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Public Attitude and Perception about Analgesic and their Side Effects

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Authors' contributions

This work was carried out in collaboration among all authors. Author MAGR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SSAS and NAO managed the analyses of the study. Author MWA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Analgesics are substances which work in various ways to relieve different types of pain experienced in the body. Non-prescription over-the-counter (OTC) drugs are widely used by patients to control pain and fever.
Study Objective: To evaluate of knowledge, attitudes and practices about analgesic and their side effects.
Methods: A cross-sectional study conducted during a period of three months from September to December 2017 in Rafha and Riyadh - Saudi Arabia on a random sample of 237 Saudi people, the data was collected by using a self-administered questionnaire in the Arabic language. Statistical analysis was done by using MS EXCEL using descriptive statistics and chi-square test.
Results: A total of 237 participants out of 260 consented to be interviewed and completed the questionnaire with a response rate (91%). Their ages ranged between 18 years and 54 years with a mean (28) and standard deviation (7.9). Majority of participants were females (92%) and about

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two thirds (66%) were highly educated. A quarter of study participants (25%) do not read leaflet of analgesic before use. About one-fifth of respondents (20%) reported that they cannot stop taking analgesic even if the pain is mild. 12% and 36% of respondents always and sometimes, respectively, use more than one type of analgesic for pain relief. 10% of respondents reported the occurrence of side effects from analgesic. The respondents use analgesic mainly for headache (43%) and toothache (25%). The chronic disease for which participants take analgesic were mainly arthritis (39%) and migraine (30%).

About three-quarters of respondents (74%) were aware that the use of analgesic is accompanied by side effects. The respondents believed that the reasons for analgesic misuse are that analgesic easily obtained without a medical prescription (40%) and there is no educational or awareness program regarding analgesic use (33%). Majority of participants believed that there is no sufficient awareness about analgesic. The source of information about analgesic for participants is physician (24%). Panadol analgesic is the most commonly used analgesic (48%) reported by participants.

Results showed that there is a significant statistical difference between male and female regard analgesic use (P=0.048) and between different level of educations and analgesic use (P=0.334).

Also, there is a highly significant statistical difference between male and female regard reading the leaflet before taking analgesic (P=0.0001) and between the educational level of participants regarding reading the leaflet before analgesic use (P=0.0008).

Conclusion: The over-the-counter (OTC) analgesic drugs are commonly used and many patients are unaware of their side effects. The findings of this study showed that people's knowledge, attitudes and practices regarding analgesic use is poor. Also, it is important to improve people's knowledge, attitudes and practices regarding analgesic use to reduce the misconceptions and misguided expectations contributing to inappropriate analgesic use. Therefore, health professional practice should play a major role in people's awareness of the appropriate use of OTC analgesic drugs.

Keywords: Public attitude; analgesic drugs; Arabic language; painkillers.

1. INTRODUCTION

Pain is a common condition and has a significant influence on the quality of life [1,2,3]. It was defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [4]. Analgesics, commonly known as painkillers, are substances which work in various ways to relieve different types of pain experienced in the body [5]. Non-prescription over-the-counter (OTC) drugs are widely used by patients to control aches, pain, and fever [6,7]. Over-the-counter (OTC) (non-prescribed) analgesics that are generally used by the public are paracetamol, weak opioids such as codeine, and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin.

Worldwide, paracetamol (acetaminophen) is one of the most frequently used OTC medications [8,9]. Likewise, consumption of paracetamol is widely popular [10]. It is generally accepted that paracetamol use is safe. Numerous benefits of the use of OTC medications have been recognized, such as the increase in patients' autonomy, the decreased frequency of physician visits, and the subsequent reduction of costs for the National Health System [11,12]. Nevertheless, no such treatment can be without the risk of adverse events and interactions with prescribed medications or other substances, mainly due to limited knowledge of the constitution of other drugs [13,14] overdosing, or side effects [15,16].

Paracetamol is used for mild pain and as an antipyretic drug. The mechanism of action of paracetamol is not clearly known, although one theory suggests that it acts as a selective inhibitor of the cyclooxygenase enzyme isoform, COX-3, found in the brain and spinal cord. Unlike NSAIDs, it has no anti-inflammatory action [17]. Paracetamol can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances [18]. To evaluate this policy, Morgan et al. [19] carried out a study 4 years after the implementation of the 1998 regulations on paracetamol to determine the effect on hospital admissions and mortality. Results demonstrated a decline in the severity of paracetamol poisoning cases, but not in

frequency. Boots have now set a new policy whereby only one packet of Co-codamol (codeine phosphate and paracetamol) is sold to one customer. Even with these restrictions in place, paracetamol is the most common deliberate self-poisoning drug in the UK with more than 70, 000 emergency department attendances every year [20]. At the toxic dose, paracetamol saturates the liver pathway normally involved in its metabolism, causing paracetamol to be metabolized by an alternative pathway, which produces a toxic metabolite, N-acetyl-p-benzoquinone imine (NABQI), which is inactivated by glutathione, rapidly preventing any harm. However, since glutathione can be depleted quickly during this process, excess NABQI leads to necrosis in the kidney tubules and in the liver [21].

NSAIDs produce analgesic effects, reduce inflammation and are anti-pyrexial [22,23]. NSAIDs inhibit COX. There are two main isoforms of COX, COX-1 (expressed in most tissue and blood platelets and with a homeostatic role) and COX-2 (induced in inflammatory cells by cytokines) [17]. The inhibition of COX-1 and COX-2 by NSAIDs causes inhibition of the biosynthesis of prostaglandins. This produces the anti-inflammatory effect of NSAIDs with a decrease in vasodilatory prostaglandins. Prostaglandins are responsible for increasing the body's core temperature setpoint during fever. NSAIDs reverse this effect by causing inhibition of prostaglandin production [21]. By contrast with the above beneficial effects, NSAIDs increase the risk of gastrointestinal mucosal damage by reducing COX-1-derived prostaglandin production. The amount of damage to the upper gastrointestinal depends on many factors, such as prior history of peptic ulcer and age [23]. Hargreave et al. [24] demonstrated that age is closely associated with continuous analgesic use, which may explain why age can also affect the prevalence of gastrointestinal damage due to the analgesics [24-55].

The primary objective of this study is to evaluate of knowledge, attitudes and practices about analgesic and their side effects and the secondary objectives are to determine the most common analgesics used among participants, determine the most common causes for analgesic use and to determine the relationship between participants demographic and analgesic use. To the best of our knowledge, there are little studies carried out in the past to evaluate the knowledge about analgesic and their side effects in Saudi Arabia.

2. MATERIALS AND METHODS

2.1 Study Design and Duration

This was a cross-sectional study conducted during a period of three months from September to December 2017 in Rafha and Riyadh - Saudi Arabia.

2.2 Study Population

Random sample of 237 Saudi people.

2.2.1 Inclusion criteria

- Age is >= 18 years
- Saudi in Nationality
- Currently or previously used analgesic
- Willing to respond to the study questionnaire

2.2.2 The exclusion criteria

- Age < 18 years
- Non Saudi
- People who are not analgesic user
- People who are not willing to give consent or refuse to answer questionnaire

2.3 Data Collection and Data Collection Tool

The data was collected by using a self-administered questionnaire in Arabic language specially designed for the research purpose.

The participants were met in hospitals (Prince Sultan Military Medical city in Riyadh and Rafha Central Hospital in Rafha), markets and malls in Rafha and Riyadh cities and given the questionnaire after taking oral consent. The questionnaire was divided into 4 main sections:

- Demographic data
- Practices of participants toward analgesic use
- Awareness and attitudes of participants toward analgesic use
- Common analgesic used by participants

2.4 Statistical Analysis

All data were analyzed by means of descriptive and inferential statistical analysis using MS EXCEL. The frequency and percentage calculated for all the participant's demographics and answers for the questionnaire with

representation for the answers by figures, chi-square test used to evaluate the influence of age, gender, education and of participants on analgesic use and practices.

3. RESULTS

3.1 Demographic Characteristics of Study Participants

A total of 237 participants out of 260 consented to be interviewed and completed the questionnaire with a response rate (91%). Demographic characteristics of the questionnaire respondents are summarized in Table 1. Their ages ranged between 18 years and 54 years with a mean (28) and standard deviation (7.9). Majority of participants were females (92%) and about two thirds (66%) were highly educated.

3.2 Practices of Participants toward Analgesic Use

Practices of participants toward analgesic use represented in details in (Table 2). About a quarter of study participants (25%) not read leaflet of analgesic before use. About one-fifth of respondents (20%) reported that they can't stop taking analgesic even the pain is mild. 28% of respondents take other drugs for health problem. 12% and 36% of respondents always and sometimes use more than one type of analgesic for pain relief. Majority of participants (99%) take the analgesic with water, only 1% take it with carbonated beverage and 0.4% take it with juice. 10% of respondents reported occurrence of side effects from analgesic use and the side effects reported were hypotension (4%), stomach pain (3%) and dyspnea (2%). Respondents reported use of analgesic once per month represented (58%), those reported twice-monthly analgesic use represented (27%) and those reported more than twice monthly represented (15%). The respondents use analgesic for Headache (43%), toothache (25%), menstruation pain (17%) and myopathy (5%). Regarding the time interval between feeling pain and taking analgesic, 45% reported >2 hrs, 41% reported 0.5 hr-1 hr and 14% reported that they take the analgesic immediately when feeling pain. The respondents reported some herbals they use instead of analgesic were myrrah (27%), Anise (22%), Trigonella foenum (17%), Cloves (14%). Details are represented in Table 2. When the respondents asked about chronic disease for which they take analgesic, they reported arthritis (39%), migraine (30%), spinal disc herniation (2%), irritable bowel syndrome (1%) osteoarthritis (1%) and cancer (0.4%). When the participants asked " Which drug do you use more analgesic or antibiotic" more than three quarters (76%) reported analgesic.

3.3 Awareness and Attitudes of Participants toward Analgesic Use

About three-quarters of respondents (74%) were aware that the use of analgesic is accompanied by side effects. The respondents believe that the causes of analgesic misuse are that analgesic easily obtained without a medical prescription (40%) and there are no educational or awareness program regarding analgesic use (33%). Majority of participants believe that there's no sufficient awareness about analgesic. More than half (59%) of participants think that advertisement increase analgesic use. About two-thirds of participants (65%) think that there's relation between analgesic misuse and abuse. More than half (53%) advise others to use the same analgesic they use. Physician represents the source of information about analgesic for 24% of participants also internet and leaflet of the drug represent a source of information about analgesic for 24% and 24% of participants. Awareness and attitudes of participants toward analgesic use are represented in (Table 3).

3.4 Common Analgesic Used by Participants

Panadol analgesic is the most commonly used analgesic (48%) followed by fevadol (26%), catafast (17%), voltaren (16%), ibuprofen (12%), flutab (5%) and adol (4%) (Table 4).

3.5 Relationship of Demographic Characteristics with Analgesic Use, Rate of Analgesic Use and Practice of Reading the Pamphlet before Using Analgesic

Results showed that there is a significant statistical difference between male and female regard analgesic use (P=0.048). With regards to age, there was no significant difference between different age groups and analgesic use (P=0.310) and also no significant difference between different level of educations and analgesic use (P=0.334).

Table 1. Demographic characteristics of study participants (n=237)

Variable	Categories	Frequency	Percentage (%)
Sex	Male	19	8%
	Female	216	92%
Education	Primary education	5	2%
	Intermediate education	15	6%
	Secondary education	50	21%
	University education	156	66%
	Other	11	5%
Age (years)	Maximum = 54	Minimum = 18	Mean (SD) = 28 (7.9)

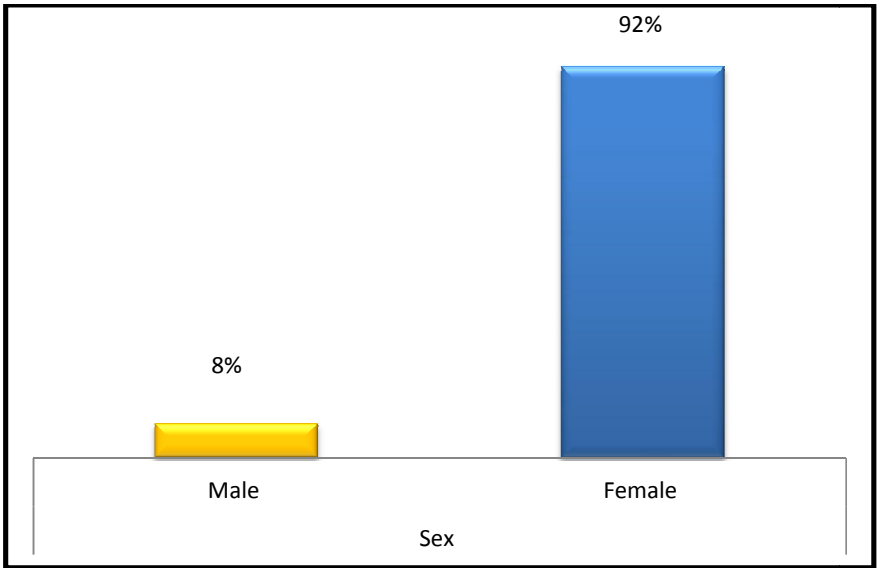

Fig. 1. Represent percentage of males and females in the study (Mainly females)

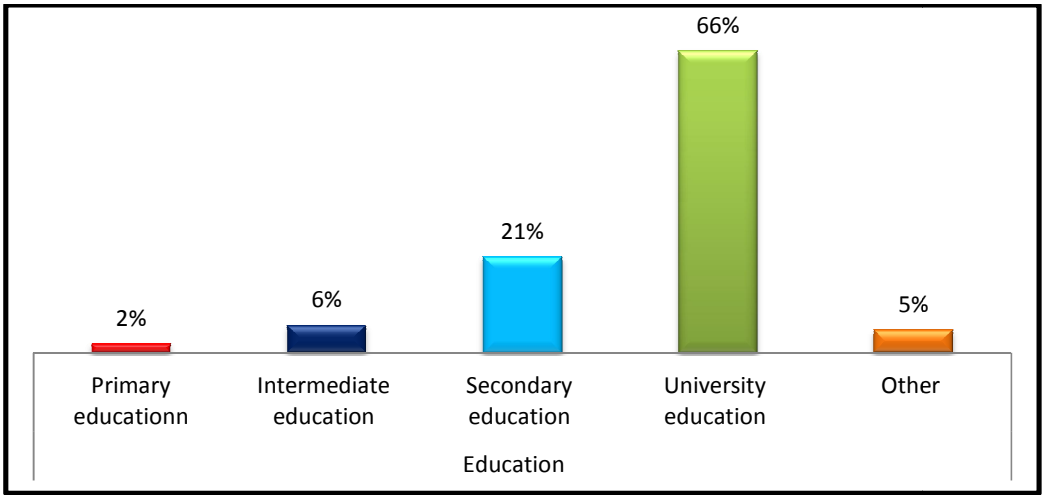

Fig. 2. Represent education of participants in the study (Mainly University education)

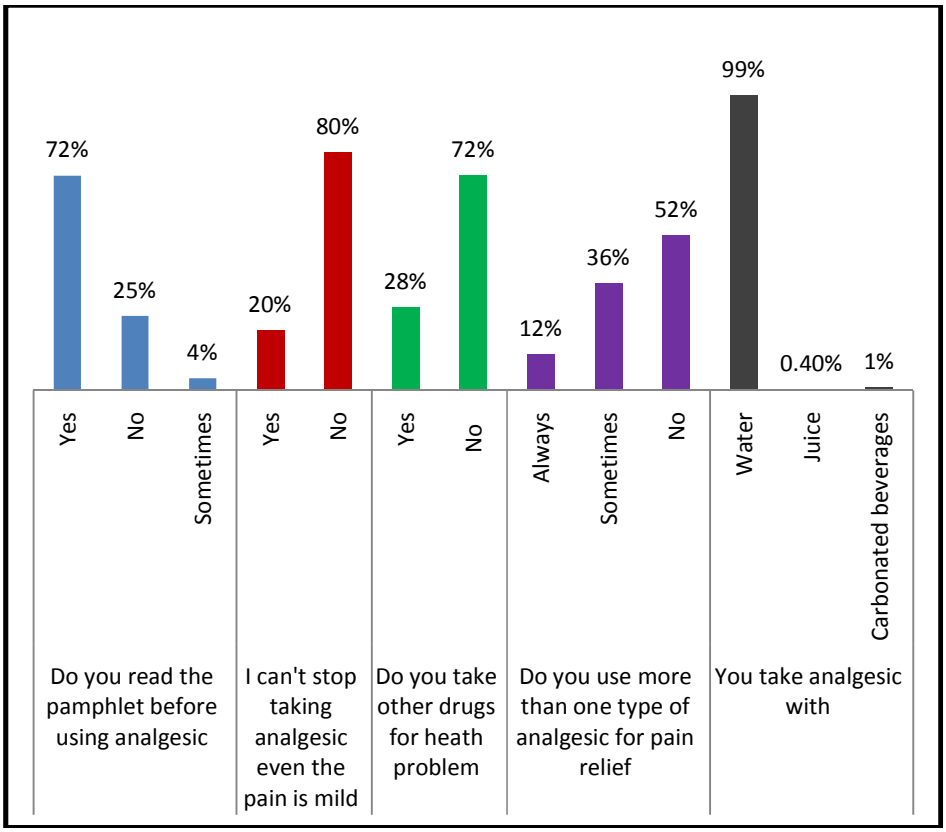

Fig. 3. Practices of participants toward analgesic use

Results revealed that there is a highly significant statistical difference between male and female regard reading the leaflet before taking analgesic (P=0.0001) and between the educational level of participants regarding reading the leaflet before analgesic use (P=0.0008) but no significant difference found between age and reading the leaflet before taking analgesic (P=0.330).

No statistical difference was found between frequency of analgesic use per month and either sex or age or educational level of participants.

4. DISCUSSION

This study conducted to evaluate of knowledge, attitudes and practices about analgesic and their side effects. Analgesics provide patients with a way to treat minor pain. While these medications are safe when used as directed, they have the potential to cause serious adverse effects when misused by susceptible populations. This study showed that no difference in age groups relating to analgesic use which is inconsistent with previous epidemiological studies which have indicated that elderly people are taking analgesics more than younger age [56,57]. The major uses for these analgesics as shown in this study are to treat general headache, toothache and body pain, a similar finding was also reported by Modupe et al. [58].

The majority of participants in this study were females and also results showed a significant difference between men and women which indicate that women consume more analgesics than men consistent with previous study results by several authors [59,60]. considers many theories underpinning that women are more consumer for analgesia than men such as the 'social support' and 'stress' theories, there is also the obvious biological difference related to women's reproductive life and the use of analgesics for menstrual pain and also may be due to cultural beliefs that men should tolerate greater pain than women. Also, in the current study, highly educated participants reported high analgesic use which may be due to the stresses they face during their study or during their work and also may be related to a higher monthly income which enable them to obtain analgesics.

Table 2. Practices of participants toward analgesic use (n=237)

Variable	Categories	Frequency	Percentage (%)
Do you read the leaflet before using analgesic	Yes	170	72%
	No	58	25%
	Sometimes	9	4%
I can't stop taking analgesic even the pain is mild	Yes	47	20%
	No	188	80%
Do you take other drugs for heath problem	Yes	66	28%
	No	171	72%
Do you use more than one type of analgesic for pain relief	Always	29	12%
	Sometimes	86	36%
	No	122	52%
You take analgesic with	Water	232	99%
	Juice	1	0.4%
	Carbonated beverages	2	1%
Do you experienced side effects from analgesic use	Yes	23	10%
	No	172	73%
	Not sure	41	17%
Side effects experienced from analgesic	Stomach pain	7	3%
	Hypotension	9	4%
	Dyspnea	4	2%
Frequency of analgesic use per month	Once	135	58%
	Twice	63	27%
	>Twice	35	15%
Indication for analgesic use	Headache	102	43%
	Myopathy	11	5%
	Toothache	58	25%
	Menstruation pain	41	17%
	Other	24	10%
Time interval between feeling pain and taking analgesic	Immediately when I feel pain	32	14%
	0.5 hr-1 hr	96	41%
	>2 hrs	104	45%
Herbals used instead of analgesic	Cumin	32	13%
	Pomegranate peel	6	3%
	Cinnamon	19	8%
	Fennel	9	4%
	Myraah	63	27%
	Camomile	7	3%
	Lepidium sativum	29	12%
	Cloves	34	14%
	Astragalus sarcocolla	26	11%
	Trigonella foenum	40	17%
	Anise	52	22%
	Ginger	24	10%
	Peppermint	26	11%
Do you have Chronic disease for	Migraine	72	30%

Variable	Categories	Frequency	Percentage (%)
which you take analgesic	Arthritis	92	39%
	Spinal disc herniation	4	2%
	Osteoarthritis	3	1%
	Cancer	1	0.4%
	Irritable bowel syndrome	3	1%
Which drug do you use more analgesic or antibiotic	Analgesic	172	76%
	Antibiotic	55	24%

Table 3. Awareness and attitudes of participants toward analgesic use (n=237)

Variable	Categories	Frequency	Percentage (%)
Use of analgesic is accompanied by side effects	Yes	174	74%
	No	14	6%
	I don't know	48	20%
In your opinion, what are the causes of misuse of analgesic?	Easily obtained without medical prescription	93	40%
	No educational or awareness program regarding analgesic use	76	33%
	I don't know	62	27%
Do you think that there's a sufficient awareness about analgesic	Yes	45	20%
	No	186	81%
Do you think that advertisement increase analgesic use	Yes	138	59%
	No	95	41%
Do you think there's a relation between analgesic misuse and abuse	Yes	151	65%
	No	34	15%
	I don't know	49	21%
Do you advise others to use the same analgesic you use	Yes	124	53%
	No	112	47%
Source of information about analgesic	Physician	56	24%
	Pharmacist	67	16%
	Television	4	2%
	Internet	57	24%
	Pamphlet	56	24%
	Family	25	11%
	Other	3	1%

Table 4. Common analgesic used by participants (n=237)

Variable	Categories	Frequency	Percentage (%)
Analgesic used	Panadol	113	48%
	Fevadol	63	26%
	Ibuprofen	29	12%
	Flutab	13	5%
	Adol	10	4%
	Voltaren	39	16%
	Catafast	40	17%
	Ketoprufen	20	8%

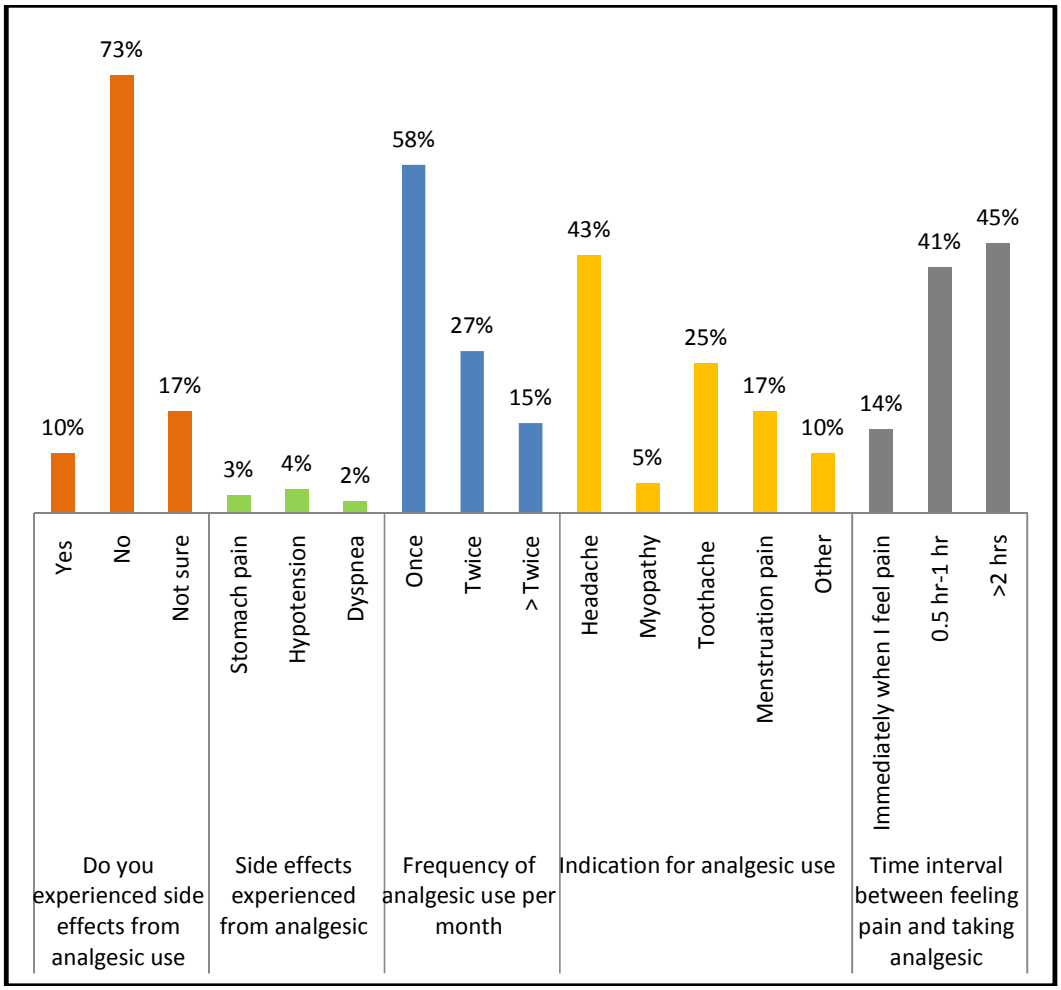

Fig. 4. Practices of participants toward analgesic use

Table 5. Relation between analgesic use and demographic characteristics of participants

Socio-demographic data	I can't stop taking analgesic even the pain is mild		P- value
	Yes (no.)	No (no.)	
Sex			**0.048***
Male	5	14	
Female	42	172	
Age			**0.310**
18 - 25 years	22	90	
26 - 30 years	6	31	
31 -54 years	23	65	
Educational level			**0.334**
Primary education	1	4	
Intermediate education	3	12	
Secondary	14	35	
University	27	127	
Other	1	10	

(*) There is a significant difference

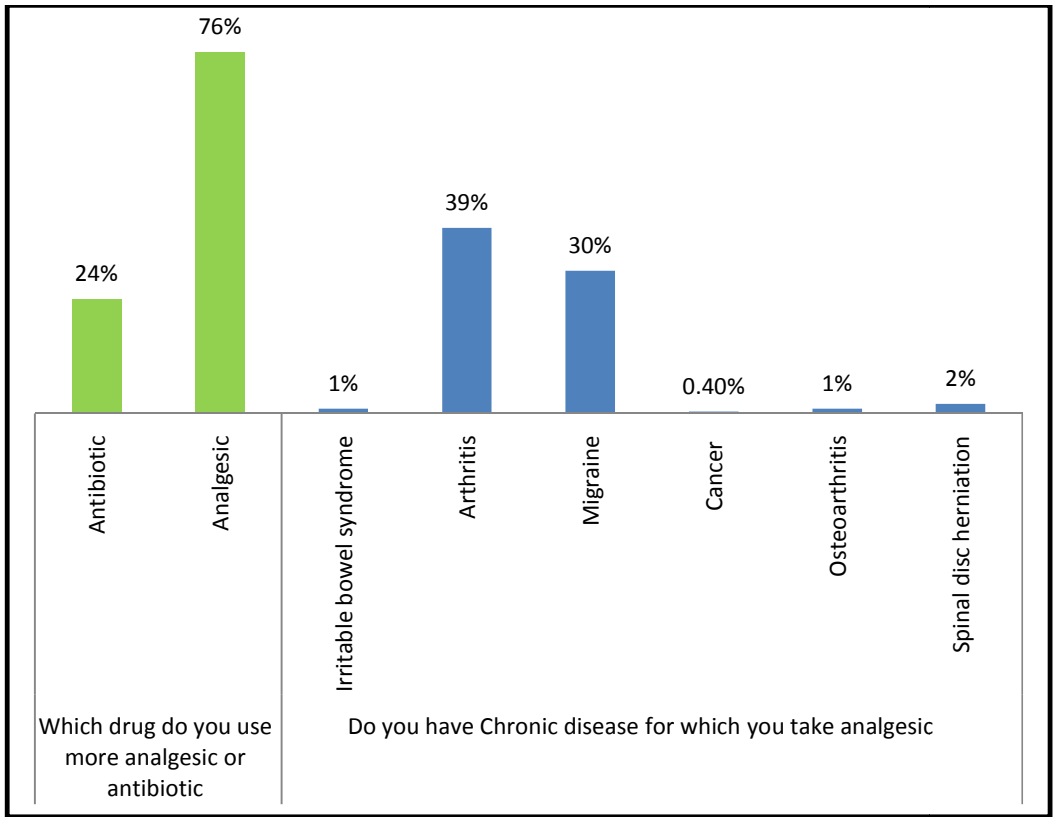

Fig. 5. Practices of participants toward analgesic use

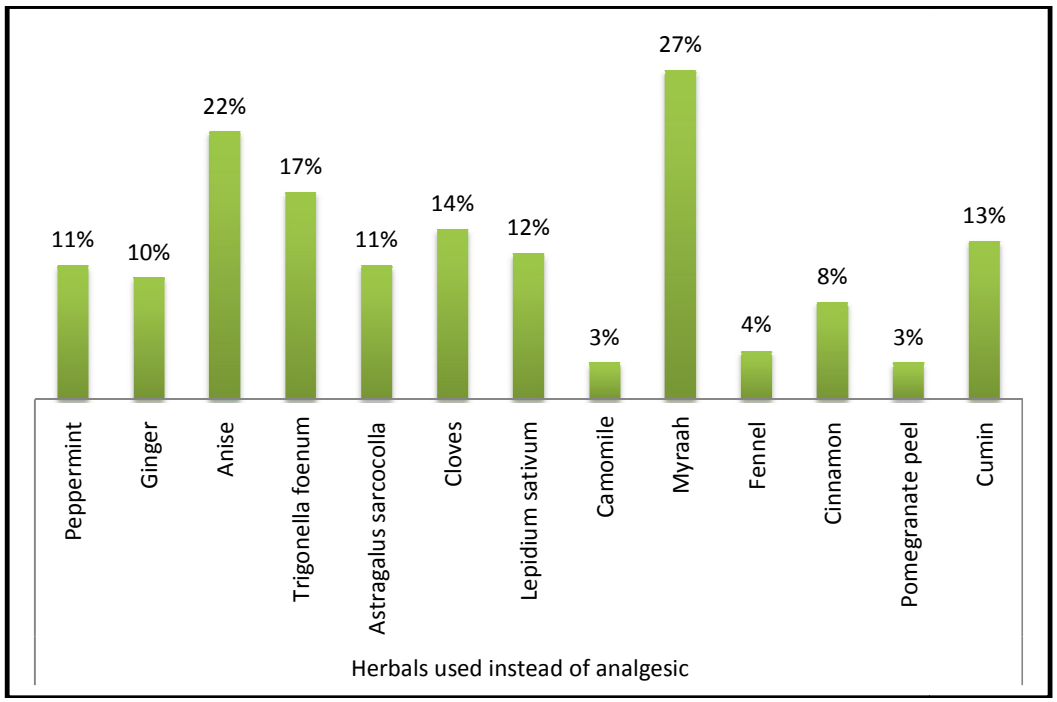

Fig. 6. Represent herbals reported to be used instead of analgesic

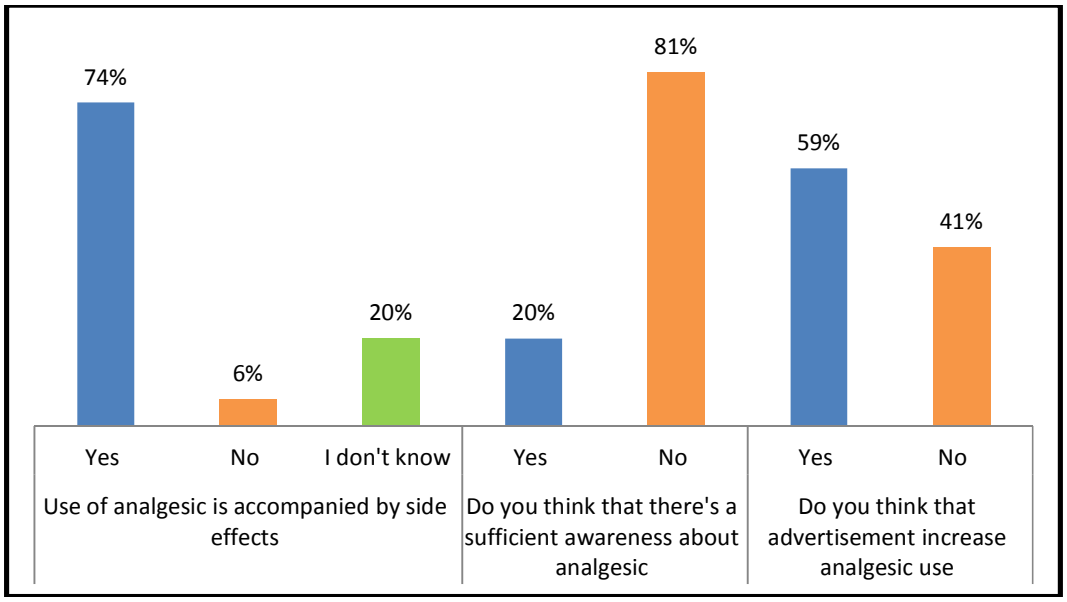

Fig. 7. Awareness and attitudes of participants toward analgesic use

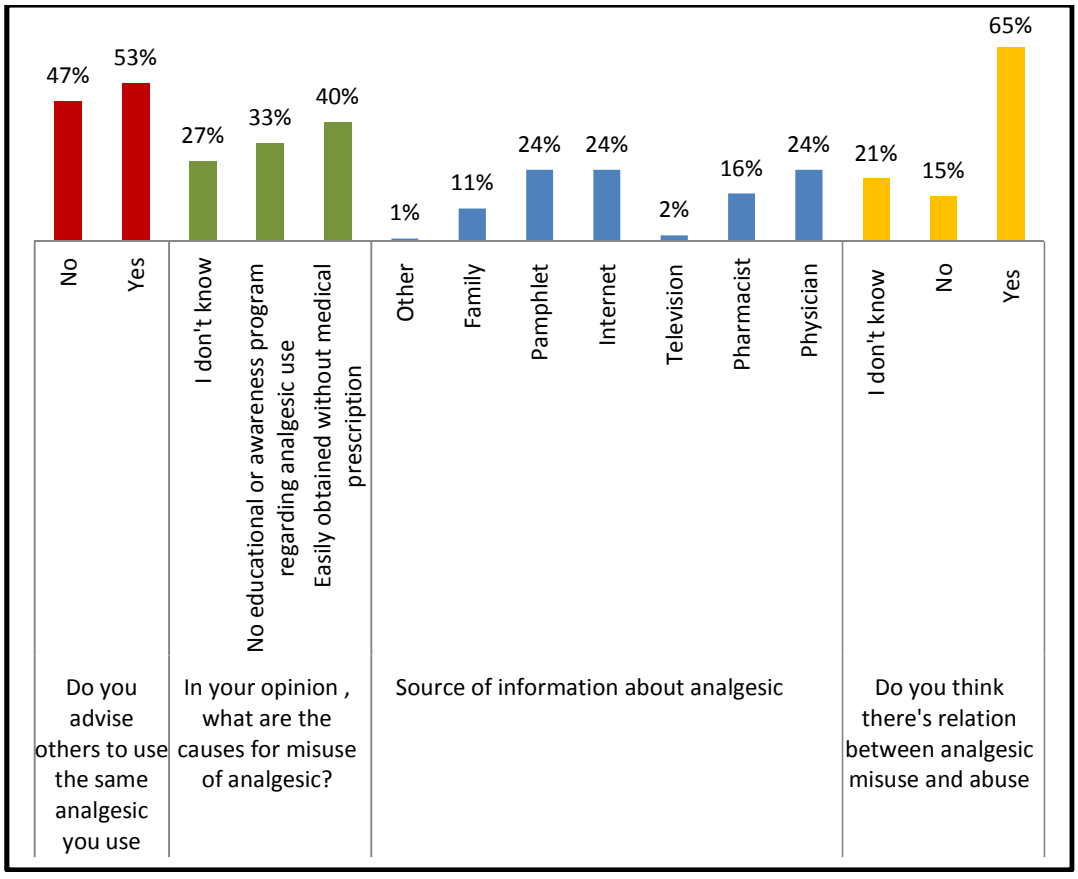

Fig. 8. Awareness and attitudes of participants toward analgesic use

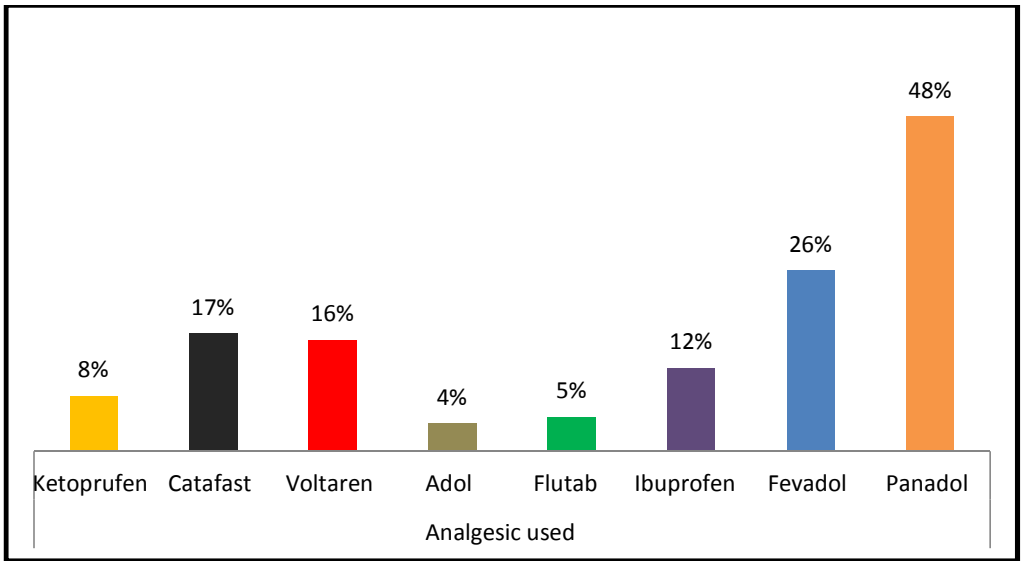

Fig. 9. Common analgesic used by participants

Table 6. Relation between demographic characteristics of participants and practice of reading the pamphlet before using analgesic

Socio-demographic data	Do you read the pamphlet before using analgesic		P- value
	Yes (no.)	No (no.)	
Sex			**0.0001***
Male	9	10	
Female	159	54	
Age			**0.330**
18 - 25 years	12	100	
26 - 30 years	5	32	
31 -54 years	28	60	
Educational level			**0.0008***
Primary education	3	2	
Intermediate education	9	6	
Secondary	32	18	
University	119	37	
Other	7	4	

(*) There is a significant difference

Acetaminophen, a common household analgesic [61] was inappropriately used for all types of pains; it was abused for tiredness, stress, weakness of the body and sleep. Of the OTC analgesics, acetaminophen has generated the greatest concern concerning renal disease because it is the major metabolite of phenacetin, although not the only metabolite [62]. About half of the participants in this study take a specific painkiller (paracetamol), consistent with other studies by Cham et al., Ozkan et al. and Paulose-Ram et al. [63-65] indicated that paracetamol is the most commonly used analgesic among the population. The selection of analgesic may not be for a specific type of pain experienced but influenced by branding and the choice of some of them based simply on what was to hand. Selection on these terms can be dangerous, as they might choose the wrong type of analgesic for the pain they are experiencing. This might lead to u nnecessarily prolonged use with the potential for side effects. This type of patients should be counselled on the signs and symptoms of common adverse events or complications which may occur by repeated or frequent use of this drug without counselling from health care provider.

Table 7. Relation between demographic characteristics of participants and frequency of analgesic use

Socio-demographic data	Frequency of analgesic use per month			P- value
	Once (no.)	Twice (no.)	Twice>(no.)	
Sex				**0.52**
Male	12	4	2	
Female	121	59	33	
Age				**0.520**
18 - 25 years	6	50	56	
26 - 30 years	7	28	2	
31 -54 years	20	27	31	
Educational level				**0.96**
Primary education	2	1	1	
Intermediate education	8	2	3	
Secondary	30	12	8	
University	87	45	23	
Other	8	3	0	

Lack of awareness about the correct consumption of analgesics can subject patients to serious side effects. 66 About one-third of study participants not interested in reading the analgesic leaflet before use which may lead them to take a higher dosage strength to mask their intense pain rapidly subsequently subject them to adverse effects or they may take a lower dosage strength which will be ineffective.

86% of the present study participants wait from half an hour to more than two hours to take analgesic after feeling pain which is higher compared to results of the previous study by Bostrom M reported that 46% of respondents would wait until “the pain gets bad” before taking their analgesics.[40].

27% of participants take analgesic twice a month and 15% take analgesic more frequent than twice a month which indicate the lower frequency of analgesic use than that reported previously in is an epidemiological study done by Christie in Australia, reported that 28% of the population admitted to taking at least 1 analgesic per week. The range was from 1 to 56 doses per week, with a median intake of 1.9 doses per week in those who took any analgesic” [66,67].

Regarding the prescription pattern of analgesics, responders prefer doctors over pharmacists to consult about the use of analgesics which is consistent with a previous study done by Mahmood Alqallaf [68] on Bahraini people who found that analgesics consumers prefer doctors rather than pharmacists. This can be explained since the patient always trust a doctor more than pharmacist in consultation regarding medicines. About 24% of responders use analgesics according to information from medical websites and 11% take advice from their relatives\friends rather than consulting a doctor or even a pharmacist and that can be attributed to their partial knowledge about analgesics, or they may have a relative that respond well to certain type of analgesics and they think the same analgesics would help them also. Those people may be subjected more than others to the side effects of these medications or may harm themselves by incorrect use since they lack the sufficient information or sometimes follow wrong, misleading information from the internet about the correct use of analgesics, side effects, and contraindications so the role of the health care providers and responsible committee's in Saudi Arabia is to raise the awareness of people to use these medications safely and decrease the percentage of people who take analgesics without consultation.

Results showed that three-quarters of the respondents have sufficient information about side effects or complications of analgesics which is inconsistent with results of study done by Cham et al., which indicate that “between 50% and 90% of NSAID users are unaware that these medications can cause ulcers or renal injury and more than half of acetaminophen users are unaware that overuse could cause liver injury” [69].

More than two thirds of participants (65%) believe that there is a relationship between

analgesic misuse and abuse and large percentage (81%) of participants reported that there's no sufficient awareness about analgesia in community, this may be related to insufficient information provided by pharmacists or other health care providers which provide the patients with dose-related information only may allow consumers to believe that they can take these medications safely. This high percentage can be decreased if pharmacists or other health care provider raise the awareness of patients about the correct use, the importance of adherence to prescription and avoid using these medications without consultation from a specialist.

Many studies proved that the analgesics use especially NSAIDs is accompanied by a high incidence of gastrointestinal (GI) irritation and ulceration [70] and even mortality [71,72]. Some participant reported stomach pain as a side effect from analgesic.

In this study, the chronic pain conditions most commonly reported by participants were arthritis and migraines. These findings were similar to those reported in other epidemiologic studies by Crook J et al and Elliott AM et al assessing the prevalence and types of chronic pain reported by community residents [73,74].

A considerable number of participants reported use of herbals instead of analgesic to relieve pain in some cases which may be explained by the fact that use of traditional medicines is an important component of Arab countries' folklore and also the thought that traditional medicines are free from side effects.

5. CONCLUSION

The over-the-counter (OTC) analgesic drugs are commonly used and many patients are unaware of their side effects. The findings of this study showed that people's knowledge, attitudes and practices regarding analgesic use is poor. Also, it is important to improve people's knowledge, attitudes and practices regarding analgesic use to reduce the misconceptions and misguided expectations contributing to inappropriate analgesic use. Therefore, health professional practice should play a major role in people awareness on the appropriate use of OTC analgesic drugs.

6. RECOMMENDATIONS

Public education on medication use and safety through educational campaigns that bring about positive changes is imperative. Multi-educational interventions can be tailored and designed according to the local social and cultural contexts. The interventions can be delivered through the well-distributed primary healthcare facilities in the cities.

Considering the potential harms of prolonged analgesic use, patterns of use at the population level need to be monitored in more detail.

Further studies on high risk groups, those with co-morbidities and those consuming multiple medicines are needed.

Furthermore, patterns of analgesic use need to be examined in the context of pain management practice.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Consent obtained from each participant during data collection. The confidentiality of the data obtained assured.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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