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## From the Editor

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In this issue of the journals a number of papers dealt with various topics including health assessment, the effect of Khat and others. In addition we have the second paper of the series on Evidence Based Medicine.

A paper from Abha City was done to assess the health aspect of male teachers (384) and to assess level of job satisfaction of male teachers in different grades in Abha city.

The study was done through a questionnaire. The average age was 39.31. The level of satisfaction regarding current job and salary of teachers which revealed that 65.6% were satisfied while 34.4% were not satisfied. The complaints or health problems among teachers as regard eyesight problems 15.4%, Hearing problems in 6.5%, Mental illness, psychological or psychiatric problem was 7.8%, The history of drug or alcohol problem 2.3%. The relation between ill health and experience years gave a significant association but with level no significant association. The relation between job satisfaction and experience years showed no significant difference with experience years but the higher rates with longer experience (70.2%) and gave significant relation with level especially at primary level.

A paper from Turkey tried to understand whether or not there are some beneficial changes of health parameters with hydroxyurea in sickle cell diseases (SCDs) cases. All SCDs cases were enrolled, and a hydroxyurea therapy was initiated. The authors studied 337 patients.. Hydroxyurea was well-tolerated with a majority of patients (80.1%). Mean number (10.3 versus 1.7 crises per year,  $p < 0.000$ ) and mean severity of painful crises decreased, significantly (7.8 versus 2.2,  $p < 0.001$ ). The authors concluded that SCDs are chronic inflammatory disorders initiating at birth. Hydroxyurea decreases frequency and severity of painful crises, WBC and PLT counts, and total and direct bilirubin and LDH levels, and it increases body weight and Hct value, all of which indicate a decreased inflammatory process in patients. Thus elective surgical procedures should be performed after a few months of treatment with hydroxyurea in non-users.

A paper from Africa looked at - Khat (*Catha edulis*) chewing as a risk factor of low birth weight among full term Newborns: A systematic review of Meta-analysis, data of 1850 neonates and their maternal history were obtained, with Khat chewers to non-chewers ratio of 1.1:1. A mean birth weight of Khat chewing mothers was found lower than the non-chewers neonates, with the mean difference of -130.74 [-189.90, -71.59] grams, Heterogeneity:  $\text{Tau}^2 = 0.00$ ;  $\text{Chi}^2 = 0.95$ ,  $\text{df} = 1$  ( $P = 0.33$ );  $I^2 = 0\%$ . In all assumptions tasted, the finding of the Meta analysis has showed consistent direction, while a reduction of 130.74 gram is the best available estimate of the effect size. The authors concluded that Khat chewing during pregnancy is found to be a significant risk factor for reduction of birth weight which may contribute a lot for infant mortality.

A retrospective study from Australia reviewing a consecutive series of Lichtenstein repairs performed by a single experienced hernia surgeon was carried out. 248 inguinal hernia patients operated on in 2005 were reviewed. Patients were contacted via telephone at a median of 50 months. A recently validated inguinal pain questionnaire was used to assess the incidence of chronic pain. 185 (75%) patients were able to be contacted for follow-up, making a total of 213 inguinal hernia repairs (including bilateral hernias). The authors concluded that chronic pain did not appear to be a major problem within this cohort of patients. The Lichtenstein technique can produce favourable results in terms of chronic pain for unilateral, bilateral and recurrent inguinal hernias in an unselected group of patients with the usual mix of risk factors and complications.

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# Preoperative management of sickle cell patients with hydroxyurea

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## Abstract

**Background:** We tried to understand whether or not there are some beneficial changes of health parameters with hydroxyurea in sickle cell diseases (SCDs) cases.

**Methods:** All SCDs cases were enrolled, and a hydroxyurea therapy was initiated.

**Results:** We studied 337 patients, totally. Hydroxyurea was well-tolerated with a majority of patients (80.1%). Mean number (10.3 versus 1.7 crises per year,  $p < 0.000$ ) and mean severity of painful crises decreased, significantly (7.8 versus 2.2,  $p < 0.001$ ). Although body weight and mean hematocrit (Hct) value increased, white blood cell (WBC) and platelet (PLT) counts and total and direct bilirubin and lactate dehydrogenase (LDH) levels decreased, significantly ( $p < 0.000$  for all). On the other hand, there were avascular necrosis of bones in 18.9%, leg ulcers in 12.7%, pulmonary hypertension in 11.5%, chronic renal disease in

8.3%, coronary heart disease in 7.7%, digital clubbing in 6.5%, stroke in 6.5%, exitus in 5.3%, chronic obstructive pulmonary disease in 4.7%, and cirrhosis in 3.2% of the patients.

**Conclusion:** SCDs are chronic inflammatory disorders initiating at birth. Hydroxyurea decreases frequency and severity of painful crises, WBC and PLT counts, and total and direct bilirubin and LDH levels, and it increases body weight and Hct value, all of which indicate a decreased inflammatory process in patients. Thus elective surgical procedures should be performed after a few months of treatment with hydroxyurea in non-users. By this way, beside decreased requirement of blood transfusions, perioperative morbidity and mortality will also be lowered due to decreased inflammatory process on capillary endothelium all over the body.

**Key words:** Sickle cell diseases, chronic endothelial inflammation, hydroxyurea

## Introduction

Systemic atherosclerosis may be the major underlying cause of aging in human beings and even in animals. It is an irreversible process initiating at birth. Although it keeps to mainly the larger, high blood pressure (BP) carrying vessels, all arteries, arterioles, and even capillaries are affected with some extent. Some of the accelerating factors of the systemic process are overweight, dyslipidemia, elevated BP, and insulin resistance for the development of terminal diseases such as obesity, hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), peripheral artery disease, and stroke, all of which are collected under the heading of metabolic syndrome (1-6). On the other hand, sickle cell diseases (SCDs) are systemic microangiopathic processes that are caused by homozygous inheritance of hemoglobin S (Hb S) (7,8). Glutamic acid is replaced with valine in the sixth position of the beta chain of the Hb S. Presence of valine promotes polymerisation of the Hb S. So Hb S causes red blood cells (RBCs) to change their normal elastic and biconcave disc shaped structures to hard bodies. The decreased elasticity of RBCs instead of their shapes may be the central pathology of the diseases. The sickling process is present in whole life, but is exaggerated during stressful conditions due to the increased basal metabolic rate. The RBCs can take their normal elastic structures after normalization of the stressful conditions, but after repeated cycles of sickling and unsickling, they become hard bodies, permanently. The hard cells induced chronic endothelial damage and infarcts at the microvascular level, even in the absence of obvious vascular occlusions due to the edematous endothelium, are the terminal consequences of the diseases, so life expectancy is decreased up to 30 years (9). We tried to understand whether or not there are some beneficial changes of health parameters with hydroxyurea therapy in the SCDs.

## Material and Methods

The study was performed in the Hematology Service of the Mustafa Kemal University between March 2007 and October 2013. All patients with SCDs were enrolled into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography. Their medical histories including smoking habit, regular alcohol consumption, and leg ulcers were learnt. Frequency of painful crises was detected as a mean number of crises per year, and severity of them as a mean degree between 0 to 10 according to patient's self-explanation. Cases with a history of three pack-year were accepted as smokers, and cases with a history of one drink a day for three years were accepted as drinkers. A check up procedure including body weight, serum creatinine value on three occasions, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, an electrocardiography, a Doppler echocardiography, an abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging of hips was performed. Other bone areas for avascular necrosis were

scanned according to the patients' complaints. Cases with acute painful crisis or any other inflammatory event were treated at first, and then the spirometric pulmonary function tests to diagnose COPD, the Doppler echocardiography to measure the systolic BP of pulmonary artery, and renal and hepatic function tests were performed on the silent phase. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (10). Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent phase is accepted as pulmonary hypertension (11). CRD is diagnosed with a permanently elevated serum creatinine level of 1.3 mg/dL or higher on the silent phase. Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, ascites, and liver biopsy in case of requirement. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of greater than 1.0 and with the presence of Schamroth's sign (12,13). A stress electrocardiography was performed in cases with an abnormal electrocardiography and/or angina pectoris. A coronary angiography was obtained just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of the cardiac walls. Then, a hydroxyurea therapy was initiated to all patients with an initial dose of 15 mg/kg/day, and then the dose was increased up to the final dose of 35 mg/kg/day according to patients' requirement and compliance. Finally, the mean number and severity of painful crises, body weight, white blood cell (WBC) and platelet (PLT) counts, hematocrit (Hct) value, mean corpuscular volume (MCV), and the total and direct bilirubin and lactate dehydrogenase (LDH) levels of the serum were compared before and after the hydroxyurea therapy. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

## Results

The study included 337 patients with the SCDs (169 females and 168 males). The mean ages of them were  $28.4 \pm 9.3$  (8-59) versus  $29.8 \pm 9.3$  (6-58) years in females and males, respectively ( $p > 0.05$ ). The hydroxyurea treatment was used and well-tolerated with a high majority of cases (80.1%), and the remaining cases could not be followed up. We have not observed any major side effect of the therapy during the follow-up period. The final dose of 35 mg/kg/day was required just in 25 cases (7.4%), and the usual dose was 500 mg twice daily during the 7-year follow-up period. During the period, the mean number of painful crises per year was significantly decreased with the treatment (10.3 versus 1.7 crises per year,  $p < 0.000$ ). The mean severity of painful crises was decreased, too (7.8 versus 2.2,  $p < 0.001$ ). Although the body weight, mean Hct value, and MCV increased, the WBC and PLT counts and the total and direct bilirubin and LDH levels of the serum decreased with the therapy, significantly ( $p < 0.000$  for all) (Table 1). On the other hand, we detected autosplenectomy in 46.8%, avascular necrosis of bones in 18.9% (90.6% at hips, 10.9% at shoulders, 9.3% at knees, 6.2% at elbows,

**Table 1: Characteristic features of sickle cell patients before and after hydroxyurea therapy**

Variables	Before hydroxyurea therapy	p-value	After hydroxyurea therapy
Mean number of painful crises per year	10.3 ± 10.6 (0-48)	<0.000	1.7 ± 1.1 (0-6)
Mean severity of painful crises	7.8 ± 2.2 (0-10)	<0.000	2.2 ± 1.7 (0-10)
Weight (kg)	59.1 ± 11.4 (37-95)	<0.000	65.2 ± 13.0 (46-107)
White blood cell (μL)	15.050 ± 6.148 (4.890-38.800)	<0.000	11.349 ± 5.029 (5.010-31.850)
Hematocrit value (%)	23.2 ± 4.0 (16-35)	<0.000	27.8 ± 3.4 (20-36)
Mean corpuscular volume (fL)	88.7 ± 9.6 (57-112)	<0.000	105.2 ± 13.6 (66-129)
Platelet (μL)	449.840 ± 217.370 (169.000-1.561.000)	<0.000	430.840 ± 142.681 (219.000-936.000)
Total bilirubin (mg/dL)	5.3 ± 5.6 (0.6-38.2)	<0.000	3.1 ± 2.2 (0.7-11.0)
Direct bilirubin (mg/dL)	2.0 ± 3.4 (0.2-15.0)	<0.000	0.9 ± 0.9 (0.2-6.0)
Lactate dehydrogenase (IU/L)	647.5 ± 265.8 (196-1.552)	<0.000	509.9 ± 315.4 (235-2.218)

**Table 2: Sickle cell patients with associated disorders**

Variables	Prevalence
Autosplenectomy	46.8% (158)
Avascular necrosis of bones	18.9% (64) (90.6% at the hips)
Leg ulcers	12.7% (43)
Pulmonary hypertension	11.5% (39)
Chronic renal disease	8.3% (28)
Coronary heart disease	7.7% (26)
Digital clubbing	6.5% (22)
Stroke	6.5% (22)
Exitus	5.3% (18)
Chronic obstructive pulmonary disease	4.7% (16)
Cirrhosis	3.2% (11)

3.1% at ankles, and 1.5% at wrists), leg ulcers in 12.7%, pulmonary hypertension in 11.5%, CRD in 8.3%, CHD in 7.7%, digital clubbing in 6.5%, stroke in 6.5%, exitus in 5.3%, COPD in 4.7%, and cirrhosis in 3.2% of the patients (Table 2). Although smoking was observed in 6.5% (22) of the patients, there was only one case (0.2%) of regular alcohol consumption, who was not cirrhotic at the time. Although antiHCV was positive in two of the cirrhotics, HCV RNA was detected as negative by polymerase chain reaction in both. Prevalences of mortality were similar in both genders (4.7% versus 5.9% in females and males, respectively,  $p>0.05$ ), and mean ages of such cases were

32.1 versus 29.1 years in females and males, respectively ( $p>0.05$ ).

## Discussion

SCDs mainly affect microvascular endothelium of the body (14), because the capillary system is the main distributor of the hard bodies to tissues, so it is destroyed much more severely than the larger vessels. Because of the microvascular nature of the diseases, we can observe healing of leg ulcers with hydroxyurea therapy in early years of life, but the healing process is difficult due to the

excessive fibrosis around the capillaries later in life. Eventually, the mean survival was 42 years in males and 48 years in females in the literature (9), whereas it was 29 and 32 years, respectively, in the present study ( $p>0.05$ ). According to our experiences, the great differences between the survival are secondary to the initiation of hydroxyurea treatment in early years of life, even at birth in developed countries. On the other hand, the prolonged survival of females with SCDs and the longer overall survival of females in the world (15) could not be explained by well known strong atherosclerotic effects of smoking alone; instead it may be explained by the dominant role of male sex in life (16). As a result of such a great variety of clinical presentations, it is not surprising to see that the mean body weight and body mass index (BMI) were retarded in the SCDs cases (17). Parallel to the lower body weight and BMI, the low density lipoprotein cholesterol, alanine aminotransferase, and systolic and diastolic BPs were also lower in the SCDs (17), which can be explained by definition of the metabolic syndrome (18,19).

Painful crises are the pathognomonic symptoms of the SCDs. Although painful crises themselves may not be life threatening directly (20), increased basal metabolic rate with any underlying cause such as infection, tissue damage, operation, or depression usually terminate with crises, so multiorgan failures on the chronic inflammatory background of the SCDs are not rare in such circumstances (21,22). Probably pain is due to the disseminated inflammatory process of the capillary endothelium, and the increased WBC and PLT counts and decreased Hct values indicate presence of a chronic inflammatory process during their whole lives in such patients. Increased WBC counts even in the absence of an infection, tissue damage, operation, or depression was an independent predictor of the disease severity (23), and it was associated with an increased risk of stroke, probably by releasing cytotoxic enzymes and causing endothelial damage in the brain (24). Due to the severity of pain, narcotic analgesics are usually required to control them (25), but according to our practice, simple RBC transfusions are highly effective during the severe crises, both to relieve pain and to prevent sudden death that may develop secondary to the multiorgan failures on the prolonged inflammatory background of the SCDs.

Hydroxyurea is an effective drug in several chronic myeloproliferative disorders and SCDs. It interferes with cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase. The deoxyribonucleotides are building blocks of DNA. Hydroxyurea mainly acts on hyperproliferative cells. Although the action of hydroxyurea is thought to be the increase of gamma globin synthesis for fetal hemoglobin (Hb F) (26,27), its main action is probably suppression of leukocytosis and thrombocytosis in the SCDs. By this way, the continuous inflammatory process of the SCDs that initiated at birth on the capillary endothelium is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferative skin cells. As in viral hepatitis cases, although pres-

ence of a continuous damage of hard RBCs on the capillary endothelium in the SCDs, the severity of destructive process is probably exaggerated by the patients' immune system, especially by the actions of WBCs and PLTs (28). So suppression of excessive proliferation of WBCs and PLTs probably limits the capillary damage-induced tissue ischemia and infarctions all over the body. Similarly, it was reported that lower neutrophil counts were associated with lower crises rates, and if a tissue infarction occurs, lower neutrophil counts may limit severity of pain and extent of tissue damage (29). On the other hand, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels, significantly (29).

Physicians at the National Institutes of Health Consensus Conference agreed that hydroxyurea is underused both in children and adults. First of all, due to the relatively younger mean ages of the SCDs patients, females and even males may not use the drug for a long period of time just to get a baby with some additional inhibitory effects of the chronic inflammatory disease on fertility. Additionally, there is fear of cancers in people, since hydroxyurea is a chemotherapeutic agent (30). However, the cancer risk has not been substantiated by more than a decade of using hydroxyurea for adults (31). Although some data show risk to fetus (32), potential benefits may outweigh potential risk even during pregnancy. According to our experiences, there are several female patients with infertility, abortus, and stillbirth in the absence of hydroxyurea therapy, and the decreased number and severity of painful crises, increased body weight, decreased WBC and PLT counts, and increased Hct value with the hydroxyurea therapy will probably result with resolution of the above problems to some extent. It is clear that there is a need for more effective treatment regimens in the SCDs, but until they become more available, hydroxyurea should be used in all cases, and its dose should be kept higher in the moderate and severe patients.

Hydroxyurea may have a critical role in the SCDs (14). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with sickle cell anemia (Hb SS), and compared the results of patients treated with hydroxyurea or placebo (33). The study especially searched effects of the drug on painful crises, acute chest syndrome, and need of RBC transfusions. The outcomes were so overwhelming in favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated to all patients. The patients treated with hydroxyurea had a 44% decrease of hospitalizations, and there was a strong and independent association of lower neutrophil counts with the lower crisis rates (33). But this study was performed just in severe Hb SS cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year (33). Whereas in our study, we used 337 patients with all subtypes and clinical severity of SCDs, and the rate of painful crises was decreased from 10.3 to 1.7 per year ( $p<0.000$ ) with an additional decreased severity of them (7.8 versus 2.2,  $p<0.000$ ). Parallel to the above results, adult SCDs patients using hydroxyurea appear to have reduced mortality rate after a 9-year follow-up period (34). Although the underlying disease severity remains critical to determine

prognosis, hydroxyurea may decrease severity of disease (34) and prolong survival (14). Probably chronic endothelial damage of the capillaries is initiated at birth, and complications may start to be seen even in infancy. For example, infants with lower hemoglobin levels were more likely to have higher incidences of acute chest syndrome, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidence of them (35). Hydroxyurea in early life may also protect splenic function, improve growth, and prevent multiorgan dysfunctions by preventing early capillary damage. Transfusion programmes also reduce the complications, but they carry risks including transmission of infections, development of allo-antibodies causing subsequent transfusions difficult, and iron overload.

As a conclusion, the SCDs are chronic inflammatory disorders initiating at birth. Hydroxyurea decreases frequency and severity of painful crises, WBC and PLT counts, and total and direct bilirubin and LDH levels, and it increases body weight and Hct value, all of which indicate a decreased inflammatory process in the patients. Thus elective surgical procedures should be performed after a few months of treatment with hydroxyurea in non-users. By this way, beside decreased requirement of blood transfusions, perioperative morbidity and mortality will also be lowered due to decreased inflammatory process on capillary endothelium all over the body.

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# Khat (*Catha edulis*) chewing as a risk factor of low birth weight among full term Newborns: A systematic review

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## Abstract

**Introduction:** Chewing the leaves of Khat (*chata edulis*) plant has been a custom of people living in east Africa and the Arabian Peninsula dating back centuries. Khat has Cathinone, an amphetamine-like alkaloid which is responsible for most of documented physiologic effect. Vasoconstriction in the utero-placental vascular bed, reduction of placental blood and myo-endometrial blood flow were among noted reproductive assaults during pregnancy.

**Methods:** The objective of this systematic review was to synthesize the best available evidence on association of Khat chewing during pregnancy and birth weight. Databases searched were PubMed, CINAHL, PopLine, LILACS, MedNar and Embase. All papers selected for inclusion in the review were subjected to a rigorous appraisal using standardized critical appraisal. Review Manager Software (Revman 5.0) was used for meta-analysis and effect size and their 95% confidence intervals were calculated.

**Result:** On Meta-analysis, data of 1850 neonates and their maternal history were obtained, with Khat chewers to non-chewers ratio of 1.1:1. A mean birth weight of Khat chewing mothers was found lower than the non-chewers neonates, with the mean difference of -130.74 [-189.90, -71.59] grams,

Heterogeneity:  $\text{Tau}^2 = 0.00$ ;  $\text{Chi}^2 = 0.95$ ,  $\text{df} = 1$  ( $P = 0.33$ );  $I^2 = 0\%$ . In all assumptions tested, the finding of the Meta analysis has shown consistent direction, while a reduction of 130.74 grams is the best available estimate of the effect size.

**Conclusion:** Khat chewing during pregnancy is found to be a significant risk factor for reduction of birth weight which may contribute a lot to infant mortality.

**Key words:** Khat chewing, birth weight, systematic review

## Introduction

Khat (*Catha edulis*) is a plant which grows wild in countries bordering the Red Sea and along the east coast of Africa and the Arabian Peninsula (1). Chewing the leaves of this plant has been a custom of people living in these countries dating back centuries. Khat Chewing in this region has mixed regulatory legislation; legal in Ethiopia, Djibouti, Kenya, Yemen and Uganda and illegal in Tanzania and Eritrea (2, 3). Globalization, hammering its restrictions has helped Khat consumption spread across countries such as the USA and Western Europe (4, 5). Khat chewing is common among all segments of the population, as high as 15% in Ethiopia and 90% in Yemen (6, 7). According to an Ethiopian national demographic survey, nearly one in ten Ethiopian women chew Khat while the corresponding figure in Yemen is 50% (6, 7). Other studies reported 26% of Ethiopian pregnant women chew Khat, less compared to Yemenis 41.0% (7-8).

Khat has an active ingredient, Cathinone, an amphetamine-like alkaloid, responsible for most of its pharmacological action (10). Additionally, various phenylalkylamines and considerable amounts of tannins and flavonoids were also found in Khat leaves (10-11). Toennes et al., reported 100 grams of Khat leaves contain, 114 mg cathinone, 83 mg cathine and 44 mg norephedrine (12). These active chemicals induce wider physiological effects. El-Guindy demonstrated an increase in temperature and pulse rate as well as mydriasis in people chewing Khat (13). Urinary retention, increased sexual desire, impotence and nocturnal emission, which involves either ejaculation during sleep for a male or lubrication of the vagina for a female, are also common with chronic Khat chewing behavior (13-14). Other studies on effects associated with Khat chewing reported sleeplessness, nervousness, nightmares, anorexia, constipation and inhibition of lactation (13-17).

Effect of Khat on reproductive function is not optimal. Jansson and colleagues in 1987 noted vasoconstriction in the utero-placental vascular bed, impairing foetal growth through reduction of placental blood flow among pregnant guinea pigs fed Khat leaves (16). They also showed an increase in the pressure of uteroplacental blood by 25% and heart rate by 9% and contrarily a reduction of Myoendometrial blood flow by 31%. Other studies also reported association between Khat chewing during pregnancy and reduced daily food intake, anaemia, and disturbance of fetal growth, low birth weight, perinatal and infant death, and other obstetric health problems (17-22). All the above cocktailed physiologic effects of Khat are untoward considering the requirements of the fetus towards optimal maternal environment for proper growth and fetal development. Furthermore, the add-on physiologic effect of Khat on existing stress due to socioeconomic misfortunes of the region should not be ignored considering highest infant mortality.

## Method

The objective of this review was to systematically identify, appraise and synthesize the best available evidence on association of Khat chewing during pregnancy and birth weight of the new born. Studies which include newborns of mothers who are adults (18 years old or older) regardless of race, country of residence, Khat dose, frequency, duration of chewing or other characteristics of Khat exposure and co-presence of other drug use were included. A three staged search strategy was used to identify all relevant published literature in English language. Databases searched were PubMed, CINAHL, PopLine, LILACS, MedNar and Embase. Secondary search were carried out from cross references and finally gray literature were sought from institutions and government websites. The search strategy used or modified for the various databases and search engines was with initial keywords/search terms: ["*Catha edulis*" or "Khat" or "Mairungi" or "Miraa" or "Qat"] and ["birth weight" or "low birth weight"]. All papers selected for inclusion in the review were subjected to a rigorous, independent appraisal by the investigator prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute (23). Quantitative papers were pooled in statistical meta-analysis using the Review Manager Software (Rev Man 5). Odds ratios and their 95% confidence intervals were calculated for analysis. Papers of optimal quality which were selected for inclusion but without optimal data set for meta-analysis were subjected to narrative synthesis.

## Result

A total of 254 relevant papers were identified in the literature search and 84 of them were retrieved for examination. Following review of titles and abstracts against the review objectives and inclusion criteria, 69 titles were excluded. The full texts of the remaining 16 studies were retrieved for detailed evaluation, after which, 11 of these were excluded. The remaining 7 studies were assessed for methodological quality using the JBI-MAStARI critical appraisal tool and, subsequently 3 were excluded; four of them were included in the review for meta-analysis.

On Meta-analysis, data of 1850 neonates and their mothers were obtained, with Khat chewers to non-chewers ratio of 1.1:1. Khat chewing mothers had a mean birth weight lower than the non-chewers with the mean difference of -346.97 [-670.29, -23.64].

The summary effect of the Meta analysis was found to be -346.97 [-670.29, -23.64] (Heterogeneity:  $\tau^2 = 103914.69$ ;  $\chi^2 = 191.95$ ,  $df = 3$  ( $P < 0.00001$ );  $I^2 = 98\%$ ). The observed heterogeneity in the meta-analysis may not be substantial as the researchers passed their critical appraisal and all have uniform direction of effect measure. However for the statistical fidelity sensitivity analysis yields a better summary of effect, tested by removing each study and analyzing the effect, accordingly, removing the study of Abdurehman and Kaima, 2009, gives a summary effect with less heterogeneity (Heterogeneity:  $\tau^2 = 19075.18$ ;

Figure 1: Forest Plot including all available relevant studies, 2015.

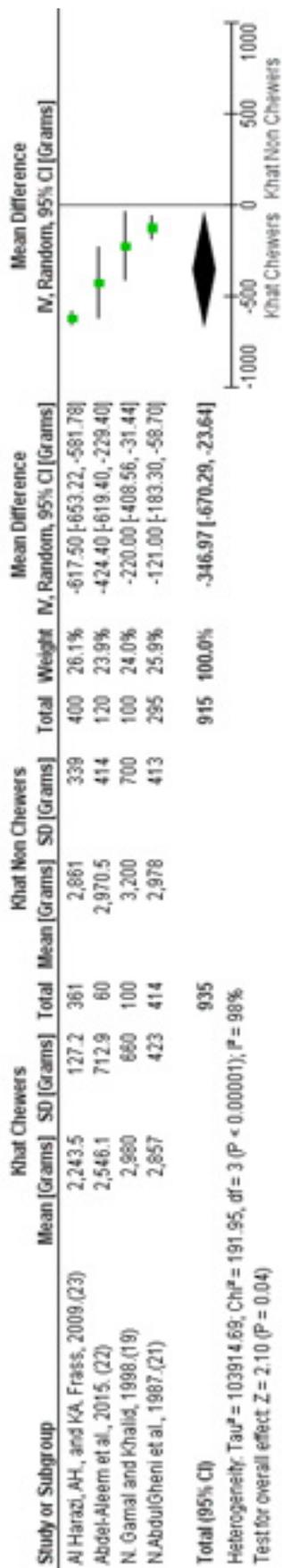


Figure 2: Forest Plot of the Meta analysis while removing a study of 'Abdurrahman and Keima' including all available relevant studies, 2015

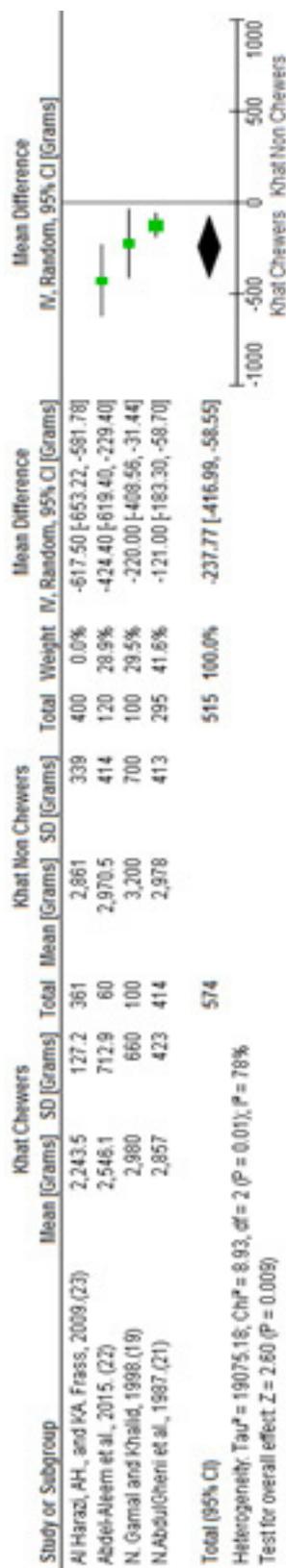
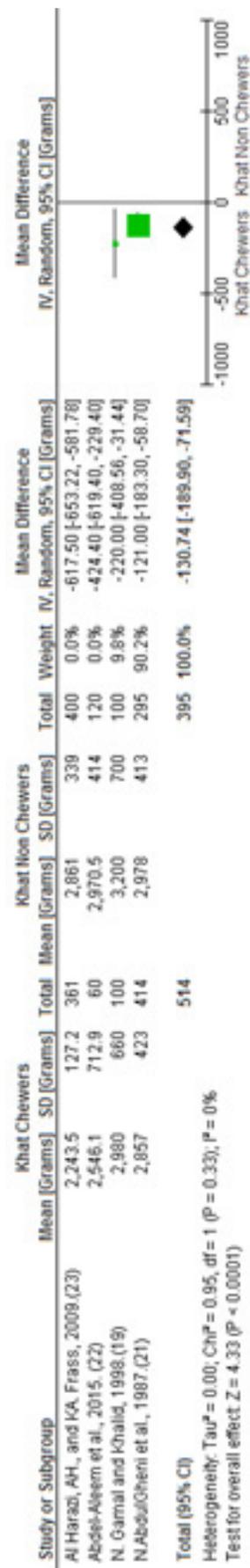


Figure 3: Subgroup analysis considering studies before millennium development, 2015



$\text{Chi}^2 = 8.93$ ,  $\text{df} = 2$  ( $P = 0.01$ );  $I^2 = 78\%$ ) of  $-237.77$  [ $-416.99$ ,  $-58.55$ ].

Furthermore, subgroup analysis by year of study (considering studies done before millennium development goal) gives a best summary effect with heterogeneity test equal to zero, (Heterogeneity:  $\text{Tau}^2 = 0.00$ ;  $\text{Chi}^2 = 0.95$ ,  $\text{df} = 1$  ( $P = 0.33$ );  $I^2 = 0\%$ ). The summary effect of the Meta analysis became  $-130.74$  [ $-189.90$ ,  $-71.59$ ].

With all the assumptions tested, the finding of the Meta analysis was consistent, neonates of Khat chewing mothers had a reduced birth weight than non-chewers ranging from  $130.74$  to  $346$  grams. However considering heterogeneity, a reduction of  $130.74$  grams is the best available estimate of the effect size when heterogeneity is zero.

## Discussion

According to WHO, low birth weight contributes to 60% to 80% of all neonatal deaths. The global prevalence of LBW is 15.5%, which amounts to about 20 million Low birth weight infants born each year, 96.5% of them in developing countries, and most in sub-Saharan countries where Khat chewing is also a social custom (24). Conventional risk factors of low birth weight were well identified and interventions have made lots of progress across countries, however, studies on setting specific substances like Khat chewing were not studied well or interventions were not yet popular or done at all.

The finding of the Meta analysis is very crucial considering every gram which accounts for immediate and longer-term health and well-being of the individual infant and has a significant impact on neonatal and infant mortality at a population level. Furthermore, the harm which is induced on the fetus reflects the physiologic stress on the mother which may hamper the capability of post-natal care, more specifically feeding. Studies have shown Khat caused reduction in breast milk production and its active substances passed through breast milk to the infant (14-17).

The finding of this review is consistent with studies done on animal experiments intended to establish cause and effect relationship by Jansson et al., who has shown a reduced maternal daily food intake and maternal weight gain among Khat fed pregnant guinea pigs than their controls (16). The study also showed, Khat feeding of the mother significantly reduced the mean birth weight of the offspring by 7% (16). Another study done by the same authors to study the Effect of Khat on utero-placental blood flow in awake, chronically catheterized, late-pregnant guinea pigs showed a reduction of blood flow by 10% at 75 min and 24% at 180 min after Khat feeding (25). Since randomized controlled trials of such studies on human subjects are questionable, such findings of animal studies are helpful in postulating cause and effect relationship, rather than epidemiologic conclusions.

Studies on human subjects with primary outcome of assessing effect of Khat on birth weight and or low birth weight among human subjects are too few or date back decades considering the very high custom of Khat chewing habits across residents of east Africa and the Arabian peninsula. However, almost all available studies describe the negative effect of Khat on fetal outcome. A study by Eriksson et al., has shown non-users of Khat, had significantly fewer low birth-weight babies (less than 2,500 gram) compared to occasional users and regular users; Khat-chewing mothers had more surviving children than the non-chewers; more children of Khat-chewers had concomitant diseases than non-chewers (26). Similarly, another study reported, mothers who chew Khat during pregnancy four times per week were twice likely to have fetal death compared to non-chewers and mothers who chewed Khat during pregnancy every day were found four times more likely to have fetal death history compared to non-chewers (27).

Experience has clearly shown that appropriate care of low birth weight infants, including their feeding, temperature maintenance, hygienic cord and skin care, and early detection and treatment of infections and complications can substantially reduce mortality (24). However, such interventions are costly compared to primary prevention options.

## Conclusion and Recommendation

In this systematic review, Khat chewing during pregnancy is found to be a significant risk factor for reduction of birth weight which may contribute high for neonatal mortality. Thus, comprehensive setting specific primary prevention of low birth weight should include novel risk factors such as Khat chewing during pregnancy. Contemporary interventions targeting Khat chewing habit, incorporating a continuum of care including prevention, treatment, and maintenance of pregnant mothers should be delivered at all levels of health care. Prevention measures designed for the general population as well as selectively for future mothers and pregnant women are important in deterring the harmful effect of Khat on fetal birth weight.

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# Chronic pain review following Lichtenstein hernia repair: A Personal Series

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## Abstract

**Introduction:** Chronic groin pain is both a topical subject and important outcome measurement following inguinal hernia repair. It has been suggested its incidence is related to the management of the nerves of the inguinal canal as well as the type of mesh used and methods of fixation for both open and laparoscopic surgery.

The level of pre-operative and post operative pain, its duration as well as complications may all be factors in predicting whether chronic pain may develop. The method of measurement of chronic pain is itself a contentious issue. It is now apparent that the measurement of activity and functional status as well as qualitative measures is important.

Uniform methods of assessing chronic post-operative pain have been proposed.

**Methods:** A retrospective study reviewing a consecutive series of Lichtenstein repairs performed by a single experienced hernia surgeon was carried out. 248 inguinal hernia patients operated on in

2005 were reviewed. Patients were contacted via telephone at a median of 50 months. A recently validated inguinal pain questionnaire was used to assess the incidence of chronic pain.

**Results:** 185 (75%) patients were able to be contacted for follow-up, making a total of 213 inguinal hernia repairs (including bilateral hernias). At the time of review 3% of patients reported having pain. No patients reported that pain or discomfort was limiting their work, exercise or activities of daily living. No patients had disabling pain.

**Conclusion:** Chronic pain did not appear to be a major problem within this cohort of patients. The Lichtenstein technique can produce favourable results in terms of chronic pain for unilateral, bilateral and recurrent inguinal hernias in an unselected group of patients with the usual mix of risk factors and complications.

**Key words:** Inguinal hernia, Lichtenstein, Local anaesthesia, Chronic pain, Bilateral inguinal hernia, Recurrent inguinal hernia

## Introduction

Inguinal hernia repairs are one of the most common surgical procedures(1). The pre-eminent status of the original Lichtenstein technique has been challenged with the introduction of other open and laparoscopic techniques, lightweight meshes and new methods of fixation with absorbable tackers and tissue glues. While there has been significant improvement in recurrence rates with most types of mesh repair(2), a variable and worrying incidence of chronic pain following open and laparoscopic repair of inguinal hernias has been documented(3).

There is still controversy regarding the true incidence of chronic pain. The lack of uniform definitions and interpretation as well as different methods of assessment has led to this(4-6). Mild, moderate and severe pain has been reported to have a prevalence of 0.7% to 43.3%(3), with some treating the presence of pain as a dichotomous (yes/no) entity.(7) An overall prevalence of 0.5 - 6% of severe debilitating pain affecting normal daily activities and work has been reported(3). It has also been suggested that the rates of severe chronic pain are lower with laparoscopic repair, compared with Lichtenstein repair or other open techniques, as well as being associated with earlier return to work and normal activities(8). This however is associated with more adverse events during surgery(9) as well as higher rates of visceral injury(10).

Other factors such as patient profile, the level of pre-operative pain, type of hernia, post-operative pain and complications are also being assessed as to their significance in assessing the risk of the development of chronic pain(8). Many methods including numerical and behavioural rating scales have been used to assess the levels of chronic pain(11), attesting to the difficulty in assessment and interpretation. Standardization of methods of measuring results is required(7).

Franneby's(11) validated chronic inguinal pain questionnaire (IPQ) was used in this study. This was chosen because of the comprehensive but simple nature of the questionnaire. This also incorporated pain behavior rather than numbers. The IPQ also addressed many of the issues surrounding this difficult concept, and went a great way towards providing accurate assessment.

Many of the multicentre trials used in larger systematic reviews(10) that govern current guidelines(12) incorporate many different surgeons of varying levels of experience(9). To gain further insight a consecutive series of patients operated on using the Tension Free Lichtenstein Technique (TFLT) with local anaesthesia and standard mesh in 2005 by a single experienced hernia surgeon were reviewed.

The primary objective of this study was to assess the incidence of chronic pain, using a validated inguinal pain questionnaire(11). This series aims to address the issues previously raised when investigating the incidence of chronic pain(13), in particular inadequate analysis. The Lichtenstein technique(14) was used in a consecutive

series of patients with unilateral, bilateral and recurrent inguinal hernias.

## Methods

Approval was obtained from The Avenue Hospital Human Research Ethics Committee, Ramsay Health, Melbourne, Australia.

### Patients Selection & Baseline Data

All patients who underwent a primary inguinal hernia, bilateral inguinal hernia, or recurrent inguinal hernia repair in 2005 were included. Patients were then contacted in 2009, at a median of 50 months post-operatively by one of the research team. The follow-up rate was 75 %. An extensive interview based on Franneby's IPQ(11) was conducted.

A review of the patient's medical records, together with audit forms completed at the time of operation was undertaken. The level of pre-operative pain, co-morbidities and type and size of the hernia had been recorded pre-operatively. The method of repair, mesh and fixation used, together with the management of the nerves was documented. The post-operative complications, post-operative pain, analgesic requirements, patient's interpretation of the pain, and return to normal activities and work had been documented during the routine post-operative visits. The level of analgesics required post-operatively and return to normal activities was reviewed.

### Inguinal Pain Questionnaire (IPQ)

The IPQ uniquely explored pain intensity rather than its presence or absence. This allowed for a more meaningful examination of pain, and pain behavior. The IPQ measured

- Pain and its impact on daily activities was examined across four different periods: preoperatively, post-operatively, time of interview, and the week preceding the interview, using the following scale;
  - i. No Pain
  - ii. Pain present but can easily be ignored
  - iii. Pain present, cannot be ignored, but does not interfere with everyday activities
  - iv. Pain present, cannot be ignored, interferes with concentration on chores and daily activities
  - v. Pain present, cannot be ignored, interferes with most activities
  - vi. Pain present, cannot be ignored, necessitates bed rest
  - vii. Pain present, cannot be ignored, prompt medical advice sought
    - When pain ceased.
    - How often had the participant felt pain in the operate groin during the past week, and how long they may have lasted.
    - Current analgesia requirements.
    - Activities of daily life associated questions.
    - Any work limitations.

## The Lichtenstein technique (14)

### Anaesthesia

All repairs were carried out using Local Anaesthetic (LA) infiltration and light intravenous sedation, including Fentanyl, Propofol or Midazolam and anti-inflammatory agents. The combination used depended largely on the anaesthetist's preference. A mixture of Lignocaine 2% with Adrenaline 1: 200,000 and plain Bupivacaine 0.5% were used. LA was directly infiltrated into the skin and subcutaneous tissues after an initial dose of sedation. The sedation avoided the possible discomfort of the injections. The ilioinguinal nerve(IIN) and the iliohypogastric nerves (IHN) were blocked by introducing the LA deep to the external oblique aponeurosis under direct vision. This gave rapid anaesthesia and displaced the IIN and IHN from the external oblique making direct injury to the nerves and their perineurium less likely. The LA helped identify and dissect the tissue planes as it was injected around the hernial sac and cord and into the region of the genital division of the GFN.

A formal ilio-inguinal nerve (IIN) block at the anterior superior iliac spine was not performed, as in the surgeon's experience patients frequently complained of post-operative pain at the site of injection. Moreover, this technique takes longer to become effective and adds to the overall volume of LA required.

### The Nerves

The identification and management of the nerves was recorded. An attempt was made to identify all 3 nerves. However an extensive search was not carried out as this could increase tissue trauma and possibly damage the nerves. In the majority of cases, all nerves were identified and spared. If the nerve had been traumatised or was compromised by the mesh or suturing, it was dissected back to the muscle, divided and removed totally, (neurectomy). Diathermy or ligation of the stump was not employed.

The IIN was usually not separated from the cord. Care was taken in closing the external oblique to avoid entrapping the IIN.

**Surgical technique:** The Lichtenstein technique has been well described(14). Some important aspects of the technique and possible differences include:

- No diathermy was used; it is believed this could cause tissue and nerve damage setting up a neuropathic and nociceptive inflammatory response.
- Adrenaline kept the blood loss to a minimum.
- Sharp dissection was used to reduce trauma.
- The Local Anaesthetic technique requires a gentler dissection.
- For indirect hernias the sac was either excised or reduced (especially for sliding hernias).
- For direct hernias the sac was reduced.
- Any additional lipoma of the cord was always excised.
- A standard Polypropylene mesh was used Prolene (trademark) mesh, Polypropylene, non-absorbable synthetic surgical mesh, Johnson & Johnson.
- A standard skin stapler (Appose 35w auto suture) was used to fix the mesh to the inguinal ligament as per the Lichtenstein technique. The mesh was placed well medial to pubic tubercle, but the staples were placed well away from the pubic tubercle.

## Results

A total of 248 patients were operated on in 2005. This equated to 283 hernias including 35 bilateral, and 23 recurrences. 185 patients were contacted in 2010. This equated to 213 hernia repairs with 28 bilateral and 16 recurrences equating to a follow-up rate of 75% (Table 1).

### Patient demographics (of original cohort)

Age distribution was between 18 - 90 years. The majority between 50 - 60 years of age n = 73 (28.85%). 241 (97%) of the patients were male, and 7 (3%) were female.

### Inguinal Pain Questionnaire (IPQ)

67% (n = 124) of patients reported pre operative pain. This ranged in severity between pain that could be easily ignored (27%) to pain which required hospitalization (3%). 33% (n = 61) of patients reported no pain at all.

**Table 1: Number of Patients, and distribution of hernia subtypes**

		Performed in 2005	Analyzed by Follow up 2010
<b>Group</b>	<b>Patients</b>	<b>248</b>	<b>185</b>
	<b>Hernias</b>	<b>283</b>	<b>213</b>
	<b>Unilateral Hernias</b>	<b>213</b>	<b>157</b>
	<b>Bilateral Hernias</b>	<b>35</b>	<b>28</b>
	<b>Recurrent</b>	<b>23</b>	<b>16</b>

**Table 2: Comparison of pain ratings**

		Pain right now	Pain in prior week
Pain Rating	No Pain	180 (97.3%)	175 (94.6%)
	Pain present, easily ignored	2 (1.1%)	4 (2.2%)
	Pain present, cannot be ignored but does not interfere with activities	3 (1.6%)	6 (3.2%)
	Pain present, cannot be ignored and interferes with concentration and activities.	0 (0%)	0 (0%)
	Pain present, interferes with most activities.	0 (0%)	0 (0%)
	Pain present necessitates bed rest now	0 (0%)	0 (0%)
	Pain present advice sought.	0 (0%)	0 (0%)

The proportion of patients with pain at time of interview was 3% (95% CI: 1% to 5%,  $P < 0.001$ ) (Table 2). Of those who reported pain:

- 1.1% ( $n = 2$ ) reported that their pain did not interfere with their normal activities and could be easily ignored.
- 1.6% ( $n = 4$ ) reported having pain, which did not interfere with their activities but could not be easily ignored (but still not sufficient to require analgesia).
- No patients reported pain that interfered with their daily activities or chores, required analgesia or required medical attention.

The proportion of patients with pain in the week prior to interview was 5% (95% CI: 2% to 7%  $P < 0.001$ ) (Table 2). Of those who reported pain:

- 2.2% ( $n = 4$ ) reported that their pain did not interfere with their normal activities and could be easily ignored.
- 3.2% ( $n = 6$ ) reported having pain, which did not interfere with their activities but could not be easily ignored (but still not sufficient to require analgesia).
- No patients reported pain that interfered with their daily activities or chores, required analgesia or required medical attention.

### Resolution of pain post-operatively

83% ( $n = 154$ ) of patients were pain free at 1 month post operatively, and 92% ( $n = 170$ ) at 2-3 months post-operatively (Table 3). Of the other 8%: 3% had intermittent pain that lasted for 6 months (not interfering with activities), 4% of patients experienced pain for up to 12 months (not interfering with activities), 1% had pain for up to 24 months post-operatively.

**Table 3: Resolution of pain post operatively. P Values calculated when cross-tabulated against preoperative pain.**

Time Since Operation	Percentage Pain Free		P Value
	1 Month	83	$p < 0.001$
2-3 Months	92	$p < 0.001$	

### Post Operative Analgesia Requirements

Patients were prescribed paracetamol and codeine tablets (500mg & 30mg combination) postoperatively, and were advised to down grade to the 500mg/8mg combination or the paracetamol 500mg only preparation as soon as pain allowed or if they were having side effects from the analgesia.

**Table 4: Post Operative Analgesia Requirements**

		n	%
Days of Analgesia	No Analgesia	36	14.2
	One Day of Analgesia	47	18.6
	2-3 Days of Analgesia	98	38.7
	>4 Days of Analgesia	15	5.9
	Incomplete data	57	22.5

**Functional status questions (at time of interview and previous week)**

- 100% (n=185) of patients had no pain when getting up from a low chair.
- 97.8% (n=180) of patients reported no pain when sitting for more than half an hour.
- 98.4% (n=182) 182 of patients did not experience any pain or discomfort when standing for more than half an hour.
- 98.9% (n=183) of patients were able to go up and down stairs without experiencing any pain in the groin.
- 98.4% (n=182) had no pain when driving.

**Complications:**

- None of the patients with significant complications developed significant chronic pain or disability.
- One patient re-operated on for bleeding, due to anti-coagulation following embolus, had occasional discomfort.
- One patient who needed removal of a staple from the mesh had no further pain
- One patient who required prostatectomy had no further pain
- Continuing audit over many years showed these to be one off events
- The patients with seromas and superficial infections had no further problems, as did the patients who developed recurrences, which were repaired.

**Treatment of Nerves**

The IIN was identified in approximately 80% of cases. In approximately 10% of these cases when the nerve was identified a neurectomy was performed, either as a result of accidental damage, excessive dissection or the fear of entrapment in the mesh.

The IHN was identified less frequently in approximately 70% of cases. It was divided accidentally or intentionally in approximately 10% of these cases mainly to avoid entrapment in fixation of the mesh as it emerged medially from the internal oblique aponeurosis.

The GFN was always identified with the cremasteric vessels and only divided and ligated in a few cases when these vessels were ligated for technical reasons.

**Discussion**

The vast majority of unilateral, bilateral or recurrent hernia patients at 50 months had no significant pain or disability. None reported that their exercise, activities or work were limited by pain. Few reported the need for analgesia on any consistent basis. The incidence of moderate or significant chronic pain was less than 1%, which the authors felt would be pain that interfered with activities or required regular analgesia. In view of the high incidence of chronic pain and disability in some series(9) there have been many attempts to identify possible risk factors and surgical materials and techniques that might predict its development. This study, because of the low incidence of chronic pain was unable to identify any previously reported risk factors, despite the cohort being a consecutive series of patients.

The authors have sought to analyze and explain why these results may be different to others. The wide discrepancy in the reported incidence of chronic pain after inguinal hernia

repair results needs to be explained particularly as recommendations may be based on these results(12).

It has been pointed out that aggressive early therapy for post-operative pain is indicated, since the intensity of post-operative pain correlates with the risk of developing chronic pain(15).

Pre-operative LA was used routinely as part of this regime ensuring the patient is pain free for at least 4-10 hours and is able to travel home in comfort without the need for analgesics. It was noted in this series that the vast majority of the patients did not consider early post-operative pain to be a major factor. The use of post-operative analgesics was: 14% needed no painkillers, 18% used pain killers for 1 day, and the majority for just a few days to a week. Even those who felt post-operative pain to be an issue did not develop significant chronic pain. Those patients who did complain of post-operative pain at one week were kept under review until the pain resolved.

The low incidence of significant early post-operative pain or perceived pain and the minimal need for analgesia in many patients, may be of significance. The LA may contribute to this early low level of pain and may be a significant factor, particularly as pre-emptive, peri-operative and post-operative analgesia considered under the title "multimodal analgesia" are being assessed as factors in preventing chronic pain(16).

Furthermore with LA many of the early side effects of general anaesthesia such as nausea, vomiting, and acute retention of urine are reduced. Less intensive post-operative nursing, including airway care is required. The majority of patients go home within 3 hours of surgery. The long acting LA lasts from 4-10 hours and many patients do not need further analgesia. Many patients preferred the LA because of previous problems with general anaesthesia. Many of the studies of the Lichtenstein method have not used local anaesthesia as described by Lichtenstein. This may diminish the benefits of the original repair and also account for a higher incidence of chronic pain found in some series.

### The nerves

The management of the 3 major nerves of the inguinal canal has been considered to be a factor in chronic pain(17). This study showed a low incidence of chronic pain despite the IIN and IHN not being formally identified or damaged and removed in up to 20% of cases.

Extensive studies concluded that identification and preservation of all 3 nerves of the inguinal canal reduces chronic incapacitating groin pain.

### Mesh, staples

Mesh and staples have also been widely implicated as significant factors in the development of chronic pain leading to a variety of new lighter weight meshes, staples and glues(16). This series with its low incidence of significant chronic pain using a standard Polypropylene mesh and non-absorbable staples raises the question as to the role of the mesh in the development of chronic pain.

### Positive Results

The positive results identified in this series may be due to the following factors;

LA infiltration allowing simpler dissection of the tissues with less trauma. Diathermy is not used, possibly reducing the inflammatory response around the nerve endings, a possible cause of nociceptive pain. Identification and management of the nerves(12). The use of the open skin stapler to fix the mesh (appose ulc 35w auto suture). The early supervised management of post-operative pain, including contact by telephone by the surgeon with all patients the day following surgery to adjust analgesia and give support as necessary.

If the results vary so much, is it possible to attribute chronic pain to the mesh/fixation alone? The results in this study, suggest that mesh and staples may not be the main factors

in determining the incidence of chronic pain, and could it just be the way the materials are used? Does it depend on the technique and the surgeon?

## Conclusion

There is strong evidence from this series, using a validated inguinal pain questionnaire, that a Lichtenstein repair using local anaesthesia can achieve a low incidence of chronic post-operative pain. Those few patients who did report pain, did not have any associated significant morbidity or impairment of activities of daily living. No obvious risk factors were identified as predicting or associated with chronic pain. There appeared to be no reason to alter the approach used to manage the nerves, the type of mesh or its method of fixation, in terms of chronic pain.

The validated IPQ provides a more detailed appreciation of pain behaviour. These types of pain measures will be useful in the future to help in assessing the role of surgical risk factors and techniques as a cause for chronic pain.

More detailed investigation using these validated tools is required in larger prospective studies, to provide more accurate and meaningful comparisons between other techniques in conjunction with greater operator experience.

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# Assessment of Health Status of Male Teachers in Abha City, Saudi Arabia

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## Summary

This study was done to assess the health aspect of male teachers (384) and to assess level of job satisfaction of male teachers in different grades in Abha city.

Following a simple random sample, the sample from primary 184 (47.9%), intermediate 132 (34.4%) and secondary 68 (17.7%) school's male teachers in Abha City were selected. All respondent teachers were exposed to the validated questionnaire to assess health problem [medical history and co-morbidities] and work place risk factors.

The background data as age was  $39.31 \pm 7.96$  [23:75] years; the average experience years were  $16.1 \pm 7.43$  [1:36] years and 71.6% have experience more than 10 years. 100 % of the sample were males due to socio-cultural matters, as regard to the educational level 47.9% were from primary schools, 34.4% from intermediate schools and 17.7% from secondary schools.

The level of satisfaction regarding current job and salary of teachers revealed that 65.6% were satisfied while 34.4% were not satisfied.

The answers about some medical history like history of having medical problems that affect teacher's

ability (9.4%), history of treatment in hospital (25.5%), sick leave 19% and all were within accepted range, apart from seeing a doctor in last year (43.2%).

The complaints or health problems among teachers as regards eyesight problems 15.4%, Hearing problems in 6.5%, Mental illness, psychological or psychiatric problem was 7.8%. The history of drug or alcohol problem was 2.3%, skin problems 12%, history of hepatitis or jaundice 1.6%. The heart or blood pressure problems were 11.32%. The history of allergies was 17.4%; asthma or chest problem was reported in 20.8% and cough for more than 3 weeks, coughed up blood or had any unexplained weight loss or fever, was 9.6%.

The history of Musculoskeletal disorders (MSD) was 21.1%, Low back pain (LBP) 21.6% and joint pain 32%. Regarding feeling well and healthy 154 (32%) gave the answer that they are NOT healthy or feeling well.

The relation between ill health and experience years gave a significant association but no significant association with teaching level.

The relation between job satisfaction and experience years showed no significant difference with experience years, but the higher rates with longer experience (70.2%) and gave significant relation with level, especially at primary level.

## Introduction

Teachers' work today is multifaceted as they undertake not only teaching but also matters associated with curriculum, students, parents, the school community and departmental initiatives [1].

These are tough times to be a teacher. Emerging issues of concern in the teaching profession are attrition rates and burnout levels. Ewing and Smith [2] reported that between 25% and 40% of beginning teachers in countries in the Western World are leaving teaching or they are burned out.

In Australia, a study [3] highlighted an upward trend in early-career teacher resignations and according to Macdonald [4] overall teacher attrition in Australian government schools ranges from 3% to 8%. When this is considered in conjunction with the impending teacher shortage in Australia [5], it is important to determine how teachers feel about their roles as this has implications for meeting society's expectations for education and for youth today; it also has implications for teacher well-being.

Well-being, according to Dunn [6] involves comparative private experiences with regard to self-perceived quality of an individual's life; it also includes both affective and cognitive components.

### **Factors that influence teacher well-being, burnout and competence**

Traditionally, the role of teaching has been one of nurturing and developing students' potential; teachers play a valuable role in helping children grow. In order to do this they must remain physically and mentally well [7]. However, there is apparent dissonance between teachers' perceived capacities and the expectations of their role. This may have implications for their physical and mental well-being and their professional competence as teachers [8].

Teacher well-being and competence have been related to job satisfaction and studies indicate that those teachers who are less satisfied are more likely to leave teaching. For example, Singh and Billingsley [9] found factors such as stress, burnout, work overload, and job dissatisfaction contribute to teacher attrition while factors such as administrative support, reasonable role expectations, and decreased workplace stress contribute to teachers' intention to stay in teaching. Principals play a pivotal role in steering the direction of their school which requires guiding the day-to-day business of the school including matters associated with both students and teachers.

The Management of Health and Safety at Work Regulations 1999 addressed various health hazards to which teachers are exposed [10].

### **Fitness criteria**

To be able to undertake teaching duties safely and effectively, it is essential that individual teachers: have the health and well-being necessary to deal with the specific types of teaching and associated duties (adjusted,

as appropriate) in which they are engaged; are able to communicate effectively with children, parents and colleagues; possess sound judgment and insight; remain alert at all times; can respond to pupils' needs rapidly and effectively; are able to manage classes and do not constitute any risk to the health, safety or well-being of children in their care.

Where disabilities exist, teachers should be enabled by reasonable adjustments, to meet these criteria. The decision on fitness should be considered using the above criteria and should be based on an individual's ability to satisfy those criteria in relation to all duties undertaken as part of their specific post and in relation to all of the individual's health problems [11]

## Review of Literature

Saudi Arabia is a country with an independent monarchy situated in South West Asia. The first feature of the educational system in Saudi Arabia is the combination of different international education systems along Islamic lines. The Ministry of Education (MOE) was founded in 1954 as a replacement to the Directory of Education. It is the responsible body for educational policy development of the curriculum and teaching methods. The educational system is highly centralized, and decision making is top-down. General education is divided into three main levels: primary level for six years, middle level for three years and secondary level for three years. The schools in each city of Saudi Arabia come under the responsibility and supervision of the Educational Administration [12].

Due to the importance of Education in the Socio-Economic development of an individual, great efforts are always made to ensure that an individual goes through the Education cycle successfully by achieving high academic results. The need for good results puts every stake-holder in the Education Sector on alert. Many mechanisms are put in place to ensure high performance and good results. Such mechanisms include: introducing performance contracts by the government, initiation of Free Primary Education (FPE) and Subsidizing Secondary Education (SSE), increasing contact hours between the teacher and learner, holiday tuition, remedial teaching during weekends, intensive testing policies [13].

In considering implications of health problems for an individual's fitness to teach, it is important to recognize that some teaching duties involve exposure to potential health hazards. The risk arising from such hazards will vary according to the specific nature of the teaching duties and the environment in which the teacher is working. Teacher training providers and employing organizations have a statutory responsibility to safeguard the health, safety and welfare of teachers, to conduct risk assessments and take steps to address potential hazards and reduce the risk of adverse health effects. Occupational health professionals have a key role in advising organizations in this regard [10].

### Physical, Chemical, Biological

Teachers are potentially exposed to a range of physical, chemical and biological hazards. The following are examples: Chemicals, plant and animal substances in those teaching the sciences, wood dusts, metal fumes, glues and noise in teachers of technical subjects, physical violence from pupils or parents, communicable diseases, ergonomic problems associated with bending, manual handling and sitting on small chairs, trauma for those involved in teaching physical education and any extra-curricular activities and voice trauma [14].

#### Physical Health

Only a few studies of varying quality have been published on teachers' physical health. When considering the main classes of diagnoses of physical diseases; musculoskeletal, respiratory, cardiovascular, nervous and hormonal disorders [14].

Moreover, when focusing on cardiovascular disorders, a study carried out in Germany showed that there was a lower risk for male teachers compared to men working in 12 other professions [15].

Another study at KSA during 1995 found the prevalence of obesity in males as 46% and females 49% [16].

About 12% of all teachers were considered hypertensive, 18% of males and 2% of females were current cigarette smokers. A greater proportion of males (57%) than females (20%) indicated they were performing a physical exercise at least one hour per week, 13% of males and 11% of females had hypercholesterolemia. Hypertriglyceridemia was found in 12% of males and 4% of females, and hyperglycemia was found in 8% of males and 4% of females.

**Conclusions:** The prevalence of cardiovascular risk factors among school teachers is not much different to that found in developed countries [16].

A study at KSA during 2006/2007 found the prevalence of hypertension (HTN) and pre-hypertension was 25.2 % in males and 43.0 % in females and diabetes was significantly associated with HTN [17].

A study conducted in Sofia , Bulgaria (1994), found that the estimated relative risk of arterial HTN for female teachers was 1.5 compared with other female employees (designers, researchers) who served as controls. This finding can classify the teaching occupation as high risk for arterial hypertension [18].

MSD represents one of the most common and most expensive occupational health problems in both developed and non-developing countries [19].

MSD is one of the leading causes for ill health retirement among school teachers [20].

Musculoskeletal complaints, especially of the lower back, neck and shoulders are also common among teachers.

Recently, Hong Kong teachers showed a higher prevalence for neck (68.9%), shoulder (73.4%) and low back pain (59.2%) in the past 30 days [21].

Epidemiological studies have demonstrated that factors such as gender, age, length of employment and awkward posture are associated with higher MSD prevalence among teachers [19].

Among workers including teachers, prolonged posture, static work and repetition are the cause of repetitive strain injuries (RSIs), which is one type of MSD that directly affects the area of upper limb, neck, shoulder and low back [22].

Smith et al., 1997 showed that compared to a control group, teachers were significantly more likely to report having 6 voice symptoms, among which hoarseness was the most frequent, and 5 related physical discomfort symptoms (tiring, effortful, ache, uncomfortable and rough) [23,24].

It is worth mentioning that there are a few additional studies that have shown a different impact of a few other diseases on teachers: an excessive rate of some major cancers, in particular breast [25] and thyroid [26] cancers and surprisingly enough, an association between school teaching and mortality from autoimmune diseases [27].

A study by Kovess-Masféty, said that teachers do not seem to have poorer mental health. However, their physical condition is characterized by a higher prevalence of health problems related to the ENT tract, and to a lesser extent, depending on the gender, to skin, eyes, legs and lower urinary tract [28].

Teachers have an important responsibility in tobacco control given that they are highly respected in their communities as they influence the evolution for each aspect of life [29].

In addition, teachers have daily interaction with students and thus represent an influential group in tobacco smoking control. However, this potential can be limited if teachers use tobacco especially in the presence of students in school premises [30].

#### Psychological

Teaching, like many jobs, is potentially stressful. Some sources of pressure are specific to teaching but others are common to various professions and management structures. Pressures which teachers have encountered include: the need to be continually vigilant when supervising pupils, verbal abuse from pupils and parents, parental expectations, the requirement to manage staff including support assistants and other teachers, the responsibility for head teachers to effectively manage a 'business', pressure from peers and colleagues, coping with change e.g. in management systems, examination formats and the curriculum and poor or inappropriate management including delays in addressing disciplinary and grievance issues [14].

## Factors Affecting Teachers' Mental Health

These include the lack of professional aptitude and spirit, occupational hazards, lack of social prestige, poor salaries, high moral expectations, workload, relationship among teachers, relationship between the administrator and teachers, insecurity of service and lack of facilities [14].

## Subjects and Methods

### Study design

Cross sectional research design

### Population and sampling

Male teachers in Abha City constitute the study population. The minimum sample size for this study has been decided according to Swanson and Cohen [31].

Following a simple random sample, the researcher selected an equal sample from primary, intermediate and secondary school male teachers in Abha City. All respondent teachers were exposed to the questionnaire.

According to the Ministry of Education in Aseer region data, the number of schools in Abha city are 96 schools divided into 46 primary, 33 intermediate and 17 secondary with 2219 teachers in all levels. So the average number in each school is about 23 teachers. Number of teachers in primary schools was 1063, intermediate schools was 763 and secondary schools was 393 teachers.

Proportionate sample was taken from each level according to the following formulas: Primary=  $384 \text{ (Sample Size)} \times 1063 / 2219 = 184$ ; Intermediate=  $384 \text{ (Sample Size)} \times 763 / 2219 = 132$ ; Secondary =  $384 \text{ (Sample Size)} \times 393 / 2219 = 68$

So in Primary level we selected 184 teachers from 8 male Schools [due to socio-cultural aspect] randomly from the total primary schools to cover their sample size and avoided non responders and 6 intermediate schools and 3 secondary schools. We asked all school teachers to participate in the research. If extra numbers will be needed, extra schools will be selected randomly soon.

### Data Collecting Tool

Sample of Employment Health Questionnaire (Department of Health) [32].

### Data Design

A self-administered questionnaire including Personal characteristics as Demographic data, medical history and co-morbidities and Special Habits, was designed.

### Administrative consideration:

The Researcher fulfilled all the required official approvals. The researcher explained to all participants how to fill out the questionnaire in the correct way and how to answer questions.

### Ethical consideration:

Before Interviewing, Informed Consent was asked from

all samples then all participants had the right not to participate in the study or to withdraw from the study prior to completion. The researcher explained the purpose to all respondents. This pre measurement education is an important part. Confidentiality and privacy were guaranteed for all participants.

### Budget

This study was carried out at the full expense of the researchers.

### Statistical Analysis

The statistical analysis of data was done by using Excel program for figures and SPSS (SPSS, Inc, Chicago, IL) program statistical package for social science version 17 [33]. The description of the data was done in form of mean (+/-) SD for quantitative data and Frequency and proportion for Qualitative data. The analysis of the data was done to test statistical significant difference between the groups. For quantitative data, student t-test was used to compare between two groups. Chi square test was used for qualitative data and odds ratio for risk assessment. Pearson Correlation was done to detect association between variables. P is significant if  $\leq 0.05$  at confidence interval 95%.

## Results

In socio-demographic data of male teachers in Abha City (N=384) we found the mean age of 39.31, Gender (male) 384 (100%), experience less than or equal to 10 years was 109 (28.4%), experience more than or equal to 10 years was 275 (71.6%) and level of schools: primary (47.9 %), intermediate (34.4 %) and secondary (17.7%) .

(Tables of Results commence next page)

## Discussion

This study was done to assess the health aspect of male teachers (384) and to assess level of job satisfaction of male teachers in different grades in Abha city.

A simple random sample, the sample from primary, intermediate and secondary school's male teachers in Abha City, was selected. All respondent teachers were exposed to the validated questionnaire to assess health problem [medical history and co-morbidities] and work place risk factors.

In our study background data is shown as age  $39.31 \pm 7.96$  [23:75] years, the average experience years were  $16.1 \pm 7.43$  [1:36] years and 71.6% have experience more than 10 years, 100 % of the sample was males due to socio-cultural matters. As regards the educational level 47.9% were from primary schools, 34.4% from intermediate schools and 17.7% from secondary schools.

The answers about some medical history like history of having medical problem that affects teacher' ability (9.4%), history of treating in hospital (25.5%), sick leave 19% are

Table 1: Medical history of male teachers in Abha City 2014

Medical History	Number	Percent (%)
Have you ever had any illness, medical problem or disability that may currently affect your ability to work safely as a teacher?	36	9.4%
Have you ever been treated in hospital?	98	25.5%
Have you seen a doctor in the last year for any kind of health problem?	166	43.2%
Are you having any treatment or investigations of any kind at the moment?	87	22.7%
Are you waiting for any treatment, operation or investigation?	48	12.5%
Have you ever had any illness or health related problem that may have been caused or made worse by your work?	44	11.5%
Have you ever been medically retired from any job, or left any job because of ill health?	7	1.8%
Have you had any days off sick in the last 2 years?	73	19%

Table 2: Medical Problems of male teachers in Abha City 2014

Medical Problems	Number	Percent
Eyesight problems not corrected with glasses	59	15.4%
Hearing problems	25	6.5%
Mental illness, psychological or psychiatric problem (depression, anxiety, nervous debility, nervous breakdown, schizophrenia or eating disorder (anorexia or bulimia )	30	7.8%
History of fits, blackouts or epilepsy	5	1.3%
Skin problems	46	12%
History of hepatitis or jaundice	6	1.6%
Current medication use	75	19.5%
CVS ( heart or HTN )	43	11.32%
Allergic to anything	67	17.4%
Chest problems (asthma or bronchitis)	80	20.8%
Difficulties (standing, bending, lifting or with any other movements )	81	21.1%
Back problems	83	21.6%
Joints problems (pain, swelling or stiffness)	123	32%

**Table 3: Relation between medical problem and experience years and level of male teachers**

Parameters		Medical Problem (54)	p
Experience years	≤10 years	27(17.5%)	<0.001***
	> 10 years	127(82.5%)	
Level	Primary	71(64.1%)	0.52
	Intermediate	58(37.7%)	
	Secondary	25(16.2%)	

all within the accepted range but seeing a doctor in last year (43.2%) seems to be higher than normal range and mostly due to respiratory infections. Kovess-Masféty, V., et al 2009 [28] reported in France that among teachers their physical condition is characterized by a higher prevalence of health problems.

Some complaints or health problems among teachers in our study regarding eyesight problems recorded (15.4%). This is lower than Chong, E. Y., & Chan, A. H. (2010) in Hong Kong who reported 32% to 43% eye problems among teachers [21].

Hearing problems in 6.5%; this is lower than Martins, R. H. G. Et al., 2007 who reported 25% compared to 10% in controls with an acoustic notch predominating (11.25%;  $p < 0.05$ ), due to excessive classroom noise (93.5%) and auditory symptoms (65%). Noise levels close to 87dBA were recorded in classes at all teaching levels [34].

Mental illness, psychological or psychiatric problem, including depression, anxiety, nervous debility, nervous breakdown, schizophrenia or eating disorder was 7.8% and is much lower than Chong, E. Y., & Chan, A. H. (2010) in Hong Kong who reported high prevalence of Pseudo-neurological and mental disorders among teachers. The lower rates in this study may be due to fear of social stigma in our society and under-estimation and ignorance about the nature of psychological diseases [21].

The skin problems (12%) may be due to exposure to various irritants, either chemical or biological factors in schools. This is lower than Chong, E. Y., & Chan, A. H. (2010) who reported skin problems among teachers in Hong Kong at 24.4% [21].

The history of hepatitis or jaundice 1.6% is much less than prevalence of all types of hepatitis especially in the southwestern area of KSA as detected by Abdo, A. A., 2012. This may explained by health appraisal and screening being done before job allocation [36].

The heart or blood pressure problems were 11.32% and this rate is lower than community prevalence and does not differ than the level in developed countries as detected by Ghabrah, T. M et al., 1998, [16] but is not in agreement with Ibrahim, N. K et al., 2008 in his study in Jeddah which

was higher. This difference may come from the detected prevalence of risk factors like obesity which was lower in our area [17].

The history of allergy was 17.4% due to exposure to different chemical and biological irritants in the school environment; this is in agreement with Chong, E. Y., & Chan, A. H. (2010).

A study in Hong Kong reported 19% prevalence of allergy among school teachers [21].

Suffering from asthma or chest problem was reported in 20.8% due to drawbacks from allergy or recurrent chest infections. This is higher than Chong, E. Y., & Chan, A. H. (2010) [21] in Hong Kong who reported 16.1%. The difference could be explained by Al Frayh, A. R., et al., 2001 [37] who reported data between Riyadh versus Hail (inland desert dry environment) and Jeddah versus Gizan (coastal humid environment) which revealed that the prevalence of asthma in the similar populations increased significantly from 8% in 1986 to 23% in 1995 due to environmental changes.

History of Musculoskeletal disorder 21.1%, Low back pain 21.6% and joint pain 32%.

These high rates due to age, length of employment and awkward posture, prolonged posture, static works and repetition are the cause of repetitive strain injuries which are associated with higher MSD prevalence rates among teachers. This is matched with Erick PN, Smith DR, 2011 who reported that the schoolteachers represent an occupational group among which there appears to be a high prevalence of MSD [19].

In our study, regarding the relation between medical problem and experience years and level among the studied Group there is a significant association between medical problem and experience years more than 10 years due to accumulation of stressors and chronic diseases so the effect may be a false association due to confounder effect of the aging process.

There was no significant association with specific educational level; this may explained by the same stressors present in all levels.

## Conclusion

The medical problems of male teachers increase with age increase. The health status of male teachers is not optimal since a high percentage of them have to see a doctor each year and one third of them are currently sick. Moreover, musculoskeletal problems are quite common among male teachers.

## Recommendations

Provision of health educational program about the risks which the teachers have been exposed to, either communicable or non-communicable. Establishment of a specific health program for teachers caring with their health status. More availability of preventive health care measures to avoid co- morbidities associated with work environment. Multidisciplinary team approach toward the screening and diagnosis of health hazards among teachers that consists of "Clinical, Laboratory, radiological, Occupational and epidemiological researcher teams".

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# How to do Systematic Review and Meta-analysis

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## Objectives

By reading this paper students and readers are expected to be able to: Differentiate narrative review, systematic review, and meta-analysis; Know the steps of conducting a systematic review and meta-analysis; Appraise a systematic review article; Interpret the forest plot and pooled result; and Understand, explore, and deal with heterogeneity.

## Clinical Scenario

In May 2007, Steven Nissen and Wolski published a systematic review in the New England Journal of Medicine entitled, "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes".<sup>(1)</sup> Rosiglitazone (Avandia) belongs to the Thiazolidinedion group that was approved by FDA in 1999 as an antidiabetic drug that increases insulin sensitivity. Physicians prescribed this drug for patients as an adjunctive therapy for those who have an uncontrolled HbA1c level (indicative of poor management of hyperglycemia) and/or for diabetics who refuse insulin injections. The result of Nissen's systematic review was shocking to all physicians who used Avandia, especially when around 7 million people were using it with sales exceeding US\$3 billion. Nissen and Wolski combined data from 42 clinical trials with a total of approximately 15,000 patients on Avandia and 12,000 on controlled treatments. Odds Ratios (OR) for acute myocardial infarction and cardiovascular death were 1.43 and 1.64, respectively. On appraising Nissen's systematic review, many flaws have been found in the methodology including: exclusion of studies with no cardiovascular events, unclear outcome definitions, problems with inclusion and exclusion criteria, study selection problems, and problems in the quality of the included studies. These caused many not to believe the results of Nissen and Wolski's systematic review.

Following Nissen and Wolski's review, other systematic reviews (with accepted quality) were published during 2007, and all supported its main conclusion of serious side-effects of Avandia. Avandia was withdrawn from the market based on the results of these systematic reviews.

## What is a Review?

A 'review' is the generic term for any attempt to synthesize the results and conclusions of two or more publications on a given topic.

If the review is synthesized using systematic methods for searching, selecting, and appraising articles, it is called Systematic Review; while, if such methods were not implemented in full, it is called Narrative Review. Combining the results of studies to produce one pooled result is called Meta-analysis.

Most of the time systematic review has a pooled result (meta-analysis). The names of systematic review and meta-analysis are exchangeable because results of both methods are frequently presented together in the same report.

### Narrative review:

It is a report or a detailed commentary written by an expert to consider the critical points of current knowledge including substantive findings of a particular topic. It may be part of a thesis and usually precedes a research proposal and results section.

### Strengths:

- It offers broad overview of a topic, similar to a textbook chapter.
- It serves as a scientific resource by providing a bridge between the scattered articles on a topic and the reader who does not have time or access to track them down.
- It provides conclusions related to the scope and theory that individual empirical reports cannot normally address.

- It usually covers multiple background aspects of a disease such as natural history, etiology, epidemiology, signs and symptoms, diagnosis, treatment, and prognosis.
- It provides a comprehensive summary of results from a pool of primary studies.

#### Limitations:

- The summarized studies are chosen at the discretion of the author.
- Usually conducted with no explicit methodology procedures reported or vote counting.

#### Systematic Review

A systematic review combines all available research in

order to answer a specific question that fits pre-defined eligibility criteria.

A systematic review can be considered a review report characterized by the following features:

1. A rigorous review of specific clinical question;
2. A systematic methodology and literature search; and
3. Explicit regarding information provided

#### Meta-analysis

Many systematic reviews contain meta-analyses. Meta-analysis is the use of statistical methods to integrate the results of independent studies into one pooled result.

**Table 1: Differences between a narrative and systematic reviews**

Item	Narrative Review	Systematic Review
The question	Many broad questions, more background type	One clinical foreground question
Search Methods	None	Explicit, comprehensive search strategy
Selection of studies	No inclusion or exclusion criteria	Explicit eligibility criteria for inclusion or exclusion of studies
Combining of results	None	The results are pooled together (meta-analysis)

### Why do we perform Systematic Reviews?

Systematic reviews and meta-analyses use systematic method of searching and locating studies to minimize bias. This is achieved by combining high quality studies by searching electronic databases preferably with no restriction to language and including both published and unpublished articles. Combining studies together increases the sample size and minimizes the effect of random error in the overall appreciation of evidence. In addition, systematic reviews also can save the costs of conducting additional randomized controlled trials (RCT) to answer the same research question.

Six steps for conducting systematic review

1. A well formulated question
2. Finding studies
3. Selecting studies
4. Data extraction
5. Appraising studies
6. Combining results

#### Step 1: A well formulated question

A well formulated question is the first step in any research. Well-formulated questions will guide many aspects of the review process, including determining eligibility criteria, searching for studies, collecting data from included studies, and presenting findings. Converting the question into PICOT format is essential to define each component well. PICO was discussed in a previous chapter and T stands for type of study and time.

PICOT defines well the Population, the Intervention, the Comparison, the Outcome, and the Type of study, its duration and time it was conducted.

The question may be broad or narrow. A broad question for example is: antibiotics for treatment of UTI; while a narrow question is like: third generation cephalosporin for treatment of childhood cystitis.

Review authors will decide about the scope of their review, bearing in mind that a too narrow question may affect the generalizability of the results, while a too broad question, may affect the manageability of the project (i.e., authors may not be able to do the review due to resources consumption).

#### Step 2: Finding studies

A comprehensive search strategy that includes most relevant electronic databases (e.g., Pubmed, Embase and Cochrane library) in addition to non-electronic resources is necessary to retrieve all relevant studies. The choice of keywords (based on PICOT) is critical for the search. A good search is one with no language restriction, no date restriction, up-to-date, and includes both published and unpublished literature.

The bottom line is not to miss any relevant study until the date of manuscript submission.

**Following are the resources to be searched:**

1. Electronic databases
2. Hand or manual search
3. Full text journals and table of contents (TOC)
4. Conference abstracts and proceedings
5. Reference lists
6. Unpublished studies
7. Clinical trial registries
8. Grey literature
9. Pharmaceutical industry trial registers

**1. Electronic databases:** The aim of thorough search is to locate, as many as possible, relevant studies and not to miss an important study. A minimum of three essential databases must be searched, which are: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. Both free-text and subject headings should be used (e.g., Medical Subject Headings (MeSH)). Searching MEDLINE alone is not sufficient to detect all RCT.

**2. Hand search:** Hand searching is complementing electronic database search because not all journals are indexed in electronic databases.

**3. Full text journal search and table of contents:** Many journals have an electronic full text either free of charge or with subscription.

**Examples of free of charge websites:**

- BioMed Central: [www.biomedcentral.com/browse/journals/](http://www.biomedcentral.com/browse/journals/)
- Public Library of Science (PLoS): [www.plos.org/journals/](http://www.plos.org/journals/)
- PubMed Central (PMC): [www.pubmedcentral.nih.gov/](http://www.pubmedcentral.nih.gov/)

**Web sites listing journals offering free full-text access includes:**

- Free Medical Journals: [freemedicaljournals.com/](http://freemedicaljournals.com/)
- HighWire Press: [highwire.stanford.edu/lists/freeart.dtl](http://highwire.stanford.edu/lists/freeart.dtl)

**There are also a number of international initiatives to provide free or low-cost online access to full-text journals (and databases) over the internet, including:**

- The Health InterNetwork Access to Research Initiative (HINARI) [www.who.int/hinari/en/](http://www.who.int/hinari/en/)
- The International Network for the Availability of Scientific Publications (INASP) [www.inasp.info/file/68/about-inasp.html](http://www.inasp.info/file/68/about-inasp.html), and
- Electronic Information for Libraries (EIFL) [www.eifl.net/cps/sections/about](http://www.eifl.net/cps/sections/about)

**Table of Contents (TOC):** Several organizations and journals, offer Table of Contents (TOC) services free of charge, normally through e-mail alerts or RSS feeds.

**Examples of organizations offering TOC services**

- British Library Direct (free): [direct.bl.uk/bld/Home.do](http://direct.bl.uk/bld/Home.do)
- British Library Direct Plus (subscription): [www.bl.uk/reshelp/atyourdesk/docsupply/roductsservices/bldplus/](http://www.bl.uk/reshelp/atyourdesk/docsupply/roductsservices/bldplus/)
- British Library Inside (to be replaced by British Library Direct Plus) (subscription): [www.bl.uk/inside](http://www.bl.uk/inside)
- Current Contents Connect (subscription): [scientific.thomson.com/products/ccc/](http://scientific.thomson.com/products/ccc/)

[thomson.com/products/ccc/](http://thomson.com/products/ccc/)

- Scientific Electronic Library Online (SciELO) - Brazil (free): [www.scielo.br/](http://www.scielo.br/)

**4. Conference abstracts and proceedings:** More than 50% of clinical trials presented in conferences failed to be published. Those that are eventually published in full have shown to be systematically different from those that are never published in full (Scherer, 2007). Conference abstracts are identified by hand search and proceedings in CD Rom. A number of websites publish these abstracts:

- The BIOSIS databases (<http://www.biosis.org/>)
- The American Society of Clinical Oncology (ASCO): [www.asco.org/ASCO/Meetings](http://www.asco.org/ASCO/Meetings)
- Biological Abstracts/RRM (Reports, Reviews, Meetings): [scientific.thomson.com/products/barrm/](http://scientific.thomson.com/products/barrm/)
- British Library Inside (to be replaced by British Library Direct Plus): [www.bl.uk/inside](http://www.bl.uk/inside)
- British Library Direct Plus: [www.bl.uk/reshelp/tyourdesk/docsupply/productsservices/bldplus](http://www.bl.uk/reshelp/tyourdesk/docsupply/productsservices/bldplus)
- ISI Proceedings: [scientific.thomson.com/products/proceedings/](http://scientific.thomson.com/products/proceedings/)

**5. Reference list:** Reference lists of published systematic reviews, studies, or guidelines are convenient resources of studies. Useful resources are the Cochrane library, Trip database, NICE guidelines, SIGN guidelines and guideline.gov.

**6. Unpublished studies:** Not all completed studies are published. Finding and including unpublished studies minimizes bias. Publication bias occurs when the decision to publish is based on study results and not how the study was conducted (the method). Are Published studies enough? Studies with positive results are submitted and get published 2.5 times more than negative ones. Negative studies are less likely to be published.(11)

**Publication Bias**

Studies with positive results are more likely to be published, published rapidly, in English, have more than one source (duplication), and are cited more than negative studies.

All trials should be registered as early as possible even at protocol stage for example:

- Clinical trial registry: [www.clinicaltrial.gov](http://www.clinicaltrial.gov)
- The National Clinical Trials Registry: Cancer trials
- National Institutes of Health Inventory of Clinical Trials and Studies
- International Registry of Perinatal Trials
- Meta-registry of Trial Registries: [www.controlled-trials.com](http://www.controlled-trials.com)

Publication bias may be presented visually by plotting and reviewing the funnel plot, which is a graph with (Y) axis representing the sample size, starting from the bottom with small sample size studies and ends at the top with large studies. The (X) axis represents effect measures of

individual studies. The line at the middle is the line of point estimate (not the line of no effect). Usually effect measures of studies will be distributed equally on both sides of the point estimate line with effect measures of small sized studies that are more in number and situated at the bottom of the curve. If publication bias is not a major issue, then an inverted funnel shaped, symmetrical curve is usually produced.

In case of publication bias, there is asymmetry of the funnel plot due to unpublished small and negative studies.

**7. Clinical trials registries** were established to prevent reporting bias including publication bias (i.e., ClinicalTrials.gov register: [clinicaltrials.gov/](http://clinicaltrials.gov/))

**8. Grey literature:** Hirtle has defined Grey Literature as: Unpublished printed reports, but circulated papers, unpublished proceedings of conferences, printed programs from conferences, and the other non-unique material which seems to constitute the bulk of our modern manuscript collections (Hirtle, 1991). Conference abstracts and other grey literature have been shown to be sources of approximately 10% of the studies referenced in Cochrane reviews (Mallett, 2002). In a recently updated Cochrane

Figure 1: Forest plot with dotted line of pooled estimate and studies distributed equally

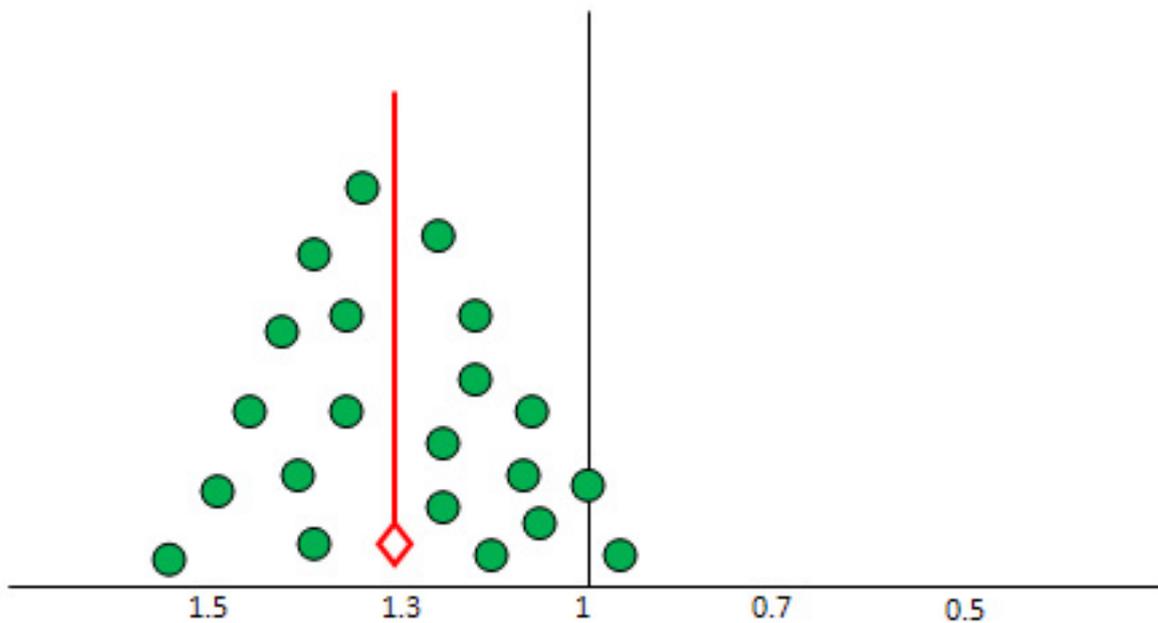
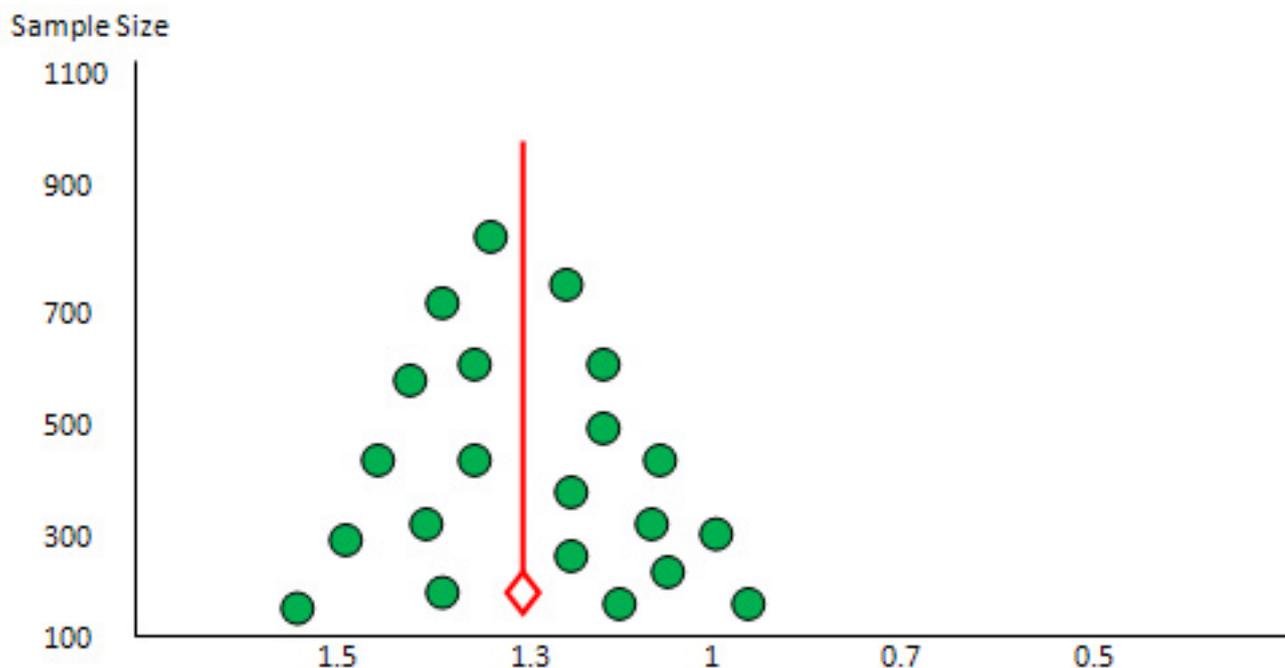
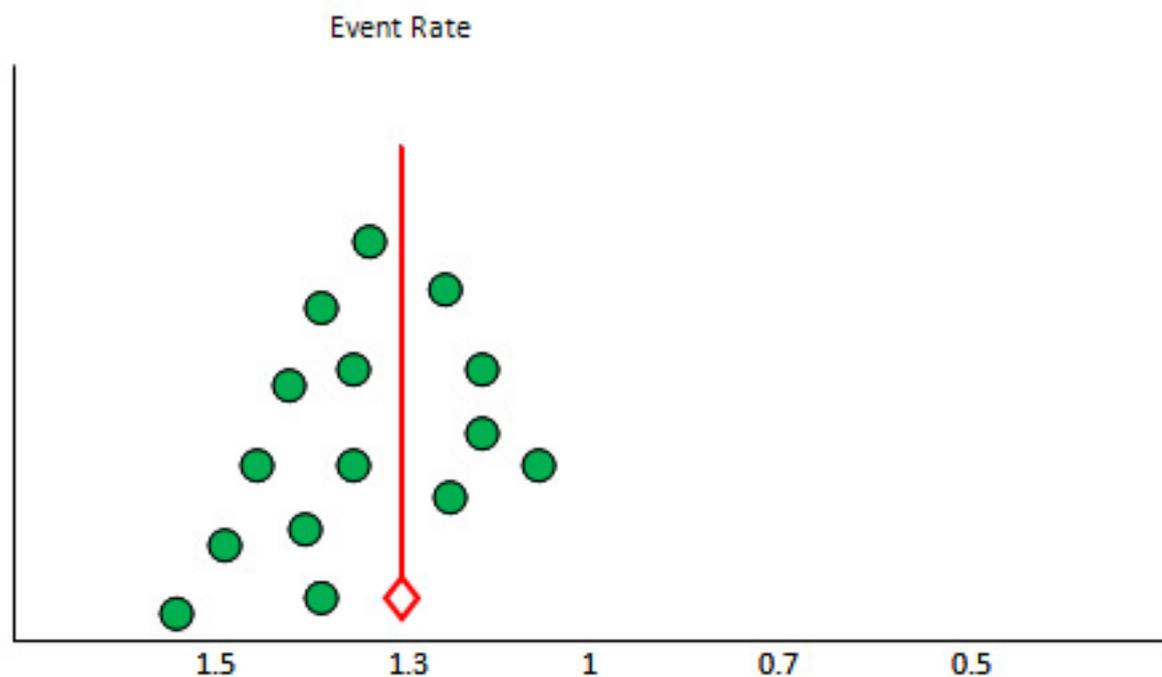


Figure 2: Funnel plot Y=100-1000, x= 1 no effect line, 1.2 1.1.6 the other side 0.8, 0.6, 0.4 with symmetrical distribution of studies



**Figure 3: Funnel plot with asymmetry due to missing studies**

methodology review, all five studies reviewed showed that published trials presented an overall greater treatment effect than grey literature trials (Hopewell 2007b). Grey literature may be found in the internet from the following resources:

- **ALA Internet Resources:** Gray Literature
- **GreyNet:** The Grey Literature Network Service
- **Science.gov** is a gateway to over 50 million pages of authoritative selected science information provided by U.S. government agencies, including research and development results.
- <http://www.scienceaccelerator.gov/> Science Accelerator searches science, including R&D results, project descriptions, accomplishments, and more, via resources made available by the Office of Scientific and Technical Information (OSTI), U.S. Department of Energy.
- **The GrayLIT network:** A science portal of technical reports. From the Office of Scientific & Technical Information at the United States Department of Energy.
- Grey Literature Library for UK Archaeology.
- The International Journal on Grey Literature published one volume in 2000. The content may be limited to subscribers.
- **CiteSeerX** indexes some of the gray literature such as technical reports in computer and information science.
- **Open Grey Repository**, formerly OpenSIGLE.

**9. Pharmaceutical industry trial registers:** Most pharmaceutical industries keep registry for all clinical trials funded by them.

### Step 3: Study selection

Researchers should apply the pre-specified inclusion and exclusion criteria in order to select the relevant studies. At least two reviewers are doing the selection of relevant studies independently.

A disagreement about whether certain studies should be included is resolved by discussion. The following steps are useful to do so:

1. Merge search results using reference management software (e.g., endnote) and remove duplicate records of the same report.
2. Examine titles and abstracts to remove obviously irrelevant reports (i.e., authors should generally be over-inclusive at this stage).
3. Retrieve full text of the potentially relevant reports.
4. Examine full-text reports for compliance of studies with eligibility criteria.
5. Correspond with investigators, where appropriate, to clarify study eligibility (it may be appropriate to request further information, such as missing results, at the same time).
6. Make final decisions on study inclusion and proceed to data collection.

### Step 4: Data extraction

The systematic review process of obtaining necessary information from retrieved articles in specific forms is called data extraction. The nature of information extracted should be tailored to the review question. Details of the data extraction process and the data extraction form should be included in the review protocol. The latter should be piloted, refined, and linked to the future assessment of the study quality prior to the start of the systematic review. The use of electronic data extraction forms can facilitate obtaining relevant information from an article in a standardized way and can reduce the time for data analysis and production of tables.

### Piloting of data extraction:

Ideally, data extraction forms should be piloted on a sample of included articles to ensure that the process will

be conducted in a comprehensive and standardized way. The process of data extraction should be assessed for both accuracy and consistency. The latter is usually evaluated by quantifying the inter-rater agreement beyond chance (Kappa) and is of particular importance in reviews where coding data will be employed.

#### **Process of data extraction:**

The primary aim of the data extraction process is to avoid human errors and subjective decisions, and hence the form should be valid and reliable as much as possible. In an ideal data extraction process, two researchers should independently perform the task; while a third researcher should be checking the forms for accuracy, completeness and consistency. The number and reasons of disagreements among data extractors should be reported and resolved by consensus among researchers first, or by arbitration in case a consensus could not be reached. If time and resources constraints limit the number of researchers involved in data extraction, the minimum acceptable process would be that one researcher should extract the data with a second researcher checking for accuracy and completeness. Blinding researchers to the journal and author details can be time-consuming but has been recommended to avoid observer bias in terms of selecting and extracting evidence from individual studies. However other investigators have reported a limited benefit of blinding in improving the accuracy of results.

#### **Nature of extracted data:**

The type of data extracted in the predefined extraction forms depends on the research question posed and the types of study designs included. The box below includes data that are most commonly extracted in systematic reviews for clinical trial.

#### **Step 5: Assess Risk of Bias (ROB)**

A bias is defined as a systematic error, or deviation from the truth, in results or inferences. Biases are not the same. Some have a minor effect on the validity of any study; while some can pose a substantial effect. Biases can lead to underestimation or overestimation of the true intervention effect. To what extent biases have affected the results of a study is difficult to answer. Studies included in systematic reviews should be classified into studies with low risk of bias, unclear, or high risk of bias.

In 1995, Moher and colleagues identified 25 scales and 9 checklists that had been used to assess the validity or 'quality' of randomized trials (Moher, 1995 and 1996).(14,15)

One commonly-used scale was developed by Jadad and colleagues for randomized trials in pain research (Jadad, 1996).(14) Cochrane collaboration discourage the use of this scale as it does not cover one of the most important potential biases in randomized trials, namely allocation concealment.

The Cochrane Collaboration's recommended tool for assessing risk of bias is neither a scale nor a checklist. It is

a domain-based evaluation, in which critical assessments are made separately for different domains.

There are 5 possible sources of biases in individual studies:

**1. Selection bias:** What differentiates RCT from other types of studies is that it starts with balanced groups, i.e., the baseline characteristics of the groups is similar. This balance is due to two processes: (1) generation of randomization list by computer then the (2) distribution of subjects to the intervention and control groups by secret methods (concealment); by using serially numbered, opaque and sealed envelopes; or, by remote telephone call. Failure to do so can affect the validity of the study and lead to selection bias.

**2. Performance bias:** The intervention and control groups must maintain balance by blinding which should be masked until the end of the study. Everyone who is dealing with a patient or his data must be blind to who is taking what. The care provided to both groups must be the same. Failure to do so, can lead to what is so called performance bias.

**3. Detection bias:** If outcome assessors know who is taking what, they may deviate from the truth, and create bias in the evaluation of outcomes. Outcome assessors must be blind especially when the outcome is subjective (e.g., assessment of pain). Failure to do so can lead to "detection" bias.

**4. Attrition bias:** Attrition refers to any situation in which the outcome data of a particular subject is not complete or corrupted. It may be due to drop-out, cross-over, or the outcome data is not complete. When any of these situations happen, an attrition bias should be suspected.

**5. Reporting bias:** There are many types of reporting biases. Publication bias was described before. Within-study publication bias describes a condition when positive findings are reported more than negative ones.

#### **Step 6: Meta-analysis**

Meta-analysis is the statistical combination of results across the combined studies. There are many statistical packages to do so, mainly RevMan (The Review Manager), produced by Cochrane collaboration. It is free of charge for Cochrane reviewers or anyone doing systematic review. Another one is the comprehensive meta-analysis software (CMA); which is a commercial software that needs to be purchased. Another software for diagnostic meta-analysis is the Metadisc software, which is also free of charge.

The principle concept of pooling results together in meta-analysis is weighted average principle.

#### **Example:**

In class A, the average score of the 20 students is 50, while in class B the average score for the 10 students is 60. What is the average of the 2 classes?

$$(50 \times 20) + (60 \times 10) / (20 + 10) = 48 \text{ (not 55)}$$

To interpret the meta-analysis, one needs to answer 4 questions:

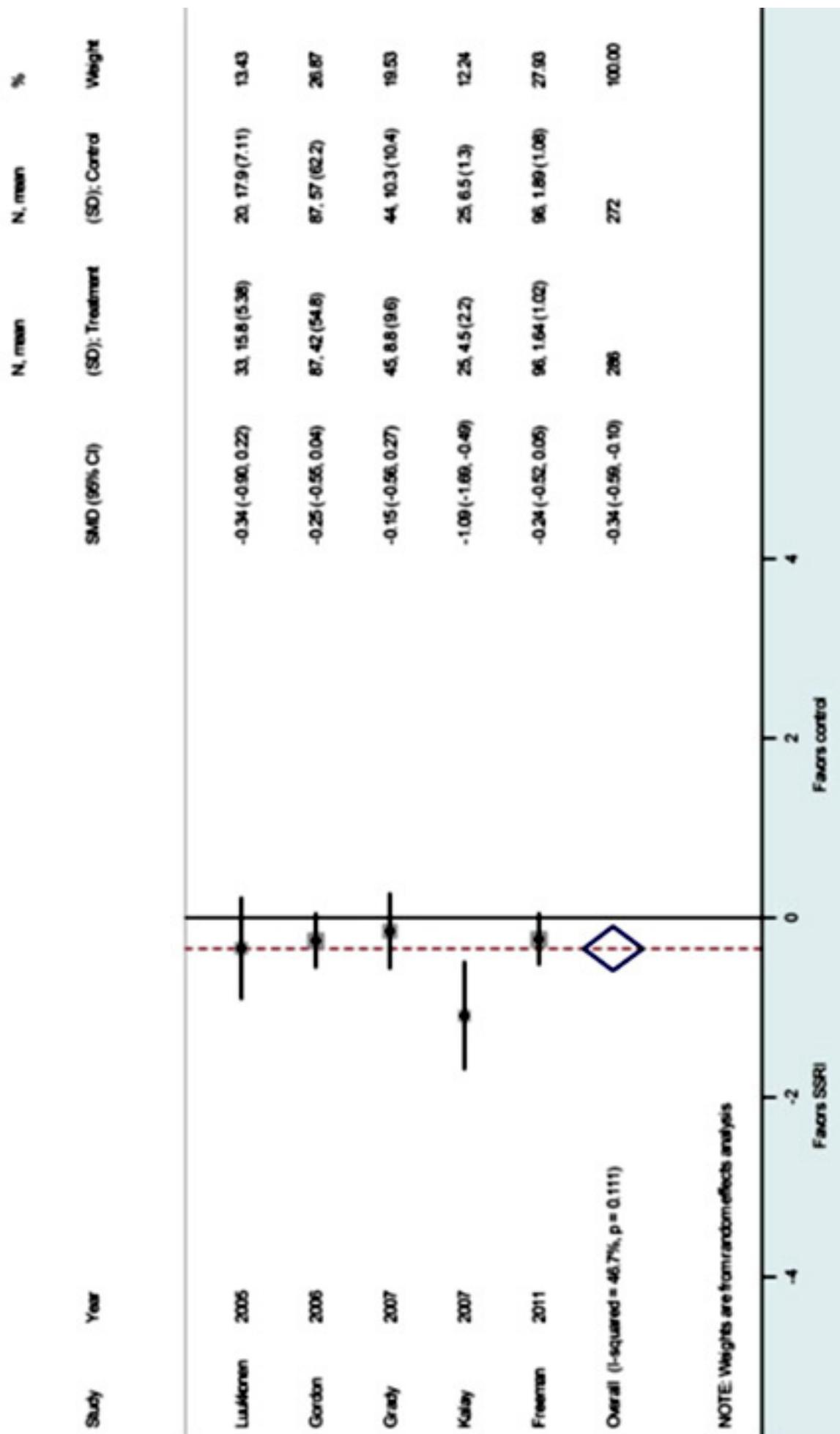


Figure 4: SSRI for hot flashes meta-analysis, improvement in standardized hot flashes

1. What is the direction of effect?
2. What is the size of effect?
3. Is the effect consistent across studies?
4. What is the strength of evidence for the effect?

**Q1. What is the direction of effect?** Is the pooled effect (point of estimate) at the site of control (favors control); or at the site of intervention (favors intervention); or crosses the no effect line (no difference of the effect between the intervention and the control). The line of no effect is (1) for dichotomous data, or (0) for continuous data.

**Q2. What is the size of effect?** The effect measure may be a relative value (RR, OR or HR) or absolute mean difference (MD) or standardized mean difference (SMD). The effect is presented as the effect measure (size) and the confidence interval (CI) or P value.

**Q3. Is the effect consistent across studies?** Inconsistency or heterogeneity across studies is the amount of variation of the results across studies. (This will be discussed later under heterogeneity.)

#### Q4. What is the strength of evidence for the effect?

This needs judgment in addition to the effect measure. It depends on the study design and risk of bias.

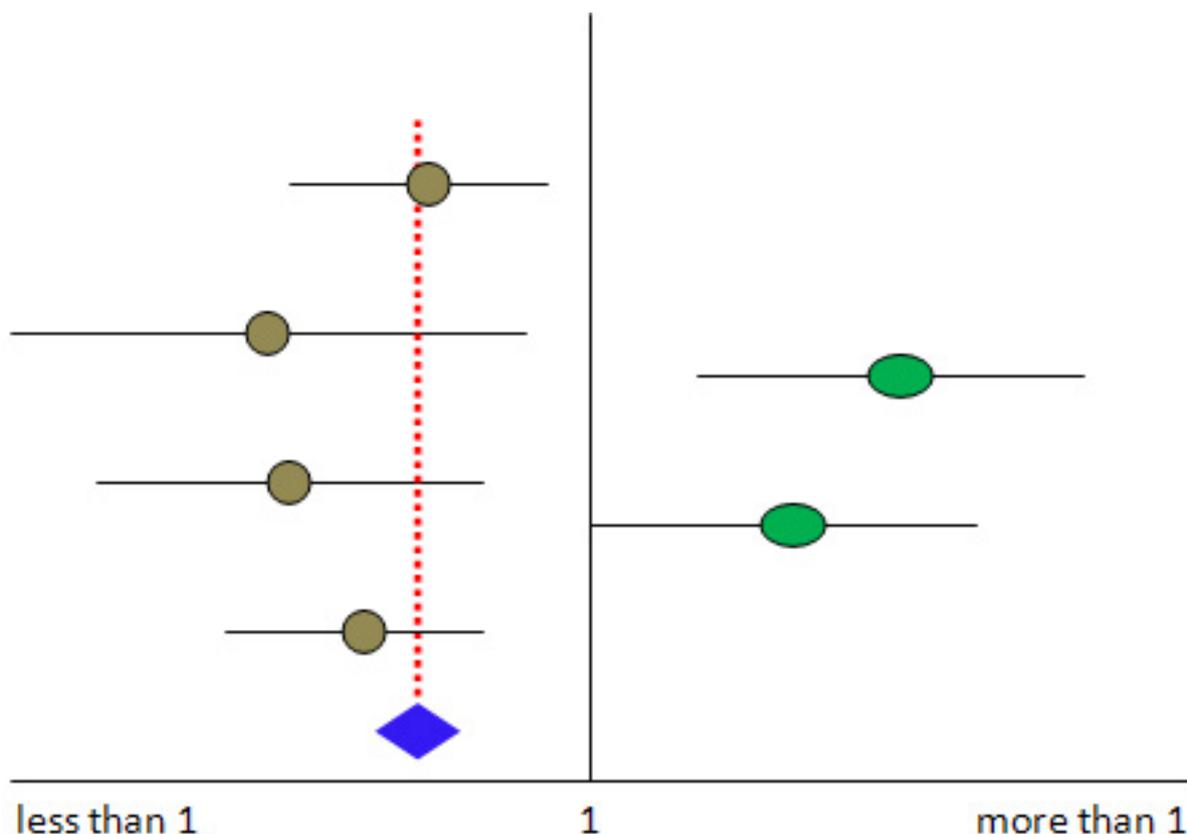
#### Heterogeneity (Inconsistency)

**1. What is heterogeneity?** Variation of results across studies that may be due to random effect (no statistical significance) or due to heterogeneity (statistical significance). It may be due to diversity in PICO elements, differences in population, intervention or outcome measures (called clinical heterogeneity); or may be due to bias, e.g., variation in study design, conduct or attrition between individual studies (called methodological heterogeneity).

#### 2. Identifying and measuring heterogeneity

There are 3 methods to identify heterogeneity:

**a. Eye ball or visual overlap:** The extent of overlap of the CI in the included studies determine its consistency. Draw an imaginary line from the pooled effect result. If there is one study or more that are not crossed by this line, it means that there is heterogeneity.



**b. P value:** The chi square test of heterogeneity, when it is less than or equal to 0.05 it indicates presence of heterogeneity.

**c. I<sup>2</sup> test:** The I<sup>2</sup> test is a modified chi square test, but it is a quantitative test, that represents the percentage of heterogeneity. It is the proportion of total variability explained by heterogeneity. How much is too much heterogeneity? Low heterogeneity, when I<sup>2</sup> is 25%, moderate when I<sup>2</sup> is 50% and high when I<sup>2</sup> is 75%.

#### 3. Strategies for addressing heterogeneity:

How to deal with heterogeneity

- a. Recheck the data of individual studies.
- b. Do not do meta-analysis in case of considerable heterogeneity, especially when the result is in favor of intervention.
- c. Do subgroup analysis: it is the splitting of all participants' data into subgroups, based on any of the PICOT elements. Subgroup analysis must be pre-specified, because ad-hoc subgroup analysis of multiple outcomes may be misleading

due to false positive and false negative results.

**d. Ignore heterogeneity:** Fixed effect-model (FEM) ignores heterogeneity.

**Fixed Effect Model:**

In non-heterogeneous studies, there is one true treatment effect.

Results are combined with the studies weighted according to the inverse of within-study variance. The statistical tests used are:

- Mantel-Haenszel method for relative risk (RR)
- Peto's method for odds ratio (OR)

**Assumptions:**

1. Only a single true value underlies all the study results;
2. If all studies were infinitely large, they would yield identical estimate of the effect; and
3. Each study estimates a difference underlying true effect and the distribution of these effects follows a normal curve.

The combined effect size is given by a weighted average of the effect from each individual study and the weight for each study is the inverse of its variance.

**e. Perform Random-effect model (REM).**

**Random Effect Model:**

While in heterogeneous studies, there are multiple true treatment effects.

Results are combined with the study weighted according to the inverse of the sum of within-study variance and among-study variance, the statistical test used is DerSimonian and Laird method.

**Assumptions:**

1. Individual studies are estimating different treatment effects;
2. The treatment of different studies has a distribution with some central value and some degree of variability.

The excess variation should be taken into consideration in computing the combined estimate.

The procedures to obtain a combined estimate is the same as a fixed-effects model, i.e., weighted average, which is the inverse variance in FEM while in REM is the inverse "variance plus the excess variation."

**e. Do Sensitivity analysis:** Heterogeneity may be due to outliers that are totally different than the rest of the studies. It is not logical to exclude them, but in a few occasions, if the outlier is blamed as the cause of the variability, it may be excluded.

If the result after excluding the study is within the CI of the result before exclusion, then the study could be excluded without affecting the result. But if the result after exclusion is changed, i.e., not included within CI of the result before exclusion, in this case you cannot exclude it.

**Figure 5-A: Hypothetical forest plot that includes 4 studies favoring one intervention while 1 study (outlier) favors another intervention; this study may be the cause of heterogeneity.**

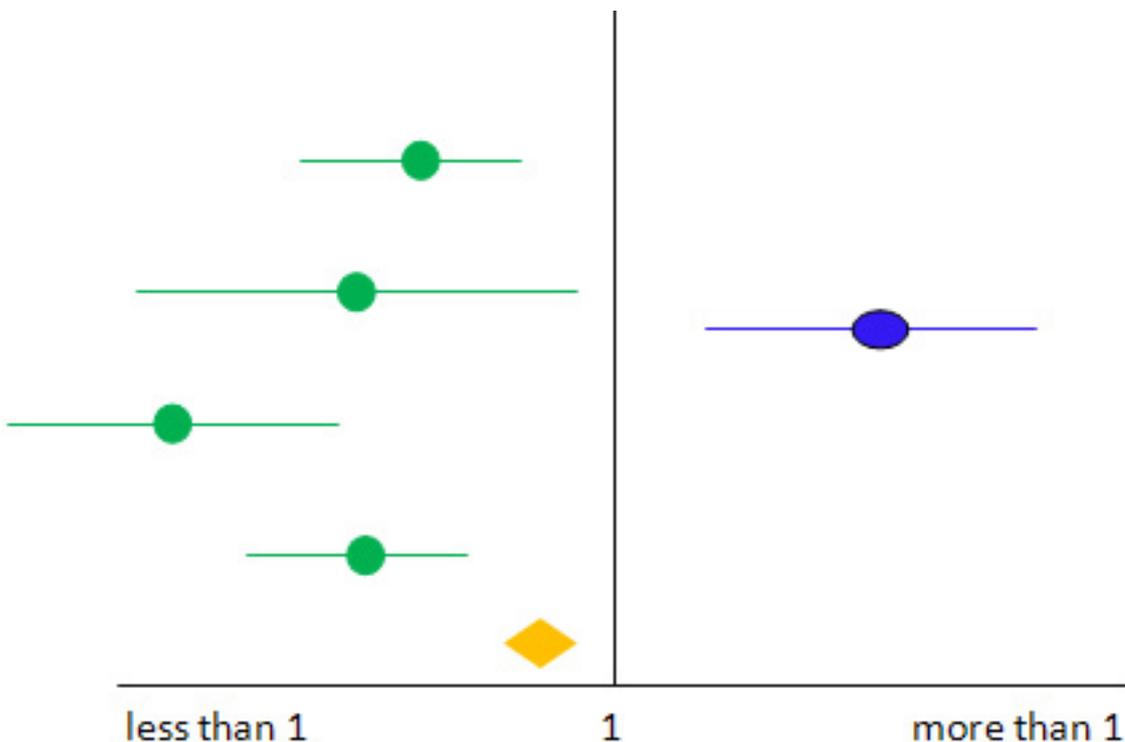


Figure 5-B: In case the outlier study is removed and the pooled result is significantly changed (the darker diamond shape), then one can't remove it

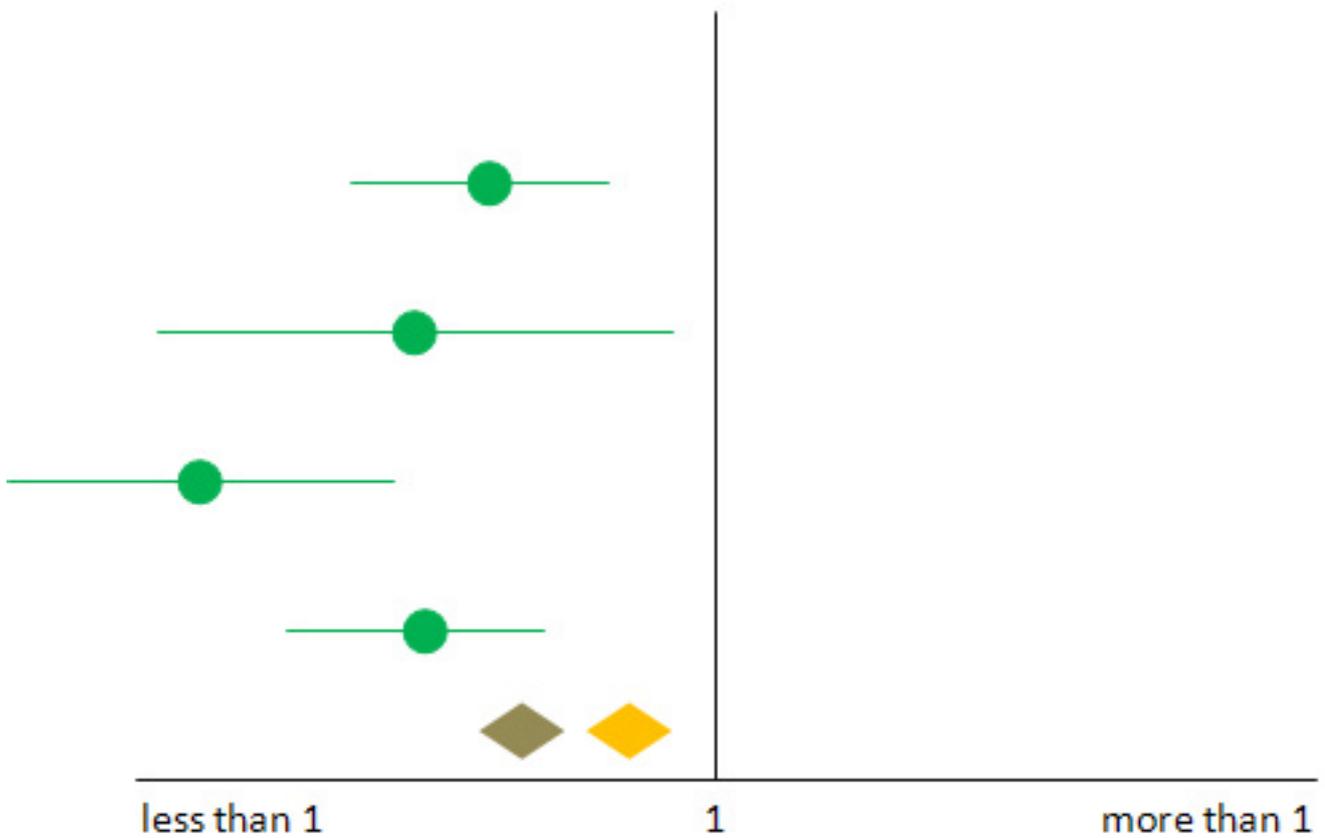
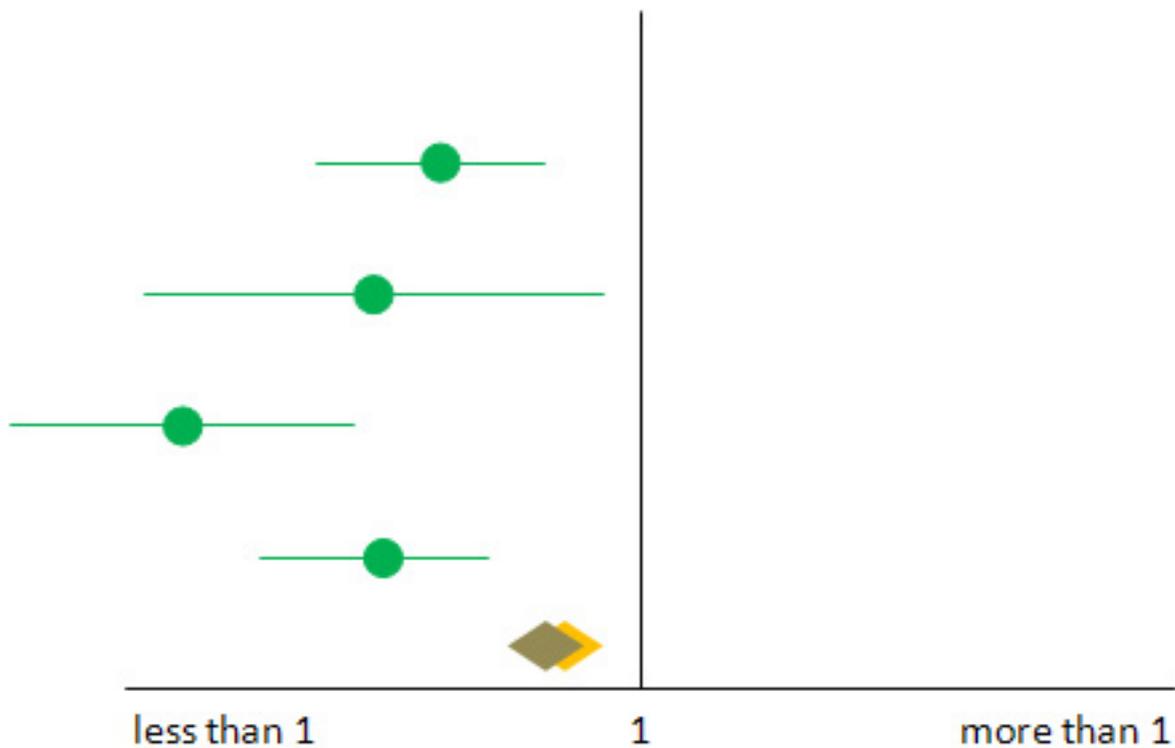


Figure 5-C: However, if the result doesn't change significantly, then one may remove the outlier safely



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# Evidence-Based Standards for Cancer Pain Management

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## Abstract

Cancer pain management is the most problematic when found in patients who have a malignant tumor, and represents the most feared consequences for patients and their families. A thorough literature review was conducted using the electronic databases of CINAHL, EBSCO, MEDLINE, and PUB MED, for articles published between 2007 and 2013. We developed quality standards; using a research study, and selected domains based on the framework of the type of cancer pain management into both types of treatment, pharmacological and non-pharmacological cancer pain management, in order to manage cancer related pain through multidisciplinary aspects and holistic approach. Pharmacological and non-pharmacological modalities give the opportunity for effective care to be provided to cancer patients. Also, these techniques may help in reducing pain and it must be encouraged as a part of the holistic cancer pain management efforts.

**Key words:** Cancer Pain, Pain Management, pharmacological and non-pharmacological cancer pain management.

## References

Cancer pain management is the most problematic when found in patients who have a malignant tumor, and represents the most feared consequences for patients and their families (Alexopoulos, et al. 2010). Cancer related pain management remains a challenge in cancer patients, their families, and oncology nurses due to lack of knowledge and assessment of pain which causes inadequate pain management (Winslow, Seymour, & Clark, 2005). However, there is inadequate pain management in different settings, especially in vulnerable populations and in low income countries. (Sydney, et al. 2008).

The most common problem facing cancer patients is bone metastases from lung, prostate, and breast cancer, that causes severe uncontrolled pain and need for multi methods of pharmacological and non pharmacological intervention to manage cancer related pain (Stenseth, Bjornnes, Kaasa, et al, 2007). The prevalence of pain among cancer patients is high worldwide: 64% in patients with metastatic or terminal disease stage, 59% in patients receiving anticancer treatment and 33% in patients who had been cured of cancer (Everdingen, Rijke, Kessels, Schouten, Kleef, & Patijn, 2007).

According to the American pain society if the plan of pain management includes both pharmacological and non-pharmacological interventions, it is considered effective and gives a positive effect on quality of life for patients and their families in order to decrease pain and remove suffering. Health care providers in this situation of performing holistic care have sustained interaction with patients and their families throughout the continuum of cancer care (American Pain Society, 2005). Thus, it is important for health care providers and decision makers to understand the updated knowledge on pain management strategies and relay their clinical services on evidence based practice in order to overcome all barriers to effective pain management among cancer patients, and select the most appropriate method to treat cancer related pain.

The purposes of this paper are to review and analyze the existing research studies on evidence based cancer pain management and to summarize the findings into evidence-based recommendations. Also, this paper is intended to answer the following questions: (1) what are the pharmacological methods that manage cancer related pain in patients with malignant tumor? (2) What is the relative efficacy of current adjuvant (non-pharmacological/non-invasive) physical or psychological (e.g., relaxation, massage, heat and cold, music, and exercise) interventions to help in managing cancer related pain?

## Methodology

A thorough literature review was conducted using the electronic databases of CINAHL, EBSCO, MEDLINE, and PUB MED, and COCHRANE DATABASE for articles published between 2007 and 2013. The following key words were used to search the electronic databases: cancer pain, pain management, pain symptoms, pharmacological and non-pharmacological cancer pain management.

Many articles were obtained and reviewed, but only 15 research articles achieved the inclusion criteria for the purpose of this study. The inclusion criteria were the following: (1) it is a research-based study; (2) written in the English language; (3) investigated the cancer pain management; (4) used either pharmacological and nonpharmacological techniques to manage cancer related pain. Based on the inclusion criteria, a total of 15 articles was selected and formed the basis for this review; a total of 14 research studies of randomized control trials (RCTs) and only one systematic review.

RCTs are considered to be the most reliable form of scientific evidence in the hierarchy of evidence that influences healthcare policy and practice because RCTs reduce spurious causality and bias (Schulz, Altman, & Moher, 2010). The articles that were included in this study were quantitative studies randomized control trials (RCTs) that were published in peer reviewed nursing and medical journals.

Countries within which the studies for this review were conducted include the United States, Australia, Canada, China, India, Greece, Egypt and Taiwan. The sample sizes in the 14 studies in this review ranged from 24 to 318 adult cancer patients aged between 18 and 60 years, and randomly assigned.

## Finding

We developed quality standards; using a research study, and selected domains based on the framework of the type of cancer pain management into both types of treatment, pharmacological and non-pharmacological cancer pain management, in order to manage cancer related pain through multidisciplinary aspects and with a holistic approach.

## Pharmacological Cancer Pain Management

Tetrodotoxin (TTX) is a potent neurotoxin that blocks voltage-gated sodium channels (Lee & Ruben 2008). Tetrodotoxin plays a crucial role in neuronal function under both physiological and pathological conditions, and is used to manage chronic pain conditions (Nieto et al., 2012).

Tetrodotoxin claims to provide effective cancer pain management and it is considered a strong analgesic that is characterized in the prolonged period to manage pain and is used in managing neuropathic pain, and improving the quality of life (Hagen et al., 2008).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used more effectively to manage cancer related pain when combined with opioids in order to give more effective pain management or to reduce the dosage of opioids that are given to cancer patients. Therefore the WHO ladder has added NSAIDs to step III to manage cancer related pain more effectively (Nabal et al., 2011).

In the study conducted by Mohamed and colleagues (2012) on patients undergoing major abdominal cancer surgery, they investigate the efficacy of intrathecally administered dexmedetomidine combined with fentanyl in control of cancer pain after surgery of 90 cancer patients.

The researcher recruited 90 cancer patients who were randomly assigned to receive intrathecally either 10 mg bupivacaine 0.5% (control group, n = 30), 10 mg bupivacaine 0.5% plus 5 u g dexmedetomidine (dexmedetomidine group, n = 30), or 10 mg bupivacaine 0.5% plus 5 ?g dexmedetomidine and 25 ?g fentanyl (dexmedetomidine= group, n = 30). The findings showed that Dexmedetomidine 5 u g given intrathecally, improves the quality and the duration of postoperative analgesia. It also provides an analgesic which indicates the usage of this drug to reduce pain in patients undergoing major abdominal cancer surgery.

Ketamine is a drug used in the induction and maintenance of general anesthesia. Other uses include sedation in the intensive care unit, especially in emergency cases (Peck et al., 2008). A study was done by Hardy and colleagues (2012) to determine whether ketamine is more effective than placebo when used in conjunction with opioids and standard adjuvant therapy in the management of cancer pain. The researcher recruited 185 participants and used randomized, double-blind, placebo-controlled design. The findings of the study found that ketamine does not have net clinical benefit when used as an adjunct to opioids and standard co analgesics in cancer pain. However current evidence is insufficient to assess the advantage and disadvantage of ketamine as an adjuvant to opioids for the relief of cancer pain.

Bisphosphonates are an antiresorptive medicine, which means they slow or stop the natural process that dissolves bone tissue, resulting in maintained or increased bone density and strength that reduces the risk of broken bones. Bisphosphonate increases bone thickness and lower the risk of fractures (Wong et al., 2002).

A randomized controlled trial was conducted on 256 patients with painful bone metastasis with solid tumors, to compare the effectiveness of the pain management effect of Bisphosphonates on incidence of skeletal-related events (Choudhury et al., 2011). The researcher found that use of Bisphosphonates for 6 months or more lead to significant improvement in relief of bone pain, and supports the effectiveness of Bisphosphonates in providing some pain relief for bone metastases that are the result of cancer spread.

Several advantages to improve quality of life and reduced chronic pain in a patient suffering from cancer related pain is when a combination of two analgesic agents was used. Most cancer types had metastasis properties to pain. (Sima et al., 2012) conducted a study of 246 patients and used a multicenter, randomized, double-blinded, placebo-controlled trial to investigate the efficacy of oxycodone/paracetamol for patients with bone-cancer pain. The researcher found that effective pain management in patients with bone-cancer pain, already on opioids, obtained clinically important, additional pain-control, with regular oxycodone/paracetamol dosing to the plan of cancer pain management.

A randomized controlled clinical trial of 153 women undergoing laparotomy for a gynecologic cancer disorder was used to establish the effect of perioperative patient-controlled epidural analgesia (PCEA) compared to postoperative intravenous (IV) patient-controlled analgesia (PCA) on postoperative recovery parameters after major open gynecologic cancer surgery. Patients were randomized to postoperative IV morphine PCA (control arm) or to postoperative morphine-bupivacaine PCEA (treatment arm). The researcher found that patients in the PCEA group had significantly less postoperative pain at rest on day 1 and during the first 3 postoperative days when coughing compared to the PCA arm ( $P < 0.05$ ). The mean pain score at rest on Day 1 was 3.3 for the PCEA group compared to 4.3 for the PCA group ( $P = 0.01$ ).

Overall, postoperative pain at rest and while coughing in the first 6 days was less in women treated with PCEA compared to PCA ( $P < 0.003$ ). PCEA offers superior postoperative pain control after laparotomy for gynecologic surgery compared to traditional IV PCA. Women requiring major open surgery for gynecologic cancer should be offered PCEA for postoperative pain management if there are no contraindications (Sarah et al., 2009)

On the other hand, in the study conducted by (Yeon et al., 2012) to evaluate the effectiveness and complications of continuous epidural analgesia in terminal cancer patients the researcher found that epidural analgesia was an effective pain management method in patients with terminal cancer stage. (Hong et al. 2008) conducted a study on 40 women with cervical cancer and found that the pain scores at 6 and 12 hours after surgery in the preemptive group were significantly lower than in the control group and preemptive epidural analgesia is a reasonable approach for potentially controlling perioperative immune function

and preventing postoperative pain in patients undergoing cancer surgery.

One hundred and eight cancer patients were included in a study conducted to compare the analgesic and adverse effects, doses, as well as cost of opioid drugs, of supportive drug therapy and other analgesic drugs in patients treated with oral sustained-release morphine, transdermal fentanyl, and oral methadone to manage cancer pain. Opioid escalation index was significantly lower in patients receiving methadone ( $p < 0.0001$ ), although requiring up and down changes in doses. At the doses used, methadone was significantly less expensive ( $p < 0.0001$ ) while the use and costs of supportive drugs and other analgesics were similar in the three groups. No relevant differences in adverse effects were observed among the groups during both the titration phase and chronic treatment. Methadone was significantly less expensive, but required more changes, up and down, of the doses, suggesting that dose titration of this drug requires major clinical expertise (Mercadante et al., 2008).

World Health Organization devised a medication algorithm known as the "3-step analgesic ladder" (WHO, 1986). The medications are required to treat mild cancer pain, non-opioids (acetaminophen, acetylsalicylic acid) and should first be introduced. If pain persists, or if at presentation it is moderate to severe, opioids should be introduced. Initially, "weak opioids" (codeine, tramadol) should be prescribed; if maximum doses are reached, the weak opioids should be rotated to "strong opioids." The strong opioids include morphine, oxycodone, hydromorphone, fentanyl, and methadone.

On their own, the strong opioids have no maximum dose. But it is important to note that, although oxycodone is a strong opioid, dosing for combination products containing both short-acting oxycodone and acetaminophen is limited by the maximum allowable daily dose of acetaminophen. Such combination agents are therefore considered appropriate for step 2 of the analgesic ladder. Although meperidine is considered a strong opioid, it is not used in the cancer pain setting, because consistent use leads to the accumulation of normeperidine in the body and a lowering of the seizure threshold (Inturrisi, 2002).

### Non-Pharmacological Cancer Pain Management

Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological agent, based on delivering low voltage electrical currents to the skin. TENS is used for the treatment of a variety of pain conditions (Bennett et al., 2010).

TENS is applied to the site of bone pain by a medical researcher for a continuous 60 minute period after 2 to 7 days placebo or active, then applied for 60 minutes. The researcher found satisfaction with patient in patients in reduced pain level, and TENS is easy to use, and has most impact on patients at rest or on movement, which application provides more benefit, and which outcome scale best represented the experience of pain intensity and relief of cancer pain.

Controversially (Robb et al., 2007), recruited 41 women with chronic pain following breast cancer treatment, and outcome measures included pain report, pain relief, pain interference, anxiety and depression.

There was little evidence to suggest that TENS or TSE were more effective than placebo. All three interventions had beneficial effects on both pain report and quality of life, a finding that may be due to either psychophysical improvements resulting from the personal interaction involved in the treatment or a placebo response, and concluded the TENS or TSE needs more research to prove the effectiveness of this method in managing cancer related pain in breast cancer.

To effective pain management among health care provider the patients play a crucial role in their pain management team because pain management consists of a multidisciplinary team that focuses on patients who are suffering from cancer related pain. (Chou et al., 2011) the researcher recruited 122 patients to evaluate the effectiveness of a pain education program to increase the satisfaction of patients with cancer and to examine how patient satisfaction with pain management mediates the barriers to using analgesics and analgesic adherence. The experimental group showed a significant improvement in the level of satisfaction they felt for physicians and nurses regarding pain management. For those in the experimental group, satisfaction with pain management was a significant mediator between barriers to using analgesics and analgesic adherence.

It is important for health providers to consider patient satisfaction when attempting to improve adherence to pain management regimes in a clinical setting. Moreover (Thomas et al., 2012) recommended nursing staff use an educational program to manage cancer pain based in this study where patients show more control of pain and reduced demand for opioids to control pain or to reduce side effect of opioids. There is a need for more research on educational programs to manage cancer pain in order to determine the type of intervention that helps patients to manage cancer pain in different types of cancer disease.

The level of evidence for the use of acupuncture and massage for the management of preoperative symptoms in cancer patients is encouraging but inconclusive.

We conducted a randomized, controlled trial assessing the effect of massage and acupuncture added to usual care vs. usual care alone in postoperative cancer patients. Cancer patients undergoing surgery were randomly assigned to receive either massage and acupuncture on postoperative Days 1 and 2 in addition to usual care, or usual care alone, and were followed over three days. Patients' pain, nausea, vomiting, and mood were assessed at four time points. Data on health care utilization were collected. Analyses were done by mixed-effects regression analyses for repeated measures. One hundred and fifty of 180 consecutively approached cancer patients were eligible and consented before surgery. Twelve patients rescheduled or declined

after surgery, and 138 patients were randomly assigned in a 2:1 scheme to receive massage and acupuncture (n=93) or to receive usual care only (n=45). Participants in the intervention group experienced a decrease of 1.4 points on a 0-10 pain scale, compared to 0.6 in the control group (P=0.038), and a decrease in depressive mood of 0.4 (on a scale of 1-5) compared to +/-0 in the control group (P=0.003).

Providing massage and acupuncture in addition to usual care resulted in decreased pain and depressive mood among postoperative cancer patients when compared with usual care alone. These findings merit independent confirmations using larger sample sizes and attention control. (Mehling et al., 2007).

Moreover to compare the efficacy of massage therapy (MT) in control of pain intensity, mood status, muscle relaxation, and sleep quality in a sample (n = 72) of Taiwanese cancer patients with bone metastases the researcher used a randomized clinical trial and found that it was statistically and clinically significant in control of pain among patients and in adding improvements in mood and relaxation over time, this study results support employing MT as an adjuvant to other therapies in improving bone pain management (Jane et al., 2011)

Beaton et al, in their systematic review found strong, high-quality evidence in favor of exercise interventions (aerobic exercises and strength training given alone or as part of a multimodal physical therapy intervention) in patients with metastatic cancer for improving physical and quality of life measures. (Beaton et al., 2009)

## Summary and Conclusions

Cancer related pain is still a permanent feared consequence for patients, their families, and health care providers. Thus, they need to be more effective method by a combination of pharmacological and non-pharmacological modalities; by using new methods to manage cancer related pain by providing a new opportunities for the patients to be more comfortable, improve quality of life, die with dignity and respect, and the health care provider needs to pay more attention and have familiarity with, and responsibilities toward these modalities for cancer patients.

The role of non-pharmacological modality in cancer pain management has an increasingly important contribution to provide holistic patient care as co-analgesics. There is evidence to support the use of patient education, cognitive behavioural therapy, relaxation, and music etc. Research on non-pharmacological modalities to cancer pain management is very important and essential.

Regarding pharmacological modality for cancer pain management many research studies recommended use of the WHO step ladder; research studies have shown effective pain management can be achieved in 90% of patients by using the WHO step ladder system. (Barakzoy and Moss, 2006).

Also, ketamine guideline, 2010 provides good opportunities to using ketamine as a third line to manage cancer related pain. (Palliative Care Guidelines: Ketamine in Palliative Care, 2013).

Pharmacological and non-pharmacological modalities give the opportunity for effective care to be provided to cancer patients. Also, these techniques may help in reducing pain and it must be encouraged as a part of the holistic cancer pain management efforts. From this point of view, it should be underlined for the patients and health care providers that these are used together as two modalities of treatment for management of cancer related pain.

## Recommendation

From this point of view, it is recommended to use various non-pharmacological methods for pain management but we need more research study results that support the efficiency of these methods. They need to conduct randomized controlled experimental studies, to examine the efficiency of these methods in cancer pain management. Also, it is recommended to use the WHO stepladder for pharmacological modality as a first line to manage cancer related pain.

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