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Editorial

Dear Readers,

The Editorial Board of ijopp wishes all the readers a very Happy and Prosperous New Year 2010!

We are mostly getting articles from academicians of Pharmacy Colleges. We also invite medical college students and teaching hospital faculty to contribute original research work. We would appreciate review /research articles from the industry colleagues as well. As we have a wide readership from academia, industry and hospital, we would like to publish articles catering to all the three sections.

We are looking forward for some interesting and informative research articles this year.

As the subscription has come to an end, we request all the subscribers to renew their subscription for this year.

Please give your feedback for the improvement of the journal.

Dr. Shobha Rani R.Hiremath
Editor-in-chief

Depressive Illness and Role of Pharmacist: An Overview

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INTRODUCTION

Depression is a "whole-body" illness, involving your body, mood, and thoughts. It affects the way you eat and sleep, the way you feel about yourself, and the way you think about things. People with a depressive illness cannot merely "pull themselves together" and get better. Without treatment, symptoms can last for weeks, months, or years. Appropriate treatment, however, can help most people who suffer from depression.

Depression causes changes in thinking, feeling, behavior, and physical well being. **Changes in Thinking**

- You may experience problems with concentration and decision-making. Some people report difficulty with short-term memory, forgetting things all the time. Negative thoughts and thinking. Some people have self-destructive thoughts during a more serious depression.

Changes in Feelings - Feel sad for no reason at all. Some people report that they no longer enjoy activities that they once found pleasurable, lack motivation, tired all the time. Sometimes irritability is a problem, in the extreme, depression is characterized by feelings of helplessness and hopelessness.

Changes in Behavior - Changes in behavior during depression are reflective of the negative emotions being experienced. You might act more apathetic; some people do not feel comfortable with other people, so social withdrawal is common. Patients may experience a dramatic change in appetite, either eating more or less. Because of the chronic sadness, excessive crying is common, lack of sexual activity.

Changes in Physical Well-being - Negative physical emotions. Chronic fatigue, despite spending more time sleeping, is common. Some people can't sleep, or don't sleep soundly. Others sleep many hours, even most of the day, although they still feel tired. Many people lose their appetite, feel slowed down by depression, and complain of many aches and pains.

Causes of depression:

Very often, a combination of biological, psychological, and environmental factors are involved in the

development of depressive disorders, as well as other psychological problems. A serious loss, chronic illness, relationship problems, work stress, family crisis, financial setback, or any unwelcome life change can trigger a depressive episode.

Types of depression:

There are several different diagnoses for depression, mostly determined by the intensity of the symptoms, the duration of the symptoms, and the specific cause of the symptoms, if that is known.

- Major Depression - This is the most serious type of depression, in terms of number of symptoms and severity of symptoms. There is no official diagnosis of "moderate depression."
- Dysthymic Disorder - This refers to a low to moderate level of depression that persists for at least two years, and often longer. While the symptoms are not as severe as a major depression, they are more enduring and resistant to treatment.
- Unspecified Depression - It includes people with a serious depression, but not quite severe enough to have a diagnosis of a major depression. It also includes people with chronic, moderate depression.
- Adjustment Disorder, with Depression - This category describes depression that occurs in response to a major life stressor or crisis.
- Bipolar Depression - This type includes both high and low mood swings, as well as a variety of other significant symptoms not present in other depressions.

Prevalence of depressive illness:

International Scenario:

In 2002, depression accounted for 4.5% of the worldwide total burden of disease (in terms of disability-adjusted life years). It is also responsible for the greatest proportion of burden attributable to non-fatal health outcomes, accounting for almost 12% of total years lived with disability worldwide²⁷.

National Scenario:

The Prevalence rates for all mental disorders were observed to be 65.4 per 1000 population. Prevalence rates for schizophrenia, affective disorders (depression), anxiety neurosis, hysteria and mental retardation were 2.3, 31.2, 18.5, 4.1 and 4.2 per 1000 population

respectively. The urban morbidity rate was 2 per 1000 higher than the rural rate²⁸.

Treatment for Depression

Psychotherapy

Psychotherapy assists the depressed individual in several ways. First, supportive counseling helps ease the pain of depression and the feelings of hopelessness are addressed. Second, cognitive therapy changes the pessimistic ideas, unrealistic expectations, and overly critical self-evaluations. Cognitive therapy helps the patient recognize which life problems are critical, and which are minor. It also helps to develop positive life goals, and a more positive self-assessment. Third, problem-solving therapy changes the stress creating areas of the person's life that are significant, and contributing to the depression. Behavioral therapy may require developing better coping skills, or interpersonal therapy, to assist in solving relationship problems.

Antidepressant Medications

There are a number of different types of antidepressant medications available. They differ in their side effects and, to some extent, in their level of effectiveness. Tricyclic antidepressants used to be the most commonly used medications for treatment of major depressions. Monoamine oxidase inhibitors (MAOIs) were often used for "atypical" depressions in which there are symptoms like oversleeping, anxiety, panic attacks, and phobias. More recently, newer antidepressants have been developed. Several of them are called "selective serotonin reuptake inhibitors" (SSRIs). Some examples of SSRIs are fluoxetine, fluvoxamine, paroxetine, and sertraline. Though structurally different from each other, all the SSRI antidepressant effects are due to their action on one specific neurotransmitter, serotonin. The FDA has also approved two other antidepressants that affect two neurotransmitters serotonin and norepinephrine. They are venlafaxine and nefazodone. All of these newer antidepressants seem to have less bothersome side effects than the older tricyclic antidepressants.

Another of the newer antidepressants, bupropion, is chemically unrelated to the other antidepressants. It has more effect on norepinephrine and dopamine than on serotonin. Bupropion has not been associated with weight gain or sexual dysfunction. It is contraindicated for individuals with, or at risk for, a seizure disorder or who have been diagnosed with bulimia or anorexia nervosa.

Role of Pharmacist

In recent years it is found that, the pharmacist services are not only restricted to drug storage and dispensing, but

also extended to the clinical activities like treatment monitoring, identifying and reporting of adverse drug reactions, patient education and counseling and also treatment planning and management.

The pharmacist mediated intervention and counseling about medication has led to significant improvement in the quality of health care and the patients now restore great faith and confidence in their pharmacists for proper and safe use of medication. Drug cannot achieve its therapeutic goal unless it is correctly prescribed, dispensed and accurately administered. This chain of responsibilities demands adequate knowledge on the part of the physician, the pharmacist, the nurse and the patient. Unfortunately, we often overlook the educational requirement of the patient and the significance of his own contribution to the success of drug therapy. Unless and until the patient learns and is motivated to take the right drug, at right time, in the right amount and for the right duration it will not be possible for rational therapy to become a reality of our health care system with enhanced level of education and awareness, patients have become cognizant of their right to make decisions regarding their drug therapy. From patient's point of view there are some basic questions, which need answer and counseling².

As pharmacist is the last health professional to come into contact with the patients, has vital role to play in patient education on drug use. Pharmacists are clearer in their instructions than physicians. Ninety percent of patients who needed more information on their medicines, besides its frequency of use, did not receive it³.

Due to lack of information or the negative attitudes of patients and health care providers, patients fail to follow drug regimens. The most patients did not ask for information about their treatment because they felt their health careers had little time for such matters⁴.

The specialized skills of clinical pharmacists have proved to be beneficial for improving treatment outcomes in a variety of health care settings. Because of their skills in identifying drug interactions, their excellent position of direct patient contact and their trust by patients, pharmacists can help patients remove evident adherence barriers and incorporate interventions into the care of their patients⁹.

The pharmacist can play important role in the management of depression with respect to below mentioned aspects.

Adverse Drug Reaction Monitoring

Study described that, pharmacist has reported 403 findings in which 47% of the findings were related to

potential adverse effects; 55% were suspected adverse drug reactions; potential interactions were 37% and 25% of people taking additional drugs, which are unknown to their physician. People taking psychotropic drugs for mental illness may be particularly susceptible to adverse drug events. The World Health Organization (WHO) has recognized including pharmacists as active members of the health care team as one approach to improving psychotropic medication use.⁵

Medication adherence and non-compliance

Non-adherence rate for antidepressants is 30-97% and side effects are common cause for non-adherence. Predicted and cognitive behavioral techniques are more successful than that of simple psycho educational interventions⁷.

Brief coaching by pharmacist with the help of informative videotape neither adherence to antidepressants nor depressive symptoms have improved in the initial sample. However, significantly better adherence was seen in patients who received care according to the intended protocol than the control group⁸.

The medication adherence rate is poor in psychiatric patients, which has led the healthcare providers to focus on enhancing intervention methods. Numerous intervention approaches have suggested that enhanced depression intervention with psychotherapy education is effective^{9,10}.

Studies showed that pharmacist's medication counseling and treatment monitoring could improve adherence to antidepressant medications among those commencing treatment. The results of this review provide some evidence that pharmacist can contribute to optimizing the use of medications for mental illness in the community setting¹¹.

Clinical pharmacist intervention in depressive patients explained that 42.2% of all encounters with patients involved counseling and education related to non antidepressant medication; 85% of encounters involved some general support activity and 50% of all encounters are of education and advocate starting antidepressants. Pharmacists spent considerable time with patients discussing their care unrelated to medication taking and also noticed some barriers to medication taking which were not evident earlier. Patients then revealed valuable information about side effects and non-adherence not discussed in their primary care physician visit¹².

Meta analysis of studies explored that out of 17 studies, 13 studies measured adherence, 7 of them reported an

increase in adherence. 11-30% higher adherence was in the intervention group. The provision of easily readable written information improved adherence by 11%. Seven of the eight studies measuring knowledge reported an overall improvement. 14-28% knowledge was increased in intervention group in comparison with control group.

One study reported an increase in satisfaction¹³.

One of the study enlightened long treatment duration, incidence of adverse effects, patients' belief that drug is not effective, poor communication between the practitioners and the patients as the major factors for non-adherence. Further it was revealed that counseling, monitoring and education showed minor effects and counseling and written or oral education can improve adherence from 0 to 44%¹⁴.

Review article on the effects of pharmacist intervention on depression medication adherence described as, in order for the medications to work patients have to take antidepressants for longer term, lack of this information may result lower rates of adherence. When patients do not see the effects immediately they may stop taking medications. Patients educated adequately on drug information will improve adherence, and pharmacist can play a better role than other healthcare providers in drug counseling¹⁵.

Patient's understanding of disease and its management

Pharmacist can provide education to patients during dispensing as well as during discharge medication counseling. Studies have demonstrated a variety of favorable outcomes like increased knowledge about illness, improved adherence to treatment, patient satisfaction, enhanced patient self rating, decreased negative symptoms and fewer side effects for patients who received education compared to those not educated. Psychiatric patient education is a rapidly growing field; it is becoming widely recognized as essential to the treatment process for serious mental illnesses. The specialized skills of clinical pharmacists have proved to be beneficial for improving treatment outcomes in a variety of health care settings. Because of their skills in identifying drug interactions, their excellent position of direct patient contact and their trust by patients, pharmacists can help patients remove barriers to adherence¹⁶.

Physician provides limited information to patients while prescribing antidepressants, often omitting critical information that may promote adherence. Mechanisms are needed to ensure that patients received pertinent

antidepressant information¹⁷.

Study on patients attitude about medication and factors affecting medication compliance showed that, out of 148 psychiatric patients, 87 patients have positive attitude about medication; 40 believed that their illness was biologically or chemically based; a large proportion believed their illness is due to situational factors, including stress (36) and family problems (18); 51 patients said they need medications to get better¹⁸.

A survey to investigate the psychiatric patients concerns, difficulties and needs in the community regarding their medication described that, out of 83 people 62% felt they had not received adequate information about their medicines and 73% considered that having access to information would improve their confidence in medicines¹⁹.

Pharmacist telemonitoring of antidepressant use showed that pharmacist guided education and monitoring had significant and positive effect on patient feedback, knowledge, medication belief and perceptions of progress. Antidepressant telemonitoring by community pharmacists can significantly and positively affect patient feedback and collaboration with pharmacists²⁰.

Coaching by community pharmacists on drug attitude of depressive primary care patients and acceptability to patients, on drug use, side effects, time taken by drug to work and other counseling. Intervention patients had more positive drug attitude than control patients and a positive attitude towards antidepressants may improve adherence rate²¹.

An evaluation of 155 primary care patients found that 28% of patients stopped taking their antidepressants within first month of therapy, and 44% had stopped by the third month. 62% did not like the side effects, 56% believed they did not need medication, 50% felt better, and 32% felt it was not effective. Such evidence confirms the large gap between ideal drug therapy and the actual use of antidepressants. Many patients do not intentionally subvert their antidepressant drug therapy, but they may often make poor decisions about their treatment due to lack of information and misconceptions about disorder, symptoms and drug therapy. Adequate patient education is critical to minimize some of these barriers to optimal outcomes. Clinicians, including pharmacists can help improve outcomes by increased patient education and more collaborative participation in their treatment²².

Study on long stay psychiatric patients knowledge and experience in the use of their antipsychotic medication

found that, most patients were aware that they have been prescribed antipsychotic drugs for their mental illness but they did not believe the explanation given to them by their psychiatrist. Patients had relatively little knowledge of the side effects of these drugs and many did not recognize the side effects as being due to medication. Just over half of the patients requested more information about their medication. Patients' knowledge of their medication, including side effects is limited and could be improved by patients' education. There is a need for a greater awareness and treatment of the side effects experienced by patients²³.

Patient care

Pharmacists significantly improved rates of antidepressant use in primary care patients, but outcome differences were too small to be statistically significant. Difficult to treat subgroups may benefit from pharmacist care²⁴.

Alleviating suicidal tendencies in depression patients

Monitoring of patients' antidepressant knowledge, beliefs, adherence, improvement in depression symptoms and orientations towards treatment progress, concludes that pharmacists could significantly and positively affect patient feedback and collaboration. Since patients usually see their pharmacist more often than their physician, pharmacists can play a significant role in suicide prevention²⁵.

Patient's reliance on Pharmacist

Pharmacist monitoring of patients antidepressant medication use is varied. More than 70% of patients reported that pharmacists asked about medication concerns; 53% of patients said pharmacists encouraged their questions; 54% said pharmacist listened to their concerns; and 32% patients said pharmacists are helpful in solving problems related to the antidepressants; 57% of patients reported that they feeling better since the time they taking antidepressants; 40% of patients said the antidepressants did not bother them; and 83% reported missing, adding or stopping of drugs during the study period²⁶.

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Uterine Fibroids: A Review

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Abstract

Uterine fibroids or Leiomyomas are benign tumors of uterus. Genetic abnormalities, alteration in growth factor (proteins formed in the body that direct the rate and extent of cell proliferation) expression, abnormalities in the vascular (blood vessel) system, and tissue response to injury have all been suggested to play a role in the development of uterine fibroids. Every year thousands of women hear the frightening diagnosis of fibroids in the uterus. In most of the women, uterine fibroids are caused when exposed to high levels of toxins, these toxins are artificial chemicals that are structurally similar to the Estrogen, naturally found in the human body. The present review focuses on the pathology, diagnosis, histology, medication options and surgical treatment of fibroids.

Key words: Estrogen, fibroids, tumors

INTRODUCTION

Uterine fibroid also referred to as uterine leiomyomata, uterine leiomyomas or uterine myomas are benign growth of womb (uterine) muscle, they are composed of smooth muscle layer accompanying connective tissues of the uterus¹. Most leiomyomas occur in the fundus and body of the uterus; only 3% occur in the cervix. They are most common towards the end of the reproductive years. They exist sometimes singly but most often are multiple, or diffuse and if the uterus contain too many leiomyomas to count, it is referred to as uterine leiomyomatosis². They are more common in obese women and probably some genetic determinant and they are less common in smokers. Majority of fibroids grow as a women gets older, and tend to shrink after menopause.³

ETIOLOGY AND PREVALENCE

The exact reason underlying in uterine fibroid remains unknown. National Institute of Child Health and human development (NICHD), part of the national institute of Health (NIH) within the US Department of health and Human service (DHHS), is trying to learn more about uterine fibroid, through research into their causes and treatments. As research works are done, NICHD scientists are exploring genetics, hormones, the immune system and environmental factors that may play a role in starting the growth of fibroids and or in continuing the growths. This information could lead to a cure for uterine fibroids that does not involve taking out of uterus. Someday, health care providers may even be able to prevent uterine fibroids from getting at all.⁴

Family history is a key factor, since there is often a history of fibroid developing in women of the same family. About 20 – 40 % of women will be diagnosed with leiomyoma.⁵ This condition is common in black women (3:1) than they do in white women (9:1)². Estrogen receptors on fibroid cause them to respond to estrogen stimulation during the reproductive years. During hypoestrogenic states such as after menopause, leiomyoma are expected to shrink. Leiomyoma are more common in overweight women because of increased estrogen from adipose aromatase activity.⁶ Researchers think that more than one factor could play a role.⁷ These factors could be:

✦ Hormonal (affected by estrogen and progesterone levels)

✦ Genetic (runs in families)

PATHOLOGY AND HISTOLOGY

Leiomyomas arise from the overgrowth of smooth muscle and connective tissue in the uterus. Histologically, a monoclonal proliferation of smooth muscle cells occurs. Estrogen and Progesterone receptors are present on fibroids. Elevated estrogen levels may cause fibroid enlargement. Infertility may occur as a result of narrowing of the isthmic portion of the fallopian tube or as a consequence of interference with implantation, especially interference caused by submucosal fibroids. Rarely, uterine leiomyoma may undergo malignant degeneration to become a sarcoma.²

Theories of fibroid formation

Until recently, the steroid hormones estrogen and progesterone were considered the most important

regulators of leiomyoma growth. There is abundant evidence that estrogen promotes fibroid growth including the clinical observations that fibroids grow in the presence of high levels of estrogen, such as during the reproductive years, and that they regress in the presence of low levels of estrogen, such as following menopause or during gonadotropin releasing hormone (GnRH) agonist therapy. Furthermore, fibroids have higher estrogen concentrations, bind more estrogen, have more estrogen receptors, and convert estradiol (a more active form of estrogen) to estrone (a less active form of estrogen) more slowly than normal myometrium.

Progesterone is also thought to play a role in fibroid growth. More specifically, clinical studies suggest progesterone facilitates the growth of fibroids. For example, fibroid size increases during treatment with synthetic progesterones. Combination GnRH agonist and progesterone therapy has been shown to have no effect on uterine volume, in contrast to GnRH agonist therapy alone which has been shown to reduce uterine volume. The observation that fibroids regress with the antiprogestosterone agent, RU-486, further supports the role of progesterone as a promoter of fibroid growth. Histologically, fibroids from patients treated with progesterone show more cellular growth than those from patients without progesterone therapy. Biochemically, fibroids have higher progesterone receptor concentrations than normal myometrium. Together, these data suggest that progesterone also enhances fibroid growth.

Other hormones such as growth hormone (GH) and prolactin (PRL) are also thought to promote fibroid growth, but their role is even less well defined.

More recently, growth factors, which are small proteins that affect cell growth, have been shown to mediate the growth-promoting effects of estrogen and to play an important role in the development of fibroid tumors. Potentially important factors in fibroid growth include transforming growth factor-beta, basic fibroblast growth factor, epidermal growth factor, insulin-like growth factor, and platelet-derived growth factor.

Overall, estrogen, progesterone, and growth factors likely promote tumor growth, but only after the initiation of tumor formation. This initiating event remains unknown, although recent evidence suggests there is a strong inherited component to fibroid development. Indirect evidence for this hypothesis is as follows. First, fibroids are at least twice as common in black women than in white women. Although racial differences in

socioeconomic status and access to health care, as well as racial differences in known risk factors for fibroids, may contribute to this finding, two recent studies suggest that these factors do not completely explain the discrepancy. Secondly, another study found a genetic predisposition for hysterectomy as indicated by a two fold higher twin pair correlation for hysterectomy in identical versus fraternal twins. Thirdly, there exists a rare heritable form of uterine fibroids in association with fibroids of the skin called Reed's syndrome. Finally, a recent Russian studies suggest that women with a family history of fibroids are twice as likely to develop fibroids than women with no family history. Unfortunately, few scientific studies directly examine the genetic component of fibroid development.

Recently, researchers at the Center for Uterine Fibroids have identified mutations in two genes, HMGI(C) and HMGI(Y), that appear to be important in the development of some fibroids. Normally, these genes code for proteins that help control cell growth by indirectly regulating DNA transcription. However, mutations in these genes are probably secondary changes in already genetically susceptible cells. Therefore, it is likely that other gene(s) crucial for fibroid development exist that have not yet been identified.⁸

Leiomyomas grossly appear as round, well circumscribed (but not encapsulated), solid nodules that are white or tan and show whorled appearance on histological section [Figure 1]. Microscopically, tumor cells resemble normal cells (elongated, spindle-shaped, with a cigar shaped nucleus) and form bundles with different (whorled). These cells are uniform in size and shape, with scarce mitosis.^{9,10}

TYPES OF UTERINE FIBROIDS

Growth and location are the main factors that determine if a fibroid leads to symptoms and problems.⁵ A small lesion can be symptomatic if located within the uterine cavity while a large lesion on the outside of the uterus may go unnoticed. Different locations [Figure 2] are classified as follows:

- Intramural fibroids are located within the wall of the uterus and are the most common type; unless they may be asymptomatic.
- Subserosal fibroids are located underneath the mucosal (peritoneal) surface of the uterus and can become very large. They can also grow out in papillary manner to become pedunculated fibroids. These pedunculated growths can actually detach from the uterus to become a parasitic leiomyoma.

Fig.1: Micrograph of a leiomyoma

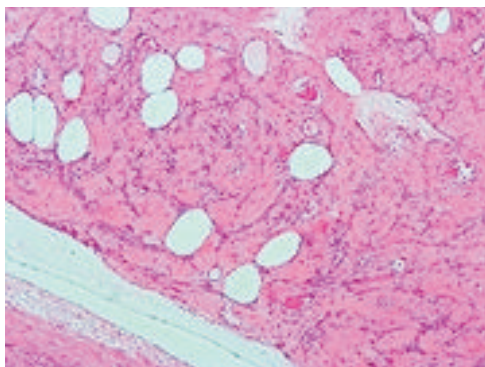
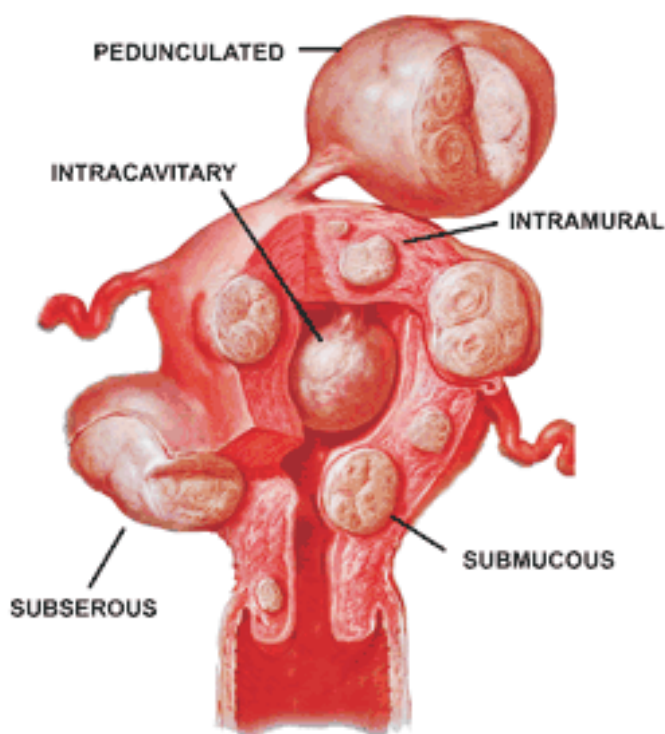


Fig.2: Types of Fibroids



- Submucosal fibroids are located in the muscle beneath the endometrium of the uterus and distort the uterine cavity; even small lesion in this location may lead to bleeding and infertility. A pedunculated lesion within the cavity is termed as intracavitary fibroid and can be passed through the cervix.
- Cervical fibroids are located in the wall of the cervix (neck of the uterus). Rarely fibroids are found in the supporting structures (round, ligament, broad ligament, or uterosacral ligament) of the uterus that also contain smooth muscle tissue.

Fibroids may be single or multiple. Most fibroids start in an intramural location that is the layer of the muscle of the uterus. With further growth, some lesions may develop towards the outside of the uterus or towards the internal cavity. Secondary changes that may develop within fibroids are hemorrhage, necrosis, calcification, and cystic changes.¹¹

SYMPTOMS OF UTERINE FIBROIDS

The most common symptoms of women with fibroids are pressure symptoms and heavy periods. An enlarged womb will place pressure on the bladder giving increased

symptoms.^{7]} Generally, symptoms include abnormal gynecologic hemorrhage, heavy or painful periods, abdominal discomfort or bloating, painful defecation, back ache, urinary frequency or retention and in some cases, infertility. There may be pain during intercourse, depending on the location of the fibroid. During pregnancy they may be miscarriage, bleeding, premature labor or interference with the position of the fetus.¹² While fibroids are common, they are not a typical cause for infertility, if a fibroid is located in a submucosal position and it is thought that this location may interfere with the function of the lining and the ability of the embryo to implant. Also larger fibroids may distort or block the fallopian tubes.¹³

DIAGNOSIS

The diagnosis is likely if bimanual pelvic examination detects an enlarged, mobile, irregular uterus that is palpable above the pelvic symphysis. Confirmation requires imaging. Gynecologic ultrasonography (ULTRASOUND) has evolved as the standard tool to evaluate the uterus for fibroids. Occasionally, when trying to determine if a fibroid is present in the uterine cavity (endometrial cavity), a hysterosalpingogram (HSG) is done. In this procedure, an ultrasound exam is done while contrast fluid is injected into the uterus from the cervix. The fluid is visualized in the endometrial cavity and thus outline any masses that are inside, such as submucosal fibroids. If ultrasonography is inconclusive, MRI, the most accurate imaging test, is done. Also magnetic resonance imaging (MRI) can be used to define the depiction of the size and location of the fibroids within the uterus.^{1,3,6}

FIBROID TREATMENT OPTIONS

Choice of treatment

Treatment should be individualized, but some factors can help with the decision:

- ☞ Asymptomatic fibroids: No treatment.
- ☞ Postmenopausal women: Trial of expectant management (because symptoms tend to remit as fibroids regress)
- ☞ Surgically accessible symptomatic fibroids, particularly if conception may be desired: Myomectomy
- ☞ Symptomatic fibroids that are not clearly surgically accessible: Uterine artery embolization or another new technique (eg, high-intensity focused sonography)
- ☞ Intolerable symptoms when other treatments were ineffective, particularly if conception is not desired: Hysterectomy, possibly preceded by drug therapy (eg,

with GnRH analogues)¹⁴

Obviously fibroids that are causing significant symptoms need treatment.

Non-surgical Treatment

Non-surgical techniques are usually hormonal in nature and include the use of drugs

- ☞ Gonadotropin-releasing hormone analogs (GnRH analogs) are the drugs that turn off the production of estrogen from the ovaries which are given for three to six months, if successful, they can shrink fibroid upto 50% and may cause osteoporosis.¹
- ☞ Aromatase inhibitors and Progesterone have been used experimentally to reduce the size of fibroids.
- ☞ Mifepristone is an antiprogestin drug which reduce the bleeding associated with fibroids, but associated with side effects such as overgrowth (hyperplasia) of the endometrium (uterine lining)¹. It was effective in a placebo-controlled pilot study.¹⁵
- ☞ Danazol (Danocrine) is an androgenic steroid hormone that has been used to reduce bleeding in women with fibroids, since the drug cause menstruation to cease. However, danazol does not appear to shrink the size of fibroids.
- ☞ Raloxifene (Evista) used to prevent and treat osteoporosis and reduce the size of fibroids in postmenopausal women.¹
- ☞ Low dose formulations of oral contraceptives pills, either combination pills with estrogen or progestin-only are prescribed to reduce uterine bleeding and cramps associated with fibroids.¹³
- ☞ Drugs which lower oestrogen levels may be used to shrink or temporarily halt fibroid growth, particularly before surgery. However, since the drugs often cause menopause-like symptoms such as hot flushes, vaginal dryness and decrease bone density. A course of treatment usually lasts only three to six months. Fibroids often continue growing once hormone therapy stops.¹⁶
- ☞ HIFU (High intensity focused ultrasound), also called Magnetic Resonance guided Focused Ultrasound (MRgFUS), is a non-invasive intervention that uses high intensity focused ultrasound waves to ablate (destroy) tissue in combination with Magnetic Resonance Imaging (MRI), which guides and monitors the treatment. This technique is relatively new; it was approved by the FDA in 2004.¹⁷ This cutting-edge technology, which offers women the option of same-day, non-surgical treatment. With increasing availability of conservative treatment choices, both patients and their physicians have the opportunity to

individualize therapy based on the goals of each patient¹⁸

✍ **Surgical Treatment**

Surgical removal of a uterine fibroid usually takes place via hysterectomy, in which entire uterus is removed, or myomectomy, in which only the fibroid is removed. It is possible to remove multiple fibroids during a myomectomy. Although a myomectomy cannot prevent the recurrence of fibroids at a later date, such surgery is increasingly recommended, especially in the case of women who have not completed bearing children or who express an explicit desire to retain the uterus. Myomectomy can be done through three different ways:

- Hysteroscopic myomectomy – Fibroid removed by the use of a resectoscope, an endoscopic instrument with a built in loop that can use high frequency electrical energy to cut tissue with either local or general anesthesia used. It is not recommended for submucosal fibroids. A French study collected results from 235 patients suffering from submucous myomas who were treated with hysteroscopic myomectomies; in none of these cases was the fibroid greater than 5 cm.¹⁹

- Laparoscopic myomectomy - It requires standard open incision into the uterus with the help of laparoscope to remove the fibroids. It is easier to remove when they are on a stalk or close to the surface. The advantage is that it lowers morbidity rates and faster recovery than laparotomic myomectomy.²⁰

- Laparotomic myomectomy – Also known as open or abdominal myomectomy is the most invasive surgical procedure to remove fibroids. Here the incision is made in the abdominal wall to remove fibroid from uterus. A particularly extensive laparotomic procedure may necessitate that any future births be conducted by Caesarean section.¹³

- Endometrial Ablation – The lining of the uterus is removed or destroyed to control heavy bleeding. This can be done with laser, wire loops, boiling water, electric current, freezing and other methods. About three in ten women have much lighter bleeding. But, a women cannot have children after this surgery.

- Myolysis – Needle is inserted into the fibroids usually guided by laproscopy, and electric current or freezing is used to destroy the fibroids.⁷

- Uterine artery embolization (UAE) – Using intervention radiology techniques, small beads of a compound called polyvinyl alcohol, which are

injected through a catheter into the arteries that feed the fibroid, these beads obstruct the blood supply to the fibroid and starve it of blood and oxygen¹. UAE results in the supposed shrinking of the fibroid and the uterus, thus alleviating the symptoms. However, it is important to note that significant adverse effects resulting from uterine artery embolization have been reported and documente in the medical literature including death, infection, misembolization, loss of ovarian function, unsuccessful fibroid expulsion, pain, foul vaginal odor, hysterectomy, and failure of embolization surgery^{5,6}

- Uterine artery occlusion (UAO) – It involves clamping the involved uterine arteries as opposed to injecting the polyvinyl alcohol beads, is currently under investigation as a potential alternative to UAE.¹

CONCLUSION

Despite the major public health impact of leiomyomas, little is known about their cause. Researchers are studying families with at least one pair of siblings affected by fibroids to search for gene(s) that predispose women to fibroid development. Ultimately, understanding the hormones, growth factors, and gene(s) involved in the formation and growth of fibroid tumors may lead to innovative, less invasive treatment options. Management depends on the symptoms, location and size of the fibroids, and the patient's desire to conceive.

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Menstrual Blood: A Valuable Source for Regenerative Medicine

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Abstract

Menstrual blood is a rich source of stem cells, the endometrium-lining of the uterus regenerates every month. Research on stem cells provides knowledge about how healthy cells replace damaged ones in adults, leading to the possibility of cell-based therapy to treat diseases. Menstrual Stem Cells (MenSCs) show multipotency by directionally differentiating into chondrogenic, adipogenic, osteogenic, neurogenic, and cardiogenic cell lineages. These studies demonstrate the plasticity of MenSCs for potential research in regenerative medicine. Researchers seeking new and more abundant sources of stem cells for use in regenerative medicine have identified a potentially unlimited, noncontroversial, easily collectable, and inexpensive source- menstrual blood.

Keywords: Menstrual Blood, stem cell, MenSCs, Regenerative Medicine

Reproductive development in woman

When a baby girl is born, she has all the eggs her body will ever use, and many more, perhaps as many as 450,000. They are stored in her **ovaries**, each inside its own sac called a **follicle**. As she matures into puberty, her body begins producing various hormones that cause the eggs to mature. This is the beginning of her first cycle; it's a cycle that will repeat throughout her life until the end of menopause¹.

The hypothalamus is a gland in the brain responsible for regulating the body's thirst, hunger, sleep patterns, libido and endocrine functions. It releases the chemical messenger **Follicle Stimulating Hormone Releasing Factor (FSH-RF)** to tell the **pituitary**, another gland in the brain, to do its job. The pituitary then secretes **Follicle Stimulating Hormone (FSH)** and a little **Leutenizing Hormone (LH)** into the bloodstream which cause the follicles to begin to mature.

The maturing follicles then release another hormone, **estrogen**. As the follicles ripen over a period of about seven days, they secrete more and more estrogen into the bloodstream. Estrogen causes the lining of the uterus to thicken. It causes the cervical mucous to change. When the estrogen level reaches a certain point it causes the hypothalamus to release **Leutenizing Hormone Releasing Factor (LH-RF)** causing the pituitary to release a large amount of **Leutenizing Hormone (LH)**. This surge of LH triggers the one most mature follicle to burst open and release an egg. This is called ovulation

Ovulation

As ovulation approaches, the blood supply to the ovary increases and the ligaments contract, pulling the ovary closer to the Fallopian tube, allowing the egg, once released, to find its way into the tube. Just before ovulation, a woman's cervix secretes an abundance of clear "fertile mucous" which is characteristically stretchy. Fertile mucous helps facilitate the sperm's movement toward the egg. Some women use daily mucous monitoring to determine when they are most likely to become pregnant. Mid cycle, some women also experience cramping or other sensations. Basal body temperature rises right after ovulation and stays higher by about 4 degrees F until a few days before the next period².

Uterine Changes

Between midcycle and menstruation, the follicle from which the egg burst becomes the corpus luteum (yellow body). As it heals, it produces the hormones oestrogen and, in larger amounts, progesterone which is necessary for the maintenance of a pregnancy. In the later stages of healing, if the uterus is not pregnant, the follicle turns white and is called the corpus albicans. Oestrogen and progesterone are sometimes called "female" hormones, but both men and women have them, just in different concentrations. Progesterone causes the surface of the uterine lining, the endometrium, to become covered with mucous, secreted from glands within the lining itself. If fertilization and implantation do not occur, the spiral arteries of the lining close off, stopping blood flow to the surface of the lining. The blood pools into "venous lakes" which, once full, burst and, with the endometrial lining, form the menstrual flow. Most periods last 4 to 8 days

Menstruation

Menstruation is the shedding of the uterine lining (endometrium). It occurs on a regular basis in reproductive-age females of certain mammal species. The **menstrual cycle** is a cycle of physiological changes that occurs in fertile females. Overt menstruation (where there is bleeding from the uterus through the vagina) is found primarily in humans and close evolutionary relatives such as chimpanzees³. The females of other placental mammal species have estrous cycles, in which the endometrium is reabsorbed by the animal (covert menstruation) at the end of its reproductive cycle.

Menstruation is the most visible phase of the menstrual cycle. Menstrual cycles are counted from the first day of menstrual bleeding, because the onset of menstruation corresponds closely with the hormonal cycle.

During pregnancy and for some time after childbirth, menstruation is normally suspended; this state is known as amenorrhoea, i.e. absence of the menstrual cycle. If menstruation has not resumed, fertility is low during lactation. The average length of postpartum amenorrhoea is longer when certain breastfeeding practices are followed; this may be done intentionally as birth control (lactational amenorrhoea method).

The menstrual cycle, under the control of the endocrine system, is necessary for reproduction. It is commonly divided into three phases: the follicular phase, ovulation, and the luteal phase; although some sources use a different set of phases: menstruation, proliferative phase, and secretory phase⁴. The length of each phase varies from woman to woman and cycle to cycle, though the average menstrual cycle is 28 days⁵. Hormonal contraception interferes with the normal hormonal changes with the aim of preventing reproduction.

Stimulated by gradually increasing amounts of estrogen in the follicular phase, menses slow then stop, and the lining of the uterus thickens. Follicles in the ovary begin developing under the influence of a complex interplay of hormones, and after several days one or occasionally two become dominant (non-dominant follicles atrophy and die). Approximately mid-cycle, 24–36 hours after the Luteinizing Hormone (LH) surges, the dominant follicle releases an ovum, or egg in an event called ovulation. After ovulation, the egg only lives for 24 hours or less without fertilization while the remains of the dominant follicle in the ovary become a corpus luteum; this body

has a primary function of producing large amounts of progesterone. Under the influence of progesterone, the endometrium (uterine lining) changes to prepare for potential implantation of an embryo to establish a pregnancy. If implantation does not occur within approximately two weeks, the corpus luteum will involute, causing sharp drops in levels of both progesterone and estrogen. These hormone drops cause the uterus to shed its lining in a process termed menstruation.

The menstrual cycle can be divided into several different phases. The average length of each phase is shown below **assuming a 28-day cycle**:

Name of phase	Average start day	Average end day
Menstrual phase (menstruation)	1	4
Proliferative phase (some sources include menstruation in this phase)	5	13
Follicular phase	1	13
Ovulatory phase (ovulation)	14	14
Luteal phase (also known as secretory phase)	15	28
Ischemic phase	27	28

In the menstrual cycle, changes occur in the female reproductive system as well as other systems (which lead to breast tenderness or mood changes, for example). A woman's first menstruation is termed menarche, and occurs typically around age 12. The end of a woman's reproductive phase is called the menopause, which commonly occurs somewhere between the ages of 45 and 55.

Menstruation is also called **menstrual bleeding**, **menses**, **catamenia** or a **period**. The flow of menses normally serves as a sign that a woman has not become pregnant. (However, this cannot be taken as certainty, as a number of factors can cause bleeding during pregnancy; some factors are specific to early pregnancy, and some can cause heavy flow)^{6,7,8}. During the reproductive years, failure to menstruate may provide the first indication to a woman that she may have become pregnant.

Bleeding - A New Theory

Some researchers view menses as the natural monthly cleansing of the uterus and vagina of sperm and bacteria they carried.

Ingesting Menstrual Blood

In the African-American hoodoo tradition, as well as in Sicilian folk-magic, menstrual blood served to a man in his coffee or tea is a sovereign recipe for capturing his sexual attention. No ritual, prayer, or invocation is necessary; simply adding some menstrual blood to the man's coffee or tea. The idea is to get her scent into the beloved's sphere of consciousness. This is nothing more or less than pheromone-magic, and as such it partakes of biology as much as it does of occultism⁹.

Menstrual Extraction

Menstrual extraction is a simple suction technique used to remove the menstrual blood from the uterus on the first day of menstruation. It can remove a fertilized egg from the uterus. A menstrual extraction can be performed by removing the rest of the retained tissue and the uterus can be able to clamp down and slow the bleeding to an acceptable level. It is usually done by an experienced group of women, as a home-care procedure in order to gain knowledge about their bodies and menstrual cycles and to exert more direct control over their reproductive cycles. The procedure is very safe; in reality it can be safer than a clinical abortion, when done correctly by a group with experience. There is no waiting for weeks as in a clinical abortion. Due to the early timing the cervix does not need to be dilated (forced open) because the smallest size canula can be used. The contents of the uterus are gently sucked out; there is no cutting or scraping of the uterine wall necessary. The contents consist of mostly blood, chorionic villi and some tissue, the amount of tissue depends on how far along the pregnancy is, the rapidly dividing cell structure is still too small to be seen.

Because the cervix is not dilated this means technically it is safe (but not advisable) to take a bath, to make love or to use a tampon. After a clinical abortion, if you do any of these things it could give you a nasty uterine infection, which is why they give women antibiotics after a clinical abortion. When the cervix is dilated the trap door of the cervix is unable to close to protect the uterus from the outside world¹⁰.

There are no drugs given. Allowing the woman to stay in touch with what is happening to her body. She is in control. She can stop at any time to take a break. The whole process could take an hour, or up to 3 hours. For every woman it is different. For some women it is mildly uncomfortable and other women experience more severe cramping, nausea, or dizziness, the experience is different for each woman.

Menstrual extractions can be done safely up to 8-9 weeks from the last menstrual period. The sooner it is done the less intense it is physically, it can be done when menstruation is due, up until 8-9 weeks from the last menstrual period. After 9 weeks the tissue is too large for the canulas used in the menstrual extraction kits. The risk of incomplete extraction can occur thus increasing the risk for possible hemorrhage or infection¹¹.

Cell Procurement and Processing

An endometrial/menstrual cell sample was procured during the first few days of a menstrual cycle. The cells were harvested with the informed consent of the donor as approved by institutional review board. The cells were transferred in phosphate-buffered saline (PBS) with penicillin/streptomycin and heparin. The sample was shipped at 4°C until it reached the processing laboratory within 24–48 h after procurement. The sample was centrifuged and supernatant was evaluated for bacteria and the cells were then cultured¹².

Stem Cells in Menstrual Blood

The feasibility of using stem cells for regenerative therapies is limited by two factors: obtaining a significant number of cells and doing so in a relatively noninvasive manner. Because our bodies freely shed a limited and select number of cells, many stem cell types must be obtained using a rather invasive procedure. Stem cell research is undoubtedly a hot and controversial topic with people nation-wide as well as internationally. The topic only grew more heated when a ban on federal funding human embryonic stem cell research and promised to remove all ideology from scientific studies. However, no matter what your position on stem cell research is, it can undoubtedly mean great things for the health industry and go on to cure many illnesses and diseases, such as diabetes, cardiac, stroke, vascular regeneration, and many cancers.

It has been hypothesized that menstrual blood contains a viable source of stem cells to be utilized or preserved for future use, providing an ideal source for a vast range of stem cell research and therapies. However, two laboratories independently reported the discovery of a new type of stem cell that may overcome both obstacles; stem cells were found to reside in menstrual blood^{13,14}. Researchers suspected stem cells to be present in menstrual blood because stem cells were previously found to be present in the lining of the uterus. The wall of the uterus is lined by a layer of cells called the endometrium (Fig. 1). To create ideal conditions for the uterus to accept and nurture an embryo, the endometrium

lining becomes thicker and increases the number of blood vessels and glands within it. However, if implantation does not occur, the endometrium lining is broken down and shed. Overall, the endometrium is quite a hyperproliferative tissue, continuously being broken down and rebuilt; it is an ideal tissue to investigate for the presence of stem cells. In the menstrual cycle, the shedding is known as menstruation, or menstrual bleeding; the excreted menstrual blood is made up of blood as well as cells from the endometrium layer. Researchers previously reported the presence of stem cells in the intact endometrium lining of the uterus^{15, 16, 17}. Because stem cells were found in the endometrium, researchers thought it likely that stem cells could also be found in the shed endometrium in the form of menstrual blood, which can be obtained in relatively large quantities in a much less invasive manner. However, the stem cells discovered in menstrual blood, MenSCs, appear to be rather different from stem cells derived from the intact endometrium.

Menstrual blood contains millions of adult stem cells that demonstrate properties similar to bone marrow and embryonic stem cells. The stem cells found in menstrual blood rapidly multiply, turning into possibly every cell type in the human body. Whether you agree with stem cell research or not, everyone supports the research to cure many illnesses and diseases and retrieving stem cells from menstrual blood would not infringe upon anyone's moral code, considering that menstrual blood is something that arrives monthly for all women. These stem cells, termed menstrual stem cells (MenSCs), are not only harvested in a noninvasive manner and relatively readily available in large quantities, but they potentially overcome the problem of immune rejection in many female patients as well.

Compared with the stem cells from other sources, such as bone marrow and cord blood, menstrual stem cells are easier to collect, do not cause any harm or pain to the donor and can be collected for more than 35 years, from 12 years old to 47 years.

Experiments in lab dishes under the right conditions showed that, menstrual stem cells could turn into more different tissue types including bone, blood vessel, fat, brain, lung, liver, pancreas and heart than other adult stem cells. The new stem cells also grow readily and rapidly, which is an important advantage because it is difficult to get some types of adult stem cells to give rise to enough cells to be of any medical value.

While stem cells from the intact endometrium appear to

be mesenchymal stem cells (MSCs), MenSCs do not; they are distinctly different not only in their undifferentiated state, but in the cells they can differentiate into as well. Researchers categorize stem cells into certain groups based off of, among other factors, their cell morphology and the proteins they express. An established stem cell group usually expresses a distinct set of proteins. MenSCs, though morphologically appearing mesenchymal, were found to express only some, but not all, proteins characteristic of MSCs. Additionally, MenSCs were reported to be able to differentiate into, or become, cells from the three different germ layers: mesoderm (muscle, bone, fat, cartilage, and endothelial cells), ectoderm (neurons) and endoderm (liver, pancreas, and lung cells)^{13, 14}. However, the mesenchymal stem cells from the intact endometrium cannot generate cells from all three germ layers. Overall, MenSCs were determined to be functionally distinct from endometrium MSCs^{13, 18}.

The MenSCs expanded rapidly and maintained greater than 50 percent of their telomerase activity when compared to human embryonic stem cells and better than bone marrow-derived stem cells. Studies have demonstrated that MenSCs are easily expandable to clinical relevance and express multipotent markers at both the molecular and cellular level. Researchers emphasized the importance of the abundance and plasticity of MenSCs. Based on the results of their studies, they noted the potential for MenSCs in regenerative transplantation therapies for many different organs and tissues. The need for regenerative therapies using cells with the ability to engraft and differentiate is vast. The ideal cell would also have the ability to be used in an allogenic manner from donors for optimal immunogenic compatibility. Due to their ease of collection and isolation, MenSCs would be a great source of multipotent cells if they exhibit this property along with their ability to differentiate¹².

Though MenSCs do not appear to be MSCs, the stem cell category MenSCs best fall into still remains unclear, along with several other basic answers concerning their stem cell identity. In addition to MSC proteins, MenSCs were also negative for proteins characteristic of hematopoietic stem cells, which are cells that give rise to the hematopoietic system. However, MenSCs were, surprisingly, positive for some proteins distinctive of embryonic stem cells^{13, 14}. The expression of these embryonic stem cell proteins is quite unusual in adult stem cells, or stem cells derived from adult tissues, such

as MenSCs¹⁴. The presence of embryonic stem cell proteins in MenSCs, combined with ability of MenSCs to differentiate into the three germ layers, led one research group to label them pluripotent¹³, though others only refer to them as multipotent¹⁴. A pluripotent stem cell is generally one that is able to differentiate into cells from any of the three germ layers, while multipotent stem cells can only differentiate into cells from one or two of the germ layers. Most adult stem cells are only multipotent. If the MenSCs are indeed pluripotent, they may have a greater potential for cell-based therapies than if only multipotent.

Some reported characterization discrepancies of the MenSCs have led researchers to suspect that there may be a bit of variability in the quality of MenSCs isolated, possibly depending on many suspected factors, though none have been fully investigated yet. Since there was not a standard method of isolation in place for these cells, there could be great variability in the actual cells isolated depending on the specifics of the isolation method used. Additionally, the quality and potency of MenSCs isolated could depend on the individual donors, possibly being related to age or other factors, though this is currently untested¹⁹. In the menstrual blood, MenSCs make up a portion of the total cells present and are mainly selected for from this collection of cells by their ability to grow on tissue culture-treated plastic. Other cell populations within this fluid have not been fully investigated; it is quite possible that the subpopulations of cells in this fluid, including the MenSCs, may also vary significantly between donors¹⁹. To complicate the identity of these stem cells even further, it has been suggested that there may be multiple different stem cell populations in the menstrual blood, as researchers have had some conflicting protein expression results¹⁹. Lastly, the origin of these stem cells is still much up for debate. Some researchers theorize that the MenSCs are shed endometrium stem cells¹⁴, though, as discussed above, they are rather distinct from these cells, while other researchers hypothesize the MenSCs originate in the endometrial glands, as many glands are observed in menstrual blood¹⁸. With a better understanding of the origins of these cells in the body, and potential variability between donors, it will be easier to properly isolate the MenSCs for use in down-stream applications.

Though many questions remain to be answered to accurately characterize these newly discovered stem cells, a great amount of interest in using these cells for

regenerative therapies has already materialized. Researchers are currently looking into using MenSCs for treating neurodegenerative and cardiovascular diseases^{18,19} and salvaging limbs^{20, 21} among several other applications²². Preliminary clinical trials for treating multiple sclerosis in humans using MenSCs have already yielded some promising results²³. With additional studies of the cells in a variety of categories, the use of these cells may lead to treatments for a number of serious diseases, such as osteoporosis, stroke, Alzheimer's and Parkinson's disease. The cells may even one day be used for customized anti-aging or sports medicine treatments. Overall, MenSCs hold great promise as a significant reservoir of stem cells obtained in a noninvasive manner that can often be patient-specific, with some evidence even suggesting them to be immune privileged, or less likely to cause an immune reaction than other stem cells.^{19,23}

Advantages of Menstrual Stem Cells

- Stem cells from menstrual blood are easier to collect through a harmless procedure. An inexpensive source, it is not painful to the donor women and can be collected for about 35 years of a woman's menstruating age. However, younger women yield better quality of endometrial progenitor cells.
- Moreover, it takes care of ethical concerns as linked to the embryonic source and there is no fear of tissue rejection too. With multitude of benefits associated with these newly discovered stem cells, potential treatments could be devised for several medical conditions.
- The MenSCs can be processed and preserved effortlessly for future implementation. Researchers say that these cells have a higher reproduction rate, doubling every 19.4 hours, compared to the elemental cells from other sources. Compared to bone marrow, menstrual blood yields almost 30 times more stem cells.
- These "pluripotent" cells can develop into cardiac, hepatic, pleural, respiratory epithelial, adipocytic, osteogenic, pancreatic, and neurocytic cells, i.e. roughly nine cell categories, so far the highest known for any stem cell source.
- This implies that many medical conditions that have no cure till date, may find a new therapy through this regenerative medium. Host rejection is not a trouble with the MenSCs because they possess an immune system suppressing effect, enabling many patients other than the donor to accept curative therapies.

CONCLUSION

Many refer menstruation as 'nature's curse on women'. It's commonly thought of as unclean. In some cultures, women are not even allowed to cook during those days of month. But, path-breaking new research could change the way people view the menstrual cycle and its here in India, for the first time ever. The blood that uselessly leaks away from a woman's body every month until she reaches menopause is a good source of stem cells, which are still at an early stage of development and retain the potential to turn into many different types of cell. Women create life; but now they will contribute medically to save lives through the Menstrual Stem Cells (MenSCs) or stem cells harvested from discarded menstrual fluid - known to be the most disgusting phase of woman's life. Menstrual blood, as researchers say, is found to be the most potent source of stem cells so far. Discovering curative power of stem cells has been a revolutionary breakthrough in the field of surgery and medicine till date, which has actually given many - the precious gift of life.

It is not hard to bank menstrual blood. The procedure is almost the same as giving a urine sample. It may be easier to harvest stem cells from menstrual blood than bone marrow or skin because it is a painless and non-invasive procedure. Preliminary research suggests that menstrual stem cells could be used to cure a woman's genetic family, such as parents, sibling or child.

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Assessment of Antimicrobials' use in Pediatrics in Moradabad city

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Abstract

This study assesses the use of antibiotics in pediatric patients and also rationality & irrationality of prescriptions. The present study was a population based analytical epidemiological design in the settings of an urban population in Moradabad, (UP) India, during Jan 2009 to April 2009. The intended work can be divided into the following steps: by selecting the antibiotics prescribed prescription then divided the prescriptions according to the following criteria; category of antibiotic used, combination of antibiotic used, site of infection diagnosed & rationality and irrationality of prescriptions. It is important to determine and reduce the antibiotic use in children as it can cause resistance to antibiotics in them that can lead to different problems. The most common antibiotics prescribed in pediatric patients belong to the class of Quinolones (43.18%), among which Norfloxacin (28.95%) predominates. Amoxicillin + Clavulanic acid (40.74%) was the most frequently used antibiotic combination. It was concluded that maximum number of prescriptions were found rational based on considering the number of antibiotics per prescription and drug interaction, while irrational prescriptions were found to be less.

Key words: antimicrobial drugs, hypersensitivity reactions, bacterial infection, rationality.

INTRODUCTION

Drugs play an important role in protecting, maintaining and restoring health of a living body. Among these different population groups, infants and children are the most vulnerable groups to contact illnesses.^{1, 2, 3, 4-5} They are mainly prone to infectious diseases. Antimicrobial agents/drugs are used to combat or treat these infectious diseases. The use of antimicrobial agents, especially antibiotics has become a routine practice for treatment of pediatric illnesses. Antibiotics are considered to be the mainstay of treatment for children⁶ and hence it is the second leading drug prescribed according to the National Ambulatory Medical Care Surveys⁷⁻⁸. The choice of antibiotics for infants and children is usually empiric. Although the antibiotics are effective and play an important role in the management of infectious diseases, they can lead to many serious consequences. One of them is the irrational use of antibiotics which can lead to destruction of gastrointestinal micro flora inducing various clinical symptoms like toxic mega colon, pseudomembranous colitis, and etc⁹. It can also lead to emergence of multi-drug resistant micro-organism which is expected to cause more serious infections than

what we have initially encountered. Now days, many pediatric physicians' include antibiotics in their prescribing pattern without considering it to be rational or irrational. Therefore, an effective step should be taken for rational and effective use of antibiotics especially in pediatric patients.

MATERIAL AND METHODS

The study was conducted by randomly collecting the 482 prescriptions of pediatric patients during Jan 2009 to April 2009. Among the collected prescriptions, antibiotic prescribed prescriptions were separated out. The prescriptions containing antibiotics were then evaluated for the category of antibiotic prescribed, most common antibiotic used and their combinations, rationality (rational use of drugs requires that patients receives appropriate medications according to their clinical needs, in doses that meet their own individual requirements for an adequate period of time) and irrationality (irrational use of drugs refers to inappropriate medications received by the patients) of prescriptions based on drug interaction and number of antibiotic prescribed in each prescription. Along with this, the site of infection was also diagnosed which included gastrointestinal infection, respiratory infection and others that included prescription with unidentified site of infection i.e. anti allergic, analgesics, etc. prescribed with antibiotics. The number of

prescriptions was than counted for each type of study and the final result was obtained.

RESULTS

The data analysis showed that among the total number of patients 24% were infants and 45% belong to the age group of 1-5 years. The most common category of antibiotic that was prescribed by maximum pediatricians was quinolones which accounts for 43.18% of the total. Among quinolones, Norfloxacin (28.95%) was the most common drug to be used. Penicillins, which accounts for 23.38% of the total, was the next category of antibiotic that was prescribed, among this category Amoxicillin

(90.5%) was the most commonly used drug. Cephalosporin (14.77%) was also preferred by many of the pediatricians, the most common drug being Cefalexin (46.15%). Macrolides, especially Azithromycin (81.8%), was also used in many of the cases and accounts for 12.5% of the total. Aminoglycosides were also prescribed in 3.41% of the cases, the most common being Gentamycin (66.7%). Tetracycline, especially Doxycyclin, and Chloramphenicol were used in 1.14% cases. The above data analysis has been represented in Table-1.

Table.1: Most Common Antibiotics Used

SL.NO.	CATEGORY	MOST COMMON DRUG USED	% OF PRESCRIBED PRESCRIPTION n=482
1	Quinolones (Qn)	Norfloxacin (28.95%)	43.18
2	Penicillin (Pn)	Amoxicillin (90.48%)	23.86
3	Cephalosporin (Cp)	Cefalexin (46.15%)	14.77
4	Macrolides (Ma)	Azithromycin (81.8%)	12.5
5	Aminoglycosides(Ag)	Gentamycin (66.7%)	3.41
6	Tetracycline's (Tc)	Doxycycline	1.14
7	Chloramphenicol (Ch)	Chloramphenicol	1.14

In most of the prescriptions which were evaluated, combination of antibiotics was found to be used. The total number of prescriptions prescribed with combination of antibiotics was considered as 100%. Amoxicillin + Clavulanic acid was the most commonly prescribed combination and it accounts for 40.74% of the total. It was than followed by the combination of Ciprofloxacin + Tinidazole in 14.81% of the cases. The combination of Theophylline + Norfloxacin was

prescribed in 11.11% cases. In 7.41% cases, the combination of Betamethasone + Gentamycin, Lomefloxacin + Benzalkonium chloride, and Norfloxacin + Tinidazole were prescribed by the pediatricians. The combination of Cetirizine + Cefalexin, Fluconazole + Azithromycin + Secnidzole, and Ampicillin + Cloxacillin was used in 3.70% cases, the data being represented in Table-2.

Table.2: Combination of Antibiotics Used

Sl No.	COMBINATIONS	% PRESCRIBED n=482
1	Amoxicillin + Clavulanic acid (Am+Ca)	40.74
2	Ciprofloxacin +Tinidazole (Ci+Ti)	14.81
3	Theophylline + Norfloxacin (Th+No)	11.11
4	Betamethasone +Gentamycin (Bm+Ge)	7.41
5	Lomefloxacin + Benzalkonium chloride (Lo+Bc)	7.41
6	Norfloxacin +Tinidazole (No+Ti)	7.41
7	Cetirizine + Cefalexin (Ce+Cf)	3.70
8	Ampicillin +Cloxacillin (Ap+Cl)	3.70
9	Azithromycin + Fluconazole +Secindazole (Az+Fl+Sn)	3.70

Among the various site of infection, gastro-intestinal tract (git) was found to be more affected. The g.i.t. infection was diagnosed in 26.86% of the cases. Respiratory organs were found to be another site of infection and it was diagnosed in 22.40% cases. Rest

50.74% cases were that of antiallergic, analgesic, antipyretic, etc. and does not show any diagnosis related to g.i.t. or respiratory infection. These were included in the category of others, refer to Table-3.

Table.3: Site of Infection Diagnosed

Sl. No.	SITE OF INFECTION	% OF CASES	n=482
1	Gastro-intestinal	26.86	
2	Respiratory	22.39	
3	Others	50.74	

The prescriptions were also evaluated for their rationality and irrationality. Based on the number of antibiotics prescribed in each prescription 71.64% prescriptions were found to be rational, the remaining of 28.36% prescriptions were found irrational with two or three

antibiotics prescribed in each prescription. When prescriptions were evaluated based on the drug interaction 58.21% prescriptions were found to be rational and 41.79% prescriptions were irrational, the data have been represented in Table-4.

Table.4: Rationality and Irrationality of Prescriptions

Sl. No.	PATTERN	RATIONAL (%)	IRRATIONAL (%)
1	Number of antibiotics prescribed	71.64	28.36
2	Drug interaction	58.21	41.79

DISCUSSION

The inappropriate utilization of antibiotics, especially in infants and children, forced many researchers to evaluate the consumption of this class of antimicrobial agent in order to control the risk and its misuse. Studying the antimicrobial prescribing pattern in an Indian tertiary hospital has showed that two antimicrobials per prescription was maximum in pediatrics, while one antimicrobial was maximum in surgery, urology and internal medicine departments. Amikacin, ciprofloxacin, cefotaxime and cloxacillin were the most preferred drugs¹⁰. The result of present study demonstrates that antibiotics are frequently used in infants and children. In

contradict to the previous observation it was found that the most widely used antibiotics belong to class of quinolones and penicillins (Pn). Norfloxacin, ciprofloxacin, ofloxacin and amoxicillin are found to be most frequently used antibiotics in pediatrics. Resistance against quinolones such as norfloxacin, ciprofloxacin, etc. develops quite slowly and hence they are widely used¹¹. Amoxicillin is active against all organisms sensitive to Pn G, in addition it inhibits many gram negative bacilli, its oral absorption is better and is not interfered by food along with this higher and more sustained blood levels are produced¹². Amoxicillin with

clavulanic acid was the commonly and most frequently used antibiotic combination. Clavulanic acid has a high affinity for and binds to certain β -lactamases that generally inactivate amoxicillin by hydrolyzing its β -lactam ring, thus it extends the antimicrobial spectrum of amoxicillin¹³. In case of gastro-intestinal infection, which is the most affected site of infection in pediatrics, the combination of norfloxacin with tinidazole or ciprofloxacin with tinidazole was highly prescribed. The combination of ciprofloxacin with tinidazole has the advantage of being effective against both bacteria and protozoa as ciprofloxacin is bactericidal against enteropathogens while tinidazole is a potent anaerobicicide, for example *Entameba* requires normal faecal flora for its survival; ciprofloxacin kills the pathogenic intestinal bacteria & alters intestinal flora, and tinidazole directly eradicate *Entameba*¹⁴. While the combination of norfloxacin with tinidazole has an extended range of antimicrobial spectrum and thus is effective in mixed gut infection as well. But in case of respiratory tract infection, which is also one of the leading sites of infection in pediatrics, the combination of norfloxacin with theophylline was found to be prescribed in number of cases. This might be because norfloxacin (though not recommended for respiratory infection) increases plasma concentration of theophylline as it exerts inhibitory effect on the cytochrome P-450 system thereby reducing theophylline clearance¹⁵. Other singly prescribed antibiotics also include cefalexin (cephalosporin) and azithromycin (macrolide) which are highly used but the frequency of consumption were bit less of them. Majority of cephalosporins need to be injected and are not metabolized but are excreted rapidly by the kidney and thus have short $t_{1/2s}$, along with this hypersensitivity reactions are most common side effects to the cephalosporins.¹⁶ On the other hand macrolides have narrow antibacterial spectrum, their absorption is incomplete and is delayed by food, along with this resistance against this class of antibiotic develops quite readily. Cephalosporins such as cefixime, cefaclor, cefpodoxime and cefadroxil were also found to be used. Aminoglycosides such as amikacin and gentamycin was also prescribed in some cases. Tetracycline (though contraindicated in infants and children as calcium-tetracycline chelates) gets deposited in developing teeth and bone and thus affect permanent anterior dentition¹⁷. Chloramphenicol, roxithromycin, nalidixic acid and cloxacillin are also rarely used in pediatrics. Besides

gastro-intestinal and respiratory infection antibiotics and their combination were also frequently used in other cases with drugs like analgesics, antiallergic, steroidal drugs and even with antineoplastic drugs. In some cases nimesulide (NSAIDs) is prescribed with amoxicillin and/or its combination with clavulanic acid but the co administration of nimesulide with amoxicillin may show additive hepatotoxic effect¹⁸, this drug interaction can be prevented either by changing the category of NSAIDs used such as replacing nimesulide by ibuprofen which does not show any interaction with amoxicillin/clavulanic acid. In many cases quinolones such as ciprofloxacin was prescribed with nimesulide but any NSAIDs when prescribed with quinolones show an increased CNS stimulation, this can be prevented by changing the category of antibiotic because if multivitamin is prescribed to combat such interaction another effect will occur leading to reduced absorption of antibiotics. In few cases omeprazole (antiulcer drug) is prescribed with Norfloxacin + Tinidazole (an antidiarrhoeal combination) but this can reduce the absorption of antibiotic from gut¹⁹, hence, in such cases antiulcer or antacids should be avoided. The use of two or more antimicrobial agents has a certain rationale and is recommended in specifically defined situation. The combination therapy is used for number of reasons such as to achieve synergism, to reduce severity or incidence of adverse effects, to prevent emergence of resistance and to broaden the spectrum of antimicrobial action. But the use of unnecessary antibiotics in pediatric patients has led to rise in irrational prescribing patterns in pediatrics for example prescribing two or more antibiotics such as azithromycin and ofloxacin or roxithromycin and cefadroxil in the same prescription was found in some cases. Many reasons account for the prescribing of antibiotics in children. Sometimes it is also prescribed in viral infection due to lack of proper diagnosis. Efforts should be employed to reduce the inappropriate use of antibiotics in children. It is well known that pediatricians or physicians may use diagnosis to justify antibiotic prescribing and it may raise estimates of appropriate antibiotic prescribing²⁰. In spite of this, pharmacists should have a role in promoting antibiotic use. They can play a major role through clinician education and focused clinical services as well as through patient counseling²¹. As this study has been performed on less number of prescriptions and is confined to a hospital i.e. the study has been conducted on small scale. Thus, a study should

be conducted on large scale including number of hospitals in different zones to actually determine the trend of antibiotic use in pediatric patients. The study can also include different parameters like age, sex, duration of therapy, route of administration, site of infection, dose of drugs, etc. in detail for actual evaluation of antibiotic prescribing pattern in children. It is important to determine and reduce the antibiotic use in children as it can cause resistance to antibiotics in them that can lead to different problems in this high risk group such as destruction of microbial flora in gut, hypersensitivity reactions, toxicity, superinfection (appearance of new infection as a result of antimicrobial therapy) and nutrition deficiency. Improving availability of diagnostic methods to differentiate between viral and bacterial infections is suggested to reduce empiric therapy numbers by antibiotic agents.

CONCLUSION

The present study concluded that the most common antibiotics prescribed in pediatric patients belongs to the class of quinolones, among which norfloxacin predominates. Amoxicillin + Clavulanic acid was the most frequently used antibiotic combination. Evaluating the prescriptions on the basis of rationality and irrationality, it was concluded that maximum number of prescriptions were found rational based on considering the number of antibiotics per prescription and drug interaction, while irrational prescriptions were found to be less.

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Pharmacoepidemiological Study of Self-Medication in Indore City

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Abstract

Self-medication and non-doctor prescribing of drugs is common in developing countries. The objectives of this research were to explore lay medication activities as an aspect of self-managed health care to identify sociomedical characteristics and to establish the prevalence, attitude knowledge, and sources of information of self-medication in Indore city. A cross-sectional study was conducted to determine the extent and pattern of self-medication. Data were collected from a random sample of 135 pharmacists from various pharmacies in city following WHO methods. The prevalence of self-medication was estimated. Respondents were questioned about the, self-treated symptomatic conditions, recent medication activities, the use of prescribed medicine in self-treated illness episodes, and the use of suitable dosage forms. The prevalence of self-medication in Indore city is high. This study contributes to a growing body of international evidence which has demonstrated that self-medication is a vital part of daily self-care behavior. Patient education and awareness campaigns are necessary to promote the role of the pharmacist in India, particularly because in modern society the pharmacist plays an active role in the provision of drug information. Strict policies need to be implemented on the advertising and selling of medications to prevent this problem from escalating.

Key words: Self-medication, Pharmacoepidemiology, Indore city

INTRODUCTION

Pharmacoepidemiology is considered newly evolving science that studies the use and effects of drugs in large numbers of people.¹ Rational use of drugs has drawn public health attention globally with the aim of maintaining quality health care at lower cost.² As dispensing medication in an appropriate way is a cornerstone of rational drug use, the dispenser should be regularly updated with information, tools and skills.³ Internationally, self-medication has been reported as being on the rise.⁴⁻⁶ Various studies have shown that the use of self-medication is twice as common as that of prescribed medication⁷⁻¹⁰, and that self-medication is often used together with prescribed medication. Self-medication is defined as obtaining and consuming drugs without the advice of a physician either for diagnosis, prescription or surveillance of treatment.¹¹ This includes acquiring medicines without a prescription, resubmitting old prescriptions to purchase medicines, sharing medicines with relatives or members of one's social circle or using leftover medicines stored at home.¹² There is much public and professional concern about the

irrational use of drugs.¹² The prevalence rates are high all over the world; up to 68% in European countries¹³ and 57% in USA,¹⁴ while much higher in the developing countries¹⁵ with rates going as high as 92% in the adolescents of Kuwait.¹⁶ The prevalence rates of self-medication and self care are 31% in India,¹⁷ 59% in Nepal¹⁴ and 51% in Pakistan.¹⁸

It is also alarming that the prevalence rates are on the rise despite efforts to limit this problem.¹⁹ Various previous studies have shown that self-medication practices are more common in women and in those; who live alone, have a lower socioeconomic status, have more chronic ailments, have psychiatric conditions, are of younger age and in students.^{15,20,21} The World Health Organization has emphasized that self medication must be correctly taught and controlled.⁴ Suspected rates of self-medication can be due to various reasons. One reason for this may be related to the availability of a wide range of non-prescription medication that can be obtained from community pharmacies without a doctor's prescription, with the notable exception of antibiotics, narcotic analgesics, steroids and major tranquillizers. Another reason could be the influence of peers and parents.

A number of studies have reported that self-medication starts with the onset of adolescence and increases with age.^{22, 23} The public health importance of self-medication has increased since the late 1980s when more drugs were changed from prescription status to be sold over-the-counter (OTC) without a prescription. This is a worldwide trend. The increased possibilities of self-medication have implications for patients, pharmacists, and physicians.²⁴ It also allows pharmaceutical companies to expand their market.²⁵

In India, pharmacists and pharmacy attendants play an important role in fostering self-medication among the public.²⁶ Combination preparations containing 'hidden' classes of drugs and food supplements or tonics of doubtful value were commonly used in India.²⁷ The nature and extent of self-medication varies in different cultural contexts and social and educational influence may be greater than the influence of medical practice. In India, it is possible to buy prescribed and non-prescribed drugs with or without prescriptions from a wide variety of sources. These drugs, if not fully used, may be kept for future use by the parents. In order to have a better understanding of the use of self-medication among patients, a study was carried out. The aims of our study were to obtain baseline data on self and non-doctor prescribing in Indore city and to obtain pharmacoepidemiological information regarding self-medication and non-doctor prescribing.

METHODS

The study design and sample size followed World Health Organization guidelines for investigation of therapeutic practice.²⁸ Accordingly, a sample of 130 pharmacies was selected randomly from Indore city, using simple random sampling technique. Indore is prime city located in the western region of Madhya Pradesh, and is close to the centre of India with a population about 35 million. A self-administered questionnaire was distributed amongst the principal pharmacist of each pharmacy after explaining the purpose of the study and taking informed consent. The study questionnaire was adapted from various similar studies conducted previously^{15, 29, 30} and pre tested on a sample of 10 participants. Any ambiguities in the questions or responses were removed before its implementation. The questionnaire was administered in english. The study consisted of a survey of the use of self-medication to ascertain:-

1. Prevalence of self-medication
2. Conditions treated by self-medication
3. Categories of medications preferred

4. Preferred dosage form during self-medication
5. Safety priority of using the drugs
6. Reasons for self medication

The prevalence of self-medication was determined as percentage of all users out of the total sample. The high prevalence of self-medication may mean that there is a high morbidity rate in the community, or that some people use medications unnecessarily. The reasons given for self-medication were analyzed.

RESULTS

All the visited pharmacists took part in the study. The conditions treated by self-medication are shown in Table-1. Conditions which were more likely to be treated by self-medication are fever, cough and cold, sex problems, infection, headache, eye problem, nutritional loss etc. Because of increasing trends of self-medication, people ask for the various medications. During the study surprising results were obtained that majority of drugs that comes under antipyretic, analgesic and anti-inflammatory, antihistaminic and anti-allergic categories are asked by patients and such drugs are dispensed by pharmacist without the proper prescription despite of the fact that these drugs requires a prescription of physician. Fifty two percent of the pharmacists believe that such medications need prescription while 48% do not. The various categories of drugs which are sold on non-prescription by pharmacists, if requested by patients are shown in Table-2. The preferred dosage form in case of prescription drug is a versatile dosage form that is tablet (98.46%). Liquid orals (55.38%) are the preferred choice after tablets. Preferred dosage forms for self-medication are shown in Table-3.

Some basic information revealed as an outcome of the study has been shown in Table-4. The number of customers coming for such medication varies from one location to another. When asked to the pharmacist, the average number of customers coming to the pharmacist shop for self-medication is about 18-26 per day. When asked about the role of advertisement on electronic media for self-medication, about 87% of pharmacists agrees the impact of advertisement, 12% says that 'Cannot say' and less than 1% believes that that there is no role of electronic media for promoting self medication. Safe use of drug should be of almost priority. But because of self-medication, these prescription drugs may cause toxicity or they may be misused. About 45% of pharmacists agree that the drugs are misused, 18% do not agree and where as 37% says 'Cannot say'. When opinion of the pharmacist

Table.1: Symptoms, disease and disorders for which medicines are asked

Sr. no	Parameters	Percentage
1	Fever	82.3
2	Cough and Cold	53.84
3	Sex problem	43.84
4	Infection	29.23
5	Headache	27.69
6	Diarrhea	22.3
7	Nutritional loss	9.23
8	Vomiting	8.46
9	Eye problem	6.92
10	Appetite loss	6.15
11	CNS depressants	3.84
12	Dental problem	1.53
13	Hypertension	1.53
14	Skin problem	0.76

Table.2: Drugs dispensed by pharmacist on patient's request

Sr. no	Parameters	Percentage
1	Antipyretic	85.38
2	Analgesic and anti-inflammatory	67.69
3	Cough and Cold Preparations	53.07
4	Sex stimulants	43.84
5	Antibiotics	40
6	Anti-allergic	26.15
7	Anti-diarrhea	23.84
8	Nutritional supplements	12.3
9	Ophthalmic preparations	8.46
10	Anti-emetic	8.20
11	Appetite stimulants	3.07
12	Dental preparations	1.53
13	Antihypertensive	1.53
14	Cosmetic preparations	0.79
15	CNS Depressants	0.76

Table.3: Choice of dosage form

Sr. no	Parameters	Percentage
1	Tablet	98.46
2	Liquid orals	55.38
3	Condom	38.46
4	Ointment	27.69
5	Capsule	21.53
6	Powders	14.61
7	Drops	7.69
8	Cream	3.07
9	Rotacap	0.78
10	Enema	0.71

Table No.4: Some basic questions related to self-medication

Sr. no	Questions	Answers	Percentage
1	What is the average number of customers coming to the pharmacist shop for self-medication in a day?	18-26	-
2	What is the impact of advertisement on electronic media for self-medication?	Increase	86.92
		Decrease	0.76
		Can not say	12.3
3	Do such medications need prescription?	Yes	52
		No	48
4	Are the drugs used for self-medication safe?	Yes	45.38
		No	17.69
		Can not say	36.92
5	Whether self-medication for prescription drug should be continued or not?	Yes	22
		No	78
6	What are the basic reasons for self-medication?	Poverty, lack of time, easy availability of drugs, minor ailments, previous treating experience, Non-availability of doctor.	-

was asked about continuation of use of prescription drugs for self-medication, majority, about 78% of pharmacists of opinion that since drugs are misused their use without prescription should be stopped, but about 22% of pharmacists are in favor of self-medication because in their opinion majority of poor people cant afford physicians fees and therefore this practice should be continued. The reasons given for self-medication were analyzed. Reasons for self-medication for prescription drugs include poverty, lack of time, easy availability of drugs, the illness was too mild and did not require the services of a doctor, previous experience of treating a similar illness and even if patients go to a doctor they will be prescribed similar medications. Non-availability of a doctor was also cited as a reason for self-medication.

DISCUSSION

We acknowledge that this type of study, using a self administered questionnaire, is largely dependent upon information given by respondents. In the present study the rate of self medication was high, due partly to the lack of enforcement of the Indian law concerning drug products requiring a prescription to be sold over the counter drugs. Due to the differing socioeconomic profiles and demographic characteristics of the populations, it was difficult to compare the results.

Antipyretics and analgesics were the most commonly used class of drugs, which is similar to findings in the literature.^{31, 32} In developing countries, antimicrobials are commonly sold drugs. In concordance with previous results,^{33,34} our results show that antimicrobials were used less than 50% for self-medication, and were mostly obtained on prescription. Factors influencing self-treatment include patient satisfaction with the healthcare provider, cost of the drugs, educational level, socioeconomic factors, age and gender.³⁵ In India, Deshpande and Tiwari reported that 26% of graduates and 23.1% of illiterate people practised self-medication.¹⁷ Another study in India in an urban slum community indicated that the practice of self medication was more prevalent among literate people.³⁶ Probably this educated group has more ability to self-medicate. Education appeared to be an important variable as the higher the purchasers' educational level, the more the complied with reading the patient information sheet, following the label instructions and reading the expiry date. Deshpande and Tiwari's study in India found that 30.8% purchased a particular medicine on advice from friends or neighbors.¹⁷ The commonest reason given for self medication was purchasers' belief that their complaint

was a minor problem, not requiring medical attention. Some of the purchasers claimed that they knew the treatment from a previous prescription while some had confidence in the pharmacist. The study indicated that purchasers attempt self-medication due to the triviality of their symptoms or to save time and money. In the slum community in India inability to pay for established medical facilities was the commonest motivation for self-medication.³⁶ Research has demonstrated that individuals have their own ideas and beliefs about drug use, which are important determinants of their use.³⁷⁻³⁹ Although it is true that self-medication can help treat minor ailments that do not require medical consultation and hence reduce the pressure on medical services particularly in the underprivileged countries with limited health care resources.⁴⁰ Moreover, the practice of self medication often has many adverse effects and can lead to many problems, including the global emergence of Multi-Drug Resistant pathogens,⁴¹ drug dependence and addiction,⁴² masking of malignant and potentially fatal diseases,⁴³ hazard of misdiagnosis,⁴⁴ problems relating to over and under dosing,⁴⁵ drug interactions⁴⁶ and tragedies relating to the side effect profile of specific drugs.⁴⁷ In the ideal setting the only justifiable rationale for self medication would be 'urgency of the problem'.

We are of the opinion that if people knew exactly how devastating self medication could be instead of just knowing that it is wrong; the prevalence rates would be much lower. Medicines that are not over-the-counter drugs should not be given without prescription and a strict system of checks and balances should be implemented to prevent this problem from escalating. A very small percentage of pharmacists actually give the appropriate medication when consulted.⁴⁸ It has also been shown by recent studies that familiarity and easy access to certain pharmaceuticals are determinants for self-medication.¹² This brings us to the issue of advertising of medicines by pharmaceutical companies. Although it was not researched in this study, previous research has demonstrated that advertising directly affects the youths decision to self-medicate.⁴⁹ Thus further research and strict rules and regulations also need to be placed in this regard. Due to the difficulty in accessing health care services, self-medication is often the simplest option for the patient. Since traditional practitioners are easily accessible, people also turn to them for their healthcare needs. However, traditional practitioners need to be educated about when to refer a patient for more

specialized care. They can also help to introduce modern concepts such as immunization among the rural population. Educational intervention to help patients decide on the appropriateness of self-medication may be helpful.

Pharmacists and to a less extent pharmacist assistants were a source of advice to purchasers in the present study. Pharmacists diagnosed certain conditions and prescribed a drug as a treatment. Purchasers also sought medication on their own initiative. In India, the pharmacist's role is mainly seen as that of a drug salesman rather than that of a health care provider. Patient education and awareness campaigns are necessary to promote the role of the pharmacist in India, particularly because in modern society the pharmacist plays an active role in the provision of drug information. In view of the wide spectrum of drugs available over the counter, it is vital that pharmacists in India assume this role after appropriate training and with continuing professional development programmes.

CONCLUSION

The prevalence of self medication practices is alarmingly high in Indore city. Fever and cough and cold were the most common reasons for non-doctor prescription. NSAIDs were the drugs most commonly used for self-medication and tonics were more frequently taken without prescription. People also emphasize to choose a suitable dosage form as per convenience. Tablets and liquid orals were mostly preferred. Few people consult pharmacists on drug information. This issue needs to be addressed by the responsible authorities in India. We recommend that a holistic approach must be taken to prevent this problem from escalating which would involve (i) awareness and education regarding the implications of self medication (ii) strategies to prevent the supply of medicines without prescription by pharmacies (iii) strict rules regarding pharmaceutical advertising and (iv) strategies to make receiving health care much less difficult. The need for promoting the appropriate use of drugs in the Indian health care system is important. It is recommended that the dispensing procedure in India needs improvement through educational, regulatory and managerial strategies. There is need for authorities to be proactive regarding over the counter, prescribed and non-prescribed drugs so as to ensure rational sale. Periodic studies on the knowledge, attitude and practice of self medication may give an insight into the changing pattern of drug use in the Indian societies and it is also hoped that this study will stimulate

more attention to, and research into, self-medication — an important but controversial medical issue.

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Comparison of quality of life and improvement in B.P and blood glucose values of patients using branded generic and generic medicines for hypertensive and diabetes treatment

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Abstract

In India most of the drugs are generics only. But these drugs are supplied with the respective company's brand names and are thus termed as branded generics. There is no practical difference between branded generics and generics. But a difference exists at the marketing level where the generics are obtained by the retailer at a lower "price to the retailer" and there could be a difference in the way healthcare professionals perceive branded generics and generics. This work consists of a comparison of therapeutic efficacy of branded generics and generics of drugs used by B.P patients and patients having B.P and diabetes by comparing their health related quality of life (HRQOL) levels and their B.P levels and blood glucose levels, before and after treatment. The hypothesis behind the work is that if there is a significant difference between the therapeutic efficacy of branded generics and generics then there should be a significant difference between the HRQOL levels and improvements in B.P levels and blood glucose levels of the patients who are using them over a long period. This work is a study of HRQOL levels as determined by SF-36 questionnaire and B.P levels and blood glucose levels as ascertained from the case sheets of patients. Statistical analysis revealed that there is no significant difference between the branded generics and generics with respect to HRQOL values or reduction in the percentage of patients from high B.P levels to low B.P levels and from high blood glucose levels to low blood glucose levels. It was concluded that there is no difference between the therapeutic efficacy of branded generic drugs and generic drugs. It is suggested that the Drugs and Cosmetics Act 1940 be amended to differentiate between generic and branded generic products and to make it compulsory for the companies to keep a lower maximum retail price (MRP) on the labels of the generic products.

Key words: HRQOL, SF-36, hypertension (B.P.), hypertension and diabetes, Branded generics (BG), Generics (G), Maximum retail price (MRP)

INTRODUCTION

Public health is a very important issue in India which is a developing country. The Global Competitiveness Report 2008-2009¹, given by the World Economic Forum ranked India 50th among 134 countries in Global Competitive Index and 100 among 134 countries in health and primary education. Thus healthcare field is one of the areas where India is performing in a poor manner and this field needs research done in a scientific manner. Generic drugs play a very important role in health care. While there are a number of articles on generic drugs (G) vs. branded generic (BG) drugs, the scientific research on BGs and Gs is mostly confined to pharmacokinetic comparison. Cost of pharmaceuticals contributes significantly to

health care expenditure and it can be definitely brought down by the increased use of generics. Almost all Indian drugs are branded generics and all of them must be inexpensive in comparison to their brands. Though it is a fact that Indian drugs are very inexpensive when seen from an international perspective the fact remains that they can be still more inexpensive. Countries such as USA, UK, Canada, Sweden, Australia and Netherlands are taking steps to ensure that their peoples have access to generics that are bioequivalent to the brands but are priced low². In India the Drugs Price Control Order 1995 does not distinguish between generics and branded generics and hence the MRPs (Maximum Retail Price) on both varieties are usually same. So there is no benefit to the patient when he purchases a generic drug. Research was carried out in our laboratories on the bioequivalence of four marketed branded generic products of sparfloxacin³ and on the bioequivalence of a generic

product and three branded generic products of amoxicillin⁴. It was found that four different BGs of sparfloracin were bioequivalent and that the four products of amoxycillin were bio-in-equivalent. But results showed that it was one of the BGs that was inequivalent. The other three amoxicillin products, including the generic amoxycillin were bioequivalent. If a study can be undertaken to ascertain the equality or inequality between generics and branded generics it will be useful to the policy makers in India, to the prescribers and to the patients in India. In the correct sense of the word "generic" all the products being compared are generic. So this may also be named as an investigation into the appropriateness of interchangeability of generics. The objective of the present work is to investigate and to find out whether, between generics and branded generics there is any difference in clinical effect as ascertained by improvement in B.P values, reduction in blood glucose values and by health related quality of life (HQOL) values which are determined by a questionnaire (SF-36).

MATERIALS AND METHODS

This research project was started with the null hypothesis that the difference observed, if any, between generic drugs and branded generic drugs is only due to chance and is not significant and was taken up as a one tailed study. For the purpose of comparison drugs for hypertension only and drugs for hypertension and diabetes were selected. The work was pursued in the following manner.

Ethics committee approval was obtained to interview patients taking generic drugs and branded generic drugs for B.P and diabetes or only for B.P. Patients were differentiated as branded generics users and generics users. The chosen instrument for study of HRQOL is SF-36 whose copy right is owned by Quality Metric. License was obtained from Quality Metric after payment of relevant fee for SF-36, its Telugu version, and its scoring manual

Hypothesis:

There is no significant difference between the HRQOL values or improvement in B.P values or reduction in blood glucose values of patients using branded generic drugs and patients using generic drugs.

Patient population selection:

The study was planned in two hospitals. One is the Health center in Andhra University (AUHC), Visakhapatnam, where the doctors use (prescribe) branded generic medicines only for all patients. The second hospital is the King George Hospital (KGH),

Visakhapatnam, where generic medicines are used. Generic medicines are not available for many medicines, because almost all companies give company names to their medicines. Only some anti-diabetic, anti-hypertensive and non steroidal anti-inflammatory medicines are available as generics and generics are available only in government hospitals. Patients using those generic medicines were selected as the second population. This research work was approved by the Institutional Ethics Committee for Human research of Andhra University as well as by the Chief Superintendent of King George Hospital.

The researcher waited in the pharmacy area in the hospitals and selected for study, those patients who are above 14 years, who were taking medicines for hypertension or for hypertension and diabetes since more than one year and who were willing to participate in the study. To those patients who gave a written informed consent, the researcher administered the SF-36, in English or in the regional language, Telugu. She obtained the answers to different questions in an average time period of 30 mins. In both the hospitals, the doctors, pharmacists and patients were very cooperative and eagerly gave answers to the questions put to them. The QOL assessment was done for each patient only once. The idea was not to pursue comparison over a period of time but it was to make a comparison between those using generics and those using branded generics in a specific period of time.

Assessment of QOL of patients:

The QOL of each participant was assessed using SF-36 which is considered by many to be a global instrument. For this study, SF-36 was typed by the researcher with a scoring scheme below each question. This facilitated easy answering of the SF-36 questions by the people. SF-36 includes 8 health concepts.

1. Physical functioning (PF) – 10 items measuring the extent to which health limits physical activities such as self-care, walking, climbing stairs, bending, lifting and moderate and vigorous exercises.
2. Role functioning (physical) (RP) – four items which measure the extent to which physical health interferes with work or other daily activities, including accomplishing less than wanted, limitations in the kind of activities or difficulty in performing activities.
3. Bodily pain (BP) - two items, measure intensity of pain and the effect of pain on normal work, both inside and out side the home
4. General health (GH) - five items reflecting the

general health perceptions of each subject. Subjects evaluate current health, health outlook and resistance to illness.

5. Vitality (VT) - four items measuring level of energy, ranging from energetic and full of pep (top level) to feeling tired and worn out (bottom level).
6. Social functioning (SF) - two items measuring how physical health and emotional problems impact on the social activities of an individual. The two items in the scale assess how health or emotional problems interfere with social activities with family, friends and neighbors.
7. Role function (emotional) (RE) - three items measuring how emotional problems (eg. feeling depressed or anxious) interfere with work or other daily activities in decreased time spent on activities and not working as carefully as usual.
8. Mental health (MH) - five items measuring general mental health (nervousness and cheerfulness, calmness, happiness) including depression, anxiety behavioral -emotional control and general positive affect.
9. Reported health transition (HT) - one item evaluating current health compared to one year ago.

Study format:

The patients studied may be grouped into two categories.

1. In this group patients taking medicines for their hypertension and diabetes for a period of more than one year were taken into the study. Fifty six patients from Andhra University Health center who were using branded generics and 75 patients from King George Hospital, Visakhapatnam, who were using generics, participated in the study.
2. In this group patients taking medicines for their hypertension for a period of more than one year were taken into the study. Ninety two patients from Andhra University Health Center who were using branded generics and 102 patients from King George Hospital, Visakhapatnam, who were using generics, participated in the study. The demographics of the patients who participated in the study are given in Table I.

The questionnaires filled were given scores by the scoring manual for SF-36. The scores obtained in 8 different domains were analyzed graphically and were compared by t test. The results are given below.

RESULTS

HRQOL

Along with the license for HRQOL instrument SF-36, the license for its scoring manual was also obtained from the company Quality Metric - Health Outcomes Solutions.

This is software which converts answers given by the patients in SF-36 into scores. The QOL is assessed in 8 domains. In each domain the maximum score is 100 and minimum score is 0. In each domain poor health status results in lesser score and higher health status results in better score. If the total score is 800, it indicates that the patient believes that he is in perfect QOL. The results from the questionnaires filled by the 325 patients were entered into the software and were scored by it.

B.P and Blood Glucose

The B.P and blood glucose values of all the patients who participated in the study were noted down from their case sheets. The values of B.P and blood glucose before the patients started treatment and the corresponding values at the time of the interview were noted.

Analysis

The HRQOL values of the patients were subjected to statistical analysis by Minitab - statistical software. The B.P and blood glucose values, before and after treatment were analyzed in the following manner. The patients were classified into four groups based on their B.P before treatment. The four classes were; normal B.P. (120/80), medium hypertension (120-140/80-100), high hypertension (140-190/100-120) and very high hypertension (190-250/120-180). After treatment, depending on the level of improvement he was given a number of pluses; for example if a patient improved from medium level to normal level he was given a single plus and so on. Finally the numbers of patients who recorded different number of pluses were tabulated for generics as well as for branded generics. A chi square test was performed on these values to determine whether there is any association between being generic or branded generic and the clinical effects. In a similar manner patients were classified into five groups based on their fasting blood glucose level; normal (80-110), medium (110-140), high (140-200), very high (200-250) and very-very high (250-550).

Based on reduction in fasting blood glucose level they were awarded a certain number of pluses and patients were classified based on the number of pluses. These values were tabulated for generics and branded generics and were analyzed by a chi square test. This analysis is shown in tables III.

Table .I: Demographics of the patients.

S.No.	Drugs type	Gender		Age in years			Exercise		
		M	F	30-49	50-69	70-89	Yes	Irregular	No
Group-I	B.G.	44	12	16	37	3	36	8	12
	G	46	29	17	52	6	29	20	26
Group-II	B.G.	70	22	28	57	7	50	15	27
	G	10	92	23	67	12	38	18	46

TABLE.II: Summary of T-Tests done on HRQOL of Patients.

Disease	Drug	S.no.	Component	N	Mean	SD	P-Value	Decision
B.P. and Diabetes.	Domain Scores	1	PF BG	56	84.2	17.2	0.674	N.S.
			PF G	75	82.9	16.5		
		2	RP BG	56	76.8	31.2	0.477	N.S.
			RP G	75	81	36.3		
		3	BP BG	56	79.9	20.8	0.124	N.S.
			BP G	75	85.2	17		
		4	GH BG	56	78	17.4	0.087	N.S.
			GH G	75	83.3	17.3		
		5	VT BG	56	78.6	19.4	0.338	N.S.
			VT G	75	75.2	20.4		
		6	SF BG	56	84.4	19.1	0.148	N.S.
			SF G	75	89.3	19.6		
		7	RE BG	56	86.3	29	0.442	N.S.
			RE G	75	90.2	28.4		
		8	MH BG	56	88.4	16.9	0.406	N.S.
			MH G	75	85.9	16.1		
		9	PF BG	92	89.1	14.7		
	PF G	102	84	16.7	0.023	S		
10	RP BG	92	85.9	28.8				
	RP G	102	81.1	38	0.325	N.S.		
11	BP BG	92	81.8	19.7				
	BP G	102	84.6	17.8	0.295	N.S.		
12	GH BG	92	84.4	15.3				
	GH G	102	83.9	14.4	0.83	N.S.		
13	VT BG	92	81.9	17.5				
	VT G	102	80.8	17.3	0.656	N.S.		
14	SF BG	92	85.3	19.8				
	SF G	102	89.7	13.8	0.078	N.S.		
15	RE BG	92	93.5	21.7				
	RE G	102	88.6	31.6	0.205	N.S.		
16	MH BG	92	89.9	13.1				
	MH G	102	85.7	17	0.057	N.S.		
	Total QOL	17	Total BG	92	691.7	78.3	0.338	N.S.
				102	678	113		

Note: - BG=branded generics, G=generics

DISCUSSION

HRQOL:

Figs 1 to 2 show comparison of HRQOLs of patients using branded generics and generics in study groups I-II. The bar diagrams in the two cases show that, the scores for branded generics and generics are nearly equal. In both the groups the importance is mixed, with branded generic users showing more score in some domains and generic users showing more score in some domains.

Comparison of Generics and Branded Generics in the two study groups with respect to different domains:

Group-1:- Patients use both antihypertensives and antidiabetics.

Fig. 1 shows a domain-wise comparison of generics and branded generic users of B.P. and anti diabetic drugs. In three domains i.e. in physical functioning, in vitality and in mental health QOLs of generics users are less but the difference is not significant. Generic users show better scores than branded generic users in all the other five domains but the difference is not significant.

Group-2:- Patients use antihypertensives only.

Fig. 2 shows a domain wise comparison of QOL scores of generic and branded generic users of B.P. drugs. In six domains i.e. in all but body pain and social functioning generic users show less QOL scores than branded generics users but the difference is significant in only one case, i.e. the case of physical function.

Fig. 3 shows a comparison of total QOL values of branded generics users and generics users of different study groups. In the first group the QOLs of the branded generics users and generic users are almost equal. In the second group the QOLs of branded generics users are a little more than the QOLs of generics users but the difference is not significant.

It may be concluded from the results that generic drugs are of equal efficacy as branded generic drugs.

Figures 4 to 7 show a comparison of total QOL scores of generic users and branded generic users. Figures 4 and 6 are individual value plots of the QOL scores of the two study groups. Figures 5 and 7 are box plots of total QOL scores of the 2 study groups.

1. The individual plot in fig. 4 and box plot in fig. 5 indicate that when the total QOLs of branded generic users and generic users of B.P. and diabetic drugs are compared, the former group has less spread and the means and medians to be almost same. There are six outliers (very low scores) in the data of generic users.
2. Individual plot fig. 6 and box plot fig. 7 indicate that the spread and median are lesser but the mean is more among the total QOLs of branded generic users of B.P.

drugs in comparison to the total QOLs of generic users of B.P. drugs. There is one outlier (very low score) in the data of generic users.

Summary of t-test values are given in table-II for the two groups. The mean QOL values in different domains and their s.d.s are calculated for users of branded generics and generics. For each domain in each group, the means, the s.d.s, p-value and the conclusion, i.e. whether the difference is significant or not is given in table-1. For each study group there are 9 comparisons, 8 comparisons for domains and 1 for comparison of total (maximum total=800) QOL. In only one case out of the 18 comparisons the difference observed is significant and in all others it is not significant. The only case of significant difference is; in study group II, physical function (B.G. = 89.1, G = 84). Patients who did regular exercise showed a higher average HRQOL value than those who did not do exercise regularly. Other demographic factors had no influence on average HRQOL values.

The interpretation of these results can only be the following:

- ✎ There is no significant difference between the HRQOL values of branded generic users and generic users, in a large member of cases, it should be concluded that branded generic drugs and generic drugs result in equally good quality of life.
- ✎ The SF-36 instrument is able to measure the QOL independent of economic status. It is really reflecting the effect of the medicine and is not impinged upon by economic or social factors. In the one case where significant difference is observed, the reflection is probably on the fact that most of the generic users are patients who depended on physical labor for their livelihood, who found a difference in their physical function QOL after the onset of the disease which the medicines could not yet repair.

BP and Blood Glucose

Group I: Table III and Figure 8 show the numbers of patients who showed different levels of improvement in their B.P values and blood glucose values. A chi square test was performed on these values to find out whether there is any association between being generic or branded generic and improvement in B.P values and blood glucose values. It was found that at 0.05 level of significance the difference observed in numbers of patients with specific levels of improvement in B.P, using Gs and BGs, was not significant enough to indicate an association. But with respect to blood glucose the difference is significant and by observation we find that

the numbers of generic users showing improvement are more than the numbers of branded generics users.

Group II: Table III and figure 8 show the numbers of patients who showed different levels of improvement in their B.P values. A chi square test was performed on these values to find out whether there is any association between being generic or branded generic and improvement in B.P values. It was found that at 0.05 level of significance the difference observed in numbers of patients with specific levels of improvement in B.P, using Gs and BGs, was significant enough to indicate an association and by observation we find that the numbers of generic users showing improvement are more than the numbers of branded generics users). Patients who did regular exercise showed better clinical outcomes than those who did not do exercise regularly. Other demographic factors had no influence on clinical outcomes.

The interpretation of these results can only be the following

Considering the results of the chi square test and after the observation of the data it may be concluded that generic drugs are not inferior to branded generic drugs in causing clinical improvement.

DISCUSSION OF THE RESULTS IN COMPARISON WITH PAST REPORTED WORK

Several studies utilized SF-36 for estimating the outcome in a variety of disease situations. Some researchers used SF-36 at two time points or three time points to prove that the treatment in question had an influence on the HRQOL of patients. Ensaf Saied Abdel-Gawad⁵ carried out a one time point QOL study and concluded that overall, diabetic patients reported mild to moderate QOL, which appears to be related to demographic, medical history and management regimens. The present work used a one time point study to assess the QOL of patients with diabetes and hypertension and patients with hypertension only that are using branded generics or generics. Berna Tander⁶ et al used HRQOL to compare the functional and psychological status of rheumatoid arthritis (RA) patients, fibromyalgia (FS) patients and controls. The scores of all SF-36 subscales except mental health scores were significantly lower in FS and RA patients than in controls. While they used QOL to compare the effect of two diseases, present work used QOL to compare the effect of two drug products of the same disease. There is no previous reported work which used QOL to compare branded generics with generics. The results of this study are in agreement with the results reported from this

laboratory^{3,4} in that there is bioequivalence between BGs and Gs.

Gyorgy jermendy⁷ et al carried out an observational study to assess the status of glycemic control and associated patient – reported outcomes in ambulatory Hungarian patients with type 2 diabetes mellitus. They concluded that patients reporting hypoglycemia were also more likely to report lower health related quality of life. In the present study patients showing better improvement in their B.P or blood glucose levels also showed better quality of life. When a rank correlation coefficient was calculated between the extent of improvement and the average HRQOL values; the coefficients ranged from 0.8 to 1.0. It may be concluded that improved clinical outcome is correlated with better HRQOL.

LIMITATIONS

1. The comparison between the patients using generics and branded generics was done on the basis of interviews done at a single point. A study extended over a period of time, by interviewing the same patients at different intervals of time (for the specific categories of drug products) would have yielded much more information but because of limitation of time it could not be done.
2. In general, patients using branded generics i.e. those who were getting their treatment from Andhra University Health Center were people belonging to an economically stable class, as they were all either employees of Andhra University or their family members. The people who were using generics, i.e. those who were taking their treatment from the King George Hospital, Visakhapatnam, which is a government hospital, were mostly people in the lower middle class or people below the poverty line and people who were going for manual labour for their livelihood. This factor could be expected to have an influence on the results of the survey by SF-36 and it did show in the low QOL with respect to physical function for the generic users. But this limitation is a natural one to this work as generics are being used in this region in government hospitals only. It is precisely to understand this situation that this research project was undertaken. But when the results were analyzed it was found that the mean QOL of generic users was, excepting one case, not only not less, but many times equal and some times more than that of the branded generic users.

Table.III: Reduction levels of B.P. and blood glucose levels in group – I and II

		B.P. reduction grade	G	B.G.
Group-I Patients having both B.P. and diabetes.	B.P. levels	0	6	5
		*	35	35
		**	15	30
		***	0	5
		Blood glucose reduction grade	G	B.G.
	Blood glucose levels	0	0	1
		*	12	21
		**	30	24
		***	20	8
		****	13	2
Group – II patients having Only B.P.	B.P. levels	B.P. reduction grade	G	B.G.
		0	1	14
		*	46	46
		**	45	31
		***	10	1

Fig.1: Comparison of QOLs of patients having BP and Diabetes using Branded Generics Vs. Generics

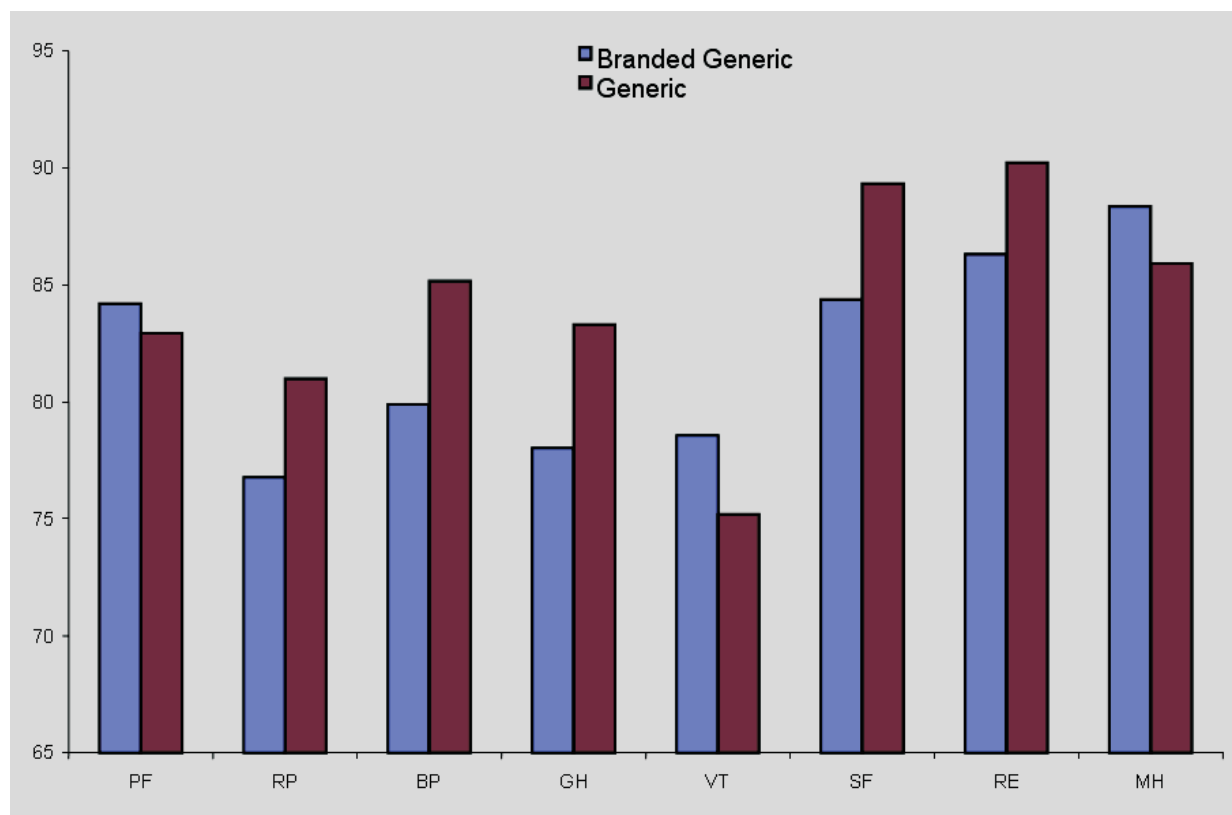


Fig.2: Comparison of QOLs of only BP patients using Branded Generics Vs. Generics (domain wise)

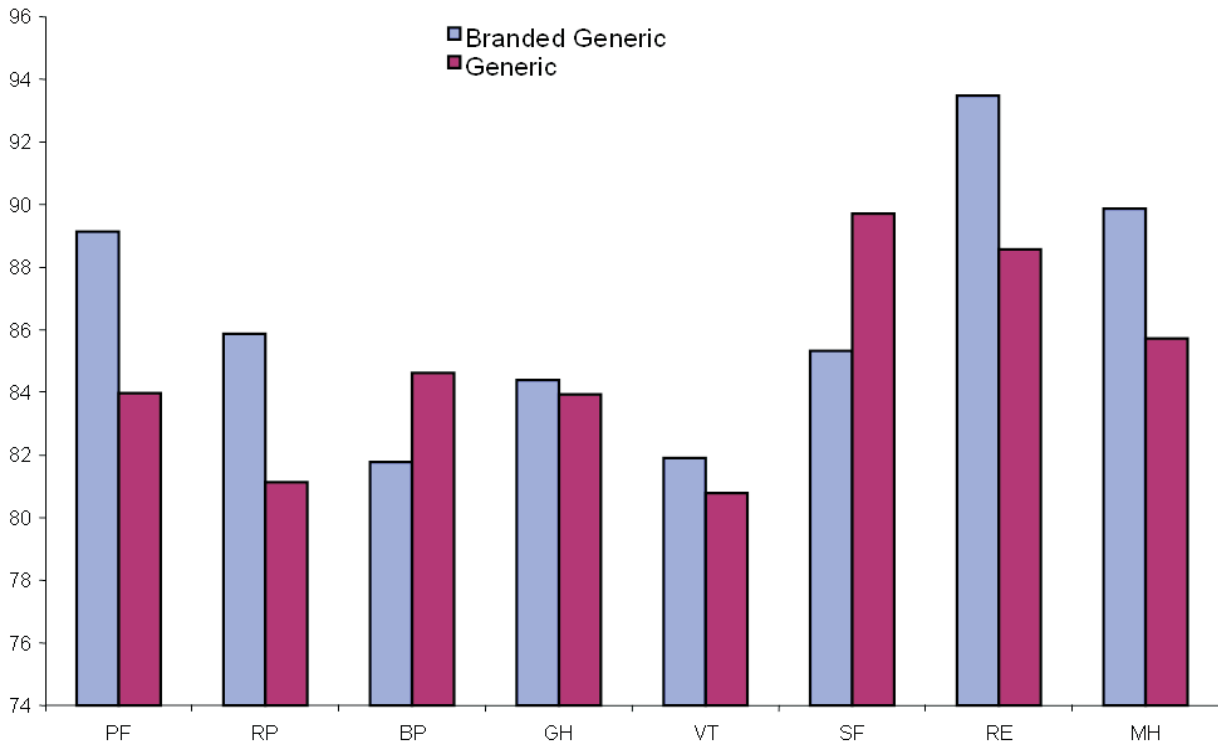


Fig.3: Comparison of total QOL of BG Vs G of different study groups (only BP and Diabetic, BP Patients)

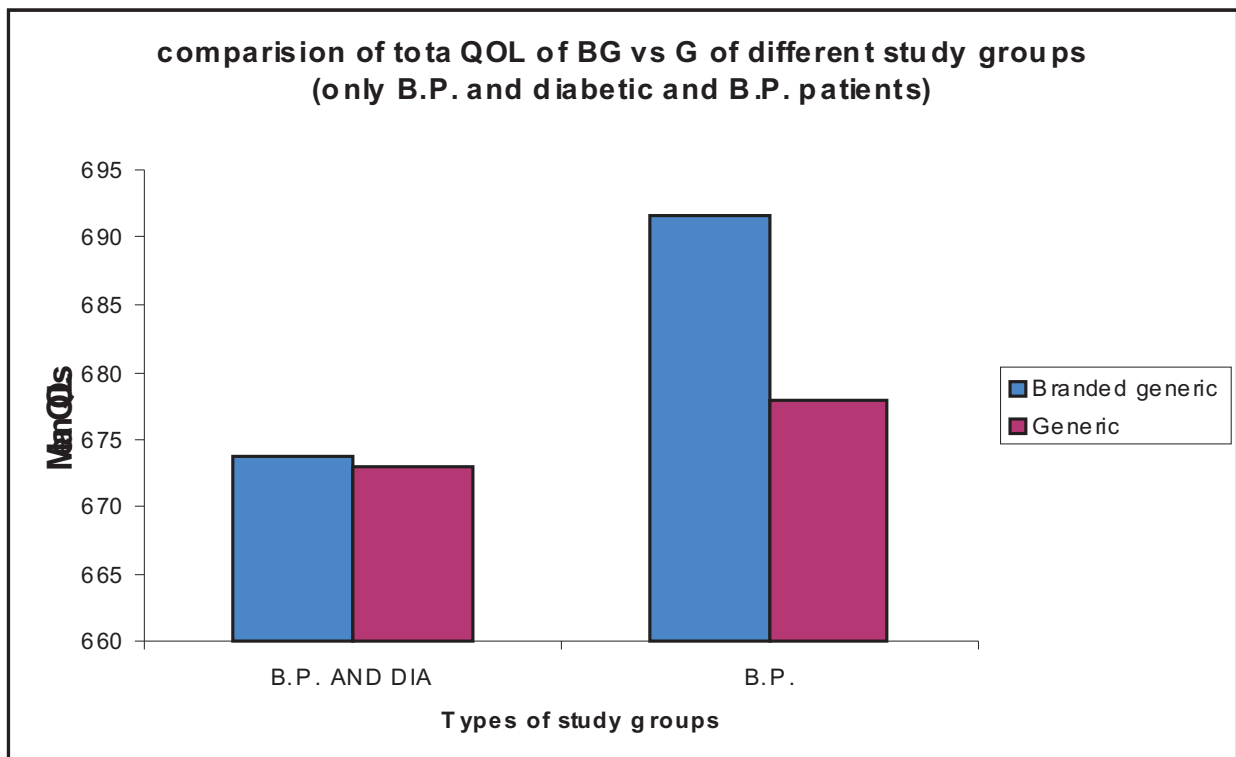


Fig.4: Individual Value Plots for QOLs of users of BP & Diabetic drugs, Branded Generics Vs. Generics

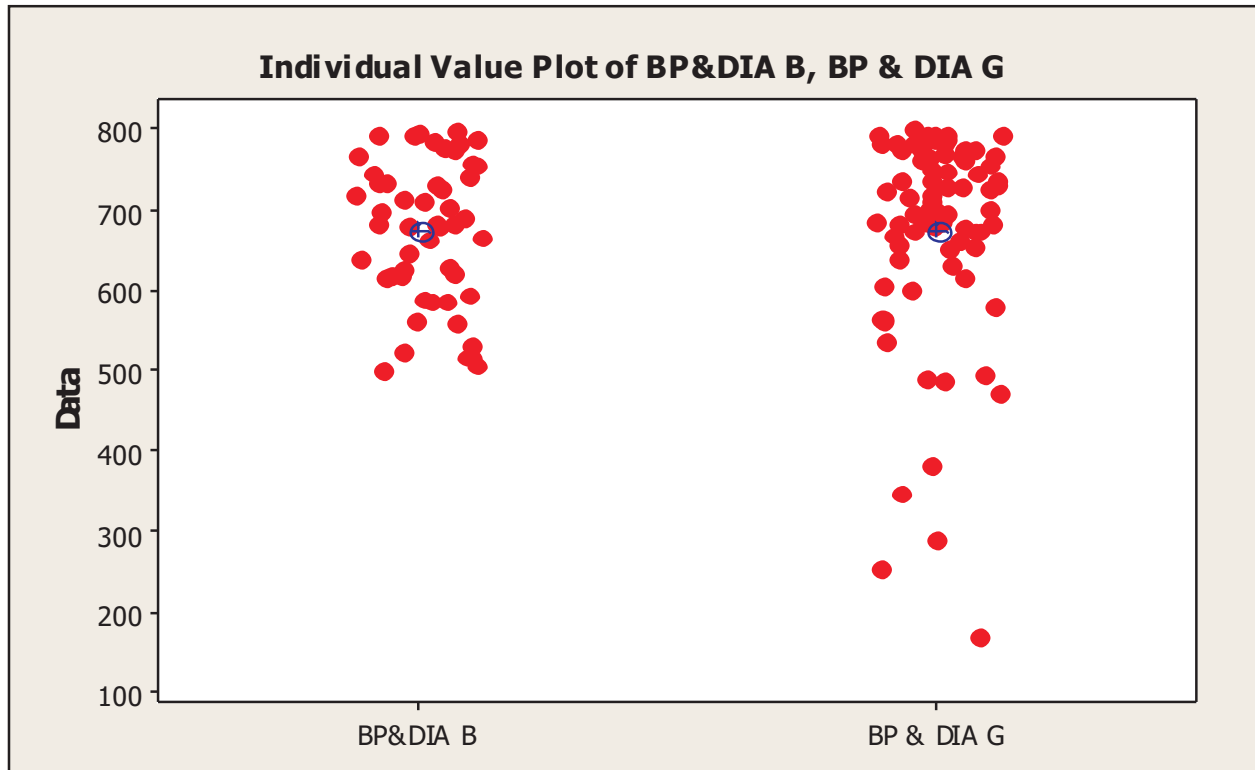


Fig.5: Box Plots for QOLs of users of BP & Diabetic drugs, Branded Generics Vs. Generics

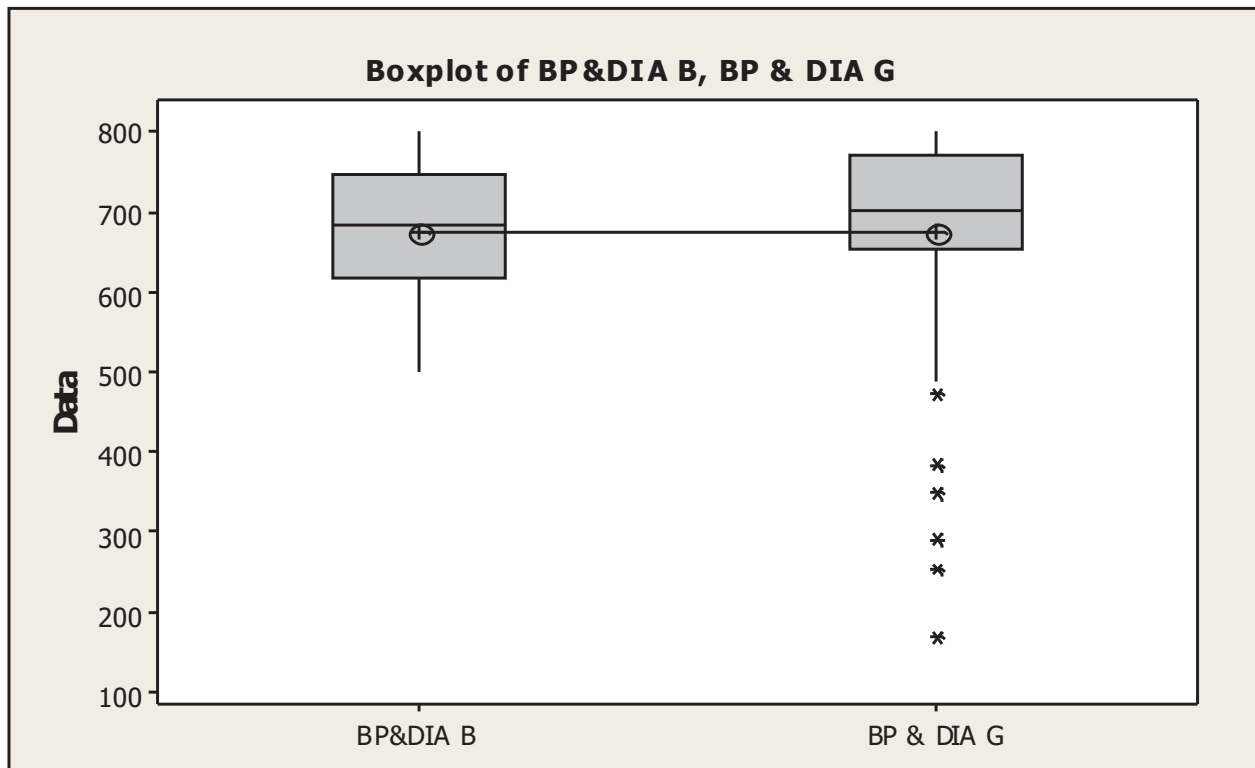


Fig.6: Individual Value Plots for QOLs of users of BP drugs, Branded Generics Vs. Generics

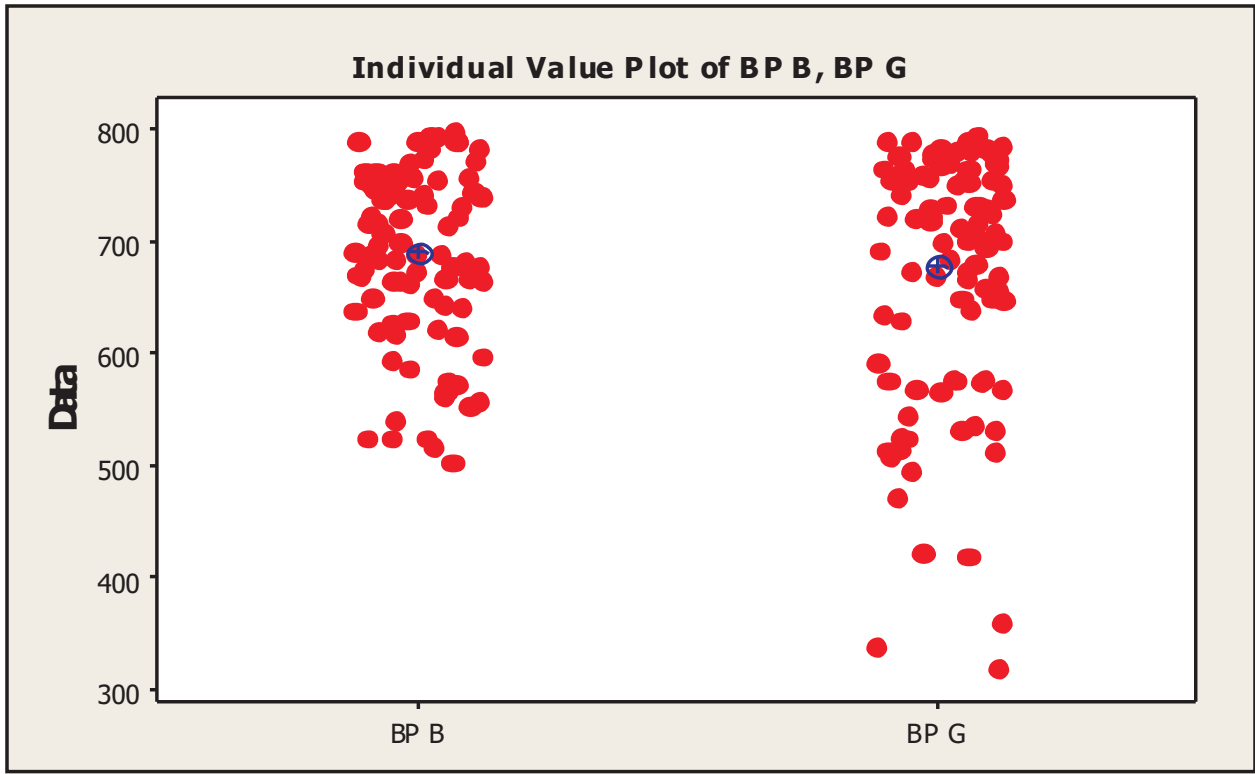


Fig.7: Box Plots for QOLs of Users of BP drugs, Branded Generics Vs. Generics

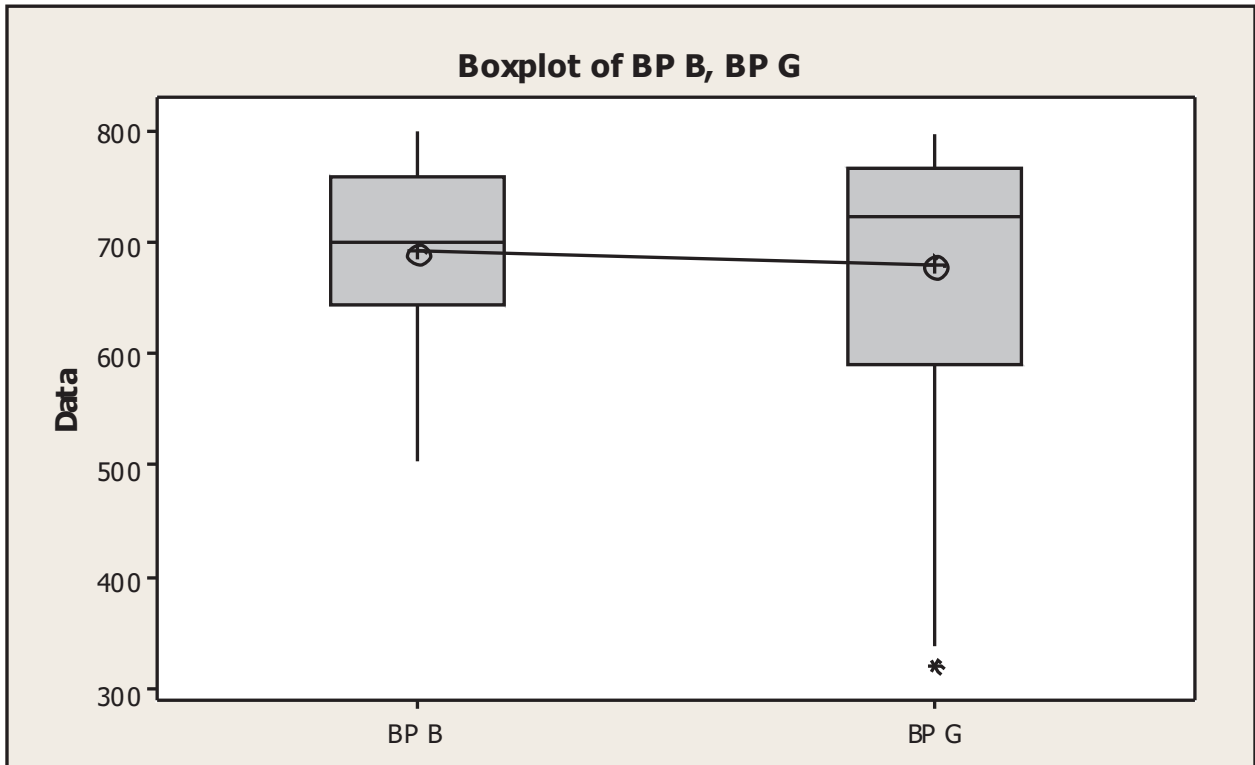
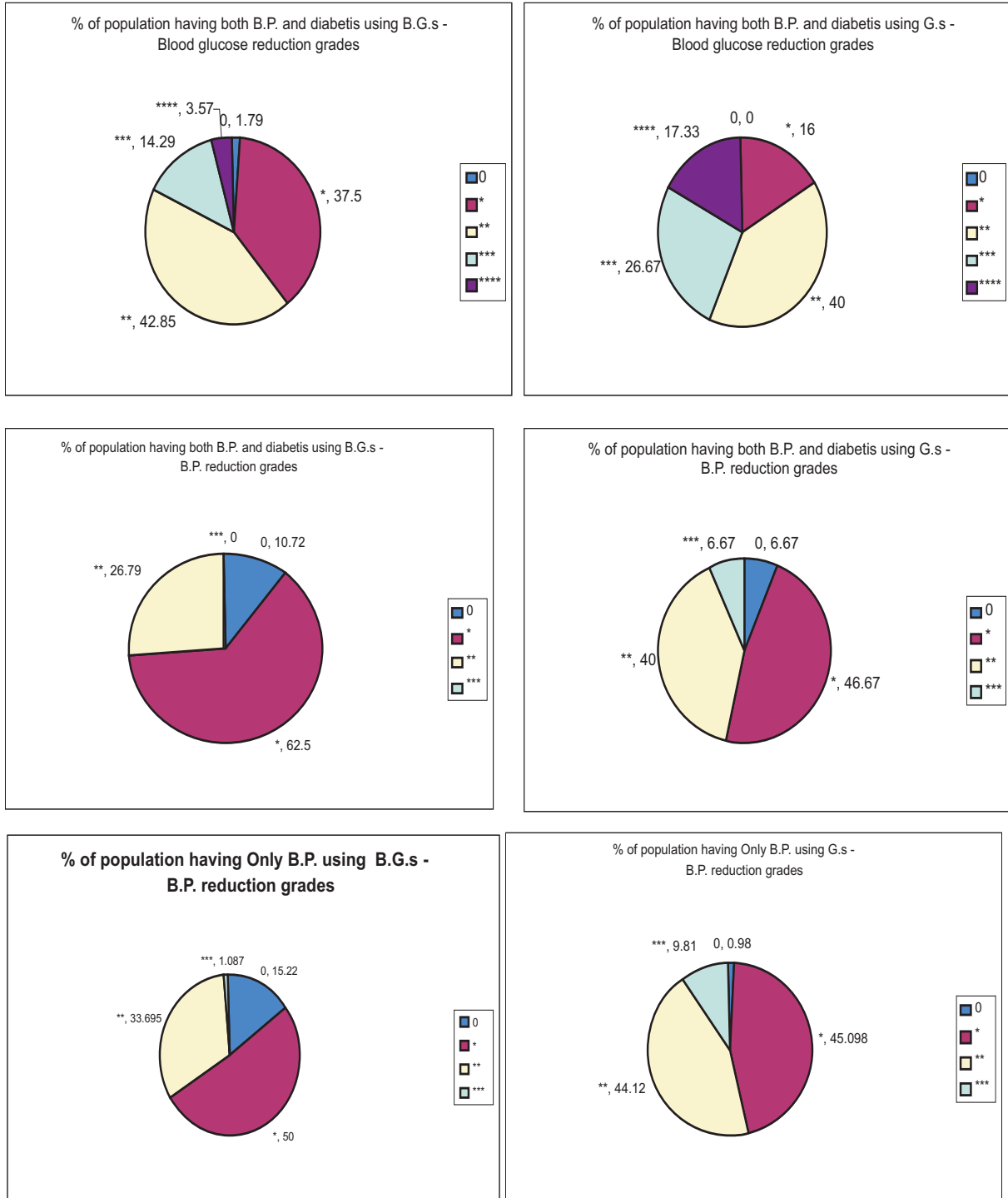


Fig.8: Reduction of BP and Blood glucose levels-% of populations in groups–I and II.



CONCLUSION

The results of this study clearly support the conclusion that there is no difference between the therapeutic efficacy of branded generic drugs and generic drugs. The Drugs and Cosmetics Act 1940 and the Drugs Price Control Order 1995 do not differentiate between BGs and Gs and do not insist on the Gs being priced lower. Hence the real situation is (Singal and Nanda)⁸ that in most cases BGs and Gs cost the same to the consumer, but to the retailer BGs cost more and Gs cost less. So the benefit that should accrue to the consumer is being snatched away by the retailer. The requirements are the Drugs and Cosmetics Act and the Drug Price Control Order should be amended to differentiate between BGs and Gs and Gs should cost less to the consumer. Then the burden on health care among patients will ease.

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Comparison of Efficacy and Safety of Atropine Sulphate and Glycopyrrolate in the Treatment of Organophosphorus Poisoning at St. Martha's Hospital, Bangalore.

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Abstract

Organophosphorus poisoning (OP) is the most common poisoning in India because of their easy availability. Atropine is considered the drug of choice in the management of OP poisoning and continues to be the standard treatment. Glycopyrrolate is a synthetic quaternary amine, a medication of the muscarinic anticholinergic group, with peripheral effects similar to those of atropine. The objective of this study was to compare the efficacy and safety of Atropine and Glycopyrrolate on OP poisoning patients. A total of 33 patients were enrolled in the study. All patients were recruited into two groups and accordingly received either Atropine or Glycopyrrolate as per the recognized dosing schedule as practiced in the hospital. The details of each OP poisoning case was observed and collected in the data collection form and assessed. All 33 patients were admitted to the ICU and the duration of hospital stay ranged from 2 to 21 days the mean ICU stay in Group-A was 5.43 ± 2.50 , in Group-B was 6.42 ± 5.13 ($P=0.511$). In Group-A, 40 patients required ventilation, whereas 40% did not and in Group-B, 36.85% required ventilation, and 63.15% did not ($P=0.304$). Among the ADRs documented the most prominent one was Altered Sensorium seen in 64.28% cases in Group-A ($P<0.001$) whereas in Group-B none had Altered sensorium. The total cost for the anticholinergic treatment in Group-A ranged from 43 rupees to 1503 rupees and in Group-B it was 639 rupees to 4032 rupees ($P<0.001$). 3 patients expired, two out of which 2 were from Group-A. The study revealed that both the groups had the same efficacy, but Atropine showed a very distinct CNS toxicity and Glycopyrrolate being a relatively expensive drug.

Key words: Organophosphorus poisoning; Atropine; Glycopyrrolate; safety; efficacy; expensive; toxicity.

INTRODUCTION

India is a predominantly agrarian country with about 60-80% rural population. Pesticides are routinely used for advanced farming. These are readily available over the counter. Therefore, a pesticide is an easy access source for suicidal purpose. Poisoning is seldom included as a priority for health research in India, though every year, hundreds of people are losing their lives prematurely from pesticide poisoning.¹

Organophosphates were first discovered more than 100 years ago, at present the predominant group of insecticides employed globally for pest control. The compounds are toxic to humans and represent an important source of poisoning domestically, in some occupations, or when ingested as a suicidal agent. Today organophosphates are used worldwide in agriculture as well as in most household gardens. This easy availability

of the compounds has resulted in a gradual increase in accidental and suicidal poisoning mainly in developed countries.²

Deliberate self-harm has often been thought as a problem particularly to the industrialized world. 75% of the world-wide total of deaths from self-harm. Pesticide poisoning from occupational, accidental and intentional exposure is a major developing world public health problem. However, it is deliberate self-poisoning that causes majority of deaths and the immense strain that pesticides put on hospital services, particularly in Asia. Many studies have shown that deliberate self-poisoning has a far higher mortality than accidental poisoning. Reducing deaths from self-harm will require interventions to both reduce the incidence of harmful behaviour and to improve medical management of acute poisoning.³

Main stay for the treatment of organophosphorus poisoning is anticholinergic treatment. Conventional

treatment being atropine administration to antagonise the excessive cholinergic effects. (bradin) *Glycopyrrolate is a synthetic quaternary amine, a medication of the muscarinic anticholinergic group, with peripheral effects similar to those of atropine. It is longer acting drug and does not cross the blood brain barrier. Thus glycopyrrolate, unlike atropine is less apt to cause altered consciousness in patients being treated for organophosphorus poisoning.*⁴

The aim of this study was to compare the efficacy of glycopyrrolate with that of atropine in patients admitted due to OP poisoning by comparing the number of days of hospital stay and ventilator requirements and to compare the safety by monitoring the side effects.

STUDY DESIGN

A comparative study on 33 patients where the efficacy and safety of the two anticholinergic drugs (Atropine and Glycopyrrolate) was studied on organophosphorus poisoning patients.

PATIENTS AND METHODS

33 patients admitted to the intensive care unit (ICU) due to organophosphorus poisoning from June 2009- Feb 2010, at St Martha's hospital, Bangalore were included in the study. Patients who consumed organophosphorus compounds were admitted to the ICU after treatment at the emergency ward by atropine along with stomach wash. After obtaining the consent from the patients attendants, they were recruited into two groups, Group-A (received atropine) and Group-B (received glycopyrrolate) as per the recognized dosing schedule as practiced in the hospital after the emergency ward treatment. The details of each OP poisoning case was observed and collected in the data collection form which included the demographic details of the patients, suspected OP compound consumed, duration of time taken to bring the patients to the hospital, patients taken to other hospital before admission, ICU stay, ventilation requirement, total hospital stay, ADRs, Pseudo-cholinesterase levels, total cumulative dose of anticholinergic treatment, duration of drug given, other clinical manifestations, complications and death.

The patients in both the groups were assessed based on the date collected.

Descriptive statistical analysis was carried out. Significance was assessed at 5 % level of significance, Student t test (two tailed, independent) was used to find the significance of study parameters on continuous scale

between two groups (Inter group analysis) Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups.

RESULTS

33 patients were recruited to receive the treatment in two groups. Among the total patients 22(66.7%) patients were male and 11(33.3%) patients were females. Age group ranged from 18 years to 39 years and above, where majority of the patients were from 18-28 years of age. The mean age being 28.76±12.14 years. 14(42.4%) patients were recruited in Group-A and received atropine and 19(57.6%) patients were recruited in Group-B and received glycopyrrolate. suspected poison consumed was Chlopyrifos (9.1%), Diazone (3.1%), Dichlovos (3.1%) and parathion seen in most of the patients (48.5%). unidentified compound accounted up to 36.4% in both the groups (Group-A-41.7% and Group-B-58.3%).

The baseline characteristics of the patients are shown in Table-1. The treatment groups were comparable in all respects. Clinical outcomes are shown in Table-2. No significant difference could be detected in the efficacy of the two drugs. All parameters in the clinical outcome was statistically significant. Incidence of Altered sensorium was significantly more in Group A when compared to Group B with P<0.00 and total cost of drug was significantly more in Group B with P<0.001. Among the three patients who died, one was geriatric patient and expired due to cardiac arrest. The second patient was a male of 34 years and died due to respiratory paralysis. The third patient was from Group-B and expired due to delay in admission to the hospital after the consumption of OP compound.

DISCUSSION

The study conducted on 33 OP poisoning patients has shown that the efficacy of the two drugs is similar. All patients were admitted to the Intensive Care Unit and the duration of stay ranged from 2 to 21 days, out of which 9(64.3%) patients from Group-A were in ICU for lesser than 5 days and 2 (14.3%) above 10 days. In Group-B 12 (63.2%) patients stayed for lesser than 5 days and 3(15.7%) above 10 days. The mean ICU stay in Group-A was 5.43±2.50, which is slightly higher than a retrospective study conducted at Hyderabad for a period of two years,⁵ where as in Group-B the mean ICU stay was 6.42±5.13; however it is statistically similar between the two groups with P=0.511.

Table.1: Baseline Characteristics

	Group-A (Atropine) N=14	Group-B (Glycopyrrolate) N=19
Time duration to admission (hours)	22*	9*
Taken to other hospital before admission (p=0.719)	10 (71.4%)	12 (63.2%)
Treatment prior hospitalisation (p=1.000)	6(42.9%)	7(36.8%)

* Mean±SD

Table.2: Clinical Outcomes

	Group-A (Atropine) N=14	Group-B (Glycopyrrolate) N=19
ICU stay (days) P=0.511	5.43±2.50*	6.42±5.13*
Ventilation requirement P=0.304	7 (50%)	8 (36.8%)
Total hospital stay (days) P=0.594	7.21±3.59*	8.16±5.78*
Altered sensorium P<0.001	9(64.3%)	0
Hyperpyrexia	1(7.1%)	0
Tachycardia	14(100%)	16(84.2%)
Cost (rupees) P<0.001	35.92±22.13*	412.58±73.74*
Other clinical manifestations		
Intermediate syndrome	1(7.1%)	2 (10.6%)
Delayed onset encephalopathy and coma P=0.620	0	2(10.6%)
Respiratory infections	1(7.1%)	0
Death	2(14.3%)	1(5.3)

* Mean±SD

In Group-A, 7(40%) patients required ventilation whereas 7 (50.0%) did not and in Group-B 8 (36.8%) required ventilation, and 13(63.2%) did not. The ventilation requirement is slightly greater for group-A when compared to group-B with P=0.304, but no statistical significance was seen.

Some of the previous studies revealed that Atropine treatment is effective but carries the risk of toxicity such as CNS effects and tachycardia.^{6,7,8} Out of all the patients included in the study altered sensorium was seen in 9 (64.3%) cases and all the 10 cases were from Group-A, none of the patients in Group-B exhibited this. Incidence

of Altered sensorium is significantly more Group A when compared to group B with P<0.001.

Among these patients, altered sensorium was seen in 2(14.3%) patients, during admission and in 7(50.0%), 48-72 hours later. Patients where altered sensorium was seen late were admitted in a time duration ranging from 20 minutes to 1 day. The type of poisoning seen in them is majorly parathion and the main neurotoxicity seen was restlessness and hallucinations.

On the other side Group-B consisted of 2(10.5%) patients with altered sensorium during admission which eventually disappeared after 48 hours. Among the ADRs

documented the most prominent one was Altered Sensorium seen in 9 (64.3%) cases in Group-A, followed by Hyperpyrexia in 1(7.1%) and Tachycardia in all patients. 2 patients (10.5%) in Group-B experienced nausea and 3(15.8%) patients did not have tachycardia. Nausea is not applicable in the comparison between the groups as patients treated with atropine were kept NPO (nil per oral).

In Group-A the dosage of anticholinergic treatment ranged from a minimum of 49mg to a maximum of 1g 792mg, total minimum cost of 43 rupees to a total maximum cost of 1503 rupees. In Group-B it ranged from a minimum of 14.5mg to maximum of 89.27mg, minimum cost of 639 rupees to a maximum of 4032 rupees. The cost of Glycopyrrolate is relatively higher than Atropine. Total cost of drug is significantly more in Group B with $P < 0.001$.

Other clinical manifestations seen were intermediate syndrome in 1(7.1%) case in Group-A and 2(10.5%) cases in Group-B. Along with this delayed onset encephalopathy and coma were seen in 2(10.5%) patients in Group-B. Among the two patients who developed delayed encephalopathy and coma one patient was admitted 6 hours after the consumption of OP compound, however such small sample size does not allow us to conclude if atropine does not manifest this clinical feature, however statistically other clinical manifestations are similar in both the groups with $P = 0.620$. A study carried out in south India reported a few cases of patients developing delayed encephalopathy and coma 4-5 days after the consumption of OP compound but this study did not suggest any other specific drug treatment for this.⁹

Respiratory infection was seen in 1(7.1%) case from Group-A. Out of 33 cases 31 patients recovered and three patients expired, out of which two were from Group-A. Incidence of mortality is also statistically similar in both groups with $P = 0.561$.

The mortality rate seen was 14.3% in Group-A and 5.3% in Group-B.

CONCLUSION

This study revealed that atropine and glycopyrrolate showed similar efficacy; however CNS toxicity was greater in the group receiving atropine. Glycopyrrolate was found to be a relatively more expensive drug than atropine.

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Effect of Insulin Therapy in Type-2 Diabetes in Improving B-Cell Function and Glycemic Control Compared with Oral Anti-Diabetic Agents with or without Insulin in Routine Clinical Practice

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Abstract

Observational studies are valuable tools for assessing the applicability of results from randomized controlled trials to broader patient populations. They are especially important in chronic diseases such as diabetes, as they can provide a comprehensive picture of the safety and effectiveness of a particular therapy across cultures and phenotypes. The aim of this study is to determine Efficacy, Safety and Tolerability of the early intervention of insulin treatment with or without Oral Anti Diabetic's (OAD) in type 2 diabetes for improving glycemic control compared with OAD's alone and to determine the persistence of effect up to 6 months in the intervention group in routine clinical practice. The effect of the anti-diabetic agents will be measured by monitoring the Fasting blood glucose level (FBG), Post prandial blood glucose level (PPBG), Glycated hemoglobin levels, C-Peptide levels and all other necessary parameters needed for diabetic management.

Key words: Type 2 Diabetes, Oral Anti Diabetics, Fasting Blood Glucose Level

INTRODUCTION

The prevalence of diabetes mellitus has dramatically increased in recent years in India, an estimated 40 million nationwide have diabetes. A similar, disproportionate number of hospitalized patients have diabetes. In the recent, the prevalence of diabetes in hospitalized adults is conservatively estimated at 12.4%- 25.0% and for every two patients diagnosed with diabetes in the hospital, there may be at least one other patient in the hospital with unrecognized diabetes, who is at risk for poor outcomes and safety issues, as well as higher health care costs. However, the prevalence and an accurate estimate of the number of patients admitted to hospitals with diabetes have never been reported because Type 2 diabetes is under diagnosed in hospital setting.

The prevalence of diabetes is increasing in India, but glycemic control appears to be deteriorating. Glycemic control remains the major therapeutic objective for diabetics. Although type 2 diabetes is a progressive disease, patients in the early stages of diabetes may advance at different rates. While prior studies have identified factors predicting glycemic control among patients with type 2 diabetes on therapy, we have not found studies that have examined predictors of disease

progression in patients with A1C >7% and not on medication therapy. Moreover, no studies have addressed this question in the "usual care" outpatient setting, where most patients first diagnosed with type 2 diabetes are initially managed. Furthermore, no recent studies have examined the factors associated with early initiation of glucose-lowering medications.

As a result of the landmark United Kingdom Prospective Diabetes Study (UKPDS), the clinical importance of glycemic control in patients with type 2 diabetes is well established. The American Diabetes Association (ADA) estimates that the risk of diabetes-related mortality increases 25% for each 1% increase in HbA1c. Each percentage point increase in HbA1c has also been estimated to correspond to a 35% increase in the risk of micro vascular complications and an 18% increase in the risk of myocardial infarction (fatal plus non-fatal).

Despite evidence that normalizing blood glucose levels as far as is practicable minimizes the risk of diabetic complications, glycemic control in patients with type 2 diabetes is commonly poor in routine clinical practice. Traditional therapy for patients with type 2 diabetes has primarily focused on controlling FPG levels with one or more oral anti-diabetic drugs (OAD's) and/or basal insulin. Although both fasting and postprandial blood glucose levels contribute to glycepmic control, these

	First visit	3rd Month	6th Month
Monitoring Parameters	Height/ Body wt	Height/ Body wt	Height/ Body wt
	Blood pressure	Blood pressure	Blood pressure
	BMI	BMI	BMI
	Blood sugar levels	Blood sugar levels	Blood sugar levels
	Random	Random	Random
	FBG	FBG	FBG
	PPBG	PPBG	PPBG
	OGTT	HbA1C	OGTT
	HbA1C	Hypoglycemia	HbA1C
	Hypoglycemia	Hyperglycemia	Fasting C-Peptide
	Hyperglycemia		Hypoglycemia
	Complications		Hyperglycemia
	Medication regimen		Complications
		Medication regimen	

RESULTS

The aim of this study was to assess effect of insulin therapy in type 2 diabetes in improving β -cell function & glycaemic control in routine clinical practice. Patients with newly diagnosed type 2 diabetes who required insulin as per the physician's decision based on the biochemical profile (if FBG > 200mg/dl or PPBG > 300mg/dl or HbA1C > 9%) were all included in this study. A total of 450 type 2 diabetic patients were recruited out of 600 screened. Out of the total study, 319 patients received complete 6 month course of treatment with regular follow-up, in these 97 patients on insulin mono-therapy, 88 patients on combination insulin + OAD and 134 patients on OAD alone received complete six month course of treatment.

Demographics and Disease character were shown in Table-1. Totally, 207 male and 112 female patients with the mean age (years) of 48.11 ± 8.33 and body weight (kgs) of 65.7 ± 9.79 were included in this study (Table - 1). Mean blood glucose level, presenting symptoms (%) and complications (%) at the time of recruitment were reported in Table -1.

Glycemic Control

Glycated Hemoglobin Level (HbA1C)

In the study Insulin treatment was compared with insulin + OAD and OAD alone in newly diagnosed type 2 diabetes with severe hyperglycemia. The patients were recruited with mean HbA1c of more than 9.00%, after 6 month intensive insulin therapy results showed that, the HbA1C level (Figure - 1) was significantly lower in the insulin group than in the insulin + OAD than OAD's (6.73

$\pm 0.99\%$ Vs. $6.81 \pm 1.02\%$ Vs $7.44 \pm 1.04\%$; ($P = 0.0001$). Our data suggests that, at the end of 6 months treatment HbA1C levels with insulin group < insulin + OAD < OAD alone (Table -2). It indicates that, the optimal blood glucose level was very well controlled with insulin group as compared to insulin + OAD or OAD alone.

Blood Glucose Levels

Fasting Blood Glucose (FBG)

The patients recruited with mean FBG of > 200 mg/dl, at the end of 6th month, FBG levels (Figure - 2) were almost similar in all three groups (85.505 ± 13.085 Vs 85.11 ± 13.949 Vs 86.694 ± 14.052 ; $P = 0.8875$). Our data suggests that, at the end of 6 months treatment the average reduction in fasting blood glucose levels were high with insulin group (132.72 mg/dl) as compared to insulin + OAD (128.65) or OAD alone (88.64 mg/dl) (Table -2).

Post Prandial Blood Glucose Level

The patients were recruited with mean PPBG of more than 200 mg/dl, at the end of 6th month, PPBG levels (Figure - 3) were almost similar in all three groups (136.16 ± 29.088 Vs 136.07 ± 28.00 Vs 137.66 ± 28.84 ; $P = 0.9927$). Our data suggests that, at the end of 6 months treatment the average reduction in postprandial blood glucose levels were high with insulin group (263.81 mg/dl) as compared to insulin + OAD (254.88 mg/dl) or OAD alone (188 mg/dl) (Table -2).

Oral Glucose Tolerance Test Levels (OGTT)

The study suggests that, at the end of 6 months treatment

2-hours OGTT levels (Figure-4) significantly reduced in Insulin group as compared to combination of Insulin + OAD and oral anti-diabetic agents alone ($389.67.53 \pm 47.05$ Vs 421.72 ± 64.27 Vs 382.1 ± 73.17 ; $P < 0.0001$). The data suggests that, at the end of 6th months insulin group has greater influence in controlling 2hrs-OGTT level as compared to insulin + OAD or OAD alone.

C- Peptide Level

At the end of 6 months treatment, Fasting C-Peptide level (Figure – 5) was significantly high with insulin group as compared to combination Insulin + OAD and OAD's (1.0312 ± 0.191 Vs 0.9684 ± 0.133 Vs 0.8976 ± 0.097 ; $P = 0.0013$). The data demonstrates that, in the early intervention of insulin treatment significantly preserves the β -cell function, and it improves the insulin secretion as compared to insulin + OAD and OAD alone.

Adverse Events

Hypoglycemia

At the end of 6 months treatment, percentage of hypoglycemia reported insulin group (15.46%), combination of insulin + OAD (22.72%) and OAD (4.47%) (Table - 2). No severe hypoglycemia occurred in either group. The overall rate of minor hypoglycemia showed no significant difference between these groups.

Weight Gain

At the end of treatment there was no significant difference in body weight from these treatment groups, insulin. (66.87 ± 9.41) Vs insulin + OAD (64.07 ± 9.09) Vs OAD alone (64.99 ± 9.97); ($P = 0.1336$). But there was a small increase in body weight in the insulin group from baseline to the end point (Table - 2).

Table.1: Demographics & Disease characteristics at the time of Recruitment

Parameters	Group I (n=97)	Group II (n=88)	Group III (n=134)
Male (%)	65 (67.01)	59 (67.04)	83 (61.94)
Female (%)	32 (32.98)	29 (32.96)	51 (38.06)
Mean age (years±SD)			
Male	49.16 ± 8.79	50.57 ± 8.59	48.80 ± 8.82
Female	46.22 ± 8.81	46.33 ± 9.40	47.60 ± 8.73
Body Wt in kgs ± SD	66.56 ± 9.93	64.86 ± 9.32	65.68 ± 10.14
Family History of Diabetes (%)	21 (21.64)	17 (19.31)	26 (19.40)
<u>Mean Blood Glucose level ± SD</u>			
FBG (mg/dl)	218.34 ± 61.14	214.36 ± 59.86	175.38 ± 28.49
PPBG (mg/dl)	394.94 ± 94.78	386.95 ± 92.35	321.73 ± 18.34
HbA1C (%)	9.61 ± 1.65	9.66 ± 1.67	9.28 ± 1.04
<u>Presenting symptoms at the time of detection (%)</u>			
Polyurea	56 (57.73)	42 (47.72)	72 (53.73)
Nocturia	26 (26.80)	14 (15.90)	33 (24.62)
Giddiness	15 (15.46)	32 (36.36)	12 (8.95)
Polyphagia	12 (12.37)	8 (9.09)	21 (15.67)
Polydypsia	17 (17.52)	6 (6.81)	14 (10.44)
Tiredness	42 (43.29)	38 (43.18)	63 (47.01)
Weight loss	13 (13.40)	7 (7.95)	16 (11.94)
Abdominal pain	6 (6.18)	4 (4.54)	12 (8.95)
Numbness	12 (12.37)	8 (9.09)	17 (12.68)
<u>Complications (%)</u>			
Hypertension	6 (6.18)	5 (5.68)	7 (5.22)
CV Events	3 (3.09)	2 (2.27)	5 (3.73)
Pain in limbs	6 (6.18)	2 (2.27)	8 (5.97)
Oedema	2 (2.06)	3 (3.40)	2 (1.49)
Respiratory Disorders	-	-	2 (1.49)

Table.2: Biochemical of the study subjects at the end of 6 months treatment.

Parameters	Insulin alone (n=97)	Insulin + OAD (n=88)	OAD Alone (n=134)
Mean Blood Glucose level			
FBG (mg/dl)	? 132.72	? 128.65	? 88.69
PPBG (mg/dl)	? 263.08	? 254.88	? 188.68
HbA1C (%)	? 2.88	? 2.85	? 1.84
2-hrs OGTT (mg/dl)	? 141.86	? 34.02	? 16.07
C-Peptide Level	1.0312	0.9684	0.8967
Adverse Events			
Hypoglycemia (%)	15.46	22.72	4.47
Body Wt in kgs ± SD	? 66.87 ± 9.41	? 64.07 ± 9.09	? 64.99 ± 9.97

Fig.1: Comparison of HbA1C levels at the end of six months treatment.

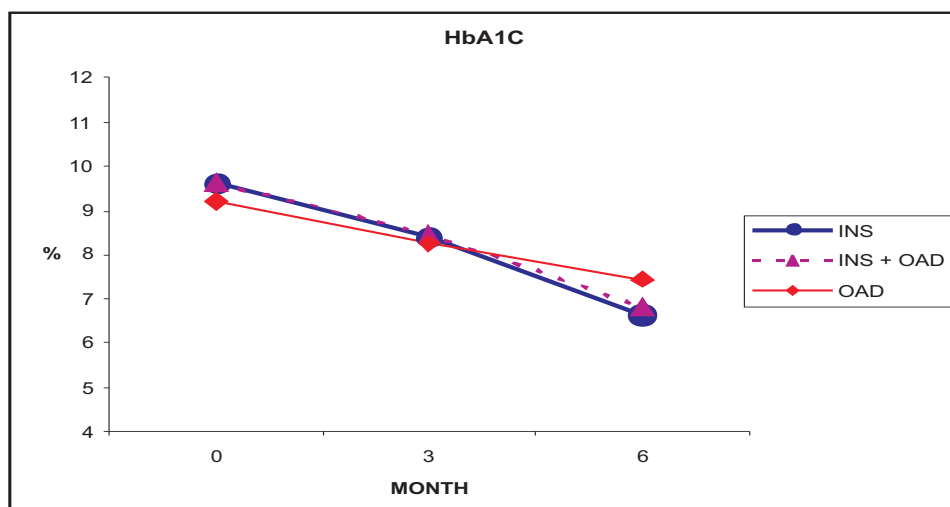


Fig.2: Comparison of FBG levels.

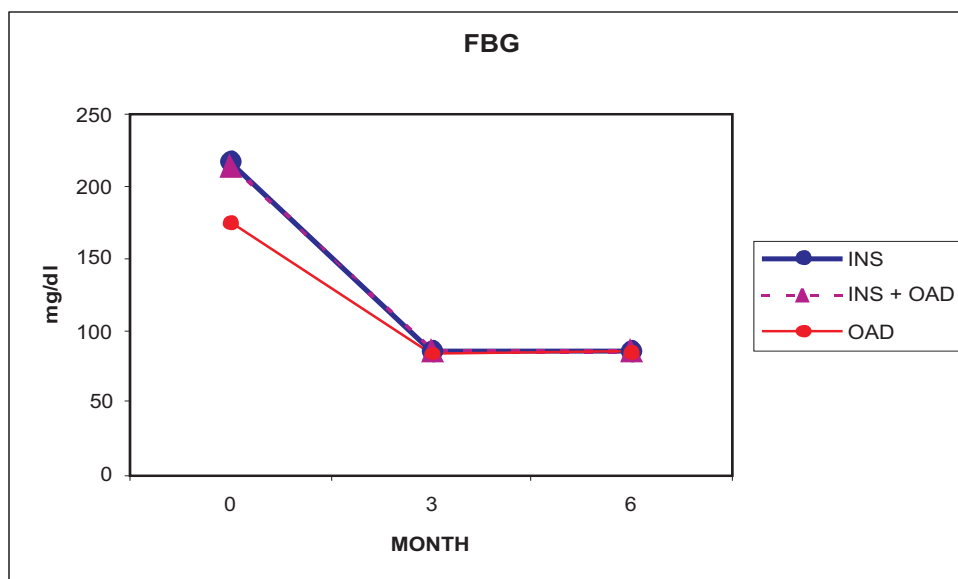


Fig.3: Comparison of PPBG levels

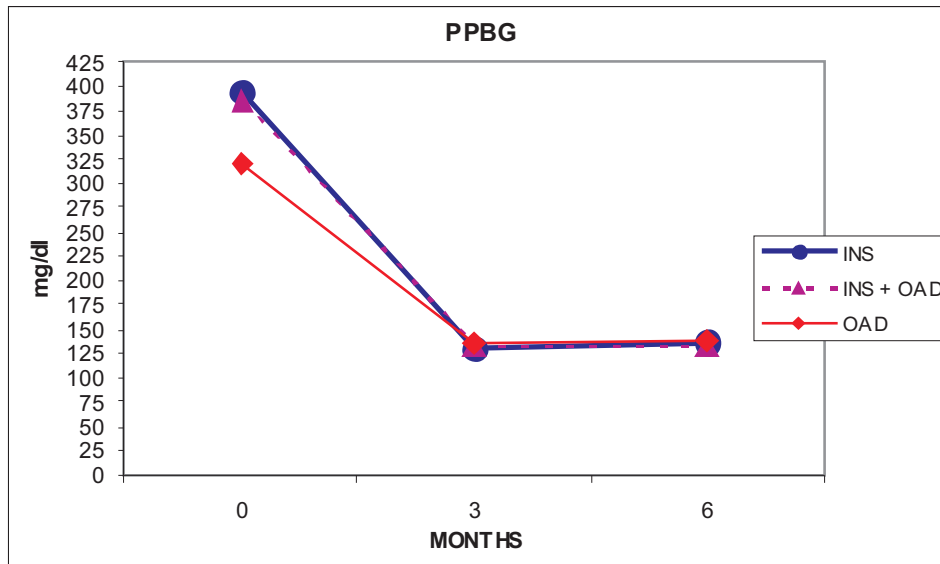


Fig.4: Comparison of OGTT Levels

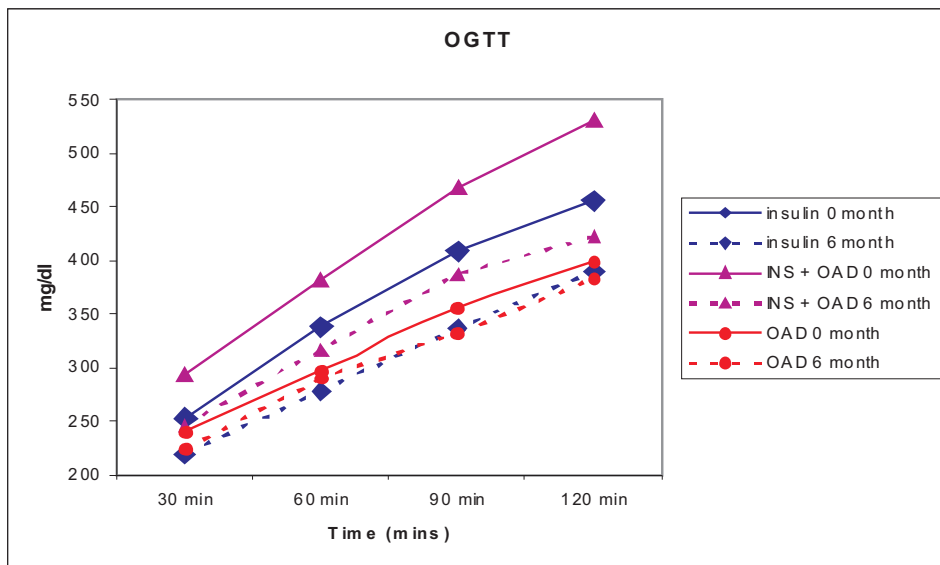
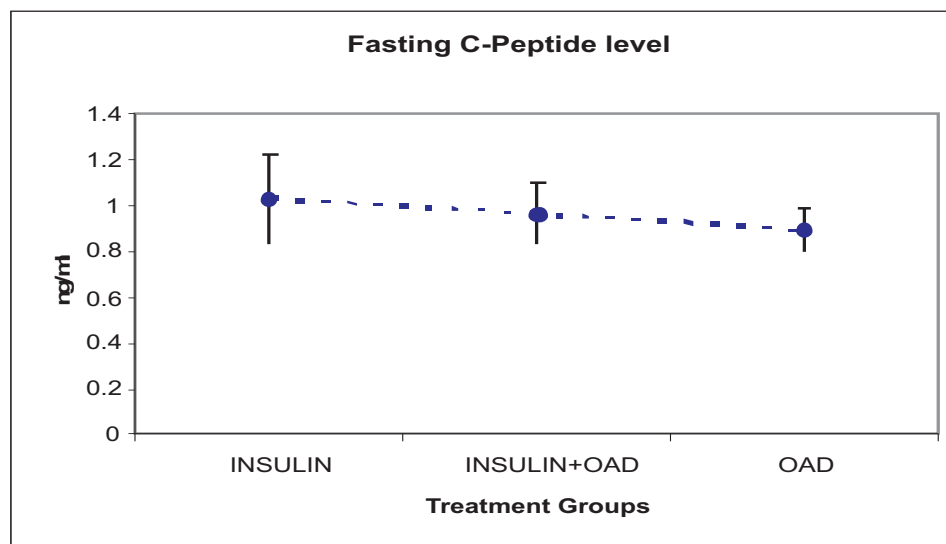


Fig.5: Comparison of fasting C-Peptide level at the end of 6 month treatment

DISCUSSION

Insulin resistance and impaired insulin secretion are the main pathophysiological defects responsible for the development of hyperglycemia in type 2 diabetes. ^(4,5)

With the continuous presence of insulin resistance, progressive loss of β -cell function is the crucial defect. The continuous decline in β -cell function is affected by glucotoxicity generated by hyperglycemia and lipotoxicity due to lipolysis ⁽⁶⁾. Impaired β -cell function appears to be reversible, particularly in the early stage of the disease, when the limiting threshold for reversibility of decreased β -cell mass has probably not been passed. So the potential benefits of early, aggressive intervention with insulin treatment to counter both β -cell dysfunction and insulin resistance must be considered. Several reports have shown that short-term intensive insulin therapy can induce long-term glycemic control in newly diagnosed type 2 diabetic patients with mild to moderate hyperglycemia ^(7,8). However, more than half of these patients require oral anti-diabetes drug (OAD) therapy within 1 year to maintain normoglycemia.

Newly diagnosed diabetes patients often get their C-peptide levels measured as a means of distinguishing type 1 diabetes and type 2 diabetes. C-peptide levels are measured instead of insulin levels because insulin concentration in the portal vein ranges from two to ten times higher than in the peripheral circulation. The liver extracts about half the insulin reaching it in the plasma,

but this varies with the nutritional state. The pancreas of patients with type 1 diabetes is unable to produce insulin and therefore they will usually have a decreased level of C-peptide, whereas C-peptide levels in type 2 patients are normal or higher than normal. Measuring C-peptide in patients injecting insulin can help to determine how much of their own natural insulin these patients are still producing. C-peptide is easily detected because antibodies that are sensitive to it are readily available, whereas antibodies to insulin are much more difficult to obtain. Can be used for identifying factitious disorder, Hypoglycemia with low C-peptide level may indicate abuse of insulin. ⁴²

When a new-onset type 2 diabetic patients presents with severe hyperglycemia, there are defects in insulin secretion and action, which is optimally treated with aggressive insulin injections, after the symptoms have been relieved, it may be possible to withdraw insulin and shift to oral agents¹. We hypothesized that continuous insulin therapy for 6 months in new-onset type 2 diabetes with severe hyperglycemia may have a prolonged glycemic control. To address this concept, we designed this 6-month study to evaluate whether treatment with insulin is advantageous compared with Insulin + OAD's and OAD's alone in newly diagnosed type 2 diabetes with severe hyperglycemia.

Glycemic Control

Blood Glucose level

There has emerged evidence that short-term intensive insulin therapy in newly diagnosed type 2 diabetes could improve glycemic control associated with improved insulin secretion⁽⁸⁻¹⁰⁾. Ryan et al.⁽⁹⁾ recently reported that, in 16 newly diagnosed type 2 diabetic case subjects with moderate hyperglycemia (mean fasting blood glucose of 239 mg/dl), a 2- to 3-week course of intensive insulin therapy was able to maintain good glycemic control at 1 year in seven of the subjects. In a similar study⁽¹⁰⁾, 138 newly diagnosed type 2 diabetic patients with fasting blood glucose >200 mg/dl (mean fasting blood glucose of 268 mg/dl, peak blood glucose of 390 mg/dl) were hospitalized and treated with continuous subcutaneous insulin infusion for 2 weeks. Optimal glycemic control was achieved within 6.3 ± 3.9 days in 126 patients. In patients with moderate hyperglycemia, a 2-week course of intensive insulin therapy achieving near-euglycemia might induce long-term glycemic control. This result may not be suitable in patients with severe hyperglycemia, such as our subjects with mean initial fasting blood glucose of >200 mg/dl and postprandial blood glucose of >300 mg/dl.⁽⁹⁾

All of our study subjects had received 6 month intensive insulin therapy to make sure the glycemic control was optimal. After recruitment, almost all of the patients were unable to maintain euglycemia without medication. (Table - 2) At the end of 6 months treatment, insulin group showed significant reduction in mean fasting and postprandial blood glucose levels as compared to combination of insulin + OAD and OAD alone. Our data revealed that 6 months of intensive insulin treatment with near-normoglycemia cannot maintain good glycemic control lasting for a long period. We suggest that short-term intensive insulin therapy may induce long-term glycemic control in newly diagnosed type 2 diabetes with moderate hyperglycemia but not in patients with severe hyperglycemia. With this evidence, further treatment with insulin for at least 6 to 12 months was necessary to maintain the euglycemia and improve β -cell function.

Glycated Hemoglobin Level (HbA1c)

In the study patients were recruited with mean HbA1c level of >9% (Table 1). HbA1c values improved from baseline for patients in each interval of the study. Mean values decreased by 2.88% for patients treated with insulin alone, by 2.85% to for patients treated with insulin + OAD, and by 1.8% for patients treated with

OAD alone (Table 3). Since the patients in the OAD group did not achieve the same glycemic target as the insulin group. At the end of the study our data suggests that mean HbA1c level was significantly lower in insulin group as compared to combination of insulin + OAD and OAD alone.

Fasting C-Peptide Level

Fasting C-Peptide level was measured at the end of six months treatment and mean values were high with insulin group as compared to combination of insulin + OAD and OAD alone. All these values were within normal limits and it indicates that, the favorable effect of insulin treatment on endogenous insulin secretion in our study could be due to better glycemic control. Glucose toxicity has been demonstrated clinically and has been investigated extensively in the laboratory. Defects in insulin secretion have been documented and directly related to hyperglycemia and are correctable with the establishment of euglycemia. Thus, the shorter the period of antecedent glucotoxicity, the more likely the full recovery of β -cell function. Our results do support the concept that correction of hyperglycemia can improve insulin secretion. Another possibility is that β -cell secretory capacity may have been restored by "rested" β -cells induced by insulin injection. In our study, most of the subjects required pharmacological therapy to maintain near-euglycemia after discontinuing insulin therapy.

Adverse Events

Hypoglycemia

No severe hypoglycemia occurred in either group. (Table - 2) Over all percentage of hypoglycemia reported insulin group (15.46%), combination of insulin + OAD (22.72%) and OAD (4.47%). The overall rate of minor hypoglycemia showed no significant difference between these groups.

Weight Gain

Insulin therapy is frequently accompanied by weight gain. The mechanisms of weight gain are not fully understood.¹⁴ Improved glycemia due to insulin treatment promotes weight gain by decreasing both the basal metabolic rate and glucosuria.¹⁴⁻¹⁹ However, newly insulin-treated patients with type 2 diabetes gain weight only during the first 2 to 3 years after the start of insulin therapy; in most cases their weight stabilizes thereafter.¹⁹⁻

²² At the end of 6 months treatment, insulin group shows marginal increase in the body. It may be due to restoring the physiological function by optimizing the blood glucose

levels (Table - 2).

CONCLUSION

In conclusion, a 6-month course of insulin mono therapy, compared with Insulin + OAD and OAD's monotherapy treatment, could more effectively maintain adequate glycemic control accompanied with significant improvement of β -cell function. Therefore, in the routine clinical practice, management of newly diagnosed type 2 diabetic patients with severe hyperglycemia, strong consideration should be given to early, aggressive insulin mono therapy for at least six months for a rapid and sustained effect on glycemic control and β -cell function and monitoring C-Peptide levels are very important in patients injecting insulin can help to determine how much of their own natural insulin these patients are still producing.

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Prevalence of Diseases and Observation of Drug Utilization

Pattern in Elderly Patients: A Home Medication Review

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Abstract

Medication related risk factors and their effect on health outcomes in geriatric patients remains unclear, which can only be identified by home visits. Therefore in the present study door to door survey was conducted in an area of 2 sq. km surrounding Shri Mahant Indiresch Hospital of Dehradun to determine drug utilization pattern and prevalence of chronic diseases in elderly by visiting them in their community. The study was primarily targeted at the elderly because, as a group they take more drugs than their younger counterparts and are known to be at risk of the side effects of many of the drugs they consume. The study shows that Cardiac disorders (34%) were most prevalent among elderly population. 40% patients were non-compliant due to poor economic status, difficulty in swallowing of the prescribed dosage forms, and disturbing side effects. The study also shows that Self-medication (38%) was a prevalent phenomenon among the elderly. 20% patients suffered from side effects of the drug were advised either to reduce their dosage regimen or to visit their physician with a request for an alternate medicine.

Present study concludes that a home medication review greatly decreases the load on tertiary care services for the elderly, which in India are sadly lacking. This may be because the Indian elderly at present are mostly in the "young elderly" age group (60 to 75 yrs old) in which there is little demand for long term health care.

Key words: Home medication review, Selfmedication, Geriatrics, and Polypharmacy

INTRODUCTION

Home Medication Review is a concept where a pharmacist has the opportunity to visit a patient in the familiar surroundings of the latter's home and questions that no one has been able to confidently answer can be answered. Medication review takes the pharmacist out of the shop into the community. Home medication review is an exciting opportunity for Indian pharmacist to contribute further to the health care of their communities. The human body is in a state of change as the years go by. There is a progressive functional decline in many organ systems with advancing age. Age-associated physiologic changes may cause reduction in functional reserve capacity (i.e. the ability to respond physiologic challenges or stresses). The cardiovascular, musculoskeletal and central nervous system appears to be most affected. The elderly have multiple and often chronic diseases. It is not surprising therefore that they are the major consumer of drugs^[1]. There has been a steady increase in the number of elderly people, defined as those over 65 years of age. Several conditions are likely to be present. A number of factors are believed to increase the risk of drug related problems in the elderly,

including suboptimal prescribing (e.g. overuse of medications or polypharmacy, inappropriate use, and under use), medication errors (both by dispensing and administration problems) and patient medication, non-adherence (both intentional and unintentional)^[2]. A number of studies have investigated medications and medication-related risk factors in patients' homes^[3, 4]; however, the medication-related problems found in those studies were not linked to patients' health outcomes. Other studies have sought to investigate the relationships between a limited number of medication-related risk factors that might be identified by a home visit and adverse health outcomes. Hospital admission secondary to adverse drug reactions was found to be related to the use of two or more pharmacies, while drug side effects were reported as the reason for non-adherence in 35% of patients whose admission was related to non-adherence^[5]. Non-adherence also precipitated about 5% of hospital readmissions in geriatric patients previously discharged on three or more drugs prescribed for chronic conditions^[6]. Similarly, poor adherence was associated with increased risk of adverse drug events (ADEs) in the elderly^[7] and hospital admission due to drug-related problems can result in patient morbidity, mortality and

increased health costs [8]. It is possible that other medication-related risk factors identified at home visits could be associated with poor health outcomes, but these medication-related risk factors have not, to date, been extensively studied.

This study has been conducted to observe the drug utilization pattern and prevalence of chronic diseases in elderly by visiting them in their community.

METHODOLOGY

A Door to door survey was conducted to identify the residents of age 65 years and above from May 2008 to July 2008. 100 subjects were included for the study after informing them about the purpose of the study and prior consent. Patients were included in this study if they satisfied one or more of the following criteria: (i) on five or more regular medications; (ii) taking twelve or more doses of medication per day; (iii) three or more medical conditions; (iv) suspected to be non-adherent with their medication regimen; (v) on medication(s) with a narrow therapeutic index or requiring therapeutic monitoring; (vi) had significant changes made to their medication regimen in the previous three months; (vii) had signs or symptoms suggestive of possible medication induced problems; (viii) had an inadequate response to medication treatment; (ix) admitted to hospital in preceding four weeks; (x) at risk in managing their own medications due to language difficulties, dexterity problems or impaired sight. A questionnaire was prepared, many practical questions regarding diseases, medication prescribed, health status involving socioeconomic status, family support, were included^[9]. The geriatric subjects were quite cooperative and confident in answering the questions since it was their familiar surrounding i.e. home. Table-1 shows the questions which were asked during medication review of

elderly patients.

RESULTS

This community based survey included 100 elderly patient. 49% were males and 51% were females. Elderly population suffers from numerous chronic disorders. The present study highlights that Cardiac disorders were most prevalent among the concerned elderly population. A Total of 120 individual drugs were prescribed to the elderly patients (Table-2), out of which Antihypertensive drugs(31%), Anti-diabetic drugs (22%), Antiplatelet agents(16%), Anti-rheumatic drugs (24%), Bronchodilators (7%), Hypolipidemic drugs (2%), Anti-tubercular drugs (1%), and drugs acting on Thyroid gland (1%) were prescribed. 60% of the patients were compliant, while the remaining 40% were non-compliant for their medication. The reasons for non-compliance are shown in Fig 2. Difficulty in swallowing tablets (25%) was the most common cause of patient non-compliance. This survey also revealed that 38% of the elderly does self-medication, out of which 32% take allopathic medicines and 6% take ayurvedic and homeopathic medicines. Reasons for self medication are listed in Table-3. Drugs like Multivitamins, Iron and Calcium supplements were taken by the elderly as Over the Counter preparation (Table-4). Analgesics and Antipyretics were commonly taken by the elderly for self medication (Table-5). From this survey, it was found that 35% of the patients faced problem with the structure and furnishing of the house, climbing stairs was a problem to them. 65% of the patients were regular with the review of their prescription order and regularly visited their physician. 25% were not regular because of lack of time and in 5% patient's family members were not supportive.

Table.1: Questionnaire

Questions were asked regarding
1. Disease of patient and medicines prescribed.
2. Patient compliance for medication. If no, then reason.
3. Any other medications (ayurvedic, allopathic, homeopathic) taken by the patient which neither pharmacist nor doctor knew.
4. Risks associated with the structure of house and furnishing (such as poor lightning, stairs obstacles etc).

Table.2 : Classification of drugs prescribed to the elderly.

DRUG CLASSIFICATION	%AGE	DRUGS	DOSE	DOSAGE FORM
1.Antihypertensive drugs	31%	Amlodipine, Atenolol, Metoprolol Ramipril	5 mg o.d 50 mg o.d 50 mg o.d 2.5 mgo.d	Tablet Tablet Tablet Tablet
2. Anti-diabetic drugs	22%	Glipizide+Metformin Glemipride+Metfprmin	5+500 mg 15+500 mg o.d	Tablet Tablet
3. Anti-platelet drugs	16%	Aspirin (10%) Clopidogrel (6%)	150mg 75 mg o.d	Tablet Tablet
4. Anti-rheumatic drugs	14%	Diclofenac Naproxen Etoricoxib	50 mg 250 mg 60 mg o.d	Tablet Tablet Tablet
5.Bronchodilators	7%	Salbutamol Theophylline Montelukast	2 mg o.d 35 mg o.d 10 mg o.d	Tablet Tablet Tablet
6. Anti-depressant drugs	4%	Fluoxetine+Alprazolam Olanzapine	20+0.25mg 5mg b.d	Tablet
7. Hypolipidemic drugs	2%	Atorvastatin	10 mg o.d	Tablet
8.Anti-parkinsonism drugs	2%	Levodopa+Carbidopa	200+50 mg t.i.d	Tablet
9. Anti-tubercular drugs	1%	Rifampicin +Isoniazid,	600+300 mg o.d	Tablet
10. Agents acting on thyroid function	2%	Thyroxine (Eltroxin)	100 mg o.d	Tablet
11. Anti-anginal drugs	1%	Nitro- glycerine	20 mg o.d	Tablet

Table.3: Reasons for Self-medication

REASONS	% PATIENTS	% MALE	% FEMALE
Lack of time	23%	15%	8%
High consultation fee	29%	14%	15%
Quick relief	18%	18%	0%
Believes in Ayurveda	16%	3%	13%
Family members are not supportive	5%	0%	5%
Unable to walk	9%	0%	9%

Table.4: Over the counter drugs used by the elderly.

DRUGS	DOSE	DOSAGE FORM
lecocule(vit.B complex)	500mg o.d	Capsule
lvion(vit.E)	500mg o.d	Capsule
lexorange(iron prep.)	50ml 2tsf b.d	Syrup
lenadon(pyridoxine)	40mg o.d	Tablet
lupracal(calcium citrate+magnesium hydroxide)	100mg b.d	Tablet
lolibala plus(Methylcobalamine+lipoic acid)	10 mg b.d	Capsule

Table.5: Drugs taken by the elderly as Self-medication

Drugs	%Male	% Female	Drugs	Dose	Dosage Form	Use
Analgesics/ antipyretic	34%	36%	Aspirin	500mg o.d	Tablet	Headache
			Nimuslide	100mg o.d	Tablet	Body pain
			Paracetamol	500mg o.d	Tablet	Fever
Antacids	5%	2%	Ranitidine	300mg o.d	Tablet	Acidity
			Aluminium hydroxide	250mg + 250mg	Syrup	
			Magnesium hydroxide	(170ml) 1tsf b.d		
Expectorant	4%	0%	Chlorpheniramine maleate +Codeine phosphate	4mg + 10mg/ml (10ml)1tsf o.d	Syrup	Cough
Multi-vitamins	2%	2%	Vit.-B complex	500mg o.d	Capsule	Weakness
			Methylcobalamin +foliacid+ vit.B ₆	(1500mcg + 1.5mg + 10mg+ 3mg+100mg) o.d	Capsule	
Ayurvedic and homeopathic drugs	10%	5%	Rasayan vishista	50ml 1 tsf	Semisolid	Hypertension
			Rumalaya forte	500mg o.d	Tablet	
			Mahayograj guggul	1 tsf	Powder	

Fig.1: Prevalence of chronic disorders among elderly

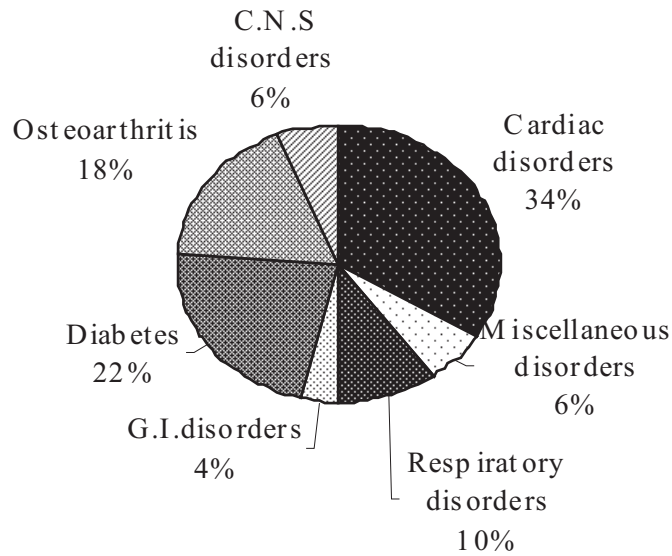
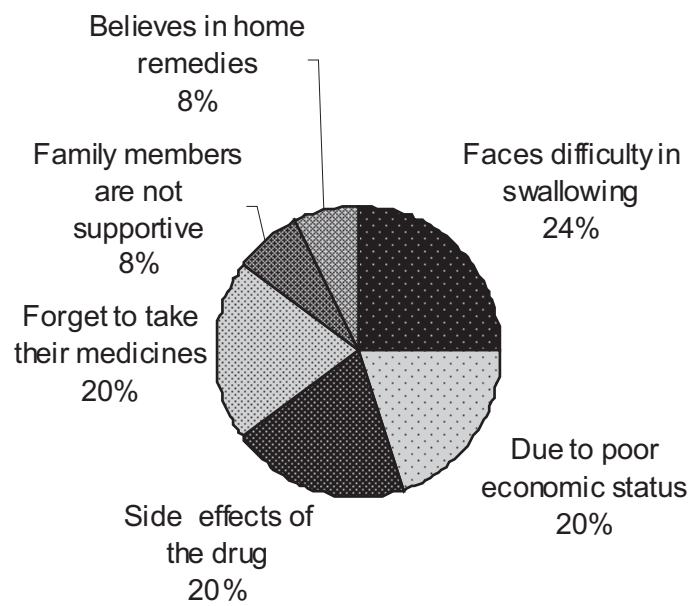


Fig.2: Reasons for non-compliance among elderly



DISCUSSION

Prescribing for geriatric patients requires an understanding of the efficacy of the medication in frail older people, assessment of the risk of adverse drug events, discussion of the harm: benefit ratio with the patient, a decision about the dose regime and careful monitoring of the patient's response. This requires evaluation of evidence from clinical trials, application of the evidence to frail older people through an understanding of changes in pharmacokinetics and Pharmacodynamic, and attention to medication management issues. Given that most disease occurs in older people, and that older people are the major recipients of drug therapy in the Western world, increased research and a better evidence base is essential to guide clinicians who manage geriatric patients.

CONCLUSION

A home medication review greatly decreases the load on tertiary care services for the elderly, which in India are sadly lacking. This may be because the Indian elderly at present are mostly in the "young elderly" age group (60 to 75 yrs old) in which there is little demand for long term health care. Several forums have discussed the need for more emphasis on geriatric medicines and management in India. The public health system needs more centers and specialist in this field." We cannot heal the old age, but let us protect it, promote it and prolong it."-Sir J Ross (9)

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