation, the

monoamine-deficiency hypothesis has proved to be the most clinically relevant neurobiological theory of depression. New findings on the role of dopamine in depression emphasize the scientific potential of this theory, and promising reports of antidepressant effects of drugs that modulate the dopaminergic system (e.g., pramipexole, modafinil) in difficult-to-treat depression underline its clinical relevance ***(Mann, 2005).***

❖ The Neuroimaging of Depression

Although many historical attempts to localize mental functions have failed, they have considerably contributed to a modern neuroscientific understanding of mental disorders. The development of neuroimaging techniques has opened up the potential to investigate structural and functional abnormalities in living depressed patients. Unfortunately, the diversity of imaging techniques used, the relatively small and heterogeneous study samples studied, and the limited overlap of results across imaging paradigms make it difficult to reliably identify neuronal regions or networks with consistently abnormal structure or function in MDD ***(Fitzgerald et al., 2008; Simpson, 2005).***

Functional imaging studies have provided the most limited overlap of findings. This may be due to methodological limitations and/or the complexity of neurocircuitry involved in MDD. A recent meta-analytic study found the best evidence for abnormal brain activity in MDD in lateral frontal and temporal cortices, insula, and cerebellum. In these brain regions, activity was decreased at rest. They showed a relative lack of activation during induction of negative emotions, and an increase in activity following treatment with serotonin reuptake inhibitors. Opposite changes may exist in ventromedial frontal areas, striatum and possibly other subcortical brain regions ***(Fitzgerald et al., 2008).***

More solid evidence has been provided by structural imaging and post-mortem studies. A recent meta-analytic study on brain volume abnormalities in MDD revealed relatively large volume reductions in the ventromedial prefrontal cortex, particularly in the left anterior cingulate and in the orbitofrontal cortex. Moderate volume reductions were found in the lateral prefrontal cortex, hippocampus and striatum ***(Fitzgerald et al., 2008).***

Post-mortem studies consistently identified a reduction in glia cell density in dorsal, orbital and subgenual prefrontal cortices, as well as in the amygdala ***(Rajkowska et al., 1999).***

Overall, functional, structural and post-mortem studies suggest that structural and functional abnormalities in the left subgenual cingulate cortex are the most solid neuroanatomical finding in MDD. Volume reduction in this region was found early in illness and in young adults at high familial risk for MDD, suggesting a primary neurobiological abnormality associated with the etiology of the illness. Humans with lesions that include the subgenual prefrontal cortex showed abnormal autonomic responses to social stimuli, and rats with left-sided lesions in this region had increased sympathetic arousal and corticosterone responses to restraint stress ***(Price and Drevets, 2010)***.

Most importantly, chronic deep brain stimulation to reduce the potentially elevated activity in the subgenual cingulated cortex produced clinical benefits in patients with treatment-resistant depression ***(Mayberg et al., 2005).***

In summary, despite the considerable heterogeneity of findings from neuroimaging studies, there is convergent evidence for the presence of abnormalities in the subgenual prefrontal cortex in some patients with

MDD. Neuroanatomical research in depression is of great clinical interest, since novel antidepressant treatments such as deep brain stimulation can target specific brain regions. In addition, there are promising leads for neuroimaging findings to predict the likelihood of responses to specific treatments ***(MacQueen, 2009).***

❖ The Neurotrophic Hypothesis of Depression

Risk factors for depressive episodes change during the course of the illness. The first depressive episode is usually "reactive", i.e., triggered by important psychosocial stressors, while subsequent episodes become increasingly "endogenous", i.e., triggered by minor stressors or occurring spontaneously. There is consistent evidence that the volume loss of the hippocampus and other brain regions is related to the duration of depression, suggesting that untreated depression leads to hippocampal volume loss, possibly resulting in increased stress sensitivity and increased risk of recurrence ***(Sheline et al., 2003).***

Glucocorticoid neurotoxicity, glutamatergic toxicity, decreased neurotrophic factors, and decreased neurogenesis have been proposed as possible mechanisms explaining brain volume loss in depression. There is no solid evidence on any of these mechanisms, since there are no imaging tools to examine directly the neurotoxic and neurotrophic processes in vivo. Brain derived neurotrophic factor (BDNF) has attracted considerable interest. Specifically, preclinical studies have shown correlations between stress-induced depressive-like behaviors and decreases in hippocampal BDNF levels, as well as enhanced expression of BDNF following antidepressant treatment. The clinician should be aware of the potentially brain-damaging effect of depression and treat

depressed patients as early and effectively as possible ***(Martinowich et al., 2007).***

❖ Altered Glutamatergic and GABAergic Neurotransmission

A series of magnetic resonance spectroscopy studies consistently showed reductions in total gamma-aminobutyric acid (GABA) concentrations in the prefrontal and occipital cortex in acute depression. This may reflect acute stress effects, since psychological stress seems to induce presynaptic down-regulation of prefrontal GABAergic neurotransmission*(**Hasler et al., 2010**).*

Alternatively, low total GABA concentration may reflect reduction in the density and size of GABAergic interneurons. In addition, chronic stress may reduce GABA-A receptor function, possibly through changes in neuroactive steroid synthesis. Contradictory evidence of the GABA hypothesis of depression includes the lack of effects of GABAergic drugs on core depressive symptoms and normal prefrontal GABA concentration in subjects with remitted MDD*(**Rajkowska et al., 2007**).*

Several lines of evidence suggest a dysfunction of the glutamate neurotransmitter system in MDD. A single dose of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist (ketamine) produced rapid and large antidepressant effects in patients with treatment-resistant MDD. Inhibitors of glutamate release (e.g., lamotrigine, riluzole) demonstrated antidepressant properties. Abnormal glutamate levels were found in depressed subjects as determined by magnetic resonance spectroscopy; and there is evidence for abnormal NMDA signaling in post-mortem tissue preparations *(**Feyissa et al., 2009**; **Rajkowska et al., 2007**).*

❖ Circadian Rhythms

Sleep disturbances and daytime fatigue are diagnostic criteria for MDD, suggesting impaired sleep-wake regulation in depressed patients. In addition, some depressive symptoms may show diurnal variations (mood, psychomotor activity, accessibility of memories of positive and negative experiences), and a subgroup of patients with MDD may have a circadian rhythm disorder. In healthy young subjects, moderate changes in the timing of the sleep-wake cycle had specific effects on subsequent mood. In depressed patients, manipulations of circadian rhythms (light therapy, sleep deprivation, phase advance treatment) can have antidepressant efficacy(***Bunney and Bunney, 2000***).

Based on these findings, circadian abnormalities have been hypothesized to be etiologically associated with MDD. The association between phase advance of the sleep-wake cycle and phase advances in nocturnal cortisol secretion; shortened REM latency in some subjects with MDD; and the effect of antidepressants on circadian rhythms of behavior, physiology, and endocrinology contribute to the biological foundation of this hypothesis(***Hasler et al., 2004***).

Despite of the many promising findings, the molecular and genetic underpinnings of this hypothesis are largely unknown. It remains to be determined whether antidepressant effects of new therapeutics such as agomelatine directly relate to normalization of circadian rhythms. Based on these findings, circadian abnormalities have been hypothesized to be etiologically associated with MDD(***Germain and Kupfer, 2008***).

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E- Assessment and Evaluation of Depression:

Management of depression involves comprehensive assessment and proper establishment of diagnosis. The assessment must be based on detailed history, physical examination and mental state examinations. History must be obtained from all sources, especially the family. The diagnosis must be recorded as per the current diagnostic criteria***(Gautam et al., 2017)***.

Depression often presents with a combination of symptoms of depressed mood, loss of interest or pleasure, decreased energy and fatigue, reduced concentration and attention, reduced self-esteem and self-confidence, ideas of guilt and unworthiness, bleak and pessimistic views of the future, ideas or acts of self-harm or suicide, disturbed sleep and diminished appetite. Depending on the severity of depression some of these symptoms may be more marked and develop characteristic features that are widely regarded as having special clinical significance***(Gautam et al., 2017)***.

These symptoms are known as somatic symptoms of depression and include: symptoms of loss of interest or pleasure in activities that are normally enjoyable, lack of emotional reactivity to normally pleasurable

surroundings and events, waking up in the morning 2 hours or more before the usual time, depression worse in the morning, objective evidence of definite psychomotor retardation or agitation (remarked on or reported by other people), marked loss of appetite, weight loss (often defined as 5% or more of body weight in the past month) and marked loss of libido. It is important to note that for the diagnosis of depressive disorder these symptoms need to be present for at least 2 weeks and need to be associated with psychosocial dysfunction***(Gautam et al., 2017).***

Some of the patients with depression may present with predominant complaints of aches, pains and fatigue and they may not report sadness of mood on their own. A careful evaluation of these patients often reveals the underlying features of depression. However, it is important to note that many patients with depression will also have associated anxiety symptoms. With increasing severity of depression, patients may report psychotic symptoms and may also present with catatonic features. Thorough assessment also ought to focus on evaluation for comorbid substance abuse/dependence. Careful history of substance intake need to be taken to evaluate the relationship of depression with substance intoxication, withdrawal and abstinence. Whenever required appropriate tests like, urine or blood screens (with prior consent) may be used to confirm the existence of comorbid substance abuse/dependence***(Fiske et al., 2009).***

Many physical illnesses are known to have high rates of depression. In some situations, the physical illnesses have causative role in development of depression, whereas in other situations the relationship/co-occurrence is due to common etiology. When depression occurs in relation to physical illness attempt may be made to clearly delineate the symptoms of depression and physical illness. Further, while

making the diagnosis, it may be clearly mentioned as to which diagnostic approach [i.e., inclusive approach (symptoms are counted whether or not they might be attributable to physical illness), substitute approach (non-somatic symptoms are substituted with somatic symptoms), exclusive approach (somatic symptoms are deleted from the diagnostic criteria) or best estimate approach] was followed(***Fiske et al., 2009***).

Further, while reviewing the treatment history of medical illnesses, medication induced depression must be kept in mind, as many medications are known to cause depression.

It is always important to consider the longitudinal life course perspective to evaluate for previous episodes and presence of symptoms of depression amounting to dysthymia. Evaluation of history also takes into consideration the relationship of onset of depression with change in season (seasonal affective disorder), peripartum period and phase of menstrual cycle. Further, the longitudinal course approach may also take into account response to previous treatment and whether the patient achieved full remission, partial remission and did not respond to treatment(***Parikh et al., 2016)***.

An important aspect of diagnosis of depression is to rule out bipolar disorder. Many patients with bipolar disorder present to the clinicians during the depressive phase of illness and spontaneously do not report about previous hypomanic or manic episodes. Careful history from the patient and other sources (family members) often provide important clues for the bipolar disorder. It is often useful to use standardized scales like mood disorder questionnaire to rule out bipolarity. Treating a patient of bipolar depression as unipolar disorder can increase the risk of antidepressant-induced switch. Presence of psychotic features, marked

psychomotor retardation, reverse neurovegetative symptoms (excessive sleep and appetite), irritability of mood, anger, family history of bipolar disorder and early age of onset need to alert the clinicians to evaluate for the possibility of bipolar disorder, before concluding that they are dealing with unipolar depression(***Gautam et al., 2017***).

Area to be covered in assessment include symptom dimensions, symptom-severity, comorbid psychiatric and medical conditions, particularly comorbid substance abuse, the risk of harm to self or others, level of functioning and the socio-cultural milieu of the patient. In case patient has received treatment in the past, it is important to evaluate the information in the form of type of antidepressant used, dose of medication used, compliance with medication, reasons for poor compliance, reasons for discontinuation of medication, response to treatment, side effects experienced etc. If the medications were changed, then the reason for change is also to be evaluated(***Gautam et al., 2017)***.

Wherever possible, unstructured assessments need to be supplemented by ratings on appropriate standardized rating scales. Depending on the need, investigations need to be carried out. The use of neuroimaging may be indicated in those with first-episode of depression seen in late or very late age; those have neurological signs, those having treatment resistant depression(***Gautam et al., 2017***).

Besides, patients, information about the illness need to be obtained from the caregivers too and their knowledge and understanding of the illness, their attitudes and beliefs regarding treatment, the impact of the illness on them and their personal and social resources need to be evaluated(***Gautam et al., 2017***).

F- The Clinical Course of Depression:

Early empirical studies investigating the course of depression were hindered by a lack of consensus about key points of change that were being observed in the results. This was resolved and the key change points were named and defined by a task force (**Table.5**) ***(Richards, 2011)***.

The CDS and the Zurich studies are the only prospective long-term studies of the natural course of depression. Participants in the CDS were recruited from individuals who sought psychiatric treatment. The survey recruited participants from several U.S. university hospitals between 1979 and 1981. Participants were then assessed every 6 months for a period of 5 years, and then further assessed annually for a 15-year period. Between 1959 and 1963***(Richards, 2011)***.

The Zurich Study recruited hospitalized patients with a diagnosis of depression. Participants were treated and followed-up every 5 years for up to 21 years. The MOS survey examined the course of several diseases in a variety of health care settings. Recruitment took place at three different U.S. cities between February and October 1986. Participants were assessed yearly for a period of 3 years(***Angst, 1986***).

Table.5: Key change points in depression and their definitions(**Richards, 2011**).

Key Terms	Definition
Episode	Defined as having a certain number of symptoms for a certain period of time, fully symptomatic. (e.g. DSM-IV criteria)

Remission	Partial remission where the individual is no longer fully symptomatic, but displays more than minimal symptoms. Full remission, is a brief period (2–8 weeks), where the individual is asymptomatic, no more than minimal symptoms
Response	A partial or full remission due to a treatment intervention
Recovery	Defined as a full remission, symptom free for a certain length of time. It designates a recovery from an episode
Relapse	Relapse An early return of symptoms following a positive response, meeting full syndrome criteria that occurs during the period of remission
Recurrence	Refers to a new episode, which can only occur during a recovery

G- The Treatment Options for Management of Depression:

Treatment options for management of depression can be broadly divided into antidepressants, electroconvulsive therapy (ECT) and psychosocial interventions. Other less commonly used treatment or treatments used in patients with treatment resistant depression include repetitive transcranial magnetic stimulation (rTMS), light therapy, transcranial direct stimulation, vagal nerve stimulation, deep brain stimulation, and sleep deprivation treatment. In many cases, benzodiazepines are used as adjunctive treatment, especially during the initial phase of treatment. Additionally in some cases, lithium and thyroid supplements may be used as an augmenting agent when patient is not responding to antidepressants(***Gautam et al., 2017***).

❖ Antidepressants

Large numbers of antidepressants are available for management of depression and in general, all the antidepressants have been shown to have nearly equal efficacy in the management of depression. Antidepressant medication may be used as initial treatment modality for patients with mild, moderate, or severe depressive episode. The selection of antidepressant medications may be based on patient specific and drug specific factors***(Price et al., 2011).***

In general, because of the side effect and safety profile, selective serotonin reuptake inhibitors (SSRIs) are considered to be the first line antidepressants. Other preferred options include tricyclic antidepressants, mirtazapine, bupropion, and venlafaxine. Usually the medication must be started in the lower doses and the doses must be titrated, depending on the response and the side effects experienced***(Price et al., 2011).***

Patients who have started taking an antidepressant medication should be carefully monitored to assess the response to pharmacotherapy as well as the emergence of side effects and safety. Factors to consider when determining the frequency of monitoring include severity of illness, patient's co-operation with treatment, the availability of social support and the presence of comorbid general medical problems. Visits may be kept frequent enough to monitor and address suicidality and to promote treatment adherence. Improvement with pharmacotherapy can be observed after 4-6 weeks of treatment. If at least a moderate improvement is not observed in this time period, reappraisal and adjustment of the pharmacotherapy should be considered***(Price et al., 2011).***

❖ Psychotherapeutic interventions

A specific, effective psychotherapy may be considered as an initial treatment modality for patients with mild to moderate depressive

disorder. Clinical features that may suggest the use of a specific psychotherapy include the presence of significant psychosocial stressors, intrapsychic conflict and interpersonal difficulties. Patient's preference for psychotherapeutic approaches is an important factor that may be considered in the decision to use psychotherapy as the initial treatment modality. Various psychotherapeutic interventions which may be considered based on feasibility, expertise available and affordability***(Olbrisch, 1977).***

Cognitive behavioral therapy (CBT) and interpersonal therapy are the psychotherapeutic approaches that have the best-documented efficacy in the literature for management of depression. When psychodynamic psychotherapy is used as specific treatment, in addition to symptom relief it is frequently with broader long term goals(***Sudak, 2012***).

The psychiatrist should take into account multiple factors when determining the frequency of sessions for individual patients, including the specific type and goals of psychotherapy, the frequency necessary to create and maintain a therapeutic relationship, the frequency of visits required to ensure treatment adherence, and the frequency necessary to monitor and address suicidality. The frequency of outpatient visits during the acute phase generally varies from once a week in routine cases to as often as several times a week. Regardless of the type of psychotherapy selected, the patient's response to treatment should be carefully monitored. For a given patient, time spent and frequency of visit may be decided by the psychiatrist***(Sudak, 2012).***

- **Psychoeducation to the patient and, when appropriate, to the family**

Education concerning depression and its treatments can be provided to all patients. When appropriate, education can also be provided to involved family members. Specific educational elements may be helpful in some circumstances, e.g. that depression is a real illness and that effective treatments are both necessary and available may be crucial for patients who attribute their illness to a moral defect or witch craft. Education regarding available treatment options will help patients make informed decisions, anticipate side effects and adhere to treatments. Another important aspect of providing education is informing the patient and especially family about the lag period of onset of action of antidepressants(***Kitts and Goldman, 2012***).

Chapter III: The Association between Chronic Low Back Pain and Depression

Low back pain is nearly ubiquitous in society. Many published guidelines for the diagnosis and management of CLBP are available. Most are straightforward, but few emphasize the fact that family physicians actually lack the richness, which comes from addressing psychosocial issues. Up to 30% of individuals, who report low back pain, go on to have recurrent or persistent symptoms. As a result, chronic low back pain is one of the most common reasons for medical visits***(Kassis, 2008)***.

Chronic non-malignant pain has been defined as pain experienced every day for three of the preceding six months. Non-organic low back pain also occurs and can be divided into several categories, including psychosomatic spinal pain (tension syndrome fibrositis, or muscle tension generated physiologically by anxiety); psychogenic spinal pain (somatization of anxiety into neck or back pain with no physiological changes, as in a conversion reaction); psychogenic modification of organic spinal pain (an emotional reaction that modifies the appreciation of an organic pain); and situational spinal pain (litigation reaction, conscious over concern of exaggeration). Emotional stress has long been recognized as a contributor to pain and/or its perception(**Rotheram-Borus, 2000**).

While burdensome in its own right, pain is also risk factor for depression, and many studies have examined the co-occurrence of pain and depression. The comorbidity is clinically well established but the

underlying mechanisms are not well understood, though a potential explanation is disruption of the mesolimbic dopamine system*(**Taylor et al., 2015**)*.

Recent data from animal models indicate that regulation of dopamine activity in the ventral tegmental area (VTA) mediates depressive and anxiogenic responses suggesting a neurological link between depression and chronic pain*(**Small et al., 2016**)*.

CLBP in particular is often co-morbid with depression, a main cause of disability worldwide. Depression increases the risk of developing LBP, and CLBP is affected by the patient's mental state*(**Matsudaira et al., 2012**)*.

In spite of that, the mental state of most CLBP patients is not routinely assessed. Thus, in chronic pain, psychosocial risk factors become relevant, and are important to explain how individuals respond to back pain. Recent studies have demonstrated that psychosocial factors are important risk factors for LBP among Japanese workers [22, 23]; however, scant data are available on the prevalence of anxiety and depression in the chronic low back pain population*(**Matsudaira et al., 2012**)*.

A-Epidemiology of Depression in CLBP:

Sagheer and colleagues conducted a prospective cross-sectional study was at Pakistan, from January to June 2010, to assess the prevalence of anxiety and depression in chronic low back pain patients was studied according to specified age and gender groups using Hospital Anxiety and Depression Scale. Abnormal level of anxiety and depression were found in 77 (55%) and 68 (48.57%) patients respectively. Out of

them 54 (38.5%) and 51 (36.4%) were borderline abnormal for anxiety and depression respectively, while 23 (16.4%) and 17 (12.1%) were abnormal for anxiety and depression respectively. Among the males, there were 20 (14.28%) and 23 (16.42%) patients with abnormal levels of the corresponding numbers among the females were 57 (40.71%) and 45 (32.14%). There was a significant association in anxiety ($p<0.01$) and depression ($p<0.01$) levels with respect to gender and no significant association with respect to age ($p>0.05$) ***(Sagheer et al., 2013)***.

Table 6 shows the reported prevalence of depression in CLBP in the published literature.

Study	Sample	Criteria	Results
(**Fishbain *et al.*, 1986**)	283 consecutive referrals to a pain clinic	DSM-Ill	5% major depression, 23% dysthymic disorder, 28% adjustment disorder
(**Katon *et al.*, 1985**)		DSM-Ill	
(**Love, 1987**)	37 admissions to an inpatient pain program	DSM-Ill	32% major depression
(**Atkinson *et al.*, 1988**)		DSM-Ill	25% major depression
(**Turner and Romano, 1984**)	68 consecutive patients	DSM-Ill	15% major depression
(**France *et al.*, 1986**)	34 consecutive patients	RDC	30% major depression
	40 consecutive patients		21% major depressive disorder, 54% intermittent depressive disorder, 4'% minor depressive disorder, 3% endogenous major depressive disorder
(**Kramlinger *et al.*, 1983**)	80 consecutive patients	RDC	
(**Krishnan *et al.*, 1985**)	100 patients	RDC	25%; major depressive disorder, 39% probable major depressive disorder
(**Atkinson *et al.*, 1986**)	71 consecutive referrals to an inpatient	RDC	
	52 consecutive admissions to an inpatient		45% major depressive disorder, 11%minor depressive disorder, 26% intermittent depressive disorder, 44% major depressive disorder, 19% minor depressive disorder

A recent study by Tsuji and colleagues extracted data from the 2014 Japan National Health and Wellness Survey (N = 30,000). Depressed CLBP patients had significantly more severe pain and higher levels of pain compared with patients without depression (P < 0.001). Depression was associated with worse HRQoL in CLBP patients. Presenteeism, overall work impairment and activity impairment were 1.8, 1.9 and 1.7 times as high, respectively, among those with depression relative to those without depression. CLBP patients with depression had almost twice as many healthcare provider visits in siz months than those without depression. The pattern of results remained consistent after adjustment for sociodemographic and general health characteristics. Analysis also indicated presenteeism was closely related to overall work impairment (correlation coefficient = 0.99) ***(Tsuji et al., 2016).***

A longitudinal, genetically informative study design included 1,269 adult twins with CLBP. The authors observed that here was a significant association between chronic LBP and the risk of depression or anxiety symptoms in the unadjusted total sample analysis (odds ratio [OR]: 1.81, 95% confidence interval [CI]: 1.34-2.44). After adjusting for confounders, the association remained significant (OR: 1.43, 95% CI: 1.05-1.95), although the adjusted co-twin case-control was non-significant in dizygotic twins (OR: 1.03, 95% CI: 0.50-2.13) and monozygotic twins (OR: 1.86, 95% CI: 0.63-5.51). They concluded that the relationship between CLBP and the future development of depression or anxiety symptoms is not causal. The relationship is likely to be explained by confounding from shared familial factors, given the non-statistically significant associations in the co-twin case-control analyses ***(Fernandez et al., 2017).***

B- Brain Changes in CLBP:

Epidemiological, cross-sectional, and prospective studies suggest that insomnia, chronic pain and depression are a cluster of symptoms that are mutually interactive. Studies using a variety of methods, including neuroimaging, suggest the mesolimbic dopamine system has been proposed as a key factor in promoting the comorbidity of this cluster of symptoms(***Finan and Smith, 2013)***

Studies of pain areas using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) are steadily revealing aspects of pain where attention should be focused. One of these is the dopamine system. Psychosocial factors such as stress and depression are clearly closely involved in CLBP, but the mechanisms have yet to be clearly elucidated. However, the relationship between psychosocial factors and chronic pain is also being steadily uncovered by recent molecular biological studies***(Apkarian et al., 2011)***.

The mesolimbic dopamine system refers to the dopamine pathway with axons extending from the ventral tegmental area to the nucleus accumbens, ventral pallidum, frontal cortex, amygdala, and other areas. When painful stimuli are applied to the body, μ-opioids are produced mainly in the nucleus accumbens. Dopamine is involved in this μ-opioid production: when painful stimuli are applied, large amounts of dopamine are released from the ventral tegmental area. With the dopamine release, μ-opioids are produced in the nucleus accumbens, the descending pain inhibitory system is activated, and pain is inhibited***(Wood, 2006)***.

The mesolimbic dopamine system functions involuntarily, but if it stops functioning for some reason, the individual becomes hypersensitive to pain. Stress, anxiety, and depression are thought to be causes of

dopamine system dysfunction. Dopamine release occurs not just with painful stimuli, but also with expectation of pleasure or reward. Scientific evidence for pleasure-related analgesia has also been obtained. Pain is inhibited by pleasurable sensations. Pleasant smells or images, favorite music, favorite foods and the like have shown clear efficacy in inhibiting pain. Interactions exist between pain and pleasure***(Leknes and Tracey, 2008)***.

The introduction to medical practice of pleasant smells (aromatherapy), images (clean or fresh sensations, beautiful pictorial images), pleasant music and similar sensations are soothing for patients with chronic pain and can exert major effects on treatment effectiveness. In the presence of depression, anxiety, or stress, the dopamine response to painful stimuli is insufficient and as a result, μ-opioids are not produced and the mechanism of pain inhibition does not work***(Leknes and Tracey, 2008)***.

Many reports have suggested dysfunction of central analgesic mechanisms in fibromyalgia patients. Hamba integrated the findings of many studies on the dopamine system and hypothesized that dysfunction of the central analgesic mechanisms is involved in the pathology of nonorganic pain. In this, she described a clinical study using PET that compared the relationship between dopamine metabolism in the brain and pain intensity between fibromyalgia patients and healthy individuals. First, physiological saline and then hypertonic saline were injected into the tibialis anterior muscle of subjects. In healthy individuals, pain is not induced with physiological saline, but occurs with injection of hypertonic saline. The amount of dopamine in the striatum increases in proportion to the increase in pain intensity. An obvious positive correlation is seen between pain intensity and the amount of dopamine. Fibromyalgia

patients, on the other hand, complain of pain even with the injection of physiological saline, and this pain intensifies with the injection of hypertonic saline. Increased amounts of dopamine are not seen in fibromyalgia patients as pain intensifies. This indicates that in fibromyalgia patients, the central analgesic mechanism is broken. In fibromyalgia patients, the number of μ-opioid receptors in their brain is significantly decreased compared with healthy people. Considering the above, the dopamine system is likely to be involved in the pathology of fibromyalgia***(Wood et al., 2007)***.

C-Evaluation by Brain Imaging:

❖ ***Functional MRI***

Focusing on research that examines chronic low back pain with the use of fMRI, negative activation of the prefrontal cortex has been demonstrated to decrease with visual attention tasks in patients with chronic low back pain. Other studies have reported that activation of the nucleus accumbens is decreased in low back pain groups and that connectivity of the prefrontal cortex and nucleus accumbens is involved in the chronicity of low back pain. Moreover, in patients with chronic pain including chronic low back pain, since multidisciplinary treatments such as pharmacotherapy and cognitive behavioral therapy have little effect, the predictive power of psychological and genetic factors in chronicity is low, and brain tests are effective(***Baliki et al., 2006***).

No investigation has clarified whether differences exist between chronic low back pain patients with and without psychiatric problems. Since pain and psychosocial aspects cannot be clearly separated in terms of patient background, multidimensional patient assessments are needed. The chronic low back subjects were divided into two groups using the

patient version of the BS-POP. Low back pain patients with psychiatric problems showed lower scores for the Family, Mental health and Pain-related QOL domains compared with patients without psychiatric problems using the profile scoring system mentioned above. Patients without psychiatric problems showed positive BOLD signals at the nucleus accumbens (NAc), while patients with psychiatric problems showed limited activation at the NAc(***Baliki et al., 2012***).

These results suggested that the persistence of psychiatric problems among patients with chronic low back pain might have some relationship with dysfunction of the NAc. Previous studies have shown that activation of the anterior cingulate cortex, prefrontal cortex, and nucleus accumbens is decreased in chronic low back pain patients. Since both the anterior cingulate cortex and prefrontal cortex belong to the descending inhibitory system, and the nucleus accumbens, which is involved in the dopamine system, releases μ-opioids that act to alleviate pain, decreased activation in these three brain regions may be related to decreased function of the descending inhibitory system. Other areas of focus include the existence of brain regions that are active during rest, but exhibit decreased activity during the execution of certain tasks, and much research has been conducted on default mode networks(***Vania Apkarian et al., 2013***).

Attention has been directed to default mode networks not only in pain areas, but also in the fields of neurological and psychiatric disorders. In patients with chronic low back pain, functional connectivity between the nucleus accumbens and medial prefrontal area is high, and since strengthened functional connectivity is seen in chronic pain patients, this connectivity may be effective in predicting chronicity. However, similar changes in functional connectivity are seen even with catastrophizing of

pain and depression, and disease specificity is thought to be low*(**Vania Apkarian et al., 2013**)*.

❖ ***Magnetic response spectroscopy (MRS)***

Proton MRS (1H-MRS) is used as a non-invasive tool for evaluating neural activity in chosen brain areas. A brain area is chosen and metabolites in the brain are measured using MRI. MRI installed the linear combination model (LD model) software can measure absolute concentrations of biological metabolites. N-acetylaspartate (NAA) is an amino acid specifically localized in neurons. Correlated with the MRI instrument has no LC model software, the relative to the concentration of NAA is measured ratio to the phosphocreatine complex (Cr) or choline (Cho). Cr is correlated with the density of neurons and glial cells. Cho is correlated with cell membrane metabolism. Fukui et al. reported that NAA concentrations in the thalamus, ACC, and PFC are decreased in patients with chronic pain. In the thalamus, NAA/Cr was lower in patients with lumbar spinal disease causing pain than in control subjects without pain*(**Yabuki et al., 2013**)*.

In patients with improvement of pain after surgical treatment, the NAA/Cr increased compared with the preoperative NAA/Cr by MRS. Fukui et al. measured the absolute concentration of NAA using the LC-Model, and mean NAA concentrations for normal control subjects in the thalamus, ACC and PFC have been established. The absolute concentration of NAA is useful for comparisons between patients and patient progress*(**Fukui et al., 2006**)*.

❖ ***Voxel-based morphometry (VBM)***

VBM is a morphological brain imaging method using 3D-MRI, and detects morphological changes of the brain and measures gray matter volume. Gray matter volumes of PFC and amygdala are decreased in patients with chronic pain. The intensity of morphological changes showed a negative correlation with the duration of pain. In patients with chronic low back pain, gray matter volumes of the amygdala and ACC are decreased, and these morphological changes recovered after treatment***(Baliki et al., 2011)***.

❖ ***Cerebral blood flow scintigraphy***

Cerebral blood flow is reduced in patients with chronic pain; in particular, 88% of patients with chronic pain showed reduced blood flow on cerebral blood flow scintigraphy***(Lærum et al., 2006)***.

D-Treatment of Depression in CLBP:

In light of the frequency with which depression is present in clinical samples of CLBP patients, the treatment of depression would be expected to be a major component of the therapeutic management of chronic pain patients. This however does not appear to be the case. There are indications that most depressed chronic pain patients do not receive treatment for depression. In a heterogeneous chronic pain sample, Doan and Wadden (1989) reported that depressed chronic pain, patients were more likely to be prescribed narcotics than antidepressants***(Doan and Wadden, 1989)***.

Similarly, Haley et al. (1985) reported that depressed and non-depressed chronic pain patients did not differ in the sedative and antidepressant medication they were prescribed***(Haley et al., 1985)***.

Katon et al. (1985) reported that while half of their sample of pain patients with major depression was being treated with antidepressants, the dosage levels were below recommended therapeutic levels for depression and likely accounted for the persistence of depressive symptoms***(Katon et al., 1985)***.

Multidisciplinary rehabilitation treatment programs are currently considered the treatment of choice for CLBP. These programs typically include a variety of treatment disciplines including ansthesiology, neurology/ neurosurgery, physiatry, rehabilitation nursing, physiotherapy, psychiatry, psychology, and vocational rehabilitation. Descriptions of multidisciplina~ rehabiIitation programs frequently make reference to the need to address psychosocial factors in the management of chronic pain***(Low and Macmillan, 1988)***.

Several rehabilitation programs include psychological interventions as an integral component of rehabilitation. However, the focus of psychological intervention appears to be on one or more of the following target areas: (1) coping with pain through the use of cognitive-behavioral strategies, (2) psychophysical techniques such as relaxation, or biofeedback aimed at reducing tension and anxiety, or (3) reducing pain behavior by modifying reinforcement contingencies in the patients' environment***(Ehde et al., 2014)***.

There are few, if any, discussions specifically addressing the management of depressive symptomatology in depressed chronic pain patients. Depressed chronic pain patients appear to be treated in the same manner as non-depressed patients. Antidepressants are frequently prescribed for the treatment of chronic pain. However, as with the psychological approaches to chronic pain, the focus has been on treating

pain as opposed to depression. Antidepressants have been shown to produce analgesic effects in CLBP as well as in other pain conditions***(Patetsos and Horjales-Araujo, 2016)***.

The analgesic effects of antidepressants are generally produced at dosage levels approximately l/5 to l/3 of the dosages recommended for the effective treatment of depression. It has been suggested that failure to specifically address the treatment of depression in the management of chronic pain may account for some of the treatment failures in chronic pain rehabilitation***(Atkinson et al., 1988)***.

While there have been no studies specifically designed to examine the impact of depression on rehabilitation outcome in CLBP, several studies have reported data suggesting that depression can interfere with rehabilitation outcome. Depressed chronic pain patients show a greater tendency to drop out of treatment prematurely, and may be more likely to relapse following treatment***(Painter et al., 1980)***.

Pre-treatment depression has been associated with poor outcome in chronic pain rehabilitation, and post-treatment depression has been associated with increased medication utilization and higher unemployment***(Sullivan et al., 1992)***.

A few studies have examined the efficacy of pharmacological and psychological treatment of depression in chronic low back pain. Anecdotal reports and the findings of uncontrolled studies suggest that therapeutic dosages of antidepressants and cognitive behavioral treatments may be effective means of treating pain and depression in depressed chronic pain patients(***Sullivan et al., 1992)***

One placebo-controlled trial of tricyclic antidepressants in depressed chronic pain patients has been reported. Hameroff et al. (1982) reported that doxepin, compared to placebo, led to significant reductions in pain frequency, sleep disturbance, and depressive symptoms in 15 depressed chronic pain (primarily CLBP) patients following 6 weeks of treatment. Dose level began at 50 mg/h and increased to 300 mg/day. One patient discontinued due to dry mouth(***Hameroff et al., 1982***).

Ward et al. (1984) compared the effects of doxepin and desipramine in a sample of 36 depressed CLBP patients recruited through newspaper advertisements. Patients had a diagnosis of major affective disorder, unipolar depression, or dysthymic disorder. All patients were initially given a placebo, and placebo responders (n = 4) were excluded from the study. Four patients discontinued due to side effects: 3 due to drug rash on desipramine and 1 due to sedation on doxepin. Twenty-six patients completed 4 weeks of treatment, with initial dose levels of 50 mg/day and average final dose levels of 188 mg/day and 173 mg/day of doxepin and desipramine, respectively. Significant reductions in depression were observed for patients in both drug conditions, with no significant difference between drug conditions. When success was defined as 40% reduction in pre-treatment depression scores, response rate was 73%. When success was defined as 60% reduction in pretreatment depression scores, response rate was 54%. Significant reductions in pain frequency and pain severity were also observed, although the magnitude of the analgesic effect was less pronounced than the antidepressant effect(***Ward et al., 1984***).

It has also been reported that cognitive-behavioral pain management programs may be an effective means of alleviating depression in patients with CLBP. Following a 3-week multidisciplinary inpatient pain

management program, Kramlinger et al. (1983) reported an 88% remission rate for depression in a group of 25 chronic pain (primarily CLBP) patients with major depressive disorder. It is interesting to note that response rates to antidepressants and cognitive-behavior therapy reported in depressed CLBP patients are similar to the response rates reported for depressed patients without chronic pain. Tricyclic antidepressants show response rates of approximately 55-75% in depressed patients without chronic pain***(Kramlinger et al., 1983)***.

Materials and Methods

A- Study Design and Setting:

After approval of the local ethics and research committee of Neuropsychiatry outpatient clinic in Benha University Hospital. A comparative prospective study was conducted Neuropsychiatry outpatient clinic at Benha University Hospital in Egypt. A written informed consent was taken from each patient. Data collection was started at the beginning of December 2016 and till the end of September 2017

The study involved 160 participants who constituted two groups, the case group that included patients with CLBP (n=80), and the control group that included healthy volunteers (n=80).

B- Inclusion and Exclusion Criteria:

We included patients who fulfilled the following criteria:

- Patients aged 20 to 50 years, regardless of the sex.
- Patients with diagnosed.

In addition, we recruited age and sex-matched control group to act as controls

We excluded patients with disability pension, awaiting back surgery, no longer sick listed, osteoporosis, cancer, recent low back trauma. Pregnant females were also excluded.

C- Data Collection.

The present study utilized semi-structured interview for data collection. The demographic data included age, sex, residency, occupation, marital status, off springs, and co-morbid diseases. The clinical neurological assessment including the age at onset, duration of low back pain, usage of analgesics drugs, and response to treatment.

In addition, the clinical psychiatric assessment included assessment of the severity of depressive symptoms using Depression Beck Inventory (BDI) scale, affective disorders, psychotic disorders, usage of antidepressants, and antipsychotics among others.

D- Depression Beck Inventory (BDI) scale.

In the present study, we assessed the presence and severity of depression using BDI-II scale. The BDI is self-administrated well validated in normal and psychiatric populations, which contains 21 items rated on an intensity scale of 0–3 with a maximum score of 63. Categories of depressive symptom severity include minimal (0–13), mild (14–19), moderate (20–28), and severe (29–63)(Beck et al. 1996).

A- Sample Size Calculation.

The sample size is calculated according **to Knapp and Miller (1992)**. The required sample size, n, for 2 independent proportions is given by the following formula:

$$n = [Pa \times (1 - Pa)] + [Pb \times (1 - Pb)] \times k$$

$$(Pa - Pb)2$$

Where Pa is the proportion of patients with depression, Pb is proportion of controls with depression, so (Pa − Pb) is the effect size; and k is the magic number=7.8, Pa=0.64, Pb=0.23 according to **YOSHIDA and KATO (2011).**

Using the above formula, n=18.9 so, the study included 80 patients in each group.

B- *Statistical Analysis*.

Data were collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis. Data were entered as numerical or categorical, as appropriate. Two types of statistics were done: Quantitative data were shown as mean, SD, and range. Qualitative data were expressed as frequency and percent at 95% confidence interval (95% CI).

Chi- square test and fisher exact test were used to measure association between qualitative variables. Student t-test and Mann Whitney test were done to compare means and SD of 2 sets of quantitative normally and not normally distributed data, respectively. Repeated measures ANOVA test and Friedman test was performed to differentiate changes in different follow up results of different studied quantitative variables normally and not normally distributed data, respectively. The results of comparing the correlation between two continuous variables were indicated by the correlation coefficient (r) using correlation analysis. P (probability) value was considered to be of statistical significance if it is less than 0.05.

Results

1- Demographic Characteristics

In the present prospective study, 80 CLBP patients with mean age of 41.4 (±6.3) years old were included; the majority of the included patients (70%) were female patients. Almost half of the patients were smokers and 65% of them were diabetic. The mean BMI of the included patients was 26.6 (±5.4) and more than third of them were either obese or normal weight. Fifty-five percent of the patients showed low score in sedentary life score and 65% of them were living alone. The mean BDI score was 19.4 (±9.4) and 45% of the patients showed moderate depression according to BDI score.

Table 7 shows the demographic and clinical characteristics of CLBP patients

Variables	Patients (N =80)	
	No	%
Age		
1. Mean (SD)	41.4 (6.3)	
2. Median (IQR)	43 (35.3 – 46)	
Gender		
1. Male	24	30.0
2. Female	56	70.0
Smoking		
1. Non-smokers	36	45.0
2. Smokers	44	55.0
History of DM		
1. No	28	35.0
2. Yes	52	65.0
BMI		
1. Mean (SD)	26.6 (5.4)	
2. Median (IQR)	26.9 (22 – 31)	
BMI Category		
1. Underweight	3	3.8
2. Normal	29	36.3
3. Overweight	20	25.0
4. Obese	28	35.0
Sedentary life		
1. Low	44	55.0
2. Average	28	35.0
3. High	8	10.0
Social life		
1. Live with family	28	35.0
4. Live alone	52	65.0
Duration of LBP		
1. Mean (SD)	25.25 (9.1)	
2. Median (IQR)	25 (17.3 – 30.8)	
BDI score		
1. Mean (SD)	19.4 (9.4)	
2. Median (IQR)	22.5 (9 – 27.8)	
BDI Category		
1. Normal	28	35.0
2. Mild Mood Disturbance	0	0
3. Borderline clinical depression	8	10.0
4. Moderate depression	36	45.0
5. Severe depression	8	10.0
6. Extreme depression	0	0

The study also included 80 age-matched healthy volunteers with mean age of 40.9 (±6.9) years old; the majority of the participants (70%) were females. Only 20% of the participants were smokers and 35% of them were diabetic. The mean BMI of the participants was 24.9 (±4.8) and 58% of them were normal weight. Fifty-three percent of the participants showed low soccer in sedentary life score and 25% of them were living alone. The mean BDI score was 9.7 (±6.2) and 72% of the participants showed no signs of depression according to BDI score.

Table 8 shows the demographic and clinical characteristics of healthy controls

Variables	Patients (N =80)	
	No	%
Age		
1. Mean (SD)	40.9 (6.9)	
2. Median (IQR)	42.5 (36 – 46.8)	
Gender		
1. Male	24	30.0
2. Female	56	70.0
Smoking		
1. Non-smokers	64	80.0
2. Smokers	16	20.0
History of DM		
1. No	52	65.0
2. Yes	28	35.0
BMI		
1. Mean (SD)	24.9 (4.8)	
2. Median (IQR)	23.9 (21 – 28.8)	
BMI Category		
1. Underweight	0	0
2. Normal	47	58.8
3. Overweight	18	22.5
4. Obese	15	18.8
Sedentary life		
1. Low	28	35.0
2. Average	52	65.0
3. High	0	0
Social life		
1. Live with family	60	75.0
2. Live alone	20	25.0
BDI score		
1. Mean (SD)	9.7 (6.2)	
2. Median (IQR)	8 (6 – 11)	
BDI Category		
1. Normal	58	72.5
2. Mild Mood Disturbance	14	17.5
3. Borderline clinical depression	0	0

4. Moderate depression	8	10.0
5. Severe depression	0	0
6. Extreme depression	0	0

2- Association Tests

There was no statistically significant difference between CLBP patients group and control group with regard to gender distribution and age.

Table 9 shows the distribution of gender between cases and controls

Group				Sex		P- value
				Male	Female	
CLBP patients			No.	24	56	0.999
			%	30.0%	70.0%	
Healthy Controls			No.	24	56	
			%	30.0%	70.0%	
Total	No.	48	112			
	%	30.0%	70.0%			

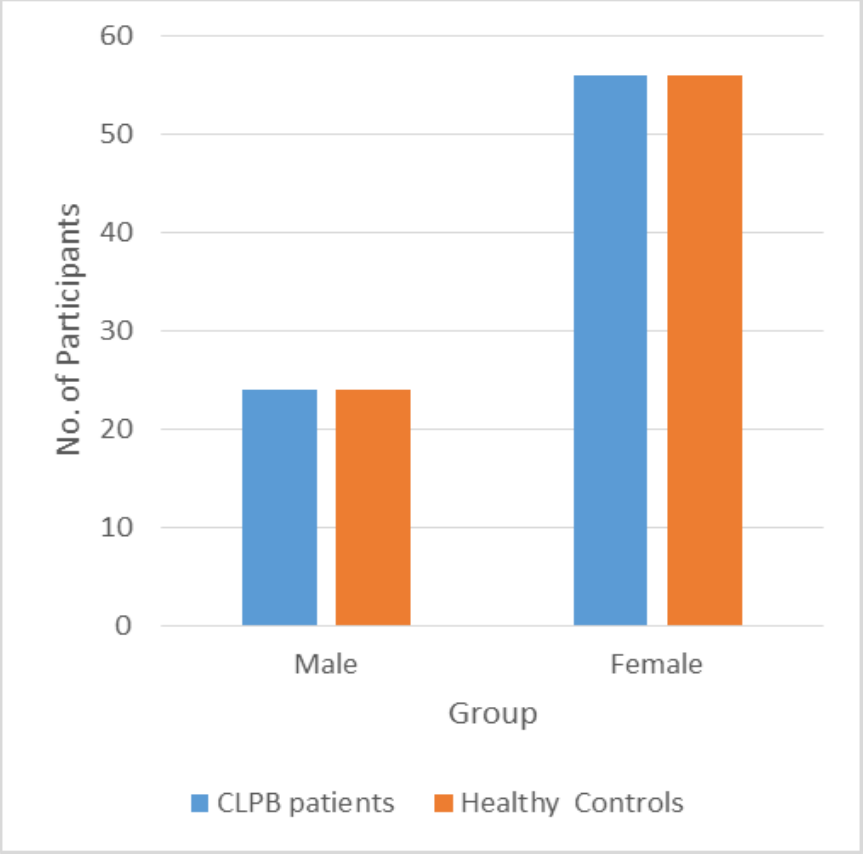

Figure 2: The distribution of gender between case and control

The number of smokers in CLBP group was significantly higher than those in control group (p <0.001).

Table 10 shows the distribution of smoking between cases and controls

Group		Smoking		P- value
		Non-smoker	Smoker	
CLBP patients	No.	36	44	< 0.001
	%	45.0%	55.0%	
Healthy Controls	No.	64	16	
	%	80.0%	20.0%	
Total	No.	100	60	
	%	62.5%	37.5%	

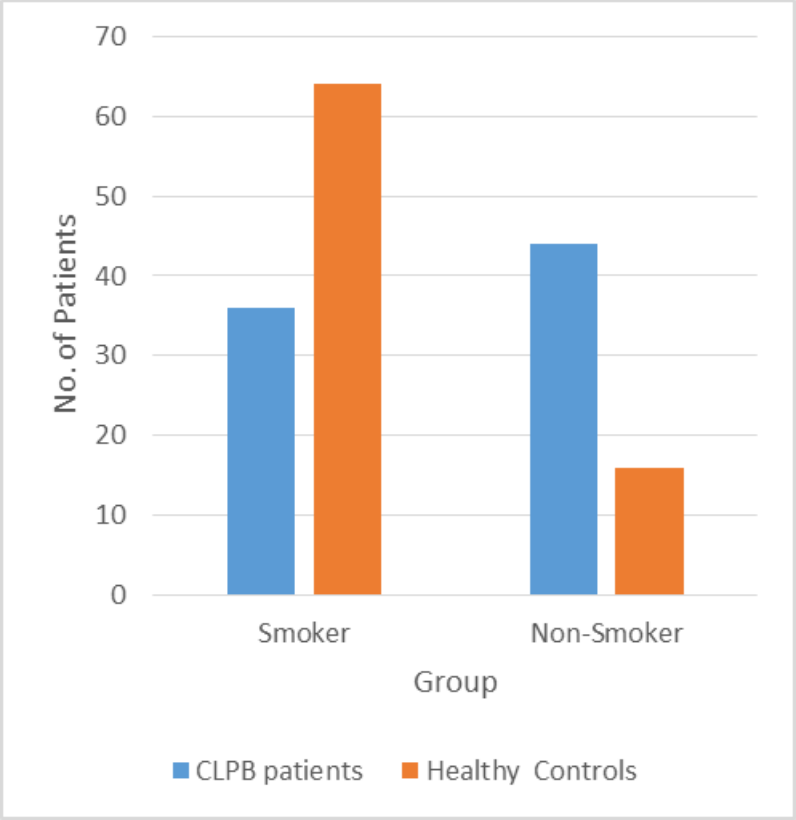

Figure 3: The distribution of smoking between cases and controls

Similarly, the number of diabetic patients in CLBP group was significantly higher than those in control group (p <0.001).

Table 11 shows the distribution of DM between cases and controls

Group		DM History		P- value
		No	Yes	
CLBP patients	No.	28	52	<0.001
	%	35.0%	65.0%	
Healthy Controls	No.	52	28	
	%	65.0%	35.0%	
Total	No.	80	80	
	%	50.0%	50.0%	

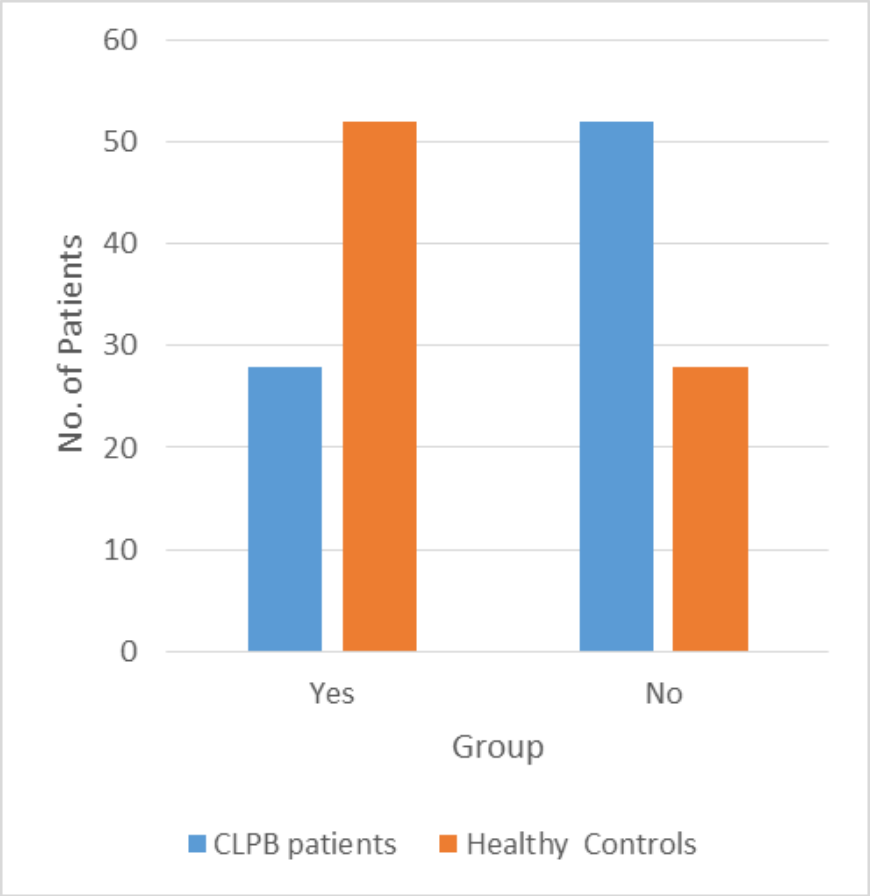

Figure 4: The distribution of DM between cases and controls

In addition, the number of patients who lived alone in CLBP group was significantly higher than those in control group (p <0.001).

Table 12 shows the distribution of social support between cases and controls

Group		Social Support		P- value
		With Family	Alone	
CLBP patients	No.	28	52	<0.001
	%	35.0%	65.0%	
Healthy Controls	No.	60	20	
	%	75.0%	25.0%	
Total	No.	28	52	
	%	35.0%	65.0%	

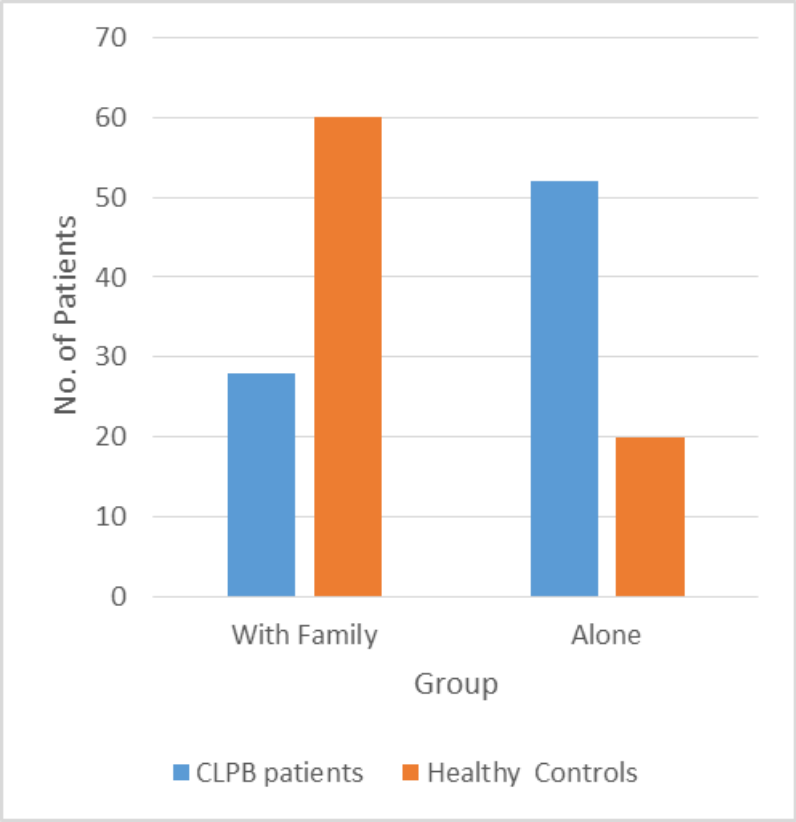

Figure 5: The distribution of social support between cases and controls

The number of patients who showed low score in sedentary life questionnaire was significantly higher in CLBP group compared to control group (p <0.001).

Table 13 shows the distribution of sedentary lifestyle between cases and controls

Group		Sedentary Life			P- value
		Low	Average	High	
CLBP patients	No.	44	28	8	<0.001
	%	55.0%	35.0%	10.0%	
Healthy Controls	No.	28	52	0	
	%	35.0%	65.0%	0.0%	
Total	No.	72	80	8	
	%	45.0%	50.0%	5.0%	

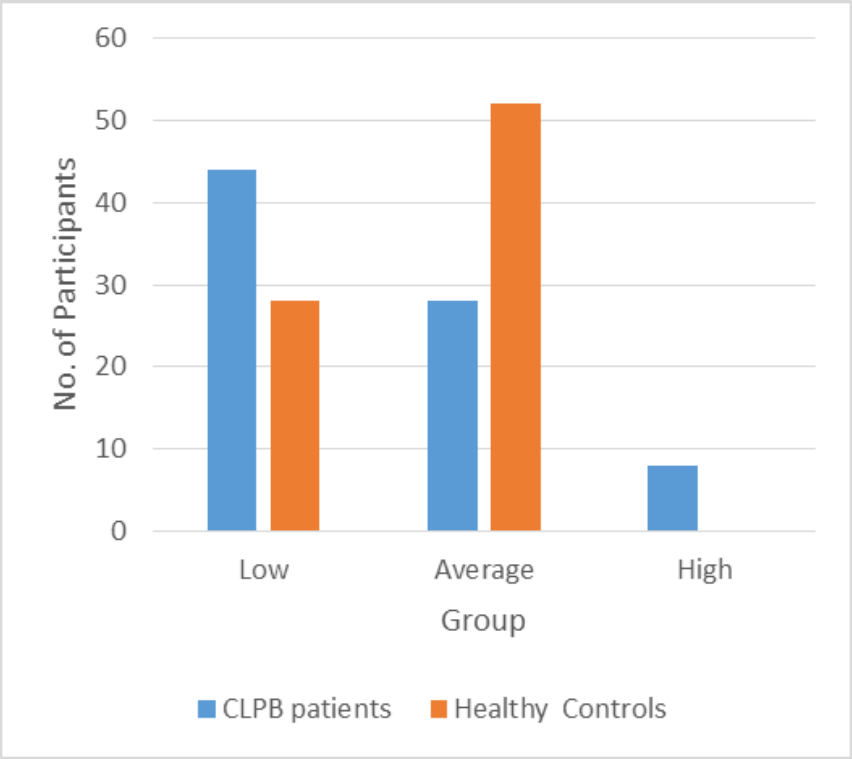

Figure 6: The distribution of sedentary lifestyle between cases and controls

Interestingly, the mean BMI was not statistically different between both groups (p =0.26); However, The number of obese patients was significantly higher in CLBP group compared to control group (p =0.01).

Table 14 shows the association between BMI and CLBP

Variable	CLBP patients	Healthy Controls	Mann-Whitney Test	P-value
BMI				
1- Mean (SD)	26.6 (5.4)	24.9 (4.8)	2548.0	0.26
2- Median (IQR)	26.9 (22 – 31)	23.9 (21 – 28.8)		

Table 15 shows the distribution of BMI category between cases and controls

Group		BMI Category				P- value
		Underweight	Normal	Overweight	Obese	
CLBP patients	No.	3	29	20	28	0.01
	%	3.8%	36.3%	25.0%	35.0%	
Healthy Controls	No.	0	47	18	15	
	%	0.0%	58.8%	22.5%	18.8%	
Total	No.	3	76	38	43	
	%	1.9%	47.5%	23.8%	26.9%	

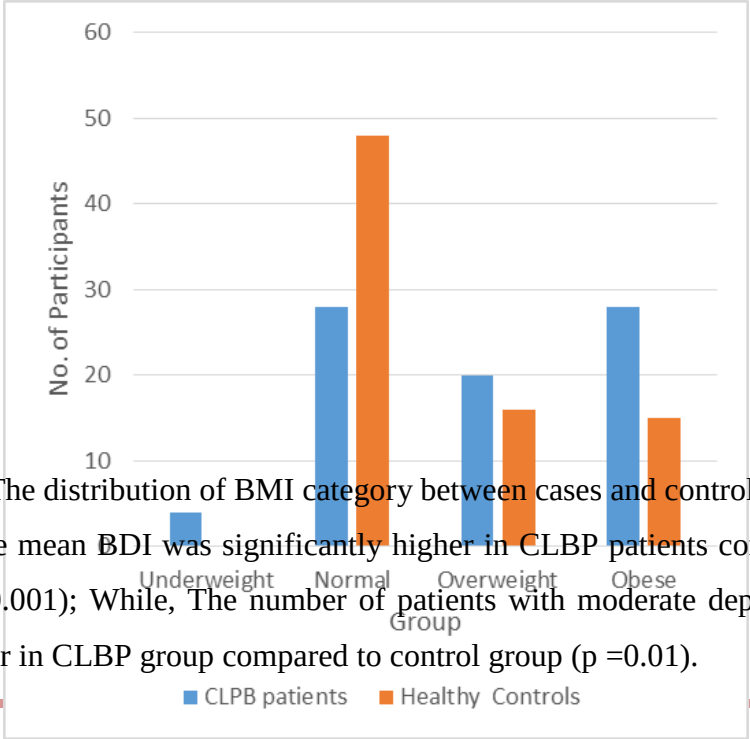

Figure 7: The distribution of BMI category between cases and controls

Importantly, the mean BDI was significantly higher in CLBP patients compared to control group (p =0.001); While, The number of patients with moderate depression was significantly higher in CLBP group compared to control group (p =0.01).

Table 16 shows the association between BDI and CLBP

Variable		CLBP patients	Healthy Controls	Mann-Whitney Test	P-value
BDI					
1-	**Mean (SD)**	19.4 (9.4)	9.7 (6.2)	1497.0	<0.001
2-	**Median (IQR)**	22.5 (9 – 27.8)	8 (6 – 11)		

Table 17 shows the association between BDI category and CLBP

Group		BDI Category						P- value
		Normal	Mild	Borderline	Moderate	Severe	Extreme	
CLBP patients	No.	28	0	8	36	8	0	<0.001
	%	35.0%	0.0%	10.0%	45.0%	10.0%	0	
Healthy Controls	No.	58	14	0	8	0	0	
	%	72.5%	17.5%	0.0%	10.0%	0.0%	0	
Total	No.	86	14	8	44	8	0	
	%	53.8%	8.8%	5.0%	27.5%	5.0%	0	

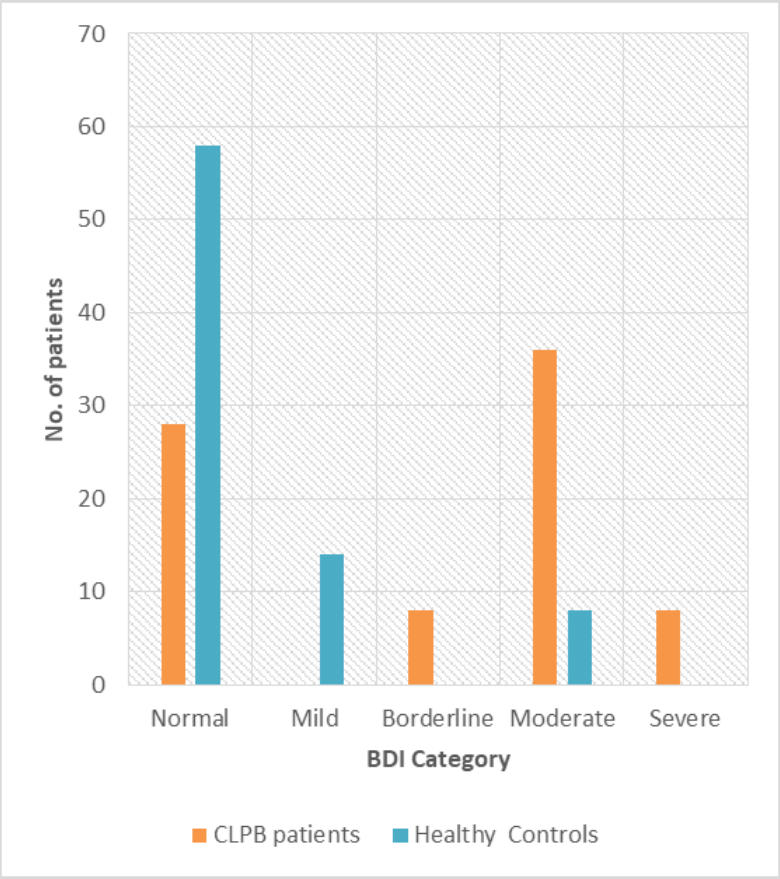

Figure 8: The association between BDI category and CLBP

3- Correlation Tests

There was a statistically significant positive correlation between BMI, duration of disease, and age with the mean BDI score (p =0.001). However, the correlation was not difference between CLBP group and control group except for BMI (p =0.47).

Table 18 shows the correlation between the clinical characteristics and BDI score

Variable	BDI
BMI	
1- Correlation Coefficient (r)	0.403
2- P-value	<0.001
Duration of disease	
1- Correlation Coefficient (r)	0.903
2- P-value	<0.001
Age	
1- Correlation coefficient (r)	0.33
2- P-value	<0.001

Table 19 shows the difference in correlation between case and controls

Variable	BDI in CLBP	BDI in healthy	P-value
BMI			
1- Correlation Coefficient (r)	0.48	0.201	0.047
Duration of disease		NA	NA
1- Correlation Coefficient (r)	0.903		
Age			
1- Correlation Coefficient (r)	0.395	0.361	0.8

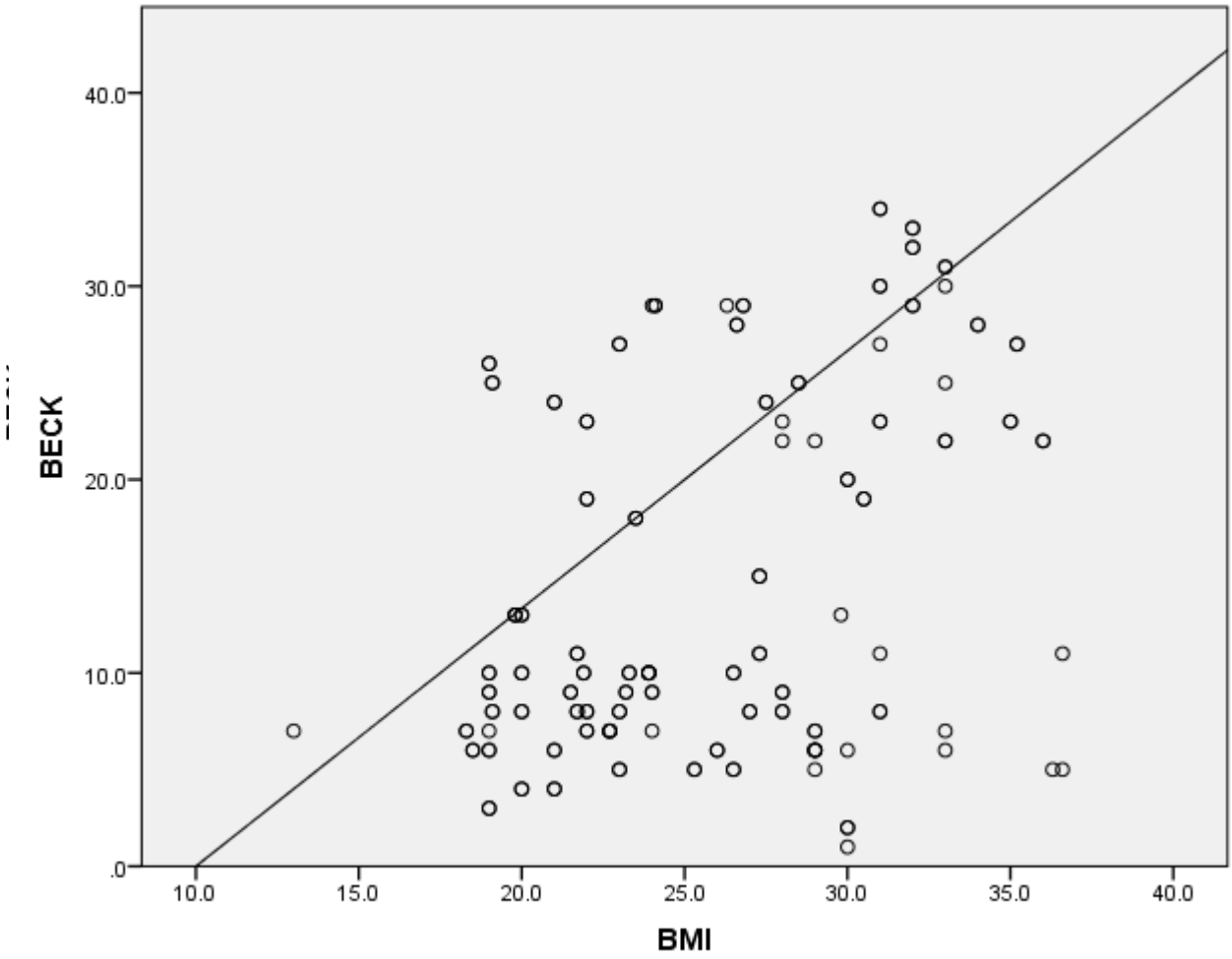

Figure 9: The correlation between Age and BDI

Figure 10: The correlation between BMI and BDI

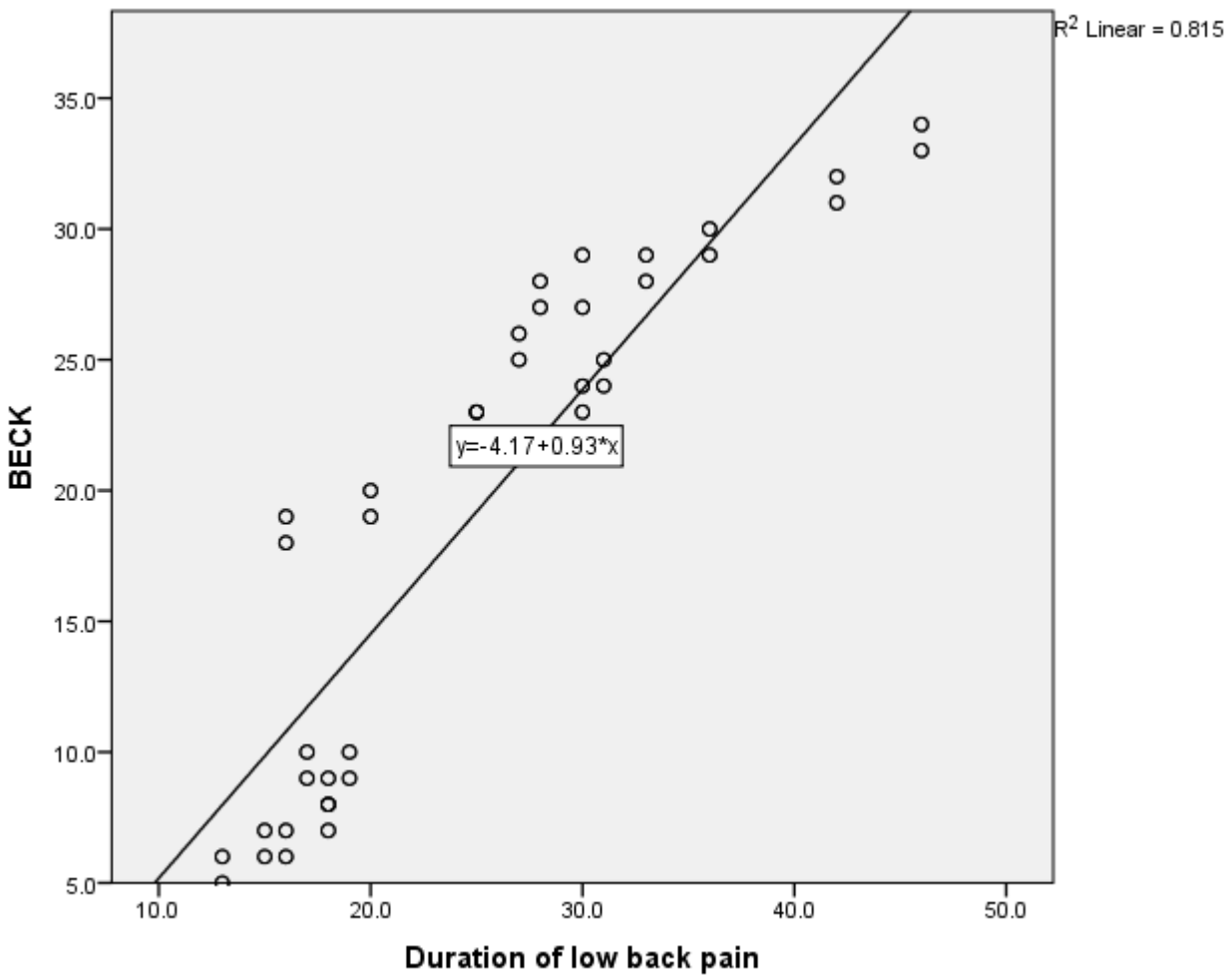

Figure 11: The correlation between disease duration and BDI

Discussion

Low back pain is one of the most commonly encountered health problems worldwide; according to 2016 National Institute of Health report, almost 8 out of 10 people at some point in their lives will suffer from back pain. In addition, more than third of United State population suffered from low back pain within the past three months of the National Center for Health Statistics (NCHS) survey***(Fleming, 2016; National Center for Health Statistics, 2015)***. Previous reports suggested that between of 5 to 10% of low back pain patients will developed CLBP(***Meucci et al., 2015***). CLBP is highly disabling and responsible for high health expenditure ($6000 per person) and low quality of life(***Shmagel et al., 2016***).

On a population level, CLBP causes significant implications on functionality and has huge socioeconomic consequences, therefore, emotional stress, including anxiety and depression, has been recognized to be significantly associated with pain, either as a risk factor or a consequence***(Kinney et al., 1993)***. There is a growing body of evidence which demonstrated a significant increase in the risk of depression among CLBP patients***(Sagheer et al., 2013)***.

In the present prospective study, we aimed to assess the risk of depression in patients with CLPB, using a psychiatric diagnostic interview; and compared 80 CLBP patients with 80 age and sex-matched healthy controls.

The mean age of CLBP patients was 41.4 (±6.3) years old, which was slightly lower than the reported average age in the global figures. According to 2016 report of Shmagel and colleagues, the risk of CLBP increases with age, with the highest likelihood in the 5th and 6th decades of life*(**Shmagel et al., 2016**)*. Moreover, another report showed that the prevalence of CLBP peaked at around 80 years of age(***Hoy et al., 2014***).

In the present study, the majority of the included patients (70%) were female patients. In their 2015 systematic review, Meucci and colleagues reported that the prevalence of CLBP was significantly higher in women than men(***Meucci et al., 2015***). A similar findings was reported by National Health and Nutrition Examination Survey*(**Shmagel et al., 2016**)*.

The higher prevalence of CLBP among women was further confirmed by a recent systematic review of Wáng and colleagues. The authors attributed the sex differences in pain to interactions between biological, psychological, and sociocultural factors. The higher CLBP prevalence in school age girls than in school age boys is likely due to psychological factors, female hormone fluctuation, and menstruation. While the further increased CLBP prevalence in females than in males after menopause age was attributed to accelerated disc degeneration due to relative estrogen deficiency*(**Wáng et al., 2016**)*.

In contrary, Hoy and colleagues reported that the prevalence of low back pain and disability-adjusted life years (DALYs) were higher in males compared to females. The authors did not provide an explanation for the discrepancy between their findings and previous reports, but this discrepancy can be attributed to the heterogeneous population included in their analysis*(**Hoy et al., 2014**)*.

The present analysis showed that the prevalence of smoking was significantly higher in CLBP patients compared to control group. It has been previously proposed that smoking is significantly associated with CLBP as smoking reduces bone mineral content, which increases the risk of osteoporosis and micro-fractures of the trabeculae of the of the vertebral bodies, cause an increase in degenerative changes in the spine(***Alkherayf and Agbi, 2009***).

In addition, Green and colleagues included 34,525 United States adults and found a statistically significant association between CLBP and smoking status*(**Green et al., 2016**)*.

Interestingly, the present study found a significant association between the history of diabetes mellitus (DM) and CLBP. Hassoon and colleagues analyzed the data of 5106 adults (4591 without DM & 515 with diagnosed DM); they found than adults with DM have higher prevalence of CLBP, and higher odds of CLBP after adjusting for LBP risk factors(***Hassoon et al., 2017***).

Eivazi and colleagues studied the prevalence of CLBP among a small outpatient clinic's sample using the Roland Morris Disability Questionnaire (RMDQ). They found that 63% of the patients with diabetes group reported LBP compared to 47% in the healthy group(***Eivazi and Abadi, 2012***). This significant association was linked to the early intervertebral disc degeneration and lumber spinal stenosis seen in DM patients*(**Hassoon et al., 2017**)*.

The lack of physical activity, which leads to weight gain, may cause extensive strain on the spine and causes degenerative changes as well leading to pain. The American Academy of Orthopedic Surgeons (2013) explains that the pain could be caused by muscle soreness, which could

have been over stretched or injured during physical activity. Alternatively, a lack of physical activity will cause weak muscles and a weak core in general leading to pain of the lower back(***Yang et al., 2016***). In the present study, the proportion of patients who showed low physical activity was significantly higher in CLBP group compared to control group.

In contrary to our results, Chen and colleagues performed a systematic review on 15 cohort and case–control studies evaluating the relationship between sedentary and low back pain. They concluded that sedentary lifestyle by itself is not associated with CLBP*(**Chen et al., 2009**).*

Obesity, defined as BMI >30 kg/m^2 is an established risk factor for CLBP, previous reports showed that obese individuals have one and half times the likelihood of developing CLBP*(**Shmagel et al., 2016***). Our analysis showed a statistically significant higher proportion of obese individuals in CLBP group compared to healthy control. Similar to our findings, a meta-analysis found a significant correlation between body weight and CLBP(***Shiri et al., 2010***). In addition, Leboeuf-Yde performed a systematic review on 65 epidemiological studies and found a weak positive association between LBP and obesity*(**Leboeuf-Yde, 2000**).*

In a study of the impact of BMI on the prevalence of low back pain in a large population, the results showed that in both sexes, a high body mass index was significantly associated with an increased prevalence of low back pain. While additional adjustments for education, smoking status, leisure time physical activity, employment status, and activity at work hardly affected these associations, there were no interactions found with most other factors. The authors concluded that this large population-

based study indicates that obesity is associated with a high prevalence of low back pain(***Heuch et al., 2010***).

The association between overweight/obesity and low back pain could be related to differences in the distribution of body fat mass or to proportion of lean body mass. In men, high BMI may reflect high muscle mass; in women, it may indicate amount of adipose tissue(***Snijder et al., 2006***).

With regard to the primary outcome, the mean BDI was significantly higher in CLBP patients compared to control group (p =0.001). Moreover, the proportion of patients with moderate depression was significantly higher in CLBP group compared to control group (45% vs. 10%, respectively; p =0.01); while, the proportion of patients with normal psychological status was higher among healthy volunteers (72.2% vs. 35%, respectively; p <0.001).

In concordance with our findings, Sagheer and colleagues conducted a prospective cross-sectional study was at Pakistan, from January to June 2010, to assess the prevalence of anxiety and depression in CLBP patients according to specified age and gender groups using Hospital Anxiety and Depression Scale. The authors concluded that individuals with CLBP were at high risk to experience anxiety and depression. This risk was higher for females (***Sagheer et al., 2013***).

In addition, the 2010 National Health and Nutrition Examination Survey found that CLBP were more likely to have depression(***Shmagel et al., 2016***). A recent study by Tsuji and colleagues, extracted data from the 2014 Japan National Health and Wellness Survey (N = 30,000), showed a strong correlation between the severity of pain and depression symptoms(***Tsuji et al., 2016***).

Although the association between the CLBP and depression appears to be clinically well established, the underlying mechanisms are not well understood, though a potential explanation is disruption of the mesolimbic dopamine system(***Taylor et al., 2015***). Recent data from animal models indicate that regulation of dopamine activity in the ventral tegmental area (VTA) mediates depressive and anxiogenic responses suggesting a neurological link between depression and chronic pain(***Small et al., 2016***).

Another possible explanation is the negative activation of the prefrontal cortex in patients with CLBP. Previous studies have reported that activation of the nucleus accumbens is decreased in low back pain groups and that connectivity of the prefrontal cortex and nucleus accumbens is involved in the CLBP***(Baliki et al., 2006)***.

No investigation has clarified whether differences exist between CLBP patients with and without psychiatric problems. Since pain and psychosocial aspects cannot be clearly separated in terms of patient background, multidimensional patient assessments are needed. However, previous report showed low back pain patients with psychiatric problems showed lower scores for the family, mental health and pain-related QOL domains compared with patients without psychiatric problems. Patients without psychiatric problems showed positive BOLD signals at the nucleus accumbens (NAc), while patients with psychiatric problems showed limited activation at the NAc(***Baliki et al., 2012***).

These results suggested that the persistence of psychiatric problems among patients with CLBP might have some relationship with dysfunction of the NAc. Previous studies have shown that activation of the anterior cingulate cortex, prefrontal cortex, and nucleus accumbens is decreased in CLBP patients. Since both the anterior cingulate cortex and

prefrontal cortex belong to the descending inhibitory system, and the nucleus accumbens, which is involved in the dopamine system, releases μ-opioids that act to alleviate pain, decreased activation in these three brain regions may be related to decreased function of the descending inhibitory system(***Vania Apkarian et al., 2013***).

Interestingly, the present results showed a statistically significant positive correlation between higher BDI score and participants who live alone. The difference in the correlation coefficient between BDI patients and healthy volunteers was significant as well. In concordance with these findings, McKillop and colleagues found that social support is an important prognostic factor for depressive symptoms and recovery from depression in patients with CLBP*(**McKillop et al., 2016**)*. Another report showed a similar findings.

In conclusion, the prevalence of depression is higher among CLBP patients compared to healthy population. Moreover, the severity of depression correlates significantly with BMI and lack of social support.

Summary and Conclusion

Previous reports suggested that between of 5 to 10% of low back pain patients will developed CLBP. CLBP is highly disabling and responsible for high health expenditure ($6000 per person) and low quality of life. There is a growing body of evidence, which demonstrated a significant increase in the risk of depression among CLBP patients. In the present prospective study, we aimed to assess the risk of depression in patients with CLPB, using a psychiatric diagnostic interview; and compared 80 CLBP patients with 80 age and sex-matched healthy controls. A comparative prospective study was conducted Neuropsychiatry outpatient clinic at Benha University Hospital in Egypt. A written informed consent was taken from each patient. Data collection was started at the beginning of December 2016 and until the end of September 2017. The mean BDI was significantly higher in CLBP patients compared to control group (p =0.001). Moreover, the proportion of patients with moderate depression was significantly higher in CLBP group compared to control group (45% vs. 10%, respectively; p =0.01); while, the proportion of patients with normal psychological status was higher among healthy volunteers (72.2% vs. 35%, respectively; p <0.001). In addition, the present results showed a statistically significant positive correlation between higher BDI score and participants who live alone. The difference in the correlation coefficient between BDI patients and healthy volunteers was significant as well. In conclusion, the prevalence of depression is higher among CLBP patients compared to healthy population. Moreover, the severity of depression correlates significantly with BMI and lack of social support.

Conclusion

In conclusion,

- The prevalence of depression is higher among CLBP patients compared to healthy population.
- Moreover, the severity of depression correlates significantly with BMI and lack of social support.
- Further well-designed studies are still needed to establish these findings.

References

Alkherayf, F. and Agbi, C. 'Cigarette smoking and chronic low back pain in the adult population.', *Clinical and investigative medicine. Médecine clinique et experimentale*, 32(5), 2009, pp. E360-7.

American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders: DSM-III-R, American Psychiatric Association*, 1987.

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-II, American Psychiatric Publications*, 1968.

American Psychiatric Association (APA) *Diagnostic and statistical manual of mental disorders: DSM-IV-TR®, American Psychiatric Association*, 2000.

Ammendolia, C., Stuber, K., De Bruin, L. K., Furlan, A. D., Kennedy, C. A., Rampersaud, Y. R., Steenstra, I. A. and Pennick, V. 'Nonoperative treatment of lumbar spinal stenosis with neurogenic claudication: A systematic review', *Spine*, 2012.

Andersson, G. B. J. 'Epidemiological features of chronic low-back pain', *The Lancet*, 354(9178), 1999, pp. 581–585.

Andrews, G., Slade, T. and Peters, L. 'Classification in psychiatry: ICD-10 versus DSM-IV. Editorial', *British Journal of Psychiatry*, 1999, pp. 3–5.

Angst, J. 'The Course of Major Depression, Atypical Bipolar Disorder,

and Bipolar Disorder', in *New Results in Depression Research*. Berlin, Heidelberg: Springer Berlin Heidelberg, 1986, pp. 26–35.

Apkarian, A. V., Hashmi, J. A. and Baliki, M. N. 'Pain and the brain: Specificity and plasticity of the brain in clinical chronic pain', *Pain*, 2011.

Atkinson, J. H., Ingram, R. E., Kremer, E. F. and Saccuzzo, D. P. 'MMPI subgroups and affective disorder in chronic pain patients.', *The Journal of nervous and mental disease*, 174(7), 1986, pp. 408–13.

Atkinson, J. H., Slater, M. a, Grant, I., Patterson, T. L. and Garfin, S. R. 'Depressed mood in chronic low back pain: relationship with stressful life events.', *Pain*, 35(1), 1988, pp. 47–55.

Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B. and Apkarian, A. V. 'Chronic Pain and the Emotional Brain: Specific Brain Activity Associated with Spontaneous Fluctuations of Intensity of Chronic Back Pain', *Journal of Neuroscience*, 26(47), 2006, pp. 12165–12173.

Baliki, M. N., Petre, B., Torbey, S., Herrmann, K. M., Huang, L., Schnitzer, T. J., Fields, H. L. and Apkarian, A. V. 'Corticostriatal functional connectivity predicts transition to chronic back pain', *Nature Neuroscience*, 15(8), 2012, pp. 1117–1119.

Baliki, M. N., Schnitzer, T. J., Bauer, W. R. and Apkarian, A. V. 'Brain morphological signatures for chronic pain', *PLoS ONE*, 6(10), 2011.

Battié, M. C., Videman, T., Kaprio, J., Gibbons, L. E., Gill, K.,

Manninen, H., Saarela, J. and Peltonen, L. 'The Twin Spine Study: Contributions to a changing view of disc degeneration†', *Spine Journal*, 2009, pp. 47–59.

Bebbington, P. E., Dunn, G., Jenkins, R., Lewis, G., Brugha, T., Farrell, M. and Meltzer, H. 'The influence of age and sex on the prevalence of depressive conditions: Report from the National Survey of Psychiatric Morbidity', *Psychological Medicine*, 28(1), 1998, pp. 9–19.

Bell, C. C. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, JAMA: The Journal of the American Medical Association*, 1994.

Belmaker, R. H. and Agam, G. 'Major depressive disorder.', *The New England journal of medicine*, 358(1), 2008, pp. 55–68.

Biglarian, A., Seifi, B., Bakhshi, E., Mohammad, K., Rahgozar, M., Karimlou, M. and Serahati, S. 'Low back pain prevalence and associated factors in Iranian population: Findings from the national health survey', *Pain Research and Treatment*, 2012.

Blackwell, D. L., Lucas, J. W. and Clarke, T. C. 'Summary health statistics for U.S. adults: National health interview survey, 2012.', *Vital and health statistics. Series 10, Data from the National Health Survey*, 10(260), 2014, pp. 1–171.

Boland, R. J. and Keller, M. B. 'Course and outcome of depression', in *Handbook of Depression*, 2009, pp. 23–43.

Borenstein, D. G., Wiesel, S. W., Scott, D. and Boden, M. B. *Low Back and Neck Pain: Comprehensive Diagnosis and Management: Third*

Edition, Low Back and Neck Pain: Comprehensive Diagnosis and Management: Third Edition, 2004.

Bunney, W. E. and Bunney, B. G. 'Molecular clock genes in man and lower animals: Possible implications for circadian abnormalities in depression', *Neuropsychopharmacology*, 2000, pp. 335–345.

Burke, J. D., Burke, J. D., Rae, D. S. and Regier, D. A. 'Comparing Age at Onset of Major Depression and Other Psychiatric Disorders by Birth Cohorts in Five US Community Populations', *Archives of General Psychiatry*, 48(9), 1991, pp. 789–795.

Charney, D. S. and Manji, H. K. 'Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention.', *Science's STKE : signal transduction knowledge environment*, 2004(225), 2004, p. re5.

Chen, S.-M., Liu, M.-F., Cook, J., Bass, S. and Lo, S. K. 'Sedentary lifestyle as a risk factor for low back pain: a systematic review', *International Archives of Occupational and Environmental Health*, 82(7), 2009, pp. 797–806.

Chou, R., Atlas, S. J., Stanos, S. P. and Rosenquist, R. W. 'Nonsurgical interventional therapies for low back pain: A review of the evidence for an American pain society clinical practice guideline', *Spine*, 2009, pp. 1078–1093.

Chou, R., Qaseem, A., Snow, V., Casey, D., Cross, T. J., Shekelle, P. and Owens, D. K. 'Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society', *Annals of Internal Medicine*, 2007, pp. 478–491.

Cohen, S. P., Argoff, C. E. and Carragee, E. J. 'Management of low back pain.', *BMJ (Clinical research ed.)*, 2008.

Copeland, J. R. M., Beekman, A. T. F., Braam, A. W., Dewey, M. E., Delespaul, P., Fuhrer, R., Hooijer, C., Lawlor, B. A., Kivela, S.-L., Lobo, A., Magnusson, H., Mann, A. H., Meller, I., Prince, M. J., Reischies, F., Roelands, M., Skoog, I., Turrina, C., deVries, M. W., *et al.* 'Depression among older people in Europe: the EURODEP studies.', *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 3(1), 2004, pp. 45–9.

Côté, P., Cassidy, J. D. and Carroll, L. 'The Saskatchewan health and back pain survey: The prevalence of neck pain and related disability in Saskatchewan adults', *Spine*, 23(15), 1998, pp. 1689–1698.

Croft, P. R., Papageorgiou, A. C., Ferry, S., Thomas, E., Jayson, M. I. and Silman, A. J. 'Psychologic distress and low back pain. Evidence from a prospective study in the general population', *Spine*, 20(24), 1995, pp. 2731–2737.

Dagenais, S., Caro, J. and Haldeman, S. 'A systematic review of low back pain cost of illness studies in the United States and internationally', *Spine Journal*, 2008, pp. 8–20.

Delitto, A., George, S. Z., Van Dillen, L. R., Whitman, J. M., Sowa, G., Shekelle, P., Denninger, T. R., Godges, J. J. and Orthopaedic Section of the American Physical Therapy Association 'Low back pain.', *The Journal of orthopaedic and sports physical therapy*, 42(4), 2012, pp. A1-57.

Devillé, W. L. J. M., Van Der Windt, D. A. W. M., Džaferagić, A., Bezemer, P. D. and Bouter, L. M. 'The test of Lasegue: Systematic

review of the accuracy in diagnosing herniated discs', *Spine*, 25(9), 2000, pp. 1140–1147.

Deyo, R. A., Mirza, S. K. and Martin, B. I. 'Back pain prevalence and visit rates: Estimates from U.S. national surveys, 2002', *Spine*, 31(23), 2006, pp. 2724–2727.

Deyo, R. A. and Weinstein, J. N. 'Low back pain.', *The New England journal of medicine*, 344(5), 2001, pp. 363–70.

Doan, B. D. and Wadden, N. P. 'Relationships between depressive symptoms and descriptions of chronic pain', *Pain*, 36(1), 1989, pp. 75–84.

Donnelly, P. 'Progress and challenges in genome-wide association studies in humans', *Nature*, 2008, pp. 728–731.

Du, J. and Leigh, J. P. 'Incidence of workers compensation indemnity claims across socio-demographic and job characteristics', *American Journal of Industrial Medicine*, 54(10), 2011, pp. 758–770.

Dyrbye, L. N., Thomas, M. R. and Shanafelt, T. D. 'Systematic review of depression, anxiety, and other indicators of psychological distress among U.S. and Canadian medical students.', *Academic medicine : journal of the Association of American Medical Colleges*, 81(4), 2006, pp. 354–373.

Eaton, W. W., Kramer, M., Anthony, J. C., Dryman, A., Shapiro, S. and Locke, B. Z. 'The incidence of specific DIS/DSM-III mental disorders: data from the NIMH Epidemiologic Catchment Area Program', *Acta Psychiatrica Scandinavica*, 79(2), 1989, pp. 163–178.

Ehde, D. M., Dillworth, T. M. and Turner, J. A. 'Cognitive-behavioral therapy for individuals with chronic pain: Efficacy, innovations, and directions for research', *American Psychologist*, 69(2), 2014, pp. 153–166.

Eivazi, M. and Abadi, L. 'Low back pain in diabetes mellitus and importance of preventive approach.', *Health promotion perspectives*, 2(1), 2012, pp. 80–88.

Fava, M., Uebelacker, L. A., Alpert, J. E., Nierenberg, A. A., Pava, J. A. and Rosenbaum, J. F. 'Major depressive subtypes and treatment response', *Biological Psychiatry*, 42(7), 1997, pp. 568–576.

Fernandez, M., Colodro-Conde, L., Hartvigsen, J., Ferreira, M. L., Refshauge, K. M., Pinheiro, M. B., Ordoñana, J. R. and Ferreira, P. H. 'Chronic low back pain and the risk of depression or anxiety symptoms: insights from a longitudinal twin study', *The Spine Journal*, 17(7), 2017, pp. 905–912.

Feyissa, A. M., Chandran, A., Stockmeier, C. A. and Karolewicz, B. 'Reduced levels of NR2A and NR2B subunits of NMDA receptor and PSD-95 in the prefrontal cortex in major depression', *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 33(1), 2009, pp. 70–75.

Finan, P. H. and Smith, M. T. 'The comorbidity of insomnia, chronic pain, and depression: Dopamine as a putative mechanism', *Sleep Medicine Reviews*, 2013, pp. 173–183.

Fishbain, D. A., Goldberg, M., Robert Meagher, B., Steele, R. and Rosomoff, H. 'Male and female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria', *Pain*, 26(2), 1986, pp. 181–

197.

Fiske, A., Wetherell, J. and Gatz, M. 'Depression in older adults', *Annual review of clinical …*, 5, 2009, pp. 363–389.

Fitzgerald, P. B., Laird, A. R., Maller, J. and Daskalakis, Z. J. 'A meta-analytic study of changes in brain activation in depression', *Human Brain Mapping*, 29(6), 2008, pp. 683–695.

Fleming, R. *National Institute of Arthritis and Musculoskeletal and Skin Disease (NIH), Questions and Answers about Acne*, 2016.

France, R. D., Houpt, J. L., Skott, a, Krishnan, K. R. and Varia, I. M. 'Depression as a psychopathological disorder in chronic low back pain patients.', *Journal of psychosomatic research*, 30(2), 1986, pp. 127–133.

Freburger, J. K., Holmes, G. M., Agans, R. P., Jackman, A. M., Darter, J. D., Wallace, A. S., Castel, L. D., Kalsbeek, W. D. and Carey, T. S. 'The rising prevalence of chronic low back pain', *Archives of Internal Medicine*, 169(3), 2009, pp. 251–258.

Fukui, S., Matsuno, M., Inubushi, T. and Nosaka, S. 'N-Acetylaspartate concentrations in the thalami of neuropathic pain patients and healthy comparison subjects measured with 1H-MRS', *Magnetic Resonance Imaging*, 24(1), 2006, pp. 75–79.

Gautam, S., Jain, A., Gautam, M., Vahia, V. N. and Grover, S. 'Clinical Practice Guidelines for the management of Depression.', *Indian journal of psychiatry*. Wolters Kluwer -- Medknow Publications, 59(Suppl 1), 2017, pp. S34–S50.

Germain, A. and Kupfer, D. J. 'Circadian rhythm disturbances in

depression', *Human Psychopharmacology*, 2008, pp. 571–585.

Goffaux, P., Michaud, K., Gaudreau, J., Chalaye, P., Rainville, P. and Marchand, S. 'Sex differences in perceived pain are affected by an anxious brain', *Pain*, 152(9), 2011, pp. 2065–2073.

Gold, P. W. and Chrousos, G. P. 'The endocrinology of melancholic and atypical depression: Relation to neurocircuitry and somatic consequences', in *Proceedings of the Association of American Physicians*, 1999, pp. 22–34.

Green, B. N., Johnson, C. D., Snodgrass, J., Smith, M. and Dunn, A. S. 'Association Between Smoking and Back Pain in a Cross-Section of Adult Americans', *Cureus*, 2016.

Haldeman, S. and Dagenais, S. 'A supermarket approach to the evidence-informed management of chronic low back pain', *Spine Journal*, 2008, pp. 1–7.

Haley, W. E., Turner, J. A. and Romano, J. M. 'Depression in chronic pain patients: relation to pain, activity, and sex differences', *Pain*, 23(4), 1985, pp. 337–343.

Hameroff, S. R., Cork, R. C., Scherer, K., Crago, B. R., Neuman, C., Womble, J. R. and Davis, T. P. 'Doxepin effects on chronic pain, depression and plasma opioids', *Journal of Clinical Psychiatry*, 43(8 II), 1982, pp. 22–27.

Hasler, G., Bonwetsch, R., Giovacchini, G., Toczek, M. T., Bagic, A., Luckenbaugh, D. A., Drevets, W. C. and Theodore, W. H. '5-HT1A Receptor Binding in Temporal Lobe Epilepsy Patients With and Without Major Depression', *Biological Psychiatry*, 62(11),

2007, pp. 1258–1264.

Hasler, G., Drevets, W. C., Manji, H. K. and Charney, D. S. 'Discovering endophenotypes for major depression', *Neuropsychopharmacology*, 2004, pp. 1765–1781.

Hasler, G., van der Veen, J. W., Grillon, C., Drevets, W. C. and Shen, J. 'Effect of acute psychological stress on prefrontal GABA concentration determined by proton magnetic resonance spectroscopy.', *The American journal of psychiatry*, 167(10), 2010, pp. 1226–31.

Hassoon, A., Bydon, M., Kerezoudis, P., Maloney, P. R., Rinaldo, L. and Yeh, H. C. 'Chronic low-back pain in adult with diabetes: NHANES 2009–2010', *Journal of Diabetes and its Complications*, 31(1), 2017, pp. 38–42.

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H. and Nemeroff, C. B. 'The link between childhood trauma and depression: Insights from HPA axis studies in humans', *Psychoneuroendocrinology*, 33(6), 2008, pp. 693–710.

Heuch, I., Hagen, K., Heuch, I., Nygaard, Ø. and Zwart, J. A. 'The impact of body mass index on the prevalence of low back pain: The HUNT study', *Spine*, 35(7), 2010, pp. 764–768.

Hoy, D., Bain, C., Williams, G., March, L., Brooks, P., Blyth, F., Woolf, A., Vos, T. and Buchbinder, R. 'A systematic review of the global prevalence of low back pain', *Arthritis and Rheumatism*, 2012, pp. 2028–2037.

Hoy, D., March, L., Brooks, P., Blyth, F., Woolf, A., Bain, C.,

Williams, G., Smith, E., Vos, T., Barendregt, J., Murray, C., Burstein, R. and Buchbinder, R. 'The global burden of low back pain: Estimates from the Global Burden of Disease 2010 study', *Annals of the Rheumatic Diseases*, 73(6), 2014, pp. 968–974.

Hsiao, C.-J., Cherry, D. K., Beatty, P. C. and Rechtsteiner, E. a 'National Ambulatory Medical Care Survey: 2007 summary.', *National health statistics reports*, (27), 2010, pp. 1–32.

John, U., Alte, D., Hanke, M., Meyer, C., Völzke, H. and Schumann, A. 'Tobacco smoking in relation to analgesic drug use in a national adult population sample', *Drug and Alcohol Dependence*, 85(1), 2006, pp. 49–55.

Kassis, A. 'Antidepressants to treat nonspecific low back pain', *American Family Physician*, 78(1), 2008, pp. 51–53.

Katon, W., Egan, K. and Miller, D. 'Chronic pain: Lifetime psychiatric diagnoses and family history', *American Journal of Psychiatry*, 142(10), 1985, pp. 1156–1160.

Kendall, N. A. S. 'Psychosocial approaches to the prevention of chronic pain: The low back paradigm', *Bailliere's Best Practice and Research in Clinical Rheumatology*, 1999, pp. 545–554.

Kendler, K. S., Gardner, C. O. and Prescott, C. A. 'Toward a comprehensive developmental model for major depression in men', *American Journal of Psychiatry*, 163(1), 2006, pp. 115–124.

Kendler, K. S., Thornton, L. M. and Prescott, C. A. 'Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects', *American Journal of*

Psychiatry, 158(4), 2001, pp. 587–593.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., Rush, a J., Walters, E. E. and Wang, P. S. 'The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R).', *Jama*, 289(23), 2003, pp. 3095–105.

Kinkade, S. 'Evaluation and treatment of acute low back pain', *American Family Physician*, 2007.

Kinney, R. K., Gatchel, R. J., Polatin, P. B., Fogarty, W. T. and Mayer, T. G. 'Prevalence of psychopathology in acute and chronic low back pain patients', *Journal of Occupational Rehabilitation*, 3(2), 1993, pp. 95–103.

Kitts, R. L. and Goldman, S. J. 'Education and Depression', *Child and Adolescent Psychiatric Clinics of North America*, 2012, pp. 421–446.

Koes, B. W., van Tulder, M., Lin, C.-W. C., Macedo, L. G., McAuley, J. and Maher, C. 'An updated overview of clinical guidelines for the management of non-specific low back pain in primary care.', *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society*, 19(12), 2010, pp. 2075–94.

Kramlinger, K. G., Swanson, D. W. and Maruta, T. 'Are patients with chronic pain depressed?', *American Journal of Psychiatry*, 140(6), 1983, pp. 747–749.

Krishnan, K. R. R., France, R. D., Pelton, S., McCann, U. D., Davidson, J. and Urban, B. J. 'Chronic pain and depression. II. Symptoms of anxiety in chronic low back pain patients and their relationship to subtypes of depression', *Pain*, 22(3), 1985, pp. 289–294.

Kristiansson, P., Svärdsudd, K. and von Schoultz, B. 'Back pain during pregnancy: a prospective study.', *Spine*, 21(6), 1996, pp. 702–9.

Lærum, E., Indahl, A. and Skouen, J. S. 'What is "the good back-consultation"? A combined qualitative and quantitative study of chronic low back pain patients' interaction with and perceptions of consultations with specialists', *Journal of Rehabilitation Medicine*, 38(4), 2006, pp. 255–262.

Larson, S. L., Clark, M. R. and Eaton, W. W. 'Depressive disorder as a long-term antecedent risk factor for incident back pain: A 13-year follow-up study from the Baltimore Epidemiological catchment area sample', *Psychological Medicine*, 34(2), 2004, pp. 211–219.

Last, A. R. and Hulbert, K. 'Chronic low back pain: Evaluation and management', *American Family Physician*, 2009, pp. 1067–1074.

Leboeuf-Yde, C. 'Body weight and low back pain: A systematic literature review of 56 journal articles reporting on 65 epidemiologic studies', *Spine*, 25(2), 2000, pp. 226–237.

Leboeuf-Yde, C. 'Smoking and low back pain: A systematic literature review of 41 journal articles reporting 47 epidemiologic studies', *Spine*, 24(14), 1999, pp. 1463–1470.

Leboeuf-Yde, C., Kyvik, K. O. and Bruun, N. H. 'Low back pain and lifestyle: Part I: Smoking. Information from a population-based sample of 29,424 twins', *Spine*, 23(20), 1998, pp. 2207–2213.

Leigh, J. P., Hubert, H. B. and Romano, P. S. 'Lifestyle risk factors predict healthcare costs in an aging cohort', *American Journal of Preventive Medicine*, 29(5), 2005, pp. 379–387.

Leknes, S. and Tracey, I. 'A common neurobiology for pain and pleasure', *Nature Reviews Neuroscience*, 2008, pp. 314–320.

Lépine, J.-P. and Briley, M. 'The epidemiology of pain in depression.', *Human psychopharmacology*, 19 Suppl 1(June), 2004, pp. S3-7.

Linton, S. J. and Shaw, W. S. 'Impact of Psychological Factors in the Experience of Pain', *Physical Therapy*, 91(5), 2011, pp. 700–711.

Love, A. W. 'Depression in chronic low back pain patients: Diagnostic efficiency of three self???report questionnaires', *Journal of Clinical Psychology*, 43(1), 1987, pp. 84–89.

Low, M. B. and Macmillan, I. C. 'Entrepreneurship: Past Research and Future Challenges', *Journal of Management*, 14(2), 1988, pp. 139–161.

MacQueen, G. M. 'Magnetic resonance imaging and prediction of outcome in patients with major depressive disorder.', *Journal of psychiatry & neuroscience : JPN*, 34(5), 2009, pp. 343–349.

Magni, G., Moreschi, C., Rigatti-Luchini, S. and Merskey, H. 'Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain', *Pain*, 56(3), 1994, pp. 289–297.

Manchikanti, L., Singh, V., Datta, S., Cohen, S. P. and Hirsch, J. a 'Comprehensive review of epidemiology, scope, and impact of spinal pain.', *Pain physician*, 12(4), 2009, pp. E35–E70.

Manchikanti, L., Singh, V., Falco, F. J. E., Benyamin, R. M. and Hirsch, J. A. 'Epidemiology of low back pain in Adults', *Neuromodulation*, 17(S2), 2014, pp. 3–10.

Mann, J. J. 'The Medical Management of Depression', *New England Journal of Medicine*, 353(17), 2005, pp. 1819–1834.

Martinowich, K., Manji, H. K. and Lu, B. 'New insights into BDNF function in depression and anxiety', *Nature Neuroscience*, 10(9), 2007, pp. 1089–1093.

Matsudaira, K., Konishi, H., Miyoshi, K., Isomura, T., Takeshita, K., Hara, N., Yamada, K. and Machida, H. 'Potential Risk Factors for New-onset of Back Pain Disability in Japanese Workers: Findings from the Japan Epidemiological Research of Occupation-Related Back Pain (JOB) Study.', *Spine*, 37(15), 2012, pp. 1324–1333.

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., Schwalb, J. M. and Kennedy, S. H. 'Deep brain stimulation for treatment-resistant depression', *Neuron*, 45(5), 2005, pp. 651–660.

McGowan, P. O., Sasaki, A., D'Alessio, A. C. A. C., Dymov, S., Labonte, B., Szyf, M., Turecki, G., Meaney, M. J. and Labonté, B. 'Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse', *Nature Neuroscience*, 12(3), 2009, pp. 342–348.

McKillop, A. B., Carroll, L. J., Jones, C. A. and Battié, M. C. 'The relation of social support and depression in patients with chronic low back pain.', *Disability and rehabilitation*, 8288(August), 2016, pp. 1–7.

Melzack, R. 'From the gate to the neuromatrix', *Pain*, 82, 1999, pp. S121–S126.

Mendlewicz, J., Kriwin, P., Oswald, P., Souery, D., Alboni, S. and Brunello, N. 'Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: A pilot open-label study', *International Clinical Psychopharmacology*, 21(4), 2006, pp. 227–231.

Meucci, R. D., Fassa, A. G. and Faria, N. M. X. 'Prevalence of chronic low back pain: systematic review.', *Revista de Saúde Pública*, 2015, p. 1.

Meyer, B., Pilkonis, P. A., Krupnick, J. L., Egan, M. K., Simmens, S. J. and Sotsky, S. M. 'Treatment expectancies, patient alliance, and outcome: Further analyses from the National Institute of Mental Health Treatment of Depression Collaborative Research Program', *Journal of Consulting and Clinical Psychology*, 70(4), 2002, pp. 1051–1055.

Meyer, J. H., Ginovart, N., Boovariwala, A., Sagrati, S., Hussey, D., Garcia, A., Young, T., Praschak-Rieder, N., Wilson, A. A. and Houle, S. 'Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression.', *Arch Gen Psychiatry*, 63(11), 2006, pp. 1209–1216.

Mizoguchi, K., Ishige, A., Aburada, M. and Tabira, T. 'Chronic stress

attenuates glucocorticoid negative feedback: Involvement of the prefrontal cortex and hippocampus', *Neuroscience*, 119(3), 2003, pp. 887–897.

Morlion, B. 'Chronic low back pain: Pharmacological, interventional and surgical strategies', *Nature Reviews Neurology*, 2013, pp. 462–473.

Moseley, G. L. 'A pain neuromatrix approach to patients with chronic pain', *Manual Therapy*, 2003, pp. 130–140.

Murphy, F. C., Michael, A., Robbins, T. W. and Sahakian, B. J. 'Neuropsychological impairment in patients with major depressive disorder: The effects of feedback on task performance', *Psychological Medicine*, 33(3), 2003, pp. 455–467.

Murray, C. J. L., Atkinson, C., Bhalla, K., Birbeck, G., Burstein, R., Chou, D., Dellavalle, R., Danaei, G., Ezzati, M., Fahimi, A., Flaxman, D., Foreman, Gabriel, S., Gakidou, E., Kassebaum, N., Khatibzadeh, S., Lim, S., Lipshultz, S. E., London, S., *et al.* 'The State of US Health, 1990-2010', *JAMA*, 310(6), 2013, p. 591.

Murray, C. J. L., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S. Y., Ali, M. K., Alvarado, M., Anderson, H. R., Anderson, L. M., *et al.* 'Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010', *The Lancet*, 380(9859), 2012, pp. 2197–2223.

National Center for Health Statistics *National Center for Health Statistics. Deaths: Final Data for 2013. National Vital Statistics*

Report., *National Vital Statistics Reports*, 2015.

Nemeroff, C. B., Heim, C. M., Thase, M. E., Klein, D. N., Rush, A. J., Schatzberg, A. F., Ninan, P. T., McCullough, J. P., Weiss, P. M., Dunner, D. L., Rothbaum, B. O., Kornstein, S., Keitner, G. and Keller, M. B. 'Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma', *Proceedings of the National Academy of Sciences*, 100(24), 2003, pp. 14293–14296.

Nemeroff, C. B., Widerlöv, E., Bissette, G., Walléus, H., Karlsson, I., Eklund, K., Kilts, C. D., Loosen, P. T. and Vale, W. 'Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients', *Science*, 226(4680), 1984, pp. 1342–1344.

Neumeister, A. 'Reduced Serotonin Type 1A Receptor Binding in Panic Disorder', *Journal of Neuroscience*, 24(3), 2004, pp. 589–591.

Neumeister, A., Konstantinidis, A., Stastny, J., Schwarz, M. J., Vitouch, O., Willeit, M., Praschak-Rieder, N., Zach, J., de Zwaan, M., Bondy, B., Ackenheil, M. and Kasper, S. 'Association between serotonin transporter gene promoter polymorphism (5HTTLPR) and behavioral responses to tryptophan depletion in healthy women with and without family history of depression.', *Archives of General Psychiatry*, 2002, pp. 613–620.

Nutt, D. J. 'The role of dopamine and norepinephrine in depression and antidepressant treatment.', *The Journal of clinical psychiatry*, 67 Suppl 6, 2006, pp. 3–8.

Ochsmann, E. B., Rueger, H., Letzel, S., Drexler, H. and Muenster,

E. 'Over-indebtedness and its association with the prevalence of back pain', *BMC Public Health*, 9, 2009.

Olbrisch, M. E. 'Psychotherapeutic interventions in physical health: Effectiveness and economic efficiency', *American Psychologist*, 32(9), 1977, pp. 761–777.

Olsson, C. B., Grooten, W. J. A., Nilsson-Wikmar, L., Harms-Ringdahl, K. and Lundberg, M. 'Catastrophizing During and After Pregnancy: Associations With Lumbopelvic Pain and Postpartum Physical Ability', *Physical Therapy*, 92(1), 2012, pp. 49–57.

Painter, J. R., Seres, J. L. and Newman, R. I. 'Assessing benefits of the pain center: Why some patients regress', *Pain*, 8(1), 1980, pp. 101–113.

Palmer, K. T., Harris, C. E., Harris, E. C., Griffin, M. J., Bennett, J., Reading, I., Sampson, M. and Coggon, D. 'Case-control study of low-back pain referred for magnetic resonance imaging, with special focus on whole-body vibration.', *Scandinavian journal of work, environment & health*, 34(5), 2008, pp. 364–73.

Parikh, S. V., Quilty, L. C., Ravitz, P., Rosenbluth, M., Pavlova, B., Grigoriadis, S., Velyvis, V., Kennedy, S. H., Lam, R. W., MacQueen, G. M., Milev, R. V., Ravindran, A. V. and Uher, R. 'Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 2. Psychological treatments', *Canadian Journal of Psychiatry*, 2016, pp. 524–539.

Patetsos, E. and Horjales-Araujo, E. 'Treating chronic pain with SSRIs: What do we know?', *Pain Research and Management*, 2016.

Paulson, P. E., Minoshima, S., Morrow, T. J. and Casey, K. L. 'Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans', *Pain*, 76(1–2), 1998, pp. 223–229.

Pergolizzi, J. V., Raffa, R. B. and Taylor, R. 'Treating acute pain in light of the chronification of pain', *Pain Management Nursing*, 2014, pp. 380–390.

Price, A., Rayner, L., Okon-Rocha, E., Evans, A., Valsraj, K., Higginson, I. J. and Hotopf, M. 'Antidepressants for the treatment of depression in neurological disorders: A systematic review and meta-analysis of randomised controlled trials', *Journal of Neurology, Neurosurgery and Psychiatry*, 2011, pp. 914–923.

Price, J. L. and Drevets, W. C. 'Neurocircuitry of mood disorders', *Neuropsychopharmacology*, 2010, pp. 192–216.

Raadsheer, F. C., Hoogendijk, W. J. G., Stam, F. C., Tilders, F. J. H. and Swaab, D. F. 'Increased Numbers of Corticotropin-Releasing Hormone Expressing Neurons in the Hypothalamic Paraventricular Nucleus of Depressed Patients', *Neuroendocrinology*, 60(4), 2008, pp. 436–444.

Rajkowska, G., Miguel-Hidalgo, J. J., Wei, J., Dilley, G., Pittman, S. D., Meltzer, H. Y., Overholser, J. C., Roth, B. L. and Stockmeier, C. A. 'Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression', *Biological Psychiatry*, 45(9), 1999, pp. 1085–1098.

Rajkowska, G., O'Dwyer, G., Teleki, Z., Stockmeier, C. A. and Miguel-Hidalgo, J. J. 'GABAergic neurons immunoreactive for

calcium binding proteins are reduced in the prefrontal cortex in major depression', *Neuropsychopharmacology*, 32(2), 2007, pp. 471–482.

Richards, D. 'Prevalence and clinical course of depression: A review', *Clinical Psychology Review*, 2011, pp. 1117–1125.

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., Griem, A., Kovacs, M., Ott, J. and Merikangas, K. R. 'Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis.', *JAMA : the journal of the American Medical Association*, 301(23), 2009, pp. 2462–2471.

Ritzwoller, D. P., Crounse, L., Shetterly, S. and Rublee, D. 'The association of comorbidities, utilization and costs for patients identified with low back pain', *BMC Musculoskeletal Disorders*, 7, 2006.

Robins, L. N. and Regier, D. A. *Psychiatric disorders in America : the epidemiologic catchment area study*, *Journal of Psychiatry and Neuroscience*, 1991.

Robins, L. N., Wing, J., Wittchen, H. U., Helzer, J. E., Babor, T. F., Burke, J., Farmer, A., Jablenski, A., Pickens, R. and Regier, D. A. 'The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures.', *Archives of general psychiatry*, 45(12), 1988, pp. 1069–77.

Rotheram-Borus, M. J. 'Variations in perceived pain associated with emotional distress and social identity in AIDS', *AIDS Patient Care*

and STD's, 14(12), 2000, pp. 659–65.

Sagheer, M. A., Khan, M. F. and Sharif, S. 'Association between chronic low back pain, anxiety and depression in patients at a tertiary care centre.', *JPMA. The Journal of the Pakistan Medical Association*, 63(6), 2013, pp. 688–90.

Santamaria, J., Tolosa, E. and Valles, A. 'Parkinson's disease with depression: a possible subgroup of idiopathic parkinsonism', *Neurology*, 36(8), 1986, p. 1130–3.

Seifert, F. and Maihöfner, C. 'Central mechanisms of experimental and chronic neuropathic pain: Findings from functional imaging studies', *Cellular and Molecular Life Sciences*, 2009, pp. 375–390.

Sheline, Y. I., Gado, M. H. and Kraemer, H. C. 'Untreated depression and hippocampal volume loss', *American Journal of Psychiatry*, 160(8), 2003, pp. 1516–1518.

Shiri, R., Karppinen, J., Leino-Arjas, P., Solovieva, S. and Viikari-Juntura, E. 'The association between obesity and low back pain: A meta-analysis', *American Journal of Epidemiology*, 171(2), 2010, pp. 135–154.

Shmagel, A., Foley, R. and Ibrahim, H. 'Epidemiology of Chronic Low Back Pain in US Adults: Data From the 2009-2010 National Health and Nutrition Examination Survey', *Arthritis Care & Research*, 68(11), 2016, pp. 1688–1694.

Simpson, D. 'Phrenology and the neurosciences: Contributions of F. J. Gall and J. G. Spurzheim', in *ANZ Journal of Surgery*, 2005, pp. 475–482.

Sitthipornvorakul, E., Janwantanakul, P., Purepong, N., Pensri, P. and Van Der Beek, A. J. 'The association between physical activity and neck and low back pain: A systematic review', *European Spine Journal*, 2011, pp. 677–689.

Small, K. M., Nunes, E., Hughley, S. and Addy, N. A. 'Ventral tegmental area muscarinic receptors modulate depression and anxiety-related behaviors in rats', *Neuroscience Letters*, 616, 2016, pp. 80–85.

Snijder, M. B., van Dam, R. M., Visser, M. and Seidell, J. C. 'What aspects of body fat are particularly hazardous and how do we measure them?', *International Journal of Epidemiology*, 2006, pp. 83–92.

Sobocki, P., Jönsson, B., Angst, J. and Rehnberg, C. 'Cost of depression in Europe', *Journal of Mental Health Policy and Economics*, 9(2), 2006, pp. 87–98.

Standaert, C. J., Friedly, J., Erwin, M. W., Lee, M. J., Rechtine, G., Henrikson, N. B. and Norvell, D. C. 'Comparative effectiveness of exercise, acupuncture, and spinal manipulation for low back pain', *Spine*, 2011.

Staud, R., Craggs, J. G., Robinson, M. E., Perlstein, W. M. and Price, D. D. 'Brain activity related to temporal summation of C-fiber evoked pain', *Pain*, 129(1–2), 2007, pp. 130–142.

Stroud, L. R., Salovey, P. and Epel, E. S. 'Sex differences in stress responses: Social rejection versus achievement stress', *Biological Psychiatry*, 52(4), 2002, pp. 318–327.

Sudak, D. M. 'Cognitive behavioral therapy for depression', *Psychiatric Clinics of North America*, 2012, pp. 99–110.

Sullivan, M. J., Reesor, K., Mikail, S. and Fisher, R. 'The treatment of depression in chronic low back pain: review and recommendations.', *Pain*, 50(1), 1992, pp. 5–13.

Sullivan, P. F., Neale, M. C. and Kendler, K. S. 'Genetic Epidemiology of Major Depression: Review and Meta-Analysis', *American Journal of Psychiatry*, 157(10), 2000, pp. 1552–1562.

Szpalski, M., Gunzburg, R., Rydevik, B. L., Le Huec, J. C. and Mayer, H. M. *Surgery for low back pain, Surgery for Low Back Pain*, 2010.

Taylor, A. M. W., Castonguay, A., Taylor, A. J., Murphy, N. P., Ghogha, A., Cook, C., Xue, L., Olmstead, M. C., De Koninck, Y., Evans, C. J. and Cahill, C. M. 'Microglia Disrupt Mesolimbic Reward Circuitry in Chronic Pain', *Journal of Neuroscience*, 35(22), 2015, pp. 8442–8450.

Tsuji, T., Matsudaira, K., Sato, H. and Vietri, J. 'The impact of depression among chronic low back pain patients in Japan.', *BMC musculoskeletal disorders*. BioMed Central, 17(1), 2016, p. 447.

van Tulder, M., Becker, A., Bekkering, T., Breen, A., del Real, M. T. G., Hutchinson, A., Koes, B., Laerum, E., Malmivaara, A. and Ma, C. B. W. G. G. 'Chapter 3 - European guidelines for the management of acute nonspecific low back pain in primary care', *European Spine Journal*, 15, 2006, pp. S169–S191.

Turner, J. A. and Romano, J. M. 'Self???report screening measures for

depression in chronic pain patients', *Journal of Clinical Psychology*, 40(4), 1984, pp. 909–913.

Urquhart, D. M., Hoving, J. L., Assendelft, W. W., Roland, M. and van Tulder, M. W. 'Antidepressants for non-specific low back pain', *Cochrane Database Syst Rev*, 2008, p. CD001703.

Ustun, T. B. 'Global burden of depressive disorders in the year 2000', *The British Journal of Psychiatry*, 184(5), 2004, pp. 386–392.

Vania Apkarian, A., Baliki, M. N. and Farmer, M. A. 'Predicting transition to chronic pain', *Current Opinion in Neurology*, 2013, pp. 360–367.

Volirath, M. and Angst, J. 'Outcome of panic and depression in a seven???year follow???up: results of the Zurich study', *Acta Psychiatrica Scandinavica*, 80(6), 1989, pp. 591–596.

Waddell, G. and Burton, A. K. 'Occupational health guidelines for the management of low back pain at work: Evidence review', *Occupational Medicine*, 51(2), 2001, pp. 124–135.

Wáng, Y. X. J., Wáng, J.-Q. and Káplár, Z. 'Increased low back pain prevalence in females than in males after menopause age: evidences based on synthetic literature review', *Quantitative Imaging in Medicine and Surgery*, 6(2), 2016, pp. 199–206.

Ward, N., Bokan, J. A., Phillips, M., Benedetti, C., Butler, S. and Spengler, D. 'Antidepressants in concomitant chronic back pain and depression: doxepin and desipramine compared.', *Journal of Clinical Psychiatry*, 45(3 Pt 2), 1984, pp. 54–59.

Webb, R., Brammah, T., Lunt, M., Urwin, M., Allison, T. and

Symmons, D. 'Prevalence and predictors of intense, chronic, and disabling neck and back pain in the UK general population', *Spine*, 28(11), 2003, pp. 1195–1202.

van Wijk, R. M. A. W., Geurts, J. W. M., Lousberg, R., Wynne, H. J., Hammink, E., Knape, J. T. A. and Groen, G. J. 'Psychological predictors of substantial pain reduction after minimally invasive radiofrequency and injection treatments for chronic low back pain', *Pain Medicine*, 9(2), 2008, pp. 212–221.

Wikström, B.-O., Kjellberg, A. and Landström, U. 'Health effects of long-term occupational exposure to whole-body vibration: A review', *International Journal of Industrial Ergonomics*, 14(4), 1994, pp. 273–292.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R. and Steinhausen, H. C. 'The size and burden of mental disorders and other disorders of the brain in Europe 2010', *European Neuropsychopharmacology*, 21(9), 2011, pp. 655–679.

Wood, P. B. 'Mesolimbic dopaminergic mechanisms and pain control', *Pain*, 2006, pp. 230–234.

Wood, P. B., Schweinhardt, P., Jaeger, E., Dagher, A., Hakyemez, H., Rabiner, E. A., Bushnell, M. C. and Chizh, B. A. 'Fibromyalgia patients show an abnormal dopamine response to pain', *European Journal of Neuroscience*, 25(12), 2007, pp. 3576–3582.

Woolf, C. J. 'Evidence for a central component of post-injury pain

hypersensitivity', *Nature*, 306(5944), 1983, pp. 686–688.

World Health Organization 'The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research', *The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research*, 1993, p. xiii+248p.

Yabuki, S., Konno, S. and Kikuchi, S. 'Assessment of pain due to lumbar spine diseases using MR spectroscopy: a preliminary report.', *Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association*, 18(3), 2013, pp. 363–8.

Yang, H., Haldeman, S., Lu, M.-L. and Baker, D. 'Low Back Pain Prevalence and Related Workplace Psychosocial Risk Factors: A Study Using Data From the 2010 National Health Interview Survey', *Journal of Manipulative and Physiological Therapeutics*, 39(7), 2016, pp. 459–472.

Zisook, S., Lesser, I., Stewart, J., Wisniewski, S., Balasubramani, G. K., Fava, M., Gilmer, W., Dresselhaus, T., Thase, M., Nierenberg, A., Trivedi, M. and Rush, A. J. 'Effect of Age at Onset on the Course of Major Depressive Disorder', *American Journal of Psychiatry*, 164(10), 2007, pp. 1539–1546.

الملخص العربي

المقدمة:

تُعد آلام أسفل الظهر السبب الثاني الأكثر شيوعا بعد نزلات البرد في الزيارات الطبية و يلجأ الكثير من المرضي إلي استشارة أطباء العظام والتخدير قبل التفكير في الطب النفسي ولا يلجؤون إلي الطبيب النفسي الا مع استمرار الآلام بالرغم من استمرار العلاج وهنا يكون التشخيص لآلام أسفل الظهر نفسي المنشأ.

وقد وجدت الدراسات ان العديد من مرضي آلام أسفل الظهر المزمنة تكون ناتجة عن الاكتئاب أو أعراض جسمانية نتيجة توتر عصبي ونفسي أو فشل في العلاج مما قد يدخل المريض في اكتئاب لاعتقاده بوجود مرض مزمن في حين يخبره الأطباء ان جميع فحوصاته جيده.

إن آلام أسفل الظهر حالة شائعة تؤثر على نسبة كبيرة من الناس يمكن أن تصل إلى ٤٠٪ وعلى الرغم من أن الأغلبية تعاني منها إلا أنها تؤثر صحيا بشكل سلبي علي الأقلية.

تنتج آلام أسفل الظهر المزمنة عن تفاعل العوامل البيولوجية والنفسية والاجتماعية وتأثير بعضها البعض مما يؤدي الي ظهور الآلام واستمرارها.

الاضطرابات النفسية أيضا أكثر انتشاراً بشكل ملحوظ في تلك الحالات مقارنة مع أولئك الذين لا يعانون من آلام أسفل الظهر المزمنة كما رأينا في ١٧ دولة في عمليات المسح العالمي للصحة النفسية وكلما قلت الأعراض العصبية بالكشف الطّبّي في حالات الآلام أسفل الظهر المزمنة كلما زادت الأعراض النفسية في تلك الحالات.

وقد وجد أنه كلما زاد عدد مرات الشكوى من آلام أسفل الظهر المزمنة كلما أدت إلي زيادة احتمالات الأمراض النفسية، وقد تم تعزيز العلاقة بين الأمراض النفسية مع آلام أسفل الظهر المزمنة مما قد تؤدي الي سوء التشخيص، وسوء النتائج ،وتؤكد المبادئ التوجيهية السريرية أهمية الفحص عن الأمراض النفسية لدى هؤلاء المرضي .

هدف الدراسة:

تحديد نسبة حدوث الاكتئاب في مرضي آلام اسفل الظهر المزمنة.

نوع و مكان الدراسة:

هذه دراسة للحالات و الشواهد تم عقدها في مستشفى بنها الجامعي.

اختيار عينة البحث :

تم اختيار80 مريضاً من مرضى آلام أسفل الظهر المزمنة ، 80 آخرون من الأفراد الأصحاء والذين تتراوح أعمارهم بين 20 و 50 عاماً.

المرضى التابعين للدراسة:

المرضي البالغين من العمر من 20 الى 50 عاماً المترددين على مستشفى بنها الجامعي والذين يعانون من آلام أسفل الظهر المزمنة.

وتم استبعاد :

- السيدات الحوامل.
- مرضى السرطان.
- المرضي المنتظرين عمليات جراحية.
- المعاقين ومرضى هشاشة العظام.

كل المرضى تم إخضاعهم للاتي:

- التاريخ المرضي بالتفصيل.
- فحص المريض فحصا شاملا.
- مقياس بيك.
- أشعه عاديه أو أشعه رنين مغناطيسي علي فقرات الظهر.
- صورة دم كاملة - نسبة السكر بالدم .

الموافقة المطلعة:

تم أخذ موافقة المرضى بعد مناقشة هدف الدراسة معهم.

أهم النتائج المستخلصة من البحث :

طبقا للعديد من الابحاث, فإن حوالى 5 الى 10% من مرضي مرضي الآلام أسفل الظهر سوف يتحولون الى مرضى مزمنين. يتسبب مرض الام أسفل الظهر المزمنة فى العديد من المعوقات الحركيه ويزيد من معدل النفقات الصحيه بصورة كبيرة. أيضا فإن الاضطرابات النفسية أكثر انتشاراً بشكل ملحوظ في تلك الحالات مقارنة مع أولئك لذين لا يعانون من الام أسفل الظهر المزمنة كما رأينا في ١٧ دولة في عمليات المسح العالمي للصحة النفسية وكلما قلت الأعراض العصبية بالكشف الطّبّي في حالات الالام أسفل الظهر المزمنة كلما زادت الأعراض النفسية في هذه الحالات. لذلك وقد تم اجراء تلك الدراسة في مستشفى بنها الجامعي حيث انضم 80 مريضاً بآلام أسفل الظهر المزمنة الدماغية و80 آخرون من الأفراد الأصحاء والذين تتراوح أعمارهم بين 20 و 50 عاماً.

أظهرت نتائج هذة الدراسه عن وجود اعراض الاكتئاب بنسب اعلى فى مرضى من الام أسفل الظهر المزمنة عن نظرائهم الاصحاء, وقد كان هذا الفرق مهم احصائيا. كما وجدت علاقه طرديه مهمه بين المرضي الذين يعيشون بمفردهم والدرجات الاعلى من اعراض الاكتئاب.

فى النهايه اظهرت تلك الدراسة وجود نسب عالية من اعراض الاكتئاب بين مرضى الام أسفل الظهر المزمنة.

نسبه انتشار الاكتئاب في مرضي الالام اسفل الظهر المزمنه

رسالة مقدمة توطئة للحصول علي درجة الماجستير في الامراض النفسية والعصبية

مقدمة من

الطبيبة/ هدي حسام الدين عبدالحفيظ

تحت اشراف

أ.د .رزق محمد خضير

أستاذ الأمراض العصبية

جامعة بنها – كلية الطب

أ.د .حسين العليمي الشيخ

أستاذ الأمراض النفسية

كلية الطب – جامعة بنها

د .ابراهيم أحمد عبدالرسول

مدرس الأمراض العصبية

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