



PHENYLTHIOCARBAMIDE TASTE SENSITIVITY AS A POTENTIAL GENETIC MARKER FOR PRESCRIPTION DRUGS AND SUBSTANCE MISUSE

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ABSTRACT

Misuse of prescription drugs and substances such as analgesics, opioids, depressants, hallucinogens, or stimulants is on the increase and a major concern for parents and the society due to its consequences on moral decay, crime, insecurity and health challenges. This study was aimed at determining the role of phenylthiocarbamide (PTC) taste sensitivity as a potential genetic marker for prescription drugs and substance misuse. Two hundred and thirty-two undergraduate students of the Nasarawa State University Keffi comprising of 133 males and 99 females were randomly selected and a structured questionnaire administered for the study. Stock solution of PTC prepared into various concentrations (0.005, 0.05, 0.25, 0.50 and 1.0) was used to determine the status of individual phenotypes. The findings of the study on the phenotypic frequency of PTC taste sensitivity on gender ($p < 0.05$), age groups of participants ($p < 0.05$) and alcohol ingestion ($p < 0.010$) showed a significant relationship while smokers were non-significant ($p > 0.346$). Results of the PTC taste sensitivity phenotype of prescription drugs/substance misuse of the sampled population ($p > 0.253$) and gender ($p > 0.216$) were non-significant whereas age groups ($p < 0.05$) revealed a significant relationship. Our view is that the outcome of this study could not present a clear picture of the relationship between the individual social life style and their inherent genetic attributes as a result of some other possible co-founding factors. Further study using larger population sample size and individual prescription drug/substance misuse is suggested.

Keywords: Prescription drug, misuse, substance, phenylthiocarbamide, phenotype, genetic marker, taste sensitivity.

INTRODUCTION

The future of any society depends largely on the quality of her adolescents and youths (NIDA, 2020). Amazingly today, youths are exposed to dangers inherent in prescription drugs and substance misuse in their formative years (NDLEA, 2014; Rudd *et al.*, 2016; NIDA, 2019; CDC wonder, 2020). Prescription drugs are defined as controlled medicines that would legally require a medical prescription from a health care provider in order to be dispensed due to their potential risks of being diverted, misused, and abused. These include but not limited to analgesics, opioids, depressants, hallucinogens and stimulants. Misuse of prescription drugs/substance therefore implies taking a medication in a manner or dose other than prescribed; taking someone else's prescription, even if for a legitimate medical complaint such as pain; or taking a medication to feel euphoria (i.e., to get high) (Jamey-Peters, 2019., NIDA, 2020).

According to results from the 2017 National Survey on Drug Use and Health, an estimated two million Americans misused prescription pain relievers for the first time within the past years, which averages to approximately 5,480 initiates per day (NIDA, 2020). Additionally, more than one million misused prescription stimulants, 1.5 million misused tranquilizers, and 271,000 misused sedatives for the first time. Misuse of prescription drugs was highest among young adults ages 18 to 25, with 14.4 percent reporting nonmedical use in the past years (Meilch *et al.*, 2017).

This night mare of prescription drug/substance misuse has intensified into an epidemic with serious consequences of moral decay, insecurity and health challenges (NDLEA, 2015; Jones and McAninch, 2015). Although misuse of prescription drugs affects many Americans, certain populations such as youth and older adults in other parts of the world may be at particular risk (Mielch *et al.*, 2015). Nigeria is not an exception.

The need for innovative measures to treat and control this menace therefore cannot be overemphasized.

One possible strategy is to identify individuals with the potentials of indulging in drug/substance misuse early in life. Recently, many polymorphic genetic markers have been deplored for better understanding of human diversity (Padmavathi, 2013). One of which is the use of Phenylthiocarbamide (PTC) sensitivity taste which in recent times has been used as a novel strategy for exploring the relationship of genetics and environmental interactions with the personality attributes of individuals and disease conditions (Hussain *et al.*, 2014; Dastan *et al.*, 2015). PTC Taste sensitivity refers to the ability of a person to detect even minute concentration of a taste substance (Murray *et al.*, 2016; Beauchamp *et al.*, 2017). "Substance" is defined as any psychoactive compound with the potential to cause health and social problems, including addiction. These substances may

be legal (e.g., alcohol and tobacco); illegal (e.g., heroin and cocaine); or controlled for use by licensed prescribers for medical purposes such as hydrocodone or oxycodone (e.g., Oxycontin, Vicodin, and Lortab). Substance misuse is however defined as a pattern of harmful use of any substance for mood-altering purposes (MClellan, 2017; Buddy, 2020).

There has therefore been an increasing interest in the study of PTC taste sensitivity and its impact on dietary choices, individuals' life styles, health and diseases. Given such outcomes', the availability of genetic markers to taste individual ability may provide insight into individual's predisposition to early lifestyles such as smoking, alcoholism, drug and substance consumption and misuse (Driscoll and Perez, 2006; Shivaprasad *et al.*, 2012; Stephen, 2013; Julliard *et al.*, 2017).

PTC tasting (or not) is conveyed by a single gene that codes for a taste receptor on the tongue. The gene, 'TAS2R38', is of two common forms or alleles of the PTC gene, and at least five rare forms (Chibuisi *et al.*, 2010). One of the common forms is a tasting allele, and the other is a non-tasting allele (Ben *et al.*, 2012). Each allele codes for a bitter taste receptor protein with a slightly different shape (Kathleen and Shana, 2016). The shape of the receptor protein determines how strongly it can bind to PTC. Since all people have two copies of every gene, combinations of the bitter taste gene variants determine whether someone finds PTC intensely bitter, somewhat bitter, or without taste at all (Bachmanov *et al.*, 2014; Riso *et al.*, 2016; Roper and Nirupa, 2017). However, it is hypothesized that the ability to taste PTC could have a protective advantage by enhancing the identification of bitter tasting of toxic compounds in plants (My 46 Trait Profile, 2019).

Though several studies on PTC taste sensitivity on dietary habits, lifestyles and disease conditions have been documented (Stephen, 2013; Kathleen and Shana, 2016), there is little or no such report linking PTC taste sensitivity on prescription drugs/substance misuse by the youths in the study location. This study is most likely the first and therefore aimed at determining the polymorphism of phenylthiocarbamide taste sensitivity as a potential genetic marker for prescription drugs/substance misuse.

MATERIALS AND METHODS

The study area

Nasarawa State University Keffi, located in the Middle Belt Region of Nigeria, coordinating latitude 8.8471°N and longitude 7.8776°E on the Northern and Eastern hemisphere respectively (Akwa *et al.*, 2007). A total of 232 students were randomly recruited for this study using a structured questionnaire. This was followed by a bitter sensitivity taste for phenylthiocarbamide. Out of this population, 133 were males and 99 were females.

Quantitative and qualitative test of phenylthiocarbamide

A stock solution containing 0.10% phenylthiocarbamide was prepared in distilled water and serial dilutions were made to obtain five concentrations in mg/ml (0.005, 0.05, 0.25, 0.50, and 1.0) and a control containing distilled water was used. Taste sensitivity to PTC was ascertained using a filter paper impregnated with different dilutions of the PTC. If a student could not taste at the lowest dilution concentration, then he/she was designated a non-taster. The experiment was commenced with the weakest PTC concentration in the order of increasing concentrations. Threshold levels for PTC were then recorded for the participants in the sampled population.

Data was analysed using the SPSS version 23.0 software package. Frequencies, percentages and Chi-square analysis were performed between individual characteristics. PTC status and prescription drug and substance misuse were also determined.

RESULTS AND DISCUSSION

The results presented in Figures 1-5, show an overview of the frequency distribution of the sampled population. A total of 232 students randomly selected through the structured questionnaire comprised of 133 (57.3%) males and 99 (42.7%) females (Fig.1). One hundred and ninety-seven (197) constituting (84.9%) were tasters while 35 constituting (15.1%) were non-tasters (Fig. 2). A general overview of the population of the age of participants was in the age range of 16-20 years with 166 (71.7%) respondents, this was followed by 21-25 years with 53 (22.8%), while the age range of 26–30 was the least with a population of 13 (5.6%) participants respectively (Fig.3).

On liquor status, the number of participants who were alcoholics were 43 (18.5%) and 189 (81.5%) were non-alcoholics respectively (Fig.4). 15 (6.5%) smokers and 217 (93.5%) non-smokers participated in the study (Fig.5).

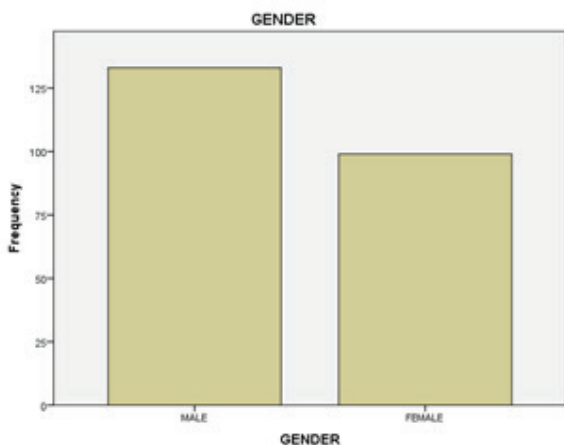


Figure 1: Frequency of gender in the sampled population

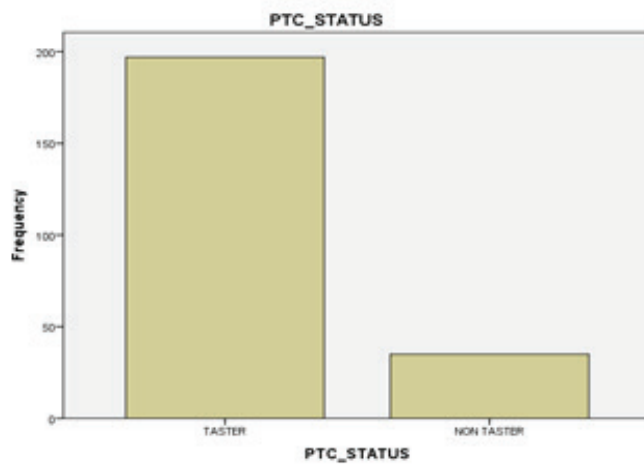


Figure 2: Distribution of respondents based on PTC status

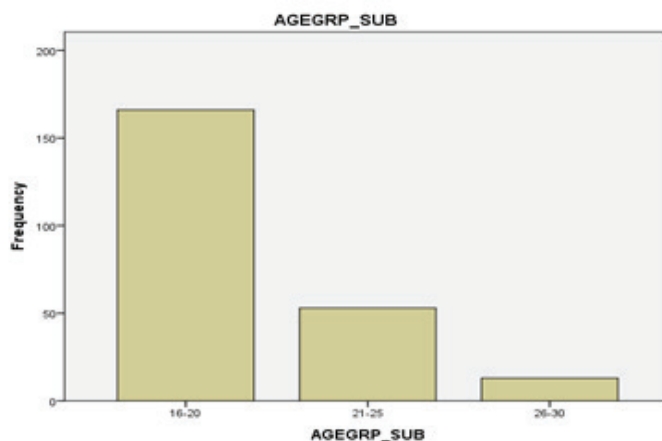


Figure 3: Frequency distribution of Age groups

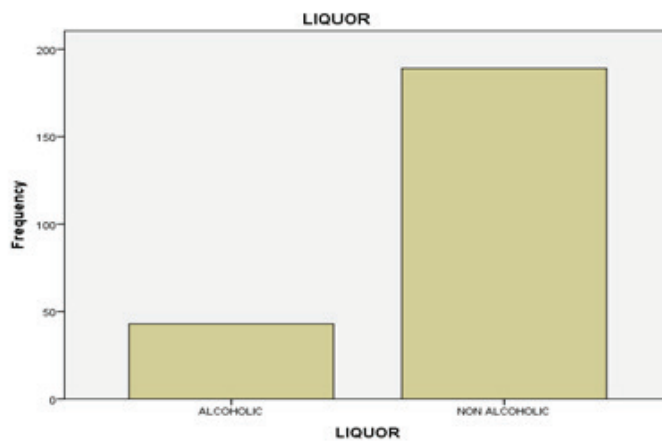


Figure 4: Distribution of status of liquor participants

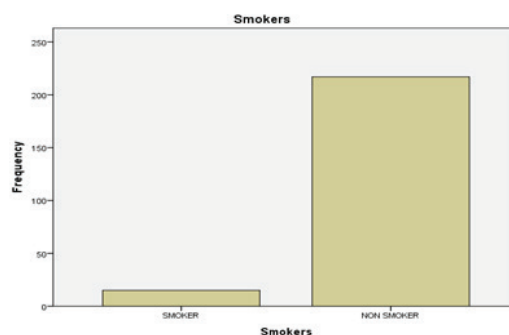


Figure 5: Distribution of Nicotine status

Table 1a: revealed the phenotypic frequency distribution of the PTC taste sensitivity status of individual respondents. Out of the 133 males 103 (52.3%) were Tasters while 30 (85.7%) were Non-Tasters, while among the 99 females, 94 (47.7%) were Tasters and 05(14.3%) non-tasters. The Chi Square value of this analysis on gender was 13.577 and a significant p-Value of $p < 0.000$ ($p < 0.005$). On liquor status, (table 1b) the alcoholics, 42 (21.3%) were Tasters and 155 (78.7%) Non-Tasters, while Non-alcoholics had 01 (2.9%) as Taster and 34 (97.1%) as Non-Tasters. The Chi square value obtained for the liquor status (alcoholic and non-alcoholic category) in the sampled population was 6.709 and a significant p-value of 0.010. The category of those analyzed for Nicotine intake had 14 (7.1%) smokers as Tasters and 183 (92.9%) as Non-Tasters while among Non-Smokers were 01 (2.9%) as a Taster and 34 (97.1%) were Non-Tasters. Respondents for the smoking and non-smoking habits pooled a Chi Square value of 0.887 and a non-significant p-value of 0.346 (Table 1b).

Table 1a: Phenotypic frequency distribution of PTC status of gender in the sampled population.

Parameters	PTC status		Chi square	P-value
Gender	Tasters	Non-tasters		
Male	103a (52.3%)	30a (85.7%)	13.577	0.000**
Female	94b (47.7%)	5b (14.3%)		

Each subscript letter denotes a subset of variables categories whose column proportions do not differ significantly from each other at the .05 level. ** indicates significant.

Table 1b: Phenotypic frequency distribution of PTC status of the sampled population of alcoholics and smokers

Parameters	PTC status		Chi square	p-Value	
	Tasters	Non-tasters			
Liquor	Alcoholics	42a (21.3%)	155b (78.7%)	6.709a	0.010**
	Non-Alcoholics	1a (2.9%)	34b (97.1%)		
Nicotine	Smokers	14a, (7.1%)	183a (92.9%)	0.887a	0.346
	Non-Smokers	1a (2.9%)	34a (97.1%)		

Table 2: Gender distribution of prescription drug and substance misused

Prescription Drugs and Substance Misuse										
			Analgesics	Opioids	Depressants	Hallucinogen	Stimulants	Total	Pearson Chi-Square	p-Value
Gender	Male	Count	68a	20a	13a	15a	17a	133	5.777a	0.216
		% within	64.2%	43.5%	54.2%	55.6%	58.6%	57.3%		
	Female	Count	38a	26a	11a	12a	12a	99		
		% within	35.8%	56.5%	45.8%	44.4%	41.4%	42.7%		
Total	Count	106	46	24	27	29	232			

Each subscript letter denotes a subset of (ALL) variables categories whose column proportions do not differ significantly from each other at the .05 level. ** indicates significant.

Figure 7: Shows the frequency distribution of the prescription drugs/substances misused by the respondents in the sampled population. 106 (45.69%) participants had experienced the use of analgesics, 46 (19.82%) opioids, 29 (12.5%) stimulants, 27 (11.64%) hallucinogens and 24 (10.34%) depressants

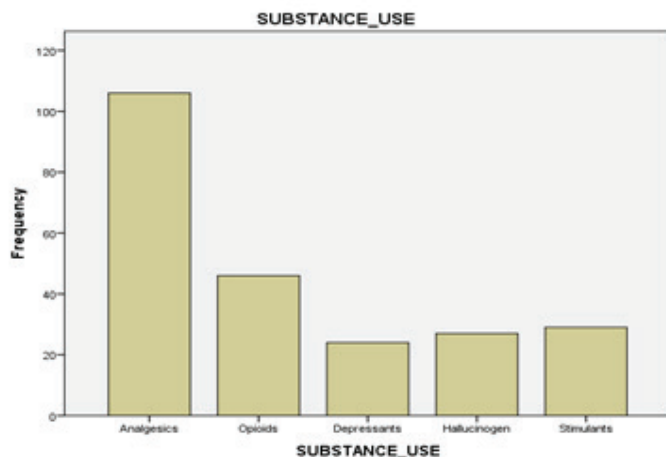


Figure 7: Frequency distribution of prescription drugs/substances misuse

Table 2 shows the frequency distribution of gender on other substances used by the respondents. In this breakdown, participants who had misused analgesics where 106(45.68%), of this figure 68 (64%) were males while 38 (35.8%) were females. Opioid users were 46 (19.82%), 20 (43.5%) were males and 26 (56%) were females respectively. This was followed by those who had experienced the misuse of stimulants (17, 58.6% male and 12, 44.4% females). The hallucinogen users were 27 in all (15, 55.6% male and 12, 41.4% females). The least group in this category were the depressant users, who had 13 (54.2%) male and 11 (45.8%) females. The analysis of the distribution of the substance use in the sampled population recorded a chi square value of 5.777 representing a non-significant value of 0.216 ($p < 0.005$).

Each subscript letter denotes a subset of Substance Use categories whose column proportions do not differ significantly from each other at the .05 level.

Table 3: The frequency distribution of Phenylthiocarbamide taste sensitivity status of the prescription substance misused respondents in the sampled population was analyzed. Respondents who had misused analgesics were more in number with 91(85.8%) as tasters and 15 (14.2%) as non-tasters. Opioid substance misusers were 36 (78.3%) tasters and 10 (14.2%) non-tasters. Those who misused stimulants were 28 (96.6%) tasters and 01 (3.4%) non-tasters. 23 (85.2%) tasters had used hallucinogen while 4 (14.8%) were non-tasters. Similarly, of the 24 respondents who had misused depressants 19(79.2%) were tasters and 5 (20.8%) were non-tasters. The Pearson chi square value for this analysis was 5.348 and a non-significant p-value of 0.253 (p<0.005)

Table 3: Distribution of Phenylthiocarbamide taste sensitivity status of other substances used

Prescription drug and substance misuse										
PTC Status	Taster	Count	Analgesics	Opioids	Depressants	Hallucinogen	Stimulants	Total	Pearson Chi-Square	p-value
		% within	85.8%	78.3%	79.2%	85.2%	96.6%	84.9%		
	Non-Taster	Count	15a	10a	5a	4a	1a	35		
		% within	14.2%	21.7%	20.8%	14.8%	3.4%	15.1%		
Total	Count		106	46	24	27	29	232		

Each subscript letter denotes a subset of prescription substance misuse categories whose column Proportions do not differ significantly from each other at the .05 level.

The distribution of the prescription drug/substance misuse according to age groups is as shown in table 4. The age group 16-20 years recorded the highest percentage of prescription drug/substance misused. 106 (100%) of the population had misused analgesics, 26 (89.7%) stimulants, 13 (48.1%) hallucinogens', 11 (45.8%) depressants and lastly 10 (21.7%) opioids respectively. The next age group was 21-25years. More of the sampled population had misused opioids (36, 78.3%) followed by hallucinogen (14, 51.9%) and stimulants (3, 10.3%). The last age group 26-30years recorded the misuse of depressants (13, 54.2%) only amongst participants. Statistical analysis on the distribution of the prescription drug/substance misuse, across the age groups revealed a Pearson chi square value of 249.684 and a significant value of 0.000 (p<0.005)

Table 4: Frequency of substance used according to age groups

Prescription drug/substance misused										
Age Group of participants		Analgesics	Opioids	Depressants	Hallucinogen	Stimulants	Total	Pearson Chi-Square	P - value	
		Count	106a	10b	11b	13b	26c			166
16-20	%within	100.0%	21.7%	45.8%	48.1%	89.7%	71.6%			
	Count	0a	36b	0a, c	14b	3c	53			
21-25	% within	0.0%	78.3%	0.0%	51.9%	10.3%	22.8%			
	Count	0a	0a	13b	0a	0a	13			
26-30	% within	0.0%	0.0%	54.2%	0.0%	0.0%	5.6%			
	Count		106	46	24	27	29	232		

Each subscript letter denotes a subset of prescription drug/substance misused categories whose column proportions do not differ significantly from each other at the .05 level.

Globally, prescription drug/substance misuse ingestion has formed a focal point for discussion considering the attending consequences associated with same. Increase in crime rate, trafficking, cattle rustling, armed robbery and banditry, kidnapping, rape, cross boarder crimes are among the so many vices accompanying prescription drug/substance misuse particularly among our youths (NIDA, 2019, Jamey-Peters, 2019) The situation is so alarming that various governments have put in so much funds and strategies towards

curbing the menace to no avail. It is as a result of the failure of earlier efforts that this work was designed towards providing a genetic perspective to identifying prospective prescription drug/substance misusers at their formative years. This study was therefore aimed at determining the polymorphism of phenylthiocarbamide taste sensitivity as a potential genetic marker for prescription drug/substance misuse. PTC-tasting ability is a simple genetic trait governed by a pair of alleles, dominant T for tasting and recessive t for non-tasting. Persons with genotypes TT and Tt are tasters, and persons with genotype tt are non-tasters.

The sampled population were regular undergraduate students of the Nasarawa State University Keffi, established in 2001. In this study, the phenotypic analysis of the sampled population recorded a high frequency of PTC tasters against non-tasters, with a significant $p < 0.000$ ($p < 0.005$) outcome.

This result is in line with the findings of Shivaprasad *et al.*, (2012), Padmavathi (2013), Hussain *et al.*, (2014) and Dastan *et al.*, (2015) who also observed high frequencies of tasters in their studies though not on prescription drug/substance misuse. We also observed in our studies that male respondents were more of tasters against female respondents. This result equally aligns with the results of Shivaprasad *et al.*, (2012) and Padmavathi (2013). In the separate study by Padmavathi (2013) the phenotypic frequency of male tasters was 68.63% and 31.37% non-tasters higher than the females. On the contrary however, Hussain *et al.*, (2014) and Dastan *et al.*, (2015) reported high incidences of female tasters in their studies. In that study, Dastan *et al.*, (2015) reported that 81.8% of the people included in their study could detect the taste PTC, whereas the remaining 18.2% couldn't detect it. Their rates were 83.4% and 16.6% in females and 79.4% and 20.6% in males, respectively. Hussain *et al.*, (2014) revealed in their study that out of 821 subjects studied, 545 (66.38%) were tasters and 276 (33.62%) were non-tasters to PTC. Among 400 males, 140 (35.00%) were non-tasters and among 421 females, 136 (32.30%) were non-tasters. This showed more males were observed to be non-tasters of PTC as compared to females. Again, females were having more tasters (285, 67.70%) than males (260, 65.00%). Padmavathi (2013), postulated that it appeared there was hormonal mediation of the tasting ability, as women were more often taste sensitive in these regards than were men. It has been suggested that PTC tasting may be related to the genetically determined level of dithiotyrosine in the saliva.

In their work on the role of phenylthiocarbamide as a genetic marker in predicting the predisposition of disease traits in humans, Shivaprasad *et al.*, (2012) observed a significantly higher incidence of PTC tasters than non-tasters among the general population in their study. The result of our findings agrees with

all but differs with Hussain *et al.*, (2014) and Dastan *et al.*, (2015) on the high phenotypic frequency of female tasters.

Many studies have reported that in world population, approximately 70% of the populations are PTC tasters and 30% non-tasters. It has also been globally postulated that human population show a tremendous variation in the frequency of tasters within the range of 10% - 98%. Our work supports the claims that there is significant higher incidence of PTC tasters than non-tasters among a general population. This is as seen from our values and different other values observed across different communities globally.

Individual susceptibility to certain personality life style such as alcoholism, smoking and prescription substance/drug abuse was analyzed in our study. Our findings on the phenotypic frequencies of alcoholics and non-alcoholics revealed a significant (0.000, $p < 0.005$) relationship with PTC sensitivity taste. It is noted that while the PTC tasters protect themselves from taking alcohol because of the irritation and bitter taste, the non-tasters are more prone to alcohol.

Our investigation on smoking phenotype recorded a Chi square value of 0.887 and a non-significant value of 0.346 ($p < 0.005$). The number of respondents in both tasters and non-taster phenotypes among the smoking participants were high in our sampled population. This result outcome is invariance with the report of Dastan *et al.*, (2015). In their findings, those who could detect the taste of PTC were 83.1% among non-smokers, a rate higher than that of smokers which was found to be significant ($p < 0.05$). Previous studies on subjects with possible connection between PTC perceptions of individuals and their susceptibility to smoking revealed that the individuals with high sensitivity of PTC perception don't consume substances such as cigarette and coffee that cause bitter taste and feeling of irritation in the mouth. It was also reported that since the PTC non-tasters could not detect the bitter taste and displeasure caused by smoking, they are therefore exposed to smoking more cigarettes, and therefore at the risk of different physiological consequences including health challenge. Padmavathi (2013) found that non-smokers and those not habituated to coffee or tea have a statistically higher percentage of tasting PTC than the general population.

The outcome of a high response of non-tasters to tasters in the student's population exposes the non-tasters to the risk of smoking with time. Today our youths perceive smoking as a social order and a cause for concern. Dastan *et al.*, (2015) posited that regular smoking habits begin almost before adolescence period. Deliberate efforts must therefore be put in place to monitor their taste sensitivity status as they are growing into adolescence to curtail addictive tendencies.

Aside alcohol and cigarette consumption, some prescription drugs/substance misuse such as

analgesics, opioids, depressants, hallucinogen and stimulants by adolescents and youths is on the increase and a major concern for parents and the society. Whereas some studies have shown that homozygous tasters experience more intense bitterness than heterozygous, other studies have indicated that another gene may be responsible for determining the taste sensitivity (Padmavathi, 2013). Attempt was therefore made in the cause of this study to establish whether PTC sensitivity taste could provide a connection to those into prescription substance/drug misuse that would confer on it the status of a potential marker.

As a result, analysis of the sampled population based on some prescription drug/substance misuse was carried out; the outcome revealed that a high proportion of the male respondents against females misused the above listed prescribed substances except, for opioids where females were more. The result of gender in relation to prescription drug/substance misuse had a Pearson chi-square value of 5.777 representing a non-significant value of $p > 0.216$ ($p < 0.005$)

The misuse of prescription drugs/substances such as analgesics, depressants, hallucinogen and stimulants by the male could be likely due to their physical disposition and work schedule. For instance, analgesics are medications that relieve pain, they don't turn off nerves, change the ability to sense one's surroundings or alter consciousness, while some are effective mild pain relievers with a low risk of side effects (e.g. paracetamol) others are strong pain relief medicine effective for both general (e.g. Tramadol) and nerve-related pain or used in the treatment of partial-onset seizures and nerve pain (e.g. Gabapentin) (CDC Vital signs, 2017; Jamey-peters, 2019), Other similar prescription drugs/substance misuse assessed were Depressants, a category of drug that includes tranquilizers, sedatives, and hypnotics substances that can slow brain activity by increasing activity at receptors for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and Hallucinogens a diverse group of drugs that alter a person's awareness of their surroundings as well as their own thoughts and feelings. They can also cause users to feel out of control or disconnected from their body and environment. Stimulants on the other hand increase alertness, attention, and energy, as well as elevate blood pressure, heart rate, and respiration (Jones and Laurie, 2016; CDC Wonder, 2020).

Multiple studies have revealed associations between prescription drug misuse and higher rates of cigarette smoking; heavy episodic drinking; and marijuana, cocaine, and other illicit drug use among U.S. adolescents, young adults, and college students (Wang *et al.*, 2015; CDC vital signs, 2017). We could not establish any such association in our study as it was not part of our objectives. However, our study observed a significant ($p < 0.000$, $p < 0.005$) relationship between age range of participants and prescription drug/substance misuse generally. It goes

to show that prescription drugs (taken nonmedically) are among the most commonly used drugs by the youths after alcohol and tobacco. Earlier, NIDA (2020) reported in their survey to monitor the future of substance misuse and attitudes in teens that about 6 percent of high school seniors reported past-year nonmedical use of the prescription stimulant 'Adderall' in 2017, while 2 percent reported misusing the opioid pain reliever 'Vicodin'. In the case of prescription opioids, receiving a legitimate prescription for these drugs during adolescence is also associated with a greater risk of future opioid misuse, particularly in young adults who have little to no history of drug use (Wang *et al.*, 2015; CDC vital signs, 2017; CDC wonder, 2020).

The outcome of the analysis of the distribution of prescription drugs/substance misuse among gender in our sampled population was not significant (0.216, $p < 0.005$). There was however, a high number of female respondents who had misused opioid; a medication which act on opioid receptors in both the spinal cord and brain to reduce the intensity of pain-signal perception, coughs and severe diarrhea. The reason for this high number of females on prescription drug misuse of opioid is not understood. We however ascribe this to feminine reproductive role particularly during their menstrual cycle or child birth to minimize the periodic pains some of them go through.

Similarly, the analysis of phenylthiocarbamide taste sensitivity and prescription drug/substance misuse revealed a non-significant ($p > 0.253$, $p < 0.005$) relationship with prescription drug/substance misuse. Our view on the outcome of this result presents a clear picture of the relationship between the social life style of the sampled population and their inherent genetic attributes. That the population is made up largely of tasters confers on it the ability to detect bitterness which serves as a survival mechanism because toxins in poisonous plants usually taste bitter and some of this prescription drugs misused may equally be bitter hence avoidable. Humans have about 30 genes that code for bitter taste receptors, making us better equipped to avoid ingesting harmful substances. As a counterpoint, animals that are strictly herbivores have fewer bitter taste receptor genes; otherwise, their food supply would be too restricted. Instead, they have larger livers capable of breaking down toxic compounds making it a survival strategy.

CONCLUSION

Nigeria as a country, has a serious substance misuse burden which is not simply financial but is deteriorating the quality of our health, educational, and social systems, that is debilitating and killing us. This burden is as intractable as poverty and ignorance, therefore, screening for drug/substance misuse and substance disorders before and during the course of prescribing, combined with patient education, are recommended

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Action:

Find below actions taken in connection with the reviewer’s comments on the article

- a1 ---- quoted
- a2----- quoted
- a3-----quoted
- a4-----quoted
- a5----- included
- a6-----inserted
- a7 -----APA referencing style applied all through
- a8 -----complied
- a9-----included
- a10-----quoted
- a11-----inserted
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- a13-----inserted
- a14-----quoted
- a15-----complied
- a16-----included
- a17-----included
- a18-----inserted
- a19-----inserted
- a20-----done
- a21 -----complied