

# Headaches and Erectile Dysfunction Medications at UTH-Kara (Togo)

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## Abstract

**Introduction:** Headaches are a common symptom affecting individuals worldwide, including in the tropical zone, and have been extensively studied in Togo. Phosphodiesterase-5 inhibitors, commonly prescribed for erectile dysfunction, are known to induce headaches, yet there is a lack of research on this topic in sub-Saharan Africa and Togo. **Methods:** A cross-sectional study conducted from February 1st to June 30th, 2023, including adult patients seeking erectile dysfunction treatment and prescribed PDE-5 inhibitors. **Results:** A total of 28 patients were included in the study, with an average age of  $34.46 \pm 7.5$  years. The age group of 30 - 39 years was the most represented (53.57%). Among the participants, 67.86% had a history of chronic headaches. During the intake of PDE-5 inhibitors, 71.43% reported the onset of headaches. Among the 19 patients with chronic headaches, 68.42% developed headaches following PDE-5 inhibitor use (RR = 0.88, 95% CI: 0.55 - 1.40, p = 0.484). The characteristics of the induced headaches were similar to the patients' pre-existing headaches in 78.95% of cases. Additional symptoms included nasal congestion (36.84%) and an urge to have a bowel movement (26.32%). Sildenafil (75.00%) and Tadalafil (25.00%) were the primarily prescribed PDE-5 inhibitors. The incidence of headaches did not significantly differ between the two groups (RR = 1.33, 95% CI: 0.67 - 2.64, p = 0.306). Treatment for the induced headaches involved self-medication with paracetamol (65.00%) and nonsteroidal anti-inflammatory drugs (NSAIDs) (35.00%). **Conclusion:** Headaches induced by PDE-5 inhibitors are a well-established reality, emphasizing the need for caution and warning in patients with pre-

existing headache conditions, while individualized approaches are necessary to address the potential interplay between migraine medications and erectile dysfunction treatments.

## **Keywords**

Headache, Phosphodiesterase-5 Inhibitors, Erectile Dysfunction, Togo, Sub-Saharan Africa

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## **1. Introduction**

Headaches are a common symptom that affects the majority of individuals at some point in their lives. They have been the subject of numerous publications in the tropical zone [1], and the Togolese literature contains a large number of them [2]-[7]. Chronic headaches are generally classified into primary headaches and secondary headaches based on their etiology. While the former are defined as having no organic cause, the latter are caused by conditions such as intracranial tumors, central nervous system infections, intracranial hypertension, metabolic abnormalities, vascular lesions, post-traumatic causes, structural abnormalities, or an overuse of medications [8]. Very rarely, even the non-abusive use of a certain category of drugs can trigger headaches. This is the case with phosphodiesterase-5 inhibitors (PDE-5 inhibitors), which are a widely prescribed class of medication for men with erectile dysfunction. Headaches are the most commonly reported side effects of PDE-5 inhibitors and are found in 30% of patients taking Sildenafil [9], 21% of patients taking Vardenafil [10], and 16% of those taking Tadalafil [11]. All types of chronic headaches have been reported to be induced by PDE-5 inhibitors, with well-detailed pathophysiological mechanisms [12]. Based on the currently available literature data, there are practically no studies on headaches induced by the use of PDE-5 inhibitors in sub-Saharan Africa, more specifically in Togo. Therefore, this study was conducted with the aim to determine the prevalence and clinical characteristics of headaches in patients undergoing treatment with PDE-5 inhibitors at University Teaching Hospital of Kara.

## **2. Methods**

### **2.1. Setting**

The study was conducted in the neurology and urology-andrology departments of the University Teaching Hospital (UTH) of Kara (UTH-Kara). UTH-Kara is the third largest university hospital center in Togo, after those in the capital city, Lomé. It serves as the referral center for the northern part of Togo. The neurology department falls under the department of medicine and medical specialties, while the urology-andrology department is part of the department of surgery and surgical specialties. In each of the two departments, consultations are held

twice a week and require prior appointment scheduling.

## **2.2. Method**

The current study was a cross-sectional, descriptive, and analytical study conducted from February 1st to June 30th, 2023, focusing on patients undergoing treatment with PDE-5 inhibitors.

## **2.3. Inclusion and Exclusion Criteria**

Adult patients aged 18 years and above who sought consultation for erectile dysfunction treatment and were prescribed a PDE-5 inhibitor were included in the study. Patients with a history of severe cardiovascular disorders, such as severe heart problems, recent stroke, or uncontrolled hypertension, were excluded to avoid increased risks associated with the use of PDE-5 inhibitors in these conditions.

## **2.4. Data Collection**

A questionnaire designed by senior neurologists and urologists was used to collect the data. This questionnaire included questions distributed in several categories: socio-demographic characteristics, personal medical history, and cardiovascular risk factors; the presence of pre-existing chronic headaches and their characteristics; the association between the intake of PDE-5 inhibitors and the occurrence of headaches; the specific type of PDE-5 inhibitor used; and the measures taken to treat headaches that occur after taking PDE-5 inhibitors.

## **2.5. Operationalization**

The presence of at least three episodes of headaches per month in the three months preceding the consultation was considered as a history of chronic headaches. The ICHD-3 criteria were used to specify the type of headaches [13]. If each instance of taking a PDE-5 inhibitor was followed by the onset of a headache, it was considered a systematic headache due to the PDE-5 inhibitor. In cases where headaches were present in a patient before taking PDE-5 inhibitors, the characteristics were studied and compared to pre-existing headaches. Additional symptoms were also investigated. Two PDE-5 inhibitor drugs were predominantly prescribed to the study patients, namely Sildenafil (100 mg) and Tadalafil (20 mg), each taken once. A comparison was made regarding the frequency of headache onset based on the type of drug prescribed to the patients.

## **2.6. Data Analysis**

Data processing and statistical analysis were performed using Epi Info software version 7.2.5 and tables were created in Microsoft Excel version 2019.

Qualitative data were compared using the chi-square test or Fisher's exact test, as appropriate based on their criteria of use. The comparison of quantitative variables was conducted using the Student's t-test.

## 2.7. Ethical Considerations

The study received ethical approval from the ethics committee prior to its initiation. Confidentiality and anonymity were ensured for each participant, and informed consent was obtained from them before collecting any information.

## 3. Results

A total of 28 patients who fulfilled the inclusion criteria of this study were enrolled. The mean age was  $34.46 \pm 7.5$  years (22 - 50 years). The age group of 30 - 39 years was the most represented, accounting for 15 patients (53.57%). Civil servants were the predominant occupation (14 patients, 50.00%), followed by farmers (8 patients, 28.57%).

Among the participants, 19 (67.86%) had a history of chronic headaches, and their characteristics were those of migraine or tension-type headaches (**Table 1**). During the intake of PDE-5 inhibitors, 20 patients (71.43%) reported the onset

**Table 1.** Socio-demographic characteristics of patients.

	Frequency	Percentage
<b>Age group</b>		
20 - <30	7	25.00
30 - <40	15	53.57
40 - <50	5	17.86
50 - <60	1	3.57
<b>Occupation</b>		
Civil servant	14	50.00
Shopkeeper	3	10.71
Farmer	8	28.57
Craftsman	3	10.71
<b>Personal medical history</b>		
None	21	75.00
Hypertension	4	14.29
Asthma	2	7.14
Smoking	1	3.57
<b>Marital status</b>		
Single	9	32.14
Married	14	50.00
Common-law partnership	5	17.86
<b>Chronic headaches</b>		
Yes	19	67.86
No	9	32.14

of headaches. Among them, 19 patients (95.00%) consistently experienced headaches after taking the PDE-5 inhibitors.

Among the 19 patients with a history of chronic headaches, 13 (68.42%) developed headaches following the use of PDE-5 inhibitors (Table 2). However, this difference was not statistically significant ( $p = 0.484$ , Fisher's exact test), with a relative risk (RR) of 0.88 (95% CI: 0.55 - 1.40) (Table 2). The characteristics of the induced headaches were similar to the patients' pre-existing headaches in 15 cases (78.95%). Some patients reported additional symptoms, including nasal congestion in 7 cases (36.84%) and an urge to have a bowel movement in 5 patients (26.32%) (Table 3).

In this study, two PDE-5 inhibitors were primarily prescribed: Sildenafil at a dosage of 100 mg and Tadalafil at a dosage of 20 mg. Sildenafil was prescribed to 21 patients (75.00%). Among those who took Sildenafil, 16 (76.19%) experienced headaches, compared to 4 patients (57.14%) in the Tadalafil group. However, this difference was not statistically significant (RR = 1.33, 95% CI: 0.67 - 2.64,  $p = 0.306$ ) (Table 2).

The main treatments used for the induced headaches were self-medication with paracetamol in 13 patients (65.00%) and nonsteroidal anti-inflammatory drugs (NSAIDs) in 7 patients (35.00%). Overall, 20 patients (71.43%) reported the onset of headaches after taking PDE-5 inhibitors, and 19 patients (76.00%) consistently experienced headaches after each medication intake.

**Table 2.** Characteristics of headaches associated with the intake of PDE\*-5 inhibitors.

	Headaches after taking PDE-5 inhibitors		p	RR (95% CI)
	Yes n (%)	No n (%)		
<b>Chronic headaches</b>				
Yes (n = 19)	13 (68.42)	6 (31.58)	0.484	0.88 (0.55 - 1.40)
No (n = 9)	7 (77.78)	2 (22.22)		
Total (n = 28)	20 (71.43)	8 (28.57)		
<b>Type of PDE*-5 inhibitor</b>				
Sildenafil (n = 21)	16 (76.19)	5 (23.81)	0.306	1.33 (0.67 - 2.64)
Tadalafil (n = 7)	4 (57.14)	3 (42.86)		
Total (n = 28)	20 (71.43)	8 (28.57)		

\*PDE: Phosphodiesterase.

**Table 3.** Additional symptoms in patients with pre-existing headaches (n = 19).

Additional symptoms	Frequency	Percentage
Urge to go to the bathroom	5	26.32
Feeling of nasal congestion	7	36.84
Sudden fatigue	2	10.53
Cold sweats	5	26.32

## 4. Discussion

This cross-sectional study, conducted over a period of 5 months, aimed to explore the inducer effect of PDE-5 inhibitors on headaches. All the 28 patients who fulfilled the study inclusion criteria were included. This study has some limitations, because it does not cover all cases of erectile dysfunction, which is a symptom that can be reported by patients consulting in other specialities than those that served as the study framework. This explains the small size of the study population and the impossibility of generalizing the results. However, the data collected allow to perform an analysis and to meet the objectives set by the study.

The mean age of the participants was  $34.46 \pm 7.5$  years, with a predominance of the 30 - 39 age group. The findings of this study support the notion that a considerable proportion of young men are affected by this condition. This finding is consistent with previous studies, such as the one conducted by Nguyen *et al.* in 2017, which reported a significant prevalence of erectile dysfunction among young individuals, accounting for up to 30% of cases [14].

Among the participants, 19 (67.86%) had a history of chronic headaches. This high proportion can be attributed to the selection bias, as the neurology department primarily receives patients suffering from headaches. Out of the 19 patients with a history of chronic headaches, 13 (68.42%) developed headaches following the use of PDE-5 inhibitors. However, there was no statistically significant difference ( $p = 0.484$ , Fisher's exact test), with RR of 0.88 (95% CI: 0.55 - 1.40). These results indicate that the presence of a history of headaches is not a reliable predictor of headache induction following PDE-5 inhibitor use. Nevertheless, the characteristics of the induced headaches were similar to the patients' pre-existing headaches in 15 cases (78.95%). This suggests that PDE-5 inhibitors have the ability to reproduce similar headaches in patients with pre-existing headache conditions.

The way PDE-5 inhibitors trigger headaches is well-known. By inhibiting the degradation of cyclic guanosine monophosphate (cGMP), PDE-5 inhibitors enhance the intracellular action of nitric oxide (NO). NO, which has a function in the relaxation of smooth muscles in the corpus cavernosum, is also known to be involved in migraines by acting on pain-sensitive perivascular nerve fibers or in the genesis of central pain [15] [16]. This effect was highlighted in the study by Kruuse *et al.* in 2003, where 12 migraine patients received a double-blind dose of 100 mg Sildenafil or placebo, resulting in the triggering of migraines in 10 of them ( $p = 0.01$ ). Additionally, all patients reported symptoms similar to their usual migraines, as observed in the current study. These findings are consistent with previous studies [17]. In addition to the usual symptoms of their headaches, some patients reported additional symptoms, including nasal congestion (7 patients, 36.84%) and an urge to have a bowel movement (5 patients, 26.32%) (see **Table 3**). Nasal congestion and vasomotor flushing are the most commonly reported additional effects in the literature [17] [18] [19] [20].

There was no significant difference in headache induction based on the type of PDE-5 inhibitor (Sildenafil or Tadalafil), with a p-value of 0.306 and a RR of 1.33, 95% CI: 0.67 - 2.64. This similarity can be attributed to the fact that both medications belong to the same class and share the same mechanism of action. The first documented case of PDE-5 inhibitor-induced cluster headache involved a patient without a history of headaches. The patient experienced episodes of cluster headaches when taking Tadalafil. Even after switching to Sildenafil, the patient continued to experience the same symptoms [21].

Since the headache-inducing effects of PDE-5 inhibitors are known, trials of preventive treatments have been undertaken. For instance, Taga *et al.* [21] reported the beneficial effect of a single dose of 50 mg indomethacin taken before using PDE-5 inhibitors in their patient, who experienced headaches regardless of the type of PDE-5 inhibitor used. Other studies recommend the use of conventional migraine treatments such as Sumatriptan, tricyclic antidepressants, and beta-blockers [17].

## 5. Conclusion

Headaches induced by PDE-5 inhibitors are a well-established reality. They tend to be more pronounced in patients with pre-existing headache conditions, highlighting the importance of providing appropriate warning and precautions before initiating treatment for erectile dysfunction with PDE-5 inhibitors. During follow-up, it is crucial to seek the minimum effective dosage while considering preventive therapy for patients who already experience headaches. However, an ongoing dilemma remains, as some migraine medications can cause erectile dysfunction, while medications for erectile dysfunction can trigger migraines. Resolving this complex issue requires an individualized and personalized approach for each patient.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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