Mediterranean Journal of Pharmacy & Pharmaceutical Sciences
www.medjpps.com

ISSN: 2789-1895 online
ISSN: 2958-3101 print

ORIGINAL RESEARCH article

Assessment of community knowledge and awareness about ranitidine recall: a cross-sectional study

Nesren A. Jaaida [1 *], Fayza R. Neser [2] and Einas R. Ibramin [3]

[1] Department of Pharmaceutics and Industrial Pharmacy, [2] Department of Pharmaceutical Chemistry and Pharmacognosy, [3] Department of Pharmacology, Faculty of Pharmacy, University of Zawia, Zawia, Libya
[*] Author to whom correspondence should be addressed

Received: 30-04-2022, **Revised:** 14-05-2022, **Accepted:** 19-05-2022, **Published:** 30-06-2022

HOW TO CITE THIS

Jaaida et al. (2022) Assessment of community knowledge and awareness about ranitidine recall: a cross-sectional study. Mediterr J Pharm Pharm Sci. 2 (2): 44-51. [Article number: 67]. https://doi.org/10.5281/zenodo.6780490

Keywords: Community awareness, Libya, NDMA, pharmacist, ranitidine recall

Abstract: In April 2020, the Food and Drug Administration (FDA) requested immediate withdrawal of all prescription and over-the-counter ranitidine products. Ranitidine was recalled due to the presence of an unacceptable level of carcinogenic substance N-nitosodimethylamine (NDMA). Several pharmaceutical manufacturers have issued ranitidine product recalls including brand and generic ranitidine. FDA alerts patients to stop using ranitidine and advises them to talk with their health care professional about alternative treatments. In Libya, limited studies have been conducted to address people's awareness and knowledge in this regard. The objective of this study was to assess people's awareness and behavior toward ranitidine recall and related issues. A cross-sectional study was conducted in Zawia city for two months. An online questionnaire was distributed to 300 participants. Descriptive statistics analysis using Statistical Package for Social Sciences (SPSS) version 26.0 was used. The study found that more than half of the participants and their family members were likely to utilize ranitidine inappropriately. They seem to consume ranitidine more often without medical consultation. The findings also showed that 82.5% of the participants who were using ranitidine obtained the drug from pharmacies after the date of announcing ranitidine withdrawal from the market by the FDA. Furthermore, the vast majority of the participants were poorly informed or even had no information about ranitidine toxicity and their perception of the dangers of continued use of this drug is limited. The participants argued that pharmacists do not provide slightly information about dispensed ranitidine. In conclusion, all results reported as benefits of the participants in the study whereas the participant's perception and awareness increased when a brief notification regarding the reason for ranitidine toxicity was provided.

Introduction

Ranitidine is a drug that belongs to histamine-2 blockers. It is commonly available as an over-the-counter (OTC) and Prescription only medication (PoM). The most popular OTC brand and generic name of ranitidine is Zantac®. It is used for relieving, preventing heartburn and in the treatment of many other situations that may pathologically raise gastric acid levels. The prescription dose of ranitidine is used to treat many pathological conditions including gastroesophageal reflux disease (GERD), gastric ulcers and duodenal ulcers as well as to prevent stress ulcers [1, 2]. Ranitidine acts through the inhibition of gastric acid and basal gastric secretion,

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Induced by secretagogues such as histamine and pentagastrin where the drug binds reversibly to histamine (H-2) receptors found on gastric parietal cells. It leads to the inhibition of histamine binding to this receptor, result in a reduction of gastric acid secretion [3]. Food and Drug Administration (FDA) approved ranitidine for short term use in 1983, many competitors manufactured and launched different generic alternatives to Zantac® after Glaxo's patent expired [4].

In 2004, FDA has approved to sell of OTC versions of ranitidine products in the United States. In September 2019, the FDA warned about the concerning amount of N-nitrosodimethylamine (NDMA) found in ranitidine products [5]. Finally, in April 2020, after several tests, the FDA directly released an official request for ranitidine products (injectable and oral dosage forms) to stop being sold in the United States [4]. FDA had set a certain limit of NDMA level at 0.096 micrograms daily intake or 0.32 ppm for ranitidine. However, after testing many ranitidine products found to have NMDA concentrations nine times greater than the FDA's recommended limit. FDA has also indicated that NDMA levels could increase the longer they are kept on a shelf even at a normal temperature range. This means that some ranitidine products could become increasingly carcinogenic the longer they are on store shelves [4]. N-nitrosodimethylamine is a known environmental contaminant found in water, foods (dairy products, vegetables, grilled meats) and in several industrial processes [6, 7]. This substance has been classified by the International Agency for Research on Cancer (IRAC) as a probable human carcinogen (group 2A) [5]. It is marked as human carcinogen associated with cancers of the stomach, esophagus, nasopharynx and bladder [8].

Ranitidine can form NDMA through a combination of nitrite and dimethylamine (DMA) that exists in its molecular structure where NDMA is created during the natural degradation of ranitidine over time [9]. Thus, many clinicians were not worried about the risk of cancer from ranitidine. However, owing to the recent detection of carcinogens in ranitidine, additional research is needed to clarify the risk of cancer from ranitidine use. N-nitrosamine precursors including NDMA detected in other drugs as indicated in the previous studies [10 - 14]. Although pharmaco-epidemiologic studies to evaluate cancer risk raised as a result of the use of this medication are limited [15].

Drug recall is the most effective process to protect the public against any harmful or toxic substances [16]. Implementation of such process in poorly developed countries is a major concern, as failure of getting warned about adverse drug reactions (ADRs) reporting, which implicates their lack of awareness and attitude toward safety issues associated with any medications. Therefore, in order to maximize drug safety, community people must be warned and educated about reported adverse drug reactions of ranitidine, especially since self-medication is becoming an increasing practice all around the world [17] and Libyan people are not an exception. For this purpose, this study conducted to assess public awareness and behavior towards ranitidine recall. On the other hand, the active interaction with healthcare providers in the same context was indirectly evaluated.

Materials and methods

Study design and setting: A cross-sectional study was conducted in Zawia city which is located on the western coast of Libya and is the largest population gathering near Tripoli. A self-designed online questionnaire was sent to a total of 300 participants. The questionnaire was written in Arabic language and posted in social media platforms to be filled by participants. A pilot study was conducted on a small random sample to evaluate feasibility and improve study design. It is carried out for one month between October and November 2020. Based on the preliminary results; old age was excluded from participation. Therefore, the survey instrument was amended to ensure that older people were included. The revised instrument was then resent and data was collected at the end of January 2021.

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Study variable: Self-administered online questionnaire consisted of 19 items that were divided into four sections as follows: Section one is related to the demographic characteristics of the participants including age, gender and educational levels. Section two was designed to obtain information about participants' behavior toward ranitidine use or intake. Section three is consisted of eight items statements that measure and investigate people' knowledge about ranitidine recall issues and their interaction with their healthcare provider. Section four was designed to estimate people's perceptions and awareness of ranitidine toxicity. Vital information about the reason of ranitidine recall was attached in the questionnaire to educate the participant and measure their response.

Study participants: A random sample of 300 individuals located in Zawia city involved an online questionnaire between November 2020 and January 2021. The procedure of the pre-validation that was accomplished to ensure that the questionnaire items measure people's knowledge and awareness regarding ranitidine recall. The questionnaire was examined by other medical researchers and practitioners and they agreed that all questionnaire questions cover and measure the concept of the study. Moreover, a pilot study questionnaire was sent to a random small sample for the purpose of improving study design and to discover any problems that arise in a large-scale survey. With regard to the ethical of approval for this study, even though the low risk of the study and nature of collected data (completely anonymous with no personal information being collected as part of their name or contact details), there is no risk of possible disclosures, the study was approved by University of Zawia and a clear statement in the Arabic language provides a clear explanation of the study purpose and ensures confidentiality was provided for all participants before they fill the questionnaire.

Statistical analysis: The collected data were analyzed using Statistical Package for the Social Sciences (SPSS) Version 26.0. Descriptive statistical analysis using frequency and percentage of the response was employed to summarize all answers in this survey.

Results

Section 1: Responding rate and demographic characteristics of the participants: In **Table 1**, the demographic characteristics of the participants were shown. Thus, out of 300 participants, 258 submitted their completed questionnaires represent a response rate of 86.5%. All the participants were located within Zawia city (northwest of Libya). The majority of the respondents were female 66.4% (n=170) while 33.6% of the participants were male (n=88).

Table 1: Demographic characteristics of the participants

Items	Frequency	Percentage
Gender		
Female	**170**	**66.0**
Male	**88**	**34.0**
Age in years		
15-35	**171**	**66.3**
36-55	**66**	**25.6**
56-75	**21**	**08.1**
Educational levels		
Basic education	**13**	**05.0**
High school education	**21**	**08.0**
University education	**178**	**69.0**
Postgraduate studies	**46**	**18.0**

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Section 2: Awareness of participants about ranitidine recall and their source of interaction: In **Table 2**, data about ranitidine recall and source of information are shown in percentage. Thus, three-fold of the participants have no idea about ranitidine withdrawal or stopped by FDA. Most of the participants has also no idea about the recall of the drug. No major specific information was found that provided for the participants to stop using ranitidine.

Section 3: Participants use and behavior toward ranitidine utilization: The results showed that 146 of the participants (57.0%) were using ranitidine (**Figure 1**) and 215 of the participants (83.5%) indicated that their family members also use ranitidine products (**Figure 2**). The usage rate of ranitidine among the participants was found high.

Section 4: Ranitidine users and their interaction with health care professionals. In **Table 3**, for those participants who used ranitidine, their behavior and interaction with healthcare providers and pharmacists are summarized. The most common behavior of the participants that used ranitidine in most of the time and in irregular patterns (73.0% and 59.0%). The tablet dosage form is used by most of the participants. Long-term use by about half of the participants is found (42.0%). A low consultation rate by participants for using ranitidine is found. In **Table 4**, No high interaction or consultation by healthcare providers as pharmacist has found. Thus, very low response from the participants with ranitidine use by health care providers (<20.0% interaction).

Table 2: Awareness of participants about ranitidine recall and their source of information

Survey items	Frequency	Percentage
Did you know that ranitidine has been stopped by the FDA?		
Yes	59	23.0
No	199	77.0
Do you know the reason?		
Yes	34	13.0
No	224	87.0
What is the source of your information?		
Social media	58	22.5
Family and friends	23	09.0
Health care professional	38	14.5
Not available	139	54.0

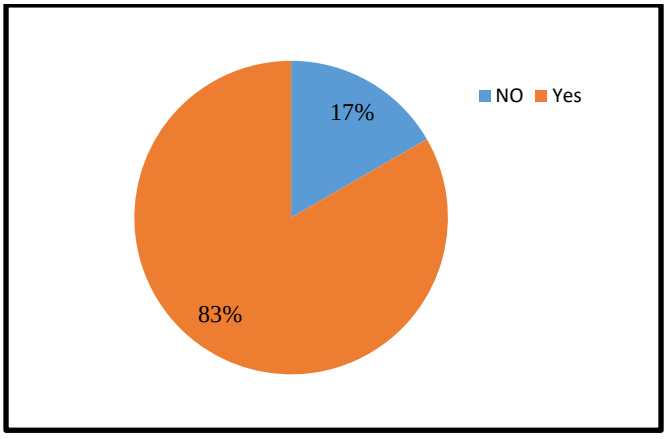

Figure 1: Ranitidine use among the participants

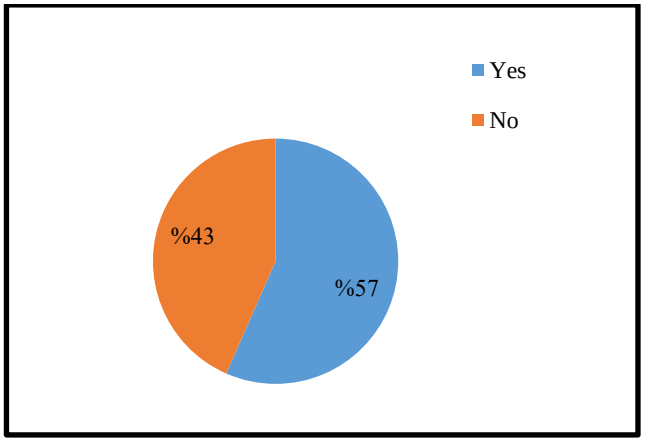

Figure 2: Ranitidine use among the participants families

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Table 3: Participants behavior toward ranitidine utilization

Survey items		Frequency	Percentage
When do use ranitidine?	Always	73	50.0
	Sometimes	59	40.5
	Rarely	14	09.5
Strength of the dose	75 mg	85	58.2
	150 mg	31	21.2
	300 mg	10	07.0
	Unspecified	20	13.6
Dosage form			
	Tablet	124	85.0
	Syrup	022	15.0
When was the last time you got ranitidine medicine?			
	< 1 month	22	15.0
	1 - 6 months	38	26.0
	> 6 months	61	42.0
	No answer	25	17.0
Did you take the drug after consultation a healthcare provider?			
	Yes	61	41.8
	No	85	58.2

Table 4: Users of ranitidine and their interaction with health professional after recalled

Survey items	Frequency	Percentage
Did you consult any health care provider to stop using ranitidine when you found out that it was withdrawn?		
Yes	029	19.9
No	117	80.1
Has any of the pharmacist told you that the FDA has stopped it from been sold?		
Yes	007	04.8
No	139	95.2
Did the pharmacist tell you about the reason?		
Yes	004	02.7
No	142	97.3
Has pharmacist stopped dispensing ranitidine to you?		
Yes	007	04.8
No	139	95.2

Section 5: Awareness data (participant's behavior toward ranitidine recalled: Two items in the questionnaire were administered to all participants to measure their awareness and behavior toward ranitidine recalled and the findings showed that only 17.0% of the participants used ranitidine stopped taken when they found out that it had been withdrawn (**Figure 2**). Furthermore, 78.0% made a decision not to use ranitidine after knowing about its toxicity through a brief notification attached in the questionnaire (**Figure 3**).

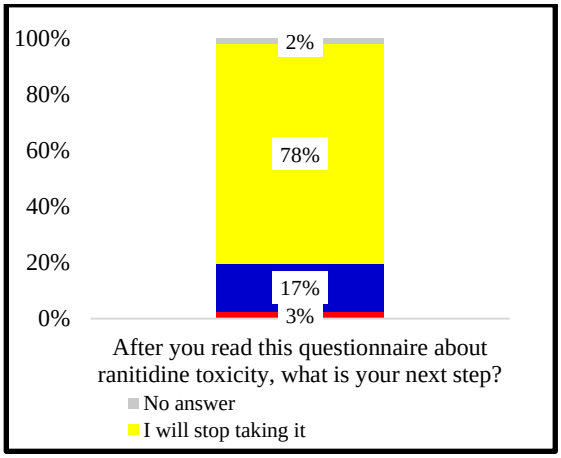

Figure 3: Participants' behavior toward continued use of ranitidine

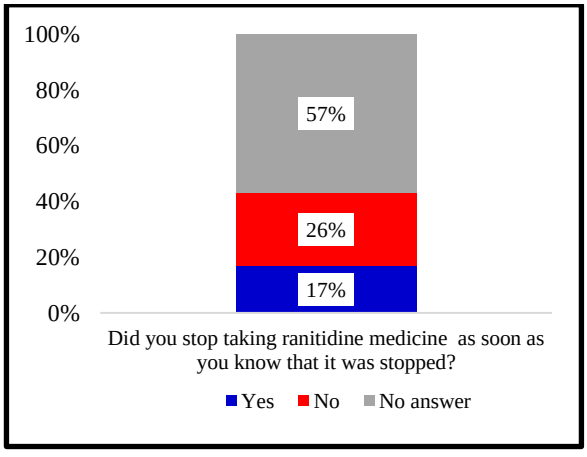

Figure 4: Participants' awareness data

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Discussion

Drug recall is the most effective process implied to ensure the safe use of drugs among people [16]. Public awareness about recalled drugs is critical to optimize patient protection against any harmful substances. Furthermore, healthcare professional and pharmacist qualifications, training and practice have a significant impact on proper drug recall implementation. The responding rate recorded to the questionnaire was high which indicates that the participants were helpful and responsive. Ranitidine is widely used among Libyan people, where more than a half of participants and most of their family members use ranitidine. Young people in the age range of 15-35 years were the most common ranitidine users. This finding is in a good agreement with the previous study indicated that highest antacid users were young adults [18]. Unfortunately, almost half of them were likely to be utilized this medicine inappropriately; they seem to be consuming ranitidine more often without medical consultation. Moreover, the study observed that about 70.0% of the participants obtain the medicine from pharmacies after April, 2020 (the period of announcing ranitidine withdrawal from the market by FDA). This refers probably that the participants either not informed or had no information about ranitidine recall.

Although most of the participants were highly educated (86.0%), they showed poor knowledge and awareness about ranitidine recall and reasons for withdrawing it. Furthermore, over half of respondents lack any source of information in this regard. A minority of the respondents (23.0%) have been aware of ranitidine recalled. In addition, the vast majority of the participants (90.0%) ensured that the pharmacists did not provide any information about ranitidine recall notification and they continued to dispense the drug to the patient. This disappointing finding could emphasize the reason for the poor knowledge of the participants and shows clearly low level of pharmacist practice and their weakness to conduct health education roles.

This is in accordance with a recent study conducted in the western region of Libya where the study aimed to evaluate Libyan pharmacists' knowledge regarding Zantac withdrawn [19]. These findings could be a consequence of weak interaction between people and healthcare providers. A previous study stated that the quality of interaction between pharmacist and patient is found to affect patients' knowledge about dispensed drugs [20]. The study ensured the availability of ranitidine products in the market and concluded that both physicians and pharmacists are still prescribing and dispensing ranitidine products. In the same context, the results of another study conducted in India to assess awareness among physicians and pharmacists regarding ranitidine recall were not satisfactory [21].

A recent study reported that providing accurate drug information to patients can improve their understanding and adherence to drug therapy. The qualification level of the dispenser could thus significantly influence knowledge score of patients in regard to the drugs dispensed [22]. To optimize patient's health and reduce health risks associated with the use of such drugs, the study recommends increasing educational coverage and the standard cross the community. This could be accomplished by providing a good standard of health services which can be achieved by improving pharmacist's communication skills, training and experiences, creating of healthcare programs concerning general health education for public, updating health care professional's information on every drug recall notification and support post-marketing surveillance through conduction of pharmacovigilance study. The study recommend that Ministry of Health decision makers and policymakers must take more responsibility to protect general public which can be accomplished by supporting educational programmers across the community, attention to health care professional qualification standards, finding effective ways to control and implement drug recall announcements as soon as possible.

Conclusion: This study revealed a decrease in community awareness about ranitidine recall in Libya. Overall, the study suggested many reasons that in turn responsible for poor knowledge and awareness among

ISSN: 2789-1895 online
ISSN: 2958-3101 print

community people, including; lack of special educational programs, availability of information resource and weak interaction between patients and pharmacists.

Acknowledgments: The authors would like to thank all the participants for their cooperation that facilitates this work.
Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author contribution: All the authors substantially contributed to the conception, compilation of data, checking, and approving the final version of the manuscript, and agreed to be accountable for its contents.
Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission were completely observed by the authors.
Author declaration: The authors confirm all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

References

1. Ridgefield CT (2013) Boehringer Ingelheim Pharmaceuticals Inc (US). Zantac® launches innovative integrated marketing campaign to educate consumers on heartburn relief. ZAN-131047.
2. Strum WB (1983) Ranitidine. Journal of the American Medical Association (JAMA) 250 (14): 1894-1896.
3. Morgan KA, Ahlawat R (2021) Ranitidine. In StatPearls [Internet]. StatPearls Publishing LLC. PMID: 30422583.
4. U.S. Food and Drug Administration (2020). FDA requests removal of all ranitidine products (Zantac) from the market. FDA advises consumers, patients and health care professionals after new FDA studies show risk to public health. FDA news release. Published April 4, 2020.
5. Liteplo RG, Meek ME, Windle W (2002) N-nitrosodimethylamine. World Health Organization. WHO Library Cataloguing-in-Publication Data. ISBN: 92 4 153038 3.
6. International Agency for Research on Cancer (1987) Overall evaluations of carcinogenicity: an updating of IARC monographs, vol. 1 to 42. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: Suppl. 7. IARC, 7: 1-440. ISBN: 978-92-832-1411-3.
7. Lips, RJ, Fennerty B, Fagan TC (1990) Clinical review of histamine-2 receptor antagonists. Archives of Internal Medicine. 150 (4): 745-751. PMID: 1970232.
8. Mirvish SS (1995) Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. Cancer Letters. 93 (1): 17-48. doi: 10.1016/0304-3835(95)03786-V
9. Wagner JA, Dinh JC, Lightdale JR, Gold BD, Colombo JM (2021) Is this the end for ranitidine? NDMA presence continues to confound. Clinical and Translational Science. 14 (4): 1197-1200. doi: 10.1111/cts.12995
10. Matsuda J, Hinuma K, Tanida N, Tamura K, Ohno T, Kano M, Shimoyama T (1990) N-nitrosamines in gastric juice of patients with gastric ulcer before and during treatment with histamine H2-receptor antagonists. Gastroenterologia Japonica. 25 (2): 162-168. doi: 10.1007/BF02776810
11. Shen R, Andrews SA (2013) Formation of NDMA from ranitidine and sumatriptan: the role of pH. Water Research. 47 (2): 802-810. doi: 10.1016/j.watres.2012.11.004
12. Zeng T, Mitch WA (2016) Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. Carcinogenesis. 37 (6): 625-634. doi: 10.1093/carcin/bgw034
13. Michaud DS, Mysliwiec PA, Aldoori W, Willett WC, Giovannucci E (2004) Peptic ulcer disease and the risk of bladder cancer in a prospective study of male health professionals. Cancer Epidemiology and Biomarkers and Prevention. 13 (2): 250-254. doi: 10.1158/1055-9965.epi-03-0174
14. Vermeer IT, Engels LG, Pachen DM, Dallinga JW, Kleinjans JC, Van Maanen JM (2001) Intragastric volatile N-nitrosamines, nitrite, pH, and Helicobacter pylori during long-term treatment with omeprazole. Gastroenterology. 121 (3): 517-525. doi: 10.1053/gast.2001.27098
15. ATSDR (2021) Agency for Toxic Substance and Disease Registry. Public Health Statement for n-Nitrosodimethylamine. Available at https:// www.atsdr.cdc.gov/PHS/PHS.asp?id=882&tid= 173. Accessed January 21, 2021.

ISSN: 2789-1895 online
ISSN: 2958-3101 print

16. US Food and drug administration (2018) FDA's role in drug recalls. Updated July 3, 2018. www.fda.gov/Drugs/DrugSafety/DrugRecalls/ucm612550.htm. Accessed May, 13rd, 2022.
17. Kasulkar AA, Gupta M (2015) Self-medication practices among medical students of a private institute. Indian Journal of Pharmaceutical Sciences. 77 (2): 178-182. doi: 10.4103/0250-474x.15656
18. irtwhistle RV (1988) Antacid use in a family-practice population. Canadian Family Physician. 34: 1681-1683. PMID: 21253067.
19. Mabroukah AI, Einass RI (2021) Attitude of Libyan pharmacist in Western Region of Libya toward Zantac withdrawal. Libyan Journal of Medical Research. 15 (1): 1-15. doi: Nil.
20. Garjani A, Rahbar M, Ghafourian T, Maleki N, Garjani A, Salimnejad M, Aghajani H (2009) Relationship of pharmacist interaction with patient knowledge of dispensed drugs and patient satisfaction. Eastern Mediterranean Health Journal. 15 (4): 934-943. PMID: 20187545.
21. Begam RF, Ravikumar Y, Velmurugan R (2021) Awareness about FDA announcement on voluntary recall of ranitidine among physicians and pharmacists in and around Chennai, India: a cross-sectional study. Future Journal of Pharmaceutical Sciences. 7: 112. doi: 10.1186/s43094-021-00267-7
22. Hirko N, Edessa D (2017) Factors influencing the exit knowledge of patients for dispensed drugs at outpatient pharmacy of Hiwot Fana specialized university hospital, Eastern Ethiopia. Patient Preference and Adherence. 11: 205-212. doi: 10.2147/PPA.S128658