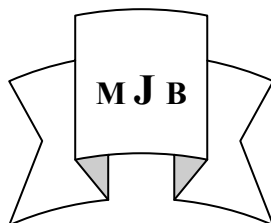


## Shall we Keep Non-Steroidal Anti-Inflammatory Drugs behind the Counter?

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### Abstract

A five hundred and thirty one (531) on the counter (OTC) non-steroidal anti-inflammatory drugs (NSAIDs) users, were directly interviewed by pre-structured questionnaires. The study was conducted at Rheumatology and rehabilitation unit of Merjan teaching hospital in period from March 2008 to August 2008. The items of pre-structured questionnaire, measures the knowledge and the attitude of patients toward the use of these medications.

The results showed that most of studied users were not using these agents correctly and frequently ignore the potential adverse effects.

Lack of knowledge of most of users, and lack of direct or labeled instructions were considered the corner stone for abusing these hazardous agents.

### الخلاصة

اجريت دراسة مسح ل ٥٣١ مستخدما للمضادات الالتهابية غير الستيرويدية (بدون وصفة طبية) بسبب الاصابة بتغيرات انحطاطية العظمية المفصلية في قسم المفاصل والتأهيل الطبي في مستشفى مرجان التعليمي من الفترة اذار الى اب لسنة ٢٠٠٨ وكان هدف الدراسة هو لتبيان موقف ومعرفة استخدام هذه العقاقير من قبل المستخدمين وقد اظهرت النتائج بأن معظم المستخدمين لم يستخدموا هذه العقاقير بصورة صحيحة ومعظمهم يجهل المضاعفات الجانبية لهذه العقاقير ، ان قلة المعرفة وعدم وجود ارشادات طبية مباشرة او في النشرة الطبية تعتبر حجر الاساس في سوء استخدام هذه العقاقير .

### Introduction

**N**on – Steroidal Anti-Inflammatory Drugs (NSAIDs) is a loosely used term denoting a varied group of agents exerting anti-pyretic, analgesic and anti-inflammatory properties [1,2]. These drugs, now days are among the most widely used medications in the world for pain relieve, stiffness, inflammation of joints, osteoarthritis (OA) and other musculo-skeletal disorders, as well as for the mounting up sport and occupational injuries. Analgesic and anti-inflammatory effect of these drugs is mainly mediated by their inhibitory effect on cyclo-oxygenases (COX) enzymes, resulting in inhibition of prostaglandins production, or through non

prostaglandin-mediated mechanism. [3,4]

The inhibition of prostaglandins production which is important for inflammation, stiffness and pain reduction, at the same time this prostaglandin inhibition also lead to serious side effects on the top of which gastrointestinal toxicity. Therefore these medications should safely be used under supervision of the patient's physician.

In addition to prescribed NSAIDs, now days over the counter (OTC)-NSAIDs "without prescription" are available and widely used medications.

OTC-NSAIDs are available in much lower doses than comparable

prescription NSAIDs. The current OTC-NSAIDs as approved by Food and Drug Administration (FDA) include: aspirin, ketoprofen, ibuprofen and naproxen.

OTC-NSAIDs are effective and usually used for treatment of mild to moderate pain of musculoskeletal system, including OA for 10-14 days.[5]

Now days we are faced with challenges of balancing the benefits and side effects of these drugs. This can be explained by easy availability of OTC-NSAIDs and the presence of common fallacy or a perception among some consumers of these drugs; that the availability of OTC-NSAIDs, without prescription, signifies that there are no risk for side effects with use of these agents.[6] This fallacy can be linked to thousands of overt morbidity or even mortality mainly from gastrointestinal toxicity and increasing-up of other side effects, specially when these drugs are used incorrectly either by taking more than recommended doses or when use continuously as in OA specially when used simultaneously with other types of NSAIDs (dual or triple NSAIDs).[7,8]

Additionally the long term use of these agents even in small doses can lead to iatrogenic gastrointestinal disorders invisible to the medical community; i.e. "a silent epidemic"

It is of interesting to mention of an excisting letter or a massage from an expert, determining the extent of mortality due to abuse of these medications, when he noted " it has been estimated that 16500 NSAIDs-related deaths occur among patients with rheumatoid arthritis RA or OA every year in united states, in spite of the mortality statistics do not include deaths ascribed to the use of OTC NSAIDs!!.[9]

### **Aim of the study**

Is to determine the extent of users knowledge and attitude regarding various aspects of chronic OTC NSAIDs use in OA.

### **Method and Patients**

A five hundred and thirty one (531) OTC NSAIDs users, were directly interviewed by pre-structured questionares. The study was conducted at Rheumatology and rehabilitation unit of Merjan teaching hospital in period from March 2008 to August 2008.

The users were selected to have more or at least one symptomatic osteoarthritic joint, who kept using NSAIDs for the last year.

The diagnosis of OA were done on clinical and radiological basis. In addition to personal data, educational level, a thorough medical history was done for each patient. The items of pre-structured questionnaire, measures the knowledge , attitude of patients toward the use of these medications, through the answers of the following questions:

- What is the name of NSAIDs used (traditional trade name), and which form (tablet, capsule, suppositories, injection)?
- What is the dose? How frequent: daily, some days/week, some days/month?
- Have the patient been discussed with health professional about various aspects of OTC NSAIDs use, mainly of importance are side effects?
- What are the patients thoughts , ideas or knowledge about potential side effects of these drugs?
- Have the patients simultaneously use more than NSAIDs (dual, triple OTC-NSAIDs)?
- Have the patient try any sort of non-pharmacologic measures to relief pain aiming to substitute or at least to reduce needed dose of NSAIDs?

- Have the patient firstly try simple analgesia in form of acetaminophen, instead of NSAIDs?

### **Results**

Data analysis showed that the number of female patients were 380, whereas males were 151 and gender ratio approximately 2.5 in favor of female. Age of patients was ranging from 25y – 76y old with mean age of 59.5y. fig. (1).

Regarding the educational level of patients, the results showed that 239 patients were illiterates, 211 patients just can write and read in Arabic language (were not passing the primary school), 56 patients were in different levels of secondary school, whereas 25 patients were graduated from high school. fig (2).

Regarding the types of NSAIDs which were used by patients in study:

446 patients used traditional non-selective NSAIDs, whereas 85 patients used selective NSAIDs COX2 inhibitors. fig (3).

The route of administration fig. (4) shows that: 96% of patients used OTC-NSAIDs orally (in form of tablet or capsule), whereas 4% of patients used OTC-NSAIDs in other form (as injection 0.6% of patients and 3.4% in form of suppositories).

Fig. (5) shows that: 210 of patients used OTC-NSAIDs daily, 216 used these medications some days/week, whereas 105 used it in frequency of some days/month. All patients didn't exceed maximum dose of specific drug per day.

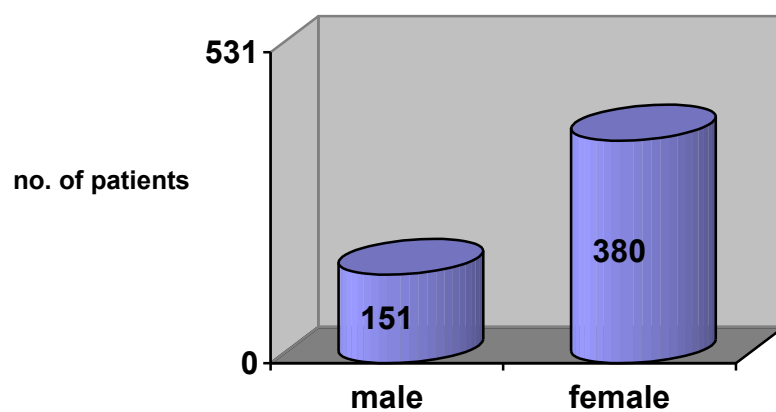
The data of study, surprisingly noted that all patients (100%) didn't read any label, or any instructions about various aspects of NSAIDs use.

Fig. (6) shows that: 132 patients (25%) were using more than one NSAIDs simultaneously, whereas 399 patients (75% ) were using just one type of NSAID at once. 55% of patients (291) were discussed or instructed by medical professional (doctors, pharmacists) about how to use these agents. "Actually all discussions were projecting the light mainly on the gastrointestinal side effect" whereas 45% (240 patients) were not discussed. fig. (7).

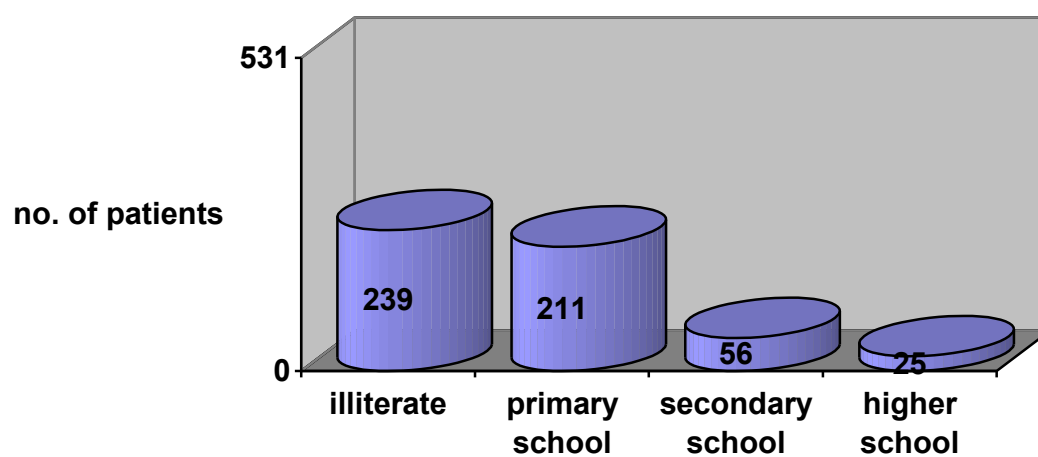
Fig. (8) shows what are patients concern or knowledge about the side effects of these medications: all patients ( 531 ) had the idea of gastric troubles that could occur with the use of this sort of medications. Whereas 42 patients know that NSAIDs may cause allergy, 21 patients concerned with renal troubles that may occur with the use of such medications. 3 patients had an idea that drugs may induce asthma or bronchospasm.

Only ( 49 patients ) 9% of patients tried some of hour-hold non-pharmacological measures in form of radiant heat, hot pack, cold pack, strengthening exercise , trial of weight reduction, using cane or stick "in case of lower limbs joints OA", spacing of activities. fig.(9 ).

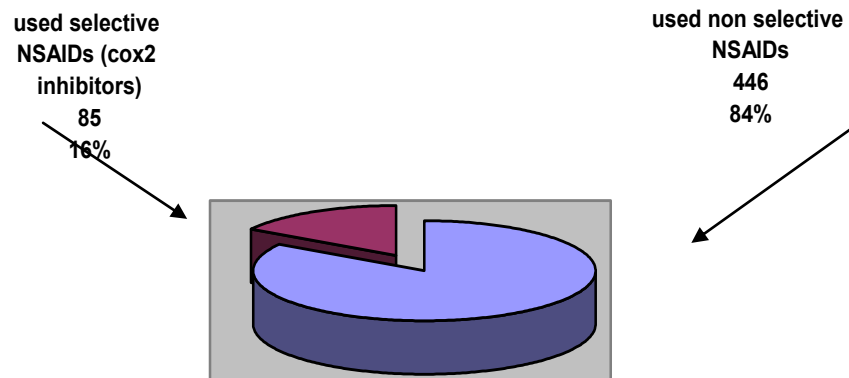
Surprisingly 98% of patients (522) had not tried acetaminophen as first line of analgesia before NSAIDs, whereas only 2% (9 patients ) had tried acetaminophen as first line of treatment. fig (10)



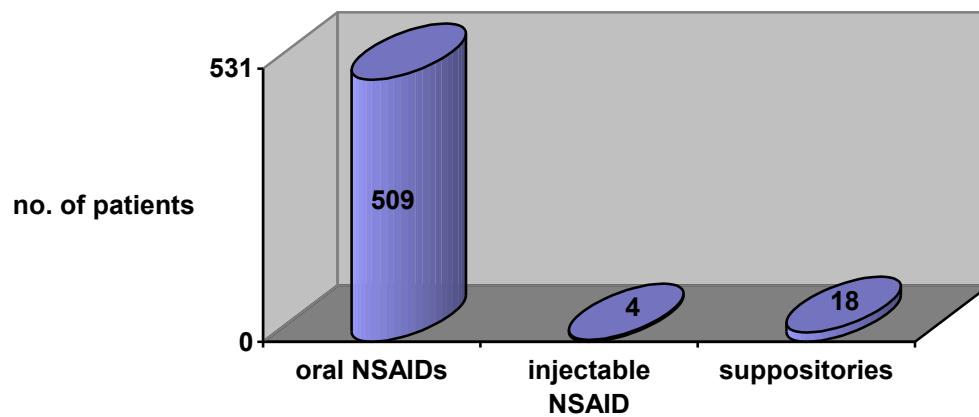
**Figure 1** Gender and number of patients



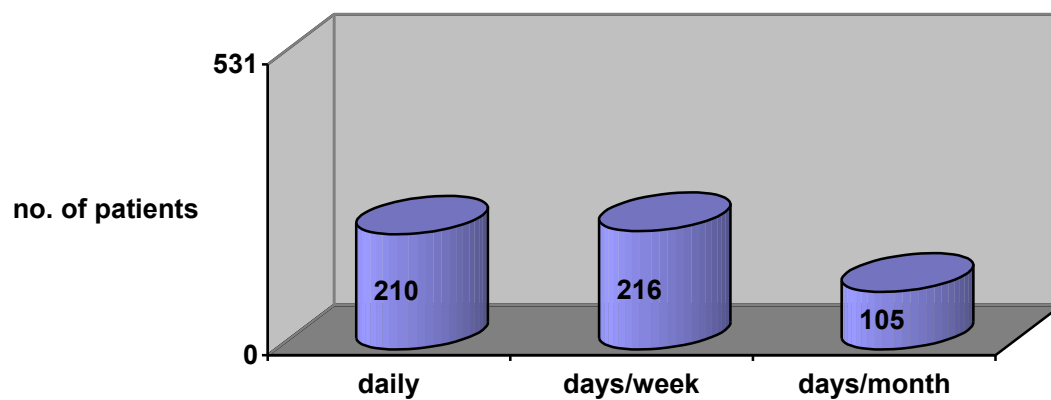
**Figure 2** The educational levels of patients



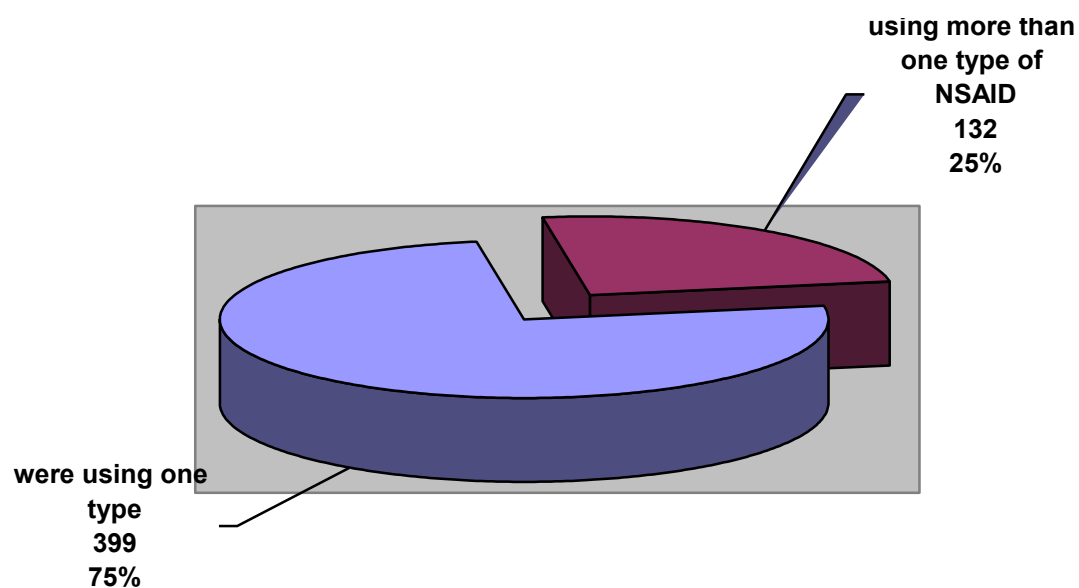
**Figure 3** Class of NSAIDs used



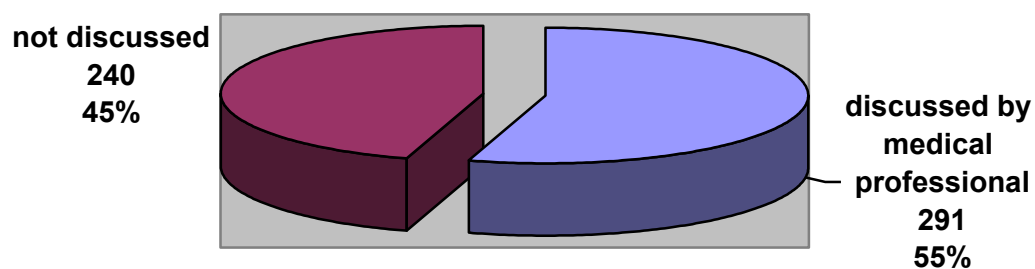
**Figure 4** Rout of administration



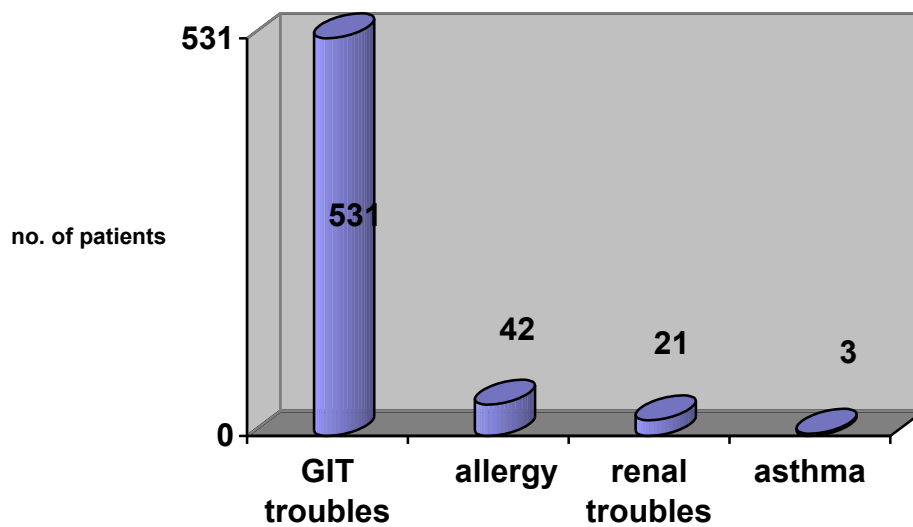
**Figure 5** Frequency of using NSAIDs



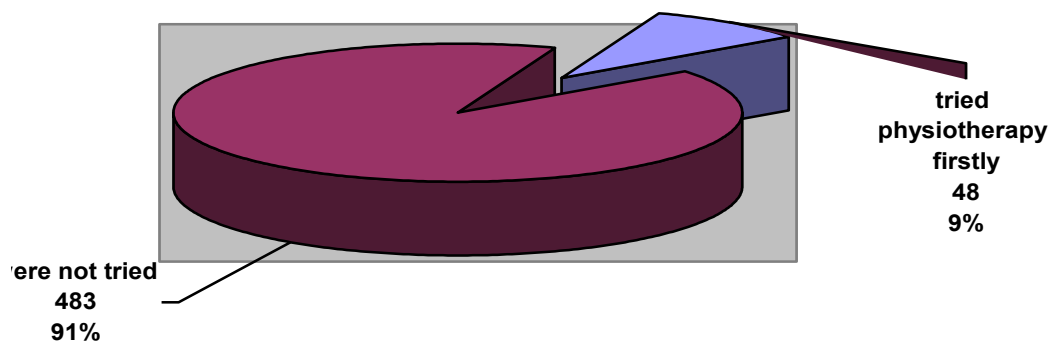
**Figure 6** Number of patients who were using more than one type of NSAIDs instantly



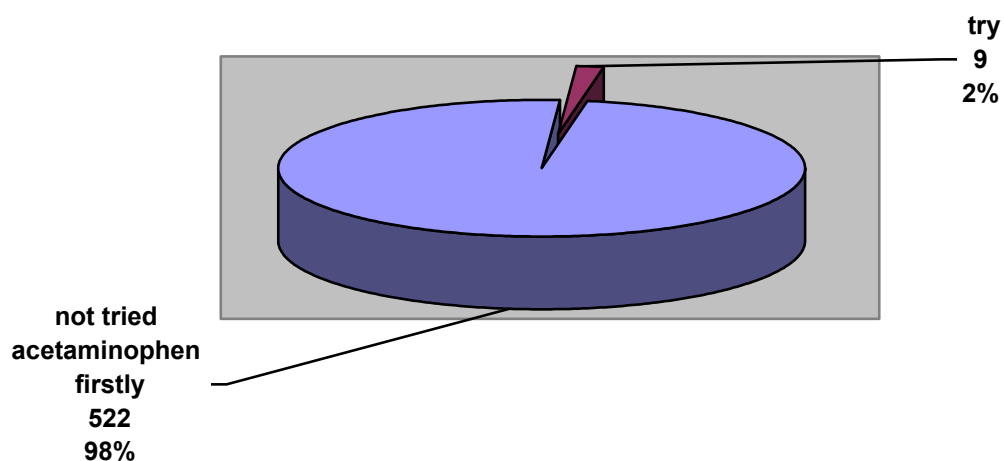
**Figure 7** Number of patients who discussed the subject with medical professional



**Figure 8** patients' knowledge about the side effects of NSAIDs



**Figure 9** Peoples who tried physiotherapy first instead of using NSAIDs



**Figure 10** Number of patients who tried simple analgesia (acetaminophen firstly)

## Discussion

The data of present study showed predominance of female gender, this may be explained by the fact that OA, especially the generalized type, have a strong genetic basis with female predominance. A well known fact that OA is more prevalent and more symptomatic in female gender, around the age of 55 years [8] which is near the mean age of patients in this study.

Although we had two cases were young (25 years, 31 years old) who represent the young onset of OA of knee joint due to the previous sport injuries resulted in internal derangement of the joint with subsequent secondary osteoarthritic changes, most of our patients were elderly, as the (primary) OA is an age-related disease [7,10] and it is well known fact that elderly require pain relieving medication, perhaps due to progressive osteoarthritic changes, this could put these categories of patients vulnerable to gastrointestinal toxicity from prolong use of OTC NSAID.

Additionally the use of polymedications by elderly patients "due to the presence of various co-morbid diseases" is considered a further risk factor for potential side effects of NSAID and/or possible of drug interactions.

Most of the studied patients had very low educational level, it clear that a lack of knowledge and ignorance were considered the main root for the risk associated with hazardous use of OTC-NSAIDs.

A 446 of studied patients (84%) used non-selective NSAID, whereas 85 patients (16%) used selective NSAID "COX-2 inhibitor".

The question is: if there is certain NSAID safer than the other? , indeed there is no clear difference in the over all safety profile of the various traditional NSAID on the market, although the side effects of individual

drug may vary. In one of epidemiological studies showed that ibuprofen (dose 1.2 g/day) has the lowest GIT complications [11], i.e. they have good beneficial/risk ratio, that is why these drugs were considered and licensed by Food and Drug Administration (FDA) as OTC-NSAIDs in united state, the same is applicable for naproxen.

One may ask why selective NSAIDs, which carry less gastrointestinal toxicity, not yet considered by FDA as OTC-NSAID, this may be related to many reports noted the probable increase risk for cardiovascular system events, i.e. that there is a "class" effect [12] for example: celecoxib, although is true selective COX-2 inhibitor, but unfortunately, have 2-3 folds for increase cardiovascular events.[13] Although the currently available COX-2 inhibitor are widely prescribed and have become first line agent for many physician, the risk-to-benefit data may not support their use as a first line agent unless the patient is at high risk for adverse events (e.g. the patient has a history of GI bleeding with no cardiovascular risk.[1,14] FDA concluded that although all types of NSAIDs may have increase risk for cardiovascular event, but naproxen and ibuprofen were selected as OTC-NSAID for which there may be an exception from increase risk for adverse cardiovascular events.

Recognizable percentage of patients used meloxicam (mobic) in form of tablets, as OTC-NSAID, this fact may explained that most of patients have an idea that this drug is completely safe regarding gastrointestinal toxicity.

As you know this is not completely true, because meloxicam is relatively selective NSAID, not purely selective, so it is not free from GIT problems, in addition to other common NSAID side effects. [15]

Unfortunately there is no any food or drug administration or organization approved which NSAIDs are safe in Iraq , that could be labeled as OTC.

Actually people select their OTC-NSAIDs for which they are familiar or may be prescribed previously by their physician.

Most of patients (509) in the study, used NSAID, by oral rout, (while only 18 patients, the administration was in form of suppositories and just 4 patients having the drugs in form of injection, hoping that they could escape from NSAID-related gastrointestinal toxicity, but this not true because the gastrointestinal-related toxicity not only due to local prostaglandin inhibition, but through systemic rout as well).

210 patients were daily OTC-NSAIDs users. All of them, fortunately didn't exceed the daily recommended dose for any particular drug. Whereas the National Consumers League, 2003 (NCL) study on OTC pain reliever conducted by Harris interactive as a matter of comparison, showed that 44% of the surveyed users had taking more than recommended dosage of OTC-NSAIDs. [16]

Unfortunately according to the definition of OTC-NSAIDs which set by FDA, all of those daily users in this study were considered "chronic users" ( as OTC-NSAID should not be used more than 10-14 days ).

It is not surprising, in present situation, to say that all the patient in study didn't read the drug label, because, actually there weren't a labels, as these drugs as well as many other drugs, dispensed in private pharmacies and out patient clinic in form of sheets, without special container, enclosing label or leaflet, that is why most of the patients didn't know about; active gradient of the drugs, long list of side

effects, drug interaction, or the dose, etc.

Whereas the NCL study showed that only 16% of adult surveyed said they read every thing on the label the first time they take an OTC, and perhaps even more worrisome, 12% said they never read label at all!!!.[16]

The FDA, continuously requesting manufacturers to revise labeling to help consumer to use these medications safely, include more specific information about GI bleeding and cardiovascular events, with strong instruction for not exceeding the recommended dose and only for limited time (not more than 10-14 days), also the label should include the contraindications for use by patients immediately following artery bypass grafting surgery. [17]

291 patients received some instructions from health professional concentrating mainly on GI troubles of NSAIDs and neglecting other aspects, while 240 patients didn't receive instructions regarding various aspects of OTC-NSAID.

While in the NCL study 40% have not discuss any of these concerns with their doctors.[16]

What is about patients knowledge, concern and attitude regarding side effects of NSAIDs? On basis of this study, although almost all users had an idea about gastric troubles which may be induced by these drugs, but the other side effects were ignored by majority of users.

Generally speaking the majority of users believed, that OTC-NSAID, are relatively safe (with exception of gastric troubles, which could be minimized by taking it after meal as with gastro-protective agents). This is a great fallacy, as like any medication, they have long list of side effects, some of these may be fatal.

Had all patients use just one NSAID instantly? The answer, No they hadn't,

as recognizable percentage they mixing this drug, i.e. more than one NSAID was used?. Either was used with salicylate, which already prescribed by physician for anti-platelet properties, or with other type of NSAIDs simultaneously, as the patient's priority is relieve of joint pain, swelling and stiffness [18] and believing that mixing more than one drug may summate the action, leading to rapid pain relieve, of course it is not true, multiple NSAIDs having no summation of action or increasing patency, in contrast increasing their side effects mainly gastrointestinal toxicity.[8] In addition of increasing of potential side effects, NSAIDs may block the cardio-protective effect of acetyl salicylic acid.[19]

Regarding the non-pharmacologic measures in management of OA; unfortunately only 4% tried simple measures, in form of heat pack, cold pack.

As you know that non-pharmacologic measures in form of weight reduction, spacing of activities, exercise, hot and cold pack, canes for management of OA, have a big role in reducing pain and minimizing the needs for pain killers, and avoiding their long list side effects, the speech mainly concern NSAIDs. [20,21]

Although NSAIDs provide much symptomatic relieve and improve clinical situation of disease activity such as joint swelling but do not improve its outcome, i.e. joint destruction, therefore successful treatment of osteoarthritis usually requires a multi disciplinary approach with physiotherapy and occupational therapy, [18]

As OTC- NSAID in the present study was mainly used for pain relieve. As NSAIDs don't alter the course or disease progression, so balancing between pain relieve and potential side effect, necessitate the search for an

alternative remedies, as simple analgesia with minimum side effect, if the pain was not relieved by non-pharmacologic measures alone.

The present study shows that 522 patients did not try acetaminophen as first drug of choice "simple analgesic" which is relatively safe drug, as patients in this study including well educating personnel believe that acetaminophen (paracetamol) is a drug designed and manufactured for treatment of headache only?!!

### **Conclusion**

Most of studied users with OA widely used OTC-NSAIDs for a period beyond that defined by FDA i.e; (10-14 days) and most of users are frequently ignore of potential adverse effects.

The hazardous effect from benefit/toxic profile remain largely "silent epidemic" as neither patients nor physician aware of the magnitude of the problem.

Absence of rigid roles in marketing these drugs and the lack of knowledge of most of users are considered the corner stone for abusing these hazardous agents.

### **Recommendations**

- The users as well as pharmacists should know that the term OTC-NSAIDs only applied to NSAIDs which named by FDA (Aspirin, Ketoprofen, Ibuprofen and Naproxen) in doses lower than prescribed doses and not more than 10-14 days.
- The label must be available and the patients should understood that any OTC-NSAIDs should be taken as directed by instructions of the label.
- Labels should include more specific information on risk including potential heart attack, stroke in addition to gastrointestinal toxicity and other side effects.

- The users have to avoid dual, triple NSAIDs therapy instantly.
- The users should be informed for not using these drugs continuously for more than 10-14 days, and must be for mild to moderate pain, other wise the patients should be seen by his/her physician.
- The "chronic users" require on going careful monitoring.
- Users should be informed about the beneficial effects of non-pharmacological measures for pain relieve, if not effective, patients can try and use acetaminophen firstly before switch to NSAIDs.

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