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"PHARMACISTS' PERSPECTIVES ON CHRONOTHERAPY IN NORTHWEST NIGERIA: A COMPREHENSIVE STUDY"

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ABSTRACT
Circadian rhythms play a pivotal role in modulating the pharmacological effects of drugs, influencing their efficacy and safety. Administering medications at specific times of the day has emerged as a critical factor in patient care and management. This systematic review explores the impact of circadian rhythms on drug therapy, aiming to enhance therapeutic outcomes. Multiple studies have demonstrated the potential for improved drug efficacy when administered at particular times of the day. Given that both pharmacokinetics and pharmacodynamics are influenced by biological rhythms, considering these variations is essential before medication administration.
Chronotherapy, an approach to optimize safe and effective pharmacotherapy by aligning drug administration with the body's biological rhythms, is gaining prominence. Circadian rhythms have been implicated in a wide range of human diseases, including insomnia, sleep disorders, jetlag, cardiovascular diseases, hypertension, metabolic disorders, neurological and psychiatric conditions, and hormone-dependent cancers. Understanding the intricate interplay between circadian rhythms and drug effects is essential for tailoring treatment strategies and improving patient outcomes.

Keywords: Circadian rhythms, Chronotherapy, Drug administration, Pharmacokinetics, Pharmacodynamics

1. Introduction

There have been advances in several aspects of science and medicine following numerous findings on how circadian rhythms affect pharmacological effects of drugs. Circadian rhythms are roughly 24 hour cycle of physiological and behavioral processes endogenously generated by an organism in response to external cues (Dibner et al., 2010). Administering medications at certain time of the day is a noteworthy factor especially during patient management and care (Kaur et al., 2016). Several studies have reported that therapeutic outcome of drugs maybe improved following medication administration at certain times of the day (Kaur et al., 2013; Hassan & Haefeli, 2010; Lemmer, 2005; Huang et al., 2011). Since it has been established that both pharmacokinetics and pharmacodynamics are affected by variations in biologic rhythms, it is therefore necessary to consider these variations prior to administration of medications.
Chronotherapy involves optimizing safe and effective pharmacotherapy by administering medications in synchronization with the biologic rhythms of the disease patterns. It has been established that circadian rhythms is relevant to human diseases and is associated with altered insomnia and sleep

syndromes (Waterhouse et al., 2007), jetlag (Portaluppi et al., 2012), cardiovascular diseases and stroke (Shea et al., 2011), hypertension (Masri & SassoneCorsi, 2013), metabolic diseases (Kronfeld-Schor & Einat, 2012), neurological and psychiatric disorders (Markt et al., 2015), and hormone-dependent cancers (Monsees et al., 2012).

Several studies have established that circadian rhythms influence both effectiveness and toxicity of many medicines, for example Acetaminophen (Kamali et al., 1987) and Theophylline (Watanabe et al., 1984) show different pharmacokinetics in the morning compared to evening. Despite the numerous findings with regards to circadian rhythms and chronotherapy, many drugs are still administered without considering the optimal time of the day suitable for their pharmacological actions. Rational drug use as defined by World Health Organization requires that patients receive appropriate prescribing and use of drugs for the appropriate diagnoses and at an affordable price (WHO, 2016). The ideal goal of rational drug use is to encourage quality pharmaceutical care, promote patient adherence and maximize therapeutic outcomes. The pharmacists collaborate with other healthcare providers to ensure that this aim is achieved using principles of rational drug use as advocated by W.H.O. These principles suggest that when prescribing, clinical guidelines should be used, patients should be educated and informed about their medications and the importance of using the medications as prescribed and at the right time (WHO. 2012).

In Nigeria, out of the seventeen universities accredited for pharmacy programme, only two are located in the Northwest geopolitical zone (PCN, 2016) and a pharmacy-based chronotherapy module is yet to be adopted in the curricula of these universities (ABU, 2017; UDUSOK, 2017) but topics on chronobiology are expected to be covered in elective courses from other departments. Community pharmacists in this region are the first contact healthcare providers that provide a variety of services which range from dispensing prescription drugs to counseling and instructing patients on how and when to use medications and medical appliances. Whilst carrying out duties as community pharmacists and pharmacy practitioners, it is expected that chronotherapeutic approach be considered when the intensity and symptoms of a disease are known to have a predictable variation during the 24-hour time period (Erkekoglu & Baydar, 2012; Stranges et al., 2015; Smolensky et al., 2015).

The aim of this study was to assess the awareness and attitudes towards chronotherapy among community pharmacists practicing in Northwest region of Nigeria. This study will identify if community pharmacists incorporate the principles of Chronotherapy into practice, since a sound knowledge and understanding of these principles could foster quality pharmaceutical care.

2. Materials & Methods

2.1 Study Setting

The study was a cross sectional study conducted between April and May, 2017. It involved consented community pharmacists practicing in Northwest region of Nigeria. Nigeria is a Sub Saharan country in the West African region with a land mass of 923,768 square kilometers (World Factbook, 2011). Nigeria comprises thirty-six states and the Federal Capital Territory and these states are grouped into six geopolitical zones. The Northwest geopolitical zone which make up about 20% of the total population of Nigeria, consist of seven states namely: Jigawa, Kaduna, Kano, Kastina, Kebbi, Sokoto and Zamfara.

List of registered pharmacists in Nigeria as at December 2016 is 5,307 out of which 474 community pharmacists are practicing in the Northwest region of Nigeria (PCN, 2016).

2.2 Data Collection

Data was collected using a modified questionnaire based on current literature (Kaur et al., 2016). Pilot tests were conducted on five community pharmacists practicing in each of the 7 states, to determine the applicability of the questionnaires. The self administered, pretested and structured questionnaire was designed to consist of twenty-seven close ended questions divided into three sections, as follows:

2.2.1 Section One- Demographics

It included 4 items that covered participants' gender, age, years of practice and level of education.

2.2.2 Section Two- Awareness

Included twelve items with two Likert scale-type response options- (Agree, Disagree), to test knowledge of
circadian rhythms and clinical case studies.

2.2.3 Section Three- Attitude

The attitude section included eleven items with five Likert scale-type options- (Strongly disagree, Disagree, Normal, Strongly agree, Agree) examined their attitude towards chronotherapy and their willingness to apply principles of chronotherapy in future practice.

2.3 Data Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 20.0 software. Descriptive statistics were used to report community pharmacists' demographics. The mean scores of awareness and attitude sections were compared with the participants' demographics using *Mann–Whitney U test* and Kruskal–Wallis test.

The variables for testing awareness of the respondents were graded on a two-point scale and the response assigned 1 and 0, where 1 was the correct answer and 0 the wrong answer. The variables for testing attitude of the community pharmacists were graded on five-point scale and the response was assigned 1,2,3,4 or 5, where 1 was the worst response and 5 the best response. During analysis, 1 and 2 were combined as the wrong/negative response and 4 and 5 as the correct/positive response. The frequency and percentage of community pharmacists with positive and negative attitudes towards chronotherapy were obtained during data analysis. Spearman's rank-order correlation was used to determine the relationship between awareness and attitudes. Statistical significance was considered at $p \leq 0.05$.

3. Results

A total of one hundred and thirty one (131) community pharmacists in Northwest region of Nigeria filled the survey instruments. Only one hundred and twenty five (125) survey instruments were included in the final analysis as six (6) were excluded due to some missing demographic data.

3.1 Demographics

Gender distribution showed that most of the participants were male (61.6%). The results showed that most of the community pharmacists who participated in this study were between 26 and 30 years old (42.4%) and only (26.4%) of the respondents were between 21 and 25 years old. The results showed

that only four (4) participants have being practicing for over 15 years (3.2%) while most of the participants have years of practice of below 6 years (56.8%). Majority of the participants have only Bachelor degree (76.0%) while only three (3) participants have PhD (2.4%). (see Table 1.)

3.2 Awareness Items

The awareness section examined the knowledge of the community pharmacists and results showed that only (46.4%) of the participants believed that disruption of the circadian rhythm of the human body can initiate disease conditions. Only (56.0%) of the participants answered correctly the question relating to pattern of peaking of cholesterol biosynthesis (item 5) and their response to that question was reflective in the next question (item 6) as only (68.8%) answered correctly, the time of the day administration of Statins with longer half life. Only (44.8%) of the participants answered correctly the clinical case question (item 12) relating to time of the day administration of a once daily dose of Perindopril for a non-dipper patient. (see Table 2.)

3.3 Attitude:

Most of the participants agreed that chronotherapy could increase the efficacy of a drug (91.2%) and reduce the incidence of adverse drug effects (88.0%). Results showed that most of the respondents agreed to statements (items 3, 4, 5) relating to counseling patients about taking their medications at more effective circadian time window. Most participants (97.6%) agreed that chronotherapy should be an area covered in the continuing pharmacy education activities for pharmacy professionals and were willing to dedicate sometime to learn about chronotherapy (95.2%). (see Table 3.)

3.4 Groups' relationship with total awareness and total attitude.

With regards to mean total awareness, results showed that there were significant differences between participants aged 21 – 25 years and 31 years & above (p=0.019) and also, participants aged 26 – 30 years and 31 years & above (p = 0.004). Results also showed that there were significant differences between participants with years of practice of 1 – 5 and 11 – 15 (p = 0.041) and also, participants who have being practicing for 6 – 10 years and 11 – 15 years (p = 0.031). (see Table 4.)

3.5 Correlation between total awareness and attitudes scores

Data analysis showed a statistically significant (p= 0.015) positive correlation (r=0.216) between awareness and attitude. This value of 'r' signifies that the correlation is weak. (see Table 5.)

Table 6. Demographic data of the community pharmacists

	Number of Community pharmacists (n=125)	**Percentage (%)**
Gender		
Female	48	38.4
Male	77	61.6
Age		
21 – 25	33	26.4
26 – 30	53	42.4
31 & Above	39	31.2

Years of practice		
1 – 5	71	56.8
6 – 10	37	29.6
11 – 15	13	10.4
16 – 20	4	3.2
Level of education		
Bachelor	95	76.0
Master	27	21.6
PhD	3	2.4

Table 7. Participants' response to awareness items

		Proportion of community pharmacists who answered items correctly (%)
1	Circadian rhythms affect human physiological processes.	68.0
2	Disease conditions cannot be initiated by the disruptions of the circadian rhythms of the human body.	46.4
3	Circadian rhythms are cycles in the physiological processes of many species, with a period (cycle duration) of roughly 24 hours.	96.8
4	With respect to pharmacokinetics of drugs, circadian rhythms can influence drug absorption.	87.2
5	In a 24-h time period, the rate of cholesterol biosynthesis follows a pattern of peaking in the morning.	56.0
6	Statins with longer half life can be taken at anytime of the day.	68.8
7	In a 24-h time period, Gastrointestinal motility follows a pattern of decreasing at night.	60.8
8	Asthma symptoms are most likely to worsen at night.	92.8
9	NSAIDs (Non steroidal anti-inflammatory drugs) are often administered for pain conditions such as rheumatoid arthritis. The most appropriate time of the day to take this medication is Evening.	82.4
10	AJ is a 25 yr old man who is diagnosed with peptic ulcers. His doctor advised him to take Omeprazole 40mg daily. Omeprazole is more effective in raising gastric pH when administered in the morning.	73.6
11	Prednisone is a corticosteroid used in wide range of condition for its anti-inflammatory and immunosuppressant effects such as asthma	74.4

	attacks. The most appropriate time to administer the drug in a non emergency situation is morning.	
12	Perindopril is angiotensin converting enzyme inhibitor used commonly for the treatment of hypertension. The best time for a non-dipper (blood pressure does not decrease during sleep) patient to take a once daily dose is evening.	43.2

Table 8. Participants' response to attitude items

	Proportion of community pharmacists who answered either 'Disagree' or 'Strongly disagree' (%)	Proportion of community pharmacists who neither 'Agree' nor 'Disagree' (%)	Proportion of community pharmacists who answered either 'Agree' or 'Strongly' (%)
Chronotherapy could increase the efficacy of a drug.	5 (4.0%)	6 (4.8%)	104 (91.2%)
Chronotherapy could reduce the incidence of adverse drug effects.	10 (8.0%)	5 (4.0%)	110 (88.0%)
At therapy initiation, doctors/general practitioners should counsel their patients about more effective 'circadian-time windows' for drugs where this is applicable.	9 (7.2%)	10 (8.0%)	106 (84.8%)
Where applicable, counseling the patients about taking their medication at more effective 'circadian-time windows' for a particular drug may lead to improved adherence.	8 (6.4%)	11 (8.8%)	106 (84.8%)
Where applicable, counseling the patients about taking their medication at more effective 'circadian-time windows' for a particular drug may lead better cost effectiveness.	15 (12.0%)	10 (8.0%)	100 (80.0%)
Counseling patients on Chronotherapy will increase the number of patients returning to your pharmacy.	13 (10.4%)	13 (10.4%)	98 (79.2%)

Chronotherapeutic information should be included in drug references.	7 (5.6%)	10 (8.0%)	108 (86.4%)
Future direction			
Chronotherapy should be an area covered in the continuing pharmacy education activities for pharmacy professionals	3 (2.4%)	0 (0.0%)	122 (97.6%)
As a pharmacist, I am willing to dedicate some time to learn about Chronotherapy.	5 (4.0%)	1 (0.8%)	119 (95.2%)
The principles of Chronotherapy should be taught in the pharmacy course.	14 (11.2)	0 (0%)	111 (88.8%)
Chronotherapeutic studies should be included as part of therapeutic goods administration (TGA) regulatory requirements for registering a drug.	16 (12.8%)	0 (0.0%)	109 (87.2%)

Table 9. Groups' relationship with total awareness and total attitude scores

	Total Awareness			**Total Attitude**		
	Mean	SD	p-value	Mean	SD	p-value
Gender						
Female	8.29	1.76	0.307	46.10	4.82	0.426
Male	8.62	1.52		46.25	6.55	
Age						
21-25	8.60*	1.57	0.019	45.67	5.18	0.351
26-30	8.90*	1.44	0.004	46.58	6.75	
31 & above	7.84	1.70		46.10	5.38	
Years of Practice						
1-5	8.77#	1.56	0.041	46.09	5.44	0.685

6-10	8.37#	1.60	0.031	45.67	7.52	
11-15	7.23	1.69		47.46	3.95	
16-20	8.75	0.50		48.50	0.57	
Education						
Bachelor	8.63	1.56	0.147	46.51	5.51	0.058
Master	8.22	1.71		46.25	5.91	
PhD	6.66	1.52		35.33	10.50	

*. Significant at p < 0.05; #. Significant at p< 0.05; SD: Standard deviation

Table 9. Correlation between total awareness and total attitude scores

	Total awareness		**Total attitude**	
	r	p- value	r	p- value
Attitude	1		0.216	0.015*
Awareness	0.216	0.015*	1	

*. Correlation is significant at the level of 0.05 (2-tailed test); r: Correlation

4. Discussion

Community pharmacists are easily accessible and often the first contact health care provider for most people living in Nigeria. To our knowledge, this is the first study assessing community pharmacists' awareness and attitudes towards principles of chronotherapy in this region. Results confirmed our hypothesis that there would be inadequate chronotherapy-related knowledge among community pharmacists practicing in this region. In addition, results indicated remarkable positive attitudes towards chronotherapy and willingness to learn and apply principles of chronotherapy in practice. This finding implies that any misconception about chronotherapy in this region could be addressed if dedicated educational programs are organized to impact more knowledge about chronotherapy.

The results of our study highlight a lack of awareness of evidence based chronotherapy-related information especially in areas involving circadian rhythms in normal physiological functions. These results are in line with previous study conducted on similar cohorts assessing their viewpoints about and experience with application of chronotherapy principles in practice (Kaur et al., 2016) and also consistent with another study that assessed the awareness and attitudes of final year pharmacy students towards chronotherapy (Kaur et al., 2016); both studies reported a lack of awareness about current therapeutic evidence on chronotherapy. This study revealed that only (44.8%) of the community pharmacists provided correct answers to evidence based recommended time for Perindopril (Hermida et al., 2011; Hassan & Haefeli, 2010).

It could be that community pharmacists in this region mostly apply the FDA approved optimal administration time (morning) for Perindopril. The implication is that they may not be able to help patients benefit maximally from their medications by suggesting appropriate administration times for such a condition in which blood pressure control is altered by disruptions in circadian BP patterns or sleep disorders. Therefore, with the development and introduction of the new evidence based clinical

guidelines for use of chronotherapies in clinical practice, it is important that information about principles of chronotherapy be updated and made available for pharmacy practitioners, as this would enhance their knowledge and quality of clinical services.

It is interesting to note that only (56.0%) of the participants know the circadian pattern of cholesterol biosynthesis as seen on (item 5) of the awareness section. Their response to that question was reflective as only (68.8%) of the respondents answered correctly 'any time of the day' administration of statins with a long half life (item 6) as approved by FDA (Plakogiannis & Cohen, 2007). This observation indicates that almost half of the participants may have forgotten or have a poor understanding of the basic pharmacology and physiology concepts. Our finding is in line with a previous study that reported a low performance by final year pharmacy students regarding 'optimal administration time' for statins with a long half life (Kaur et al., 2016) and also supports the findings from a study that was carried out on community pharmacists in an eastern state of Nigeria, where the authors reported that about 53% of the community pharmacists do not attend refresher courses, seminars and workshops frequently (Ilodigwe & Chima, 2010).

Most of the pharmacists agreed to statements relating to patient counseling and willingness to apply chronotherapy in practice. This indicates that they acknowledge their role in providing patient medication counseling, considering the fact that modern pharmacy practices have evolved from a product oriented practice to pharmaceutical care. This finding supports the result from a study carried out in Nigeria which reported that community pharmacists participate in patient education on health matters (Hunponu-Wusu et al., 2015).

This study showed that awareness was influenced by age and years of practice. Pharmacists under 31 years of age and pharmacists with less than 11 years of practice had better significant level of awareness. It could probably be because in Nigeria, the young pharmacists are the frontiers in transforming medical care systems and also, they have more access to the internet. Moreover, the teachings in the schools are now advocating evidence based facts other than the crude facts. Finally, the positive correlation between awareness and attitude scores as reported in this study is a good indication that adequate awareness can lead to positive attitude towards chronotherapy, which could eventually result in good practices.

Study limitations

This study has some limitations and shortcomings. It was difficult to get hold of the community pharmacists in charge as most of the pharmacies were managed by non pharmacists. This study may not be generalized to all parts of Nigeria considering the relative small sample size. Therefore, we suggest that similar study be carried out in other parts of the country.

Conclusion

Majority of the community pharmacists had impressive positive attitude towards chronotherapy, however, the findings from this study highlight the need for a comprehensive chronotherapy-related educational program for both future and practicing community pharmacists.

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