An audit of patients undergoing gastroscopy at Mitchells Plain District Hospital, with a focus on substance use

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Contents

Introduction

The association between peptic ulcers and the use of crystalline methamphetamine is one that is often anecdotally described by clinicians who are exposed to it. However, while the cardiovascular and neuropsychiatric implications of methamphetamine are well recognised and researched, the gastrointestinal implications remain predominantly observational. Although reference has been made to a higher rate of duodenal ulceration among methamphetamine users, case numbers are generally small with polysubstance use and confounding factors preventing definitive conclusions from being drawn or explaining the underlying aetiology.

With an increase in the use of methamphetamine reported globally and a high rate of use in Cape Town, it is becoming ever more important for clinicians to have a robust understanding of this drug and the associated health effects. Unfortunately, the manner in which substance users present in our setting and the type of gastrointestinal pathology present remains poorly understood, especially among methamphetamine users. In order to describe the demographics and pattern of disease further, a prospective, single centre audit was conducted on all patients requiring oesophagogastroduodenoscopy (OGD) during a two month period, with a focus on substance use.

Literature Review

It is estimated that of the global population between the ages of 15-64, close to 271 million individuals used drugs during 2019. While cannabis remains the most popular drug, used by 3.8% of the global population, amphetamine-type stimulants (ATS) are the second most commonly used illicit drug globally, accounting for 28.9 million users during 2017 and 0.6% of the global population (1)

Amphetamine-type stimulants (ATS) covers a broad category of stimulants including amphetamines, as well as methamphetamine in its various forms. The class of ATS also varies according to different regions, with prescription stimulants most common in North America, while crystalline methamphetamine is the most common form in East and South-East Asia and Oceania. However, they note with concern an increasing trend in the global use of crystalline methamphetamine, most notably in North America and in East and South-East Asia (1). Although Africa is not specifically discussed in the *World Drug Report,* Mitchells Plain in Cape Town and the Western Cape overall have been facing a drug crisis with high rates of crystalline methamphetamine use, especially among the youth of the area (2). Locally, crystalline methamphetamine is generally known as ‘Tik’ and is smoked in 95% of cases, while rare cases of intravenous use are reported (3).

In South Africa, most information around the pattern of substance use is provided through the South African Community Epidemiology Network on Drug Use (SACENDU), a research branch of the South African Medical Research Council focused on substance use that reports on all patients requiring admission for the treatment of substance use, including alcohol. From July-December 2019, 9692 patients required admission, with 2654 patients (27.4% of national admissions) occuring in the Western Cape. Of these, 42% reported using Tik as their primary (30%) or secondary (12%) substance of use. Although an increasing trend has been noted in the Eastern Cape where 33% of patients admitted now report Tik usage, the remaining regions of South Africa report far lower rates ranging between 6-19%. Tik has also been found to be especially prevalent in young adults with a reported mean age of 30, with males accounting for 71% of local users. It should be noted that the SACENDU reports on patients admitted specifically for assistance with substance use, and does not report on substance users admitted for other conditions, some of which may be complications arising from the use of substances (3).

Methamphetamine

Methamphetamine is a psychoactive drug derived from amphetamine that can be produced in different forms. It has been produced since the early 1900s and the ways in which it is produced and consumed has evolved over the years. This has resulted in variable isomers existing with varying central nervous system (CNS) effects and levels of addiction, which may also relate to variable levels of effect on the gastrointestinal tract. Unfortunately, the isomer is rarely identified or available for research as it is highly dependent on the purity and the supplier who will rarely report or document this due to the illicit nature of the trade in methamphetamine.

Research into methamphetamine is further limited by the high rates of poly-substance use and confounding factors among methamphetamine users. As a result, most resources report on substance users as a group and specific analysis of methamphetamine users to identify association is rarely possible. This has been confirmed locally with the majority of patients in the Western Cape using multiple substances, especially using methamphetamine with mandrax and cannabis (3).

Mechanism of action

Methamphetamine stimulates the release of catecholamines in the Central Nervous System (CNS), while also releasing dopamine, noradrenaline and serotonin into the synapse, stimulating monoamine receptors. It inhibits the reuptake of these neurotransmitters, resulting in the build-up of monoamines. Partial opioid receptor interactions have also been described and these combined effects result in its neurocognitive effect (4). Metabolised by the liver, methamphetamines are excreted renally and may still be detected in urine for 3-4 days. Outside of the CNS, the most commonly reported adverse effects relate to the sympathomimetic effects of methamphetamine, particularly on the cardiovascular system. The effects on the gastrointestinal system however are still not fully described (4).

Available research

Despite its prominence locally and globally, a search of literature on the GIT implications of methamphetamine reveals minimal detail with the most prominent references summarised in Appendix J.

Overall, illicit drugs are rarely mentioned in the majority of literature describing risk factors for peptic ulcers, despite an established association between cocaine use and the formation of peptic ulcer disease, as well as gastroduodenal perforation(5-7). While methamphetamine has certain similarities to cocaine in that it is a stimulant, they remain in distinctly different categories and research on cocaine cannot be completely extrapolated to methamphetamine. Research into the association between cannabis and peptic ulceration is ongoing, although *Joundi et al* have demonstrated a moderate association between cannabis use and the need for admission for peptic ulcer disease (8). Heroin and mandrax (methaqualone) are not mentioned or described as risk factors in the majority of available literature. Locally, *Mertens et al* described an increased lifetime risk for stomach ulcers among hazardous drug users at a primary healthcare level in Cape Town, but no mention is made of methamphetamine.

In 1996, a strong association between the abuse of cocaine and/or methamphetamine and the subsequent development of giant gastric and duodenal ulcers was demonstrated (OR 9.66). Although significant, due to the concomitant use of cocaine and methamphetamine, the authors were unable to draw definitive conclusions on the specific association with methamphetamine (9). Cocaine is however not as prevalent in the local setting, accounting for only 2.7% of substance users in the Western Cape (3).

The next major article to clearly discuss the association with methamphetamine published in 2012 by *Martinez-Aguirre et al* reviewed 42 patients admitted to their surgical service with a perforated ulcer (10). Of these, 25 of the patients reported methamphetamine usage, with methamphetamine users also showing a significantly lower age than non-users. Lastly, a case report by *Vaghefi and Mostafazadeh* in 2014 detailed a report of a patient with a perforated duodenal ulcer after using methamphetamine and methadone and called for further research into this association.(11)

A case report in 2012 by *Jones et al* of Royal Gwent Hospital also reported a patient that presented with a suspected inferior myocardial infarction subsequent to methamphetamine abuse, but was subsequently noted to have an acute abdomen due to a large perforated anterior duodenal ulcer in the second part of the duodenum (12). Another interesting case report by *Peterman et al* in 2020 describes a patient who developed a gastric methamphetamine granuloma with associated ulceration. Initially suspected as a malignancy, biopsies demonstrated mucosal ulceration with birefringent crystalline material consistent with methamphetamine on the mucosa. Managed with a proton pump inhibitor (PPI) and the cessation of methamphetamines, follow-up endoscopy demonstrated a scar with no persistent ulceration or tumour. This suggested a direct causal link between methamphetamine and the granuloma with ulceration identified (13).

There is increasing interest in the association between methamphetamine use and intestinal infarction or ischaemia, although *Brannan et al* reported a case of mesenteric infarction in a methamphetamine user presenting with shock as far back as 2004 (14). A retrospective review by *Anderson et al* in 2018 investigated Non-Occlusive Mesenteric Ischemia (NOMI) in patients with methamphetamine use, with a focus on patients requiring surgery. Patients with confirmed *H. pylori* and concomitant cocaine use were excluded. Conducted over 33 months, 10 patients were identified with a median age of 54, of which the majority were female (15). This sex distribution is not in keeping with our local prevalence of substance use.

Of the 10 patients reported, three presented during the study period with a perforated duodenal ulcer. In addition, one of these had also previously undergone bowel resection for NOMI during the same study period. Six of the ten patients died; three died within one week of admission, while the remainder died between three and eight months later. This highlights the high mortality associated with mesenteric ischaemia. While not included in their final analysis, an additional four patients were reported with confirmed methamphetamine use presenting with perforated duodenal ulcers during the study period. However they were excluded from the final analysis for two reasons, either testing positive for or not having had *H. pylori* excluded. Their ages ranged from 30-48 years, significantly lower than the included patients (15).

Four of the current theories aiming to explain the gastrointestinal complications of methamphetamine in general are discussed by *Anderson et al*, without focusing on peptic ulcers specifically. Firstly, direct ischaemia and infarction of the gastrointestinal tract are as a result of sympathomimetic mesenteric vasoconstriction. These effects are well described in the cardiovascular and cerebrovascular systems and suggestions are that the same could be happening in the gastrointestinal system, manifesting with NOMI. It however might not explain focal ischaemia resulting in a peptic ulcer.

Vasculitis has been suggested due to the vasculitic changes associated with methamphetamine-induced stroke. In order to analyse this further, the authors had all specimens examined histologically, with only four of the 10 patients showing features of vascular inflammation or injury. Interestingly, none of the patients presenting with duodenal perforation demonstrated these features.

While the underlying mechanism is not described, six patients demonstrated vascular remodelling and proliferation on histology, suggesting repeated bouts of hypoxia and subsequent bowel hypoxia. This is in keeping with the theory on sympathomimetic mesenteric vasoconstriction.

The fourth theory suggests direct cellular damage from direct toxicity of reactive oxygen species (15).

In terms of established risk factors for the development of peptic ulcers, *Helicobacter pylori* and Non-Steroidal Anti-inflammatory Drugs (NSAIDs) remain two of the most important and prevalent, while no independent association has been described for illicit drugs (16-18). *H. pylori* remains one of the most significant chronic infections worldwide, reportedly infecting more than 50% of the world's population (19). Local prevalence of *H. pylori* among patients requiring gastroscopy has been shown to be close to 70%, representing a high burden of infection (19-22). *H. pylori* has also been associated with at least 90% of duodenal ulcers, 70% of gastric ulcers and includes a significant association with non-ulcer dyspepsia and gastro-oesophageal reflux disease in the local context (19,22).

Confirming the presence of *H. pylori* remains a limitation in the South African context and is not routinely done or reported in all centres. The rapid urease test (RUT) is used in some of the academic centres in Cape Town, but is not routinely available or utilised at MPDH. At this stage a tissue biopsy remains the most commonly used method at MPDH for *H. pylori* confirmation and is only used in specific cases where *H. pylori* is a significant concern. As a result, the majority of patients with suggestive clinical findings are treated for *H. pylori* empirically. In 2020, *Palamides et al* described that 46.5% of *H. pylori* isolated in South Africa is resistant to more than one antibiotic and this remains an ongoing concern in the future management of *H. pylori* in South Africa (23).

Grand-Pa is a well-recognised brand and freely available non-steroidal anti-inflammatory drug (NSAID) combination consisting of 453mg aspirin, 324mg paracetamol and 64.8mg caffeine (24). Sold in tablet or powder form, it is marketed as a headache remedy in South Africa. It has been described as a major risk factor for peptic ulcers based on its components and excessive use due to the addictive properties of the caffeine component. Based on this, it was felt necessary to report on *Grand-Pa* use specifically, as well as general NSAID usage.

Primary aim:

The primary aim was to determine if any relationship exists between substance users and findings at index oesophagogastroduodenoscopy (OGD).

Secondary aims:

Secondary aims included a description of the demographic characteristics, urgency and endoscopic findings of patients requiring oesophagogastroduodenoscopy (OGD) at MPDH, comparing substance users and non-substance users. A sub-analysis of Methamphetamine users will also be performed.

Methods

This study was run as a prospective pilot audit of all patients receiving a complete oesophagogastroduodenoscopy (OGD) at Mitchells Plain District Hospital (MPDH) during a two month period from 1st February to 31st March 2020. While the study had intended to include patients from April 2020 as well, this was aborted due to the Covid epidemic which affected hospital services significantly.

MPDH, a 270 bed large district hospital, has been operational since late 2013. Originally designed to serve a population of 429,122, this has increased to over 830 000 and it now serves the third largest

health sub-district in the Cape Metro (25,26)**.** According to the last available Census data from 2011, Cape Town has a population of 3 740 025, with over 60% above the age of 18 and 51% females (*Census 2011 : statistical release.* 2012).

MPDH consists of a busy, specialist-led General Surgery department and the MPDH endoscopy unit performs elective as well as emergency OGD. Working predominantly during office hours Monday to Friday, the unit performs approximately 40 elective and emergency OGDs per week, with after-hours emergency OGD performed in theatre or in the emergency centre. OGD is performed by staff with different levels of experience, including Medical Officers, registrars and consultants from the surgical and medical disciplines.

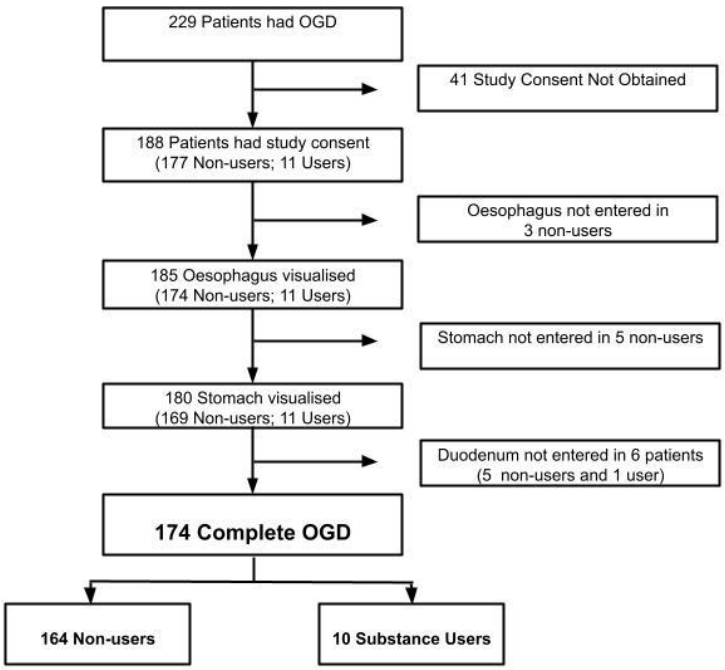
Patient numbers, as well as inclusion and exclusion criteria are summarised in Figure 1. All adult patients receiving oesophagogastroduodenoscopy (OGD) during the study period were considered for inclusion. An additional study consent and questionnaire on substance use was completed for each patient by the researchers or attending clinician (Appendix A&B). Data was collected by review of patient referral letters, records and MPDH Gastroscopy report forms (Appendix C&D). Additional information where required was obtained from electronic patient medical records via the Mitchells Plain District Hospital's Enterprise Content Management (ECM) system and patients were contacted telephonically. For an OGD to be considered 'complete', intubation of the duodenum was required and all endoscopies where this was not achieved were excluded. In patients that required more than one OGD during the study period, only the first OGD was recorded and analysed.

Patients were divided into two groups for comparison - Substance Users and Non-Users. For the purposes of this study, a "Substance abuser"was defined as a user of Methamphetamine (Tik), cannabis, mandrax, heroin or any other illicit drug and did not include patients who consumed alcohol. No distinction was made between substance use and substance abuse, with any quantity of substance use qualifying someone as a substance user.

Urgent OGD was defined as a procedure required within one week of presentation/discussion, while emergency OGD was defined as a procedure required within 24 hours of presentation, with this decision based on attending clinician judgement. Standardized reporting and clinical staging tools were used for data capture (Appendix F). The documented diagnosis was recorded as determined by the attending clinician with no subsequent external review or verification of the diagnosis performed. Although perforation has been reported in previous literature, patients with perforated ulcers requiring laparotomy were not included unless they required OGD as it is out of the scope of this audit.

All data was extracted into a spreadsheet where statistical analysis was performed. Additional statistical analysis was performed utilising R statistical software, with chi-squared and Wilcoxon test**s.** A p-value of less than 0.05 was considered significant.

Ethics approval was received from the human research ethics committee at the University of Cape Town [REF: 034/2019] and data was recorded with permission in a RedCap database managed by the Upper GIT unit at Groote Schuur Hospital (GSH) with prior ethics approval [REF: R031/2015].



Inclusion Criteria	Exclusion Criteria
1. Ability to provide informed consent	1. Inability to obtain informed consent
2. Completion of study questionnaire in full	2. Incomplete patient records and patient not contactable
3. Age over 18 years	3. Incomplete endoscopy (duodenum not visualised)

Figure 1 - Consort diagram of patients selected and distribution and breakdown of inclusion and exclusion criteria

Results

Demographics

A summary of demographics and comorbidities among both groups is provided in Table 1, while all substance users have been summarised in Appendix E.

One hundred and seventy four patients underwent complete OGD during the study period. Of these, 164 were non users, while ten were substance users. Overall the median age was 51.5 and 109 were female (66%). When compared to non-users, substance users were significantly younger (median age 38 vs 53.5; p = 0.006) and more likely to be male (90% vs 34%; p = 0.00107;X^2 2.08).

Risk Factors (Table 2)

Non-steroidal anti-inflammatory drug (NSAID) use was the most prevalent risk factor with 46.5% (n=81) of all patients using NSAIDs. Grand-Pa use was specified in 21.8% of the study population with no significant difference between users and non-users. Sixty-one patients (35.1%) were smokers and there was a significant difference in the rates of smoking between users and non=users (90% vs 32%; p = 0.0006; x^2 11.74). *H. pylori* was incidentally identified in two patients biopsied for other reasons.

Substance use (Table 2)

Tik use was reported in seven patients, four used Mandrax and seven used cannabis. Only one user used Tik alone, while polysubstance use was reported in six patients, combining tik with either

heroin, mandrax and/or cannabis (see Table 2). Six patients also consumed alcohol, resulting in a significantly higher prevalence than non-users (60% vs 18%; p = 0.004).

Table 1 – Demographics and co-morbidities comparison between substance users and non-users

	Combined	Non-users		Substance Users		p-value
		Number	(%)	Number	(%)	
Total Individuals	**174**	**164**	94.3%	**10**	5.75%	
Age						
Median (IQR)	51.5 (39-64)	53.5 (39-64)		38 (32-45)		**0.006**
Absolute range		19-80		21-59		
Gender						
Female	**110**	109	66%	1	10%	
Male	**64**	55	34%	9	90%	**0.00107**
ECOG* Status						
0	**26**	25	15%	1	10%	
1	**76**	69	42%	7	70%	
2	**53**	51	31%	2	20%	
3	**15**	15	9%	0	-	
4	**4**	4	2%	0	-	
Comorbidities						
Hypertension	**66**	66	40%	0	-	
Diabetes Mellitus	**37**	36	22%	1	10%	
HIV	**16**	16	10%	0	-	
Cardiac	**22**	22	13%	0	-	
Cholesterol	**13**	13	8%	0	-	
Arthritis	**12**	12	7%	0	-	

*Eastern Co-operative Oncology Group

Table 2 - Risk factors, substances used and pattern of substance use

	Combined	Non-users		Substance Users		p-value
		n=164	%	n=10	%	
Habits						
None	52	52	32%	-	-	
Smoker	61	52	32%	9	90%	0.0006
Ex-smokers	6	6	4%	0	-	
Steroid use	1	1	1%	0	-	
Alcohol	36	30	18%	6	60%	0.0039
NSAIDs	81	79	48%	2	20%	0.1492
Grand-Pa*	38	36	22%	2	20%	
Anti-inflammatories	12	12	7%	0	-	
Aspirin	29	28	17%	1	10%	
Combination	24	24	15%	0	-	

	Number	% Total	% Users
		n=164	n=10
Drugs Used			
Tik	**7**	4%	70%
Mandrax	4	2%	40%
Cannabis	7	4%	70%
Heroin	1	1%	10%
Drug Combinations			
Tik only	1	1%	10%
Cannabis only	**3**	2%	30%
Polysubstance use**	6	4%	60%

* Grand-Pa: A freely available headache powder containing 453mg Aspirin, 324mg paracetamol and 64.8mg caffeine
** Tik used in combination with either heroin, mandrax and/or cannabis

Presentation

One hundred and sixty eight patients underwent index OGD , five were receiving their second and one person received a fourth OGD documented on the RedCap database (not all performed during the study period). Fifty-five (31.6%) were performed on inpatients and included seven of the substance users, significantly higher than non-users (70% vs 29.3%; p = 0.015; X^2 5.8).

Ninety-six (55.2%) were determined to be routine/elective, 58 (33.3%) were urgent and 20 (11.5%) were emergencies. Only two scopes among substance users were performed electively, with three urgent and five emergency OGD required (Figure 2). Substance users accounted for 25% of the 20

emergency scopes performed and there was a significant difference in the need for emergency endoscopy (50% vs 9.1%; p = 0.0005; x^2 15.9). There was no difference in the need for urgent endoscopy and a non-significant trend was noted in the rates of elective scopes required (20% vs 57.3%; p = 0.112)

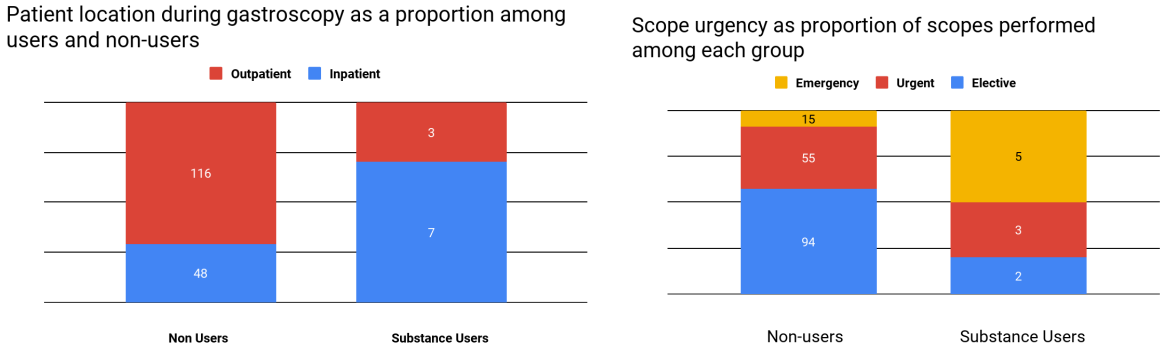


Figure 2 - Distribution of patient location and urgency of gastroscopy as a proportion

Presentations are summarised in Appendix G. Epigastric pain was the most commonly reported in 47.1%, followed by dyspepsia (35.6%). A suspected upper gastro-intestinal bleed (UGIB) was reported in 17.2% (n=30). Eight out of the ten substance users presented as suspected UGIB, significantly higher than non-users (80% vs 13.4%; p < 0.001; x^2 24.4) and accounted for 26.7% of the 30 scopes performed for a suspected UGIB (Figure 3). One substance user was attending a follow-up endoscopy six weeks post perforated gastric ulcer. Epigastric pain, the most common presentation in the study population, was less prevalent in the substance user group and only reported in one patient (10% vs 49.4%).

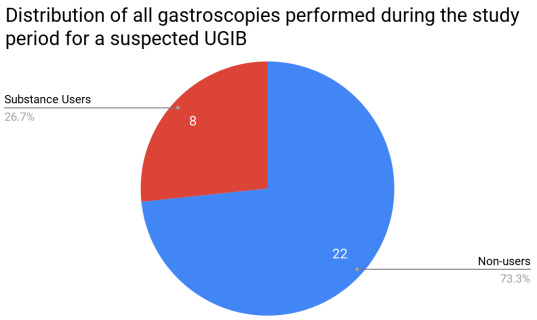


Figure 3 - Proportion of patients presenting with an UGIB

Endoscopic findings

Overall endoscopic findings are summarised in Appendix H**.** Oesophageal findings were comparable between the users and non-users with candida and oesophagitis the most common findings. Only one non-user had oesophageal varices which were Grade 1 and required no intervention.

Stomach findings were reported as normal in only 22 patients, with 75% of all patients felt to have some form of gastritis. A gastric ulcer was identified in 10.9% (n=19) of all patients (Figure 4), with no significant difference among users and non-users (20% vs 10%; p = 0.629; x^2 0.23). Partial gastric outlet obstruction (GOO) was identified on one scope, with duodenal intubation possible. Of note,

six patients were excluded from analysis due to GOO, including one patient that used tik alone and had recurrent presentations with a gastric ulcer which subsequently showed *H. pylori* associated chronic active gastritis on biopsy.

Duodenal ulcers were confirmed in seven patients (Figure 4), with three being among substance users and resulting in a significant association (30% vs 3.45%; p = 0.0005; x^2 11.9). Two of the three substance users with duodenal ulcers used Tik, while one used cannabis only, resulting in 28.5% of all Tik users presenting with duodenal ulcers. Duodenitis was present in 35% of patients, with no significant difference between users and non-users (20% vs 36%; p=0.476).

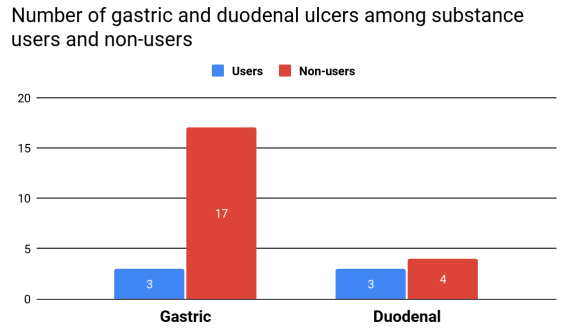


Figure 4 - Number of gastric and duodenal ulcers among both groups

Twenty-six of the twenty-seven ulcers were classified as Forrest 3, with only one Forrest 1a ulcer. This patient was a substance user and received endoscopic injection of his ulcer only. A repeat OGD conducted four days later reported a Forrest 3 duodenal ulcer (not included in our analysis). No complications were reported in any of the scopes and none of the substance users had a negative/normal OGD.

Management

Management consisted of PPI and eradication in 77% (n=134) of patients with chronic PPI alone recommended in 15.5%. A follow-up scope was scheduled for ten patients and additional investigations were recommended in 35 (21.3%). Transfusion was required in a total of 20 patients, with fourteen (70%) of these required among the 33 patients presenting with an UGIB (42.4%). Four patients in the substance user group required blood transfusion with two units of packed Red Blood Cells (RBC) each for a low Hb (6.1-8.8). All four had confirmed ulcers. When compared to non-user UGIBs, there was no major difference in rates of transfusion required (40% vs 43%).

Methamphetamine Users

A sub analysis was performed comparing the seven patients who used methamphetamine to the 167 patients that did not use methamphetamine and findings were similar to the substance user analysis. Most notably, all methamphetamine users smoked and five also consumed alcohol. Emergency endoscopy was significantly more common among methamphetamine users (71% vs 9%; p = 0.000003; x^2 25.4) and an UGIB was the presentation for six of the seven methamphetamine users (86% vs 14%; p = 0.00001; x^2 18.9). The need for inpatient endoscopy among methamphetamine users was slightly less significant (71 vs 29%; p = 0.05; x^2 3.83). Duodenal ulcers were the only significant difference in endoscopic findings among methamphetamine users (29% vs 2.9%; p = 0.01764; x^2 5.63).

Discussion

Significant differences were noted among substance users when compared to non-users, representing a younger, male population group. There was a significant association with presenting with an upper gastrointestinal bleed and with requiring emergency, inpatient endoscopy. In keeping with available literature, a strong association with duodenal ulcers has also been described. These findings were present among all substance users, as well as when methamphetamine users were compared directly.

Duodenal Ulcers

The association of duodenal ulcers with substance use was the most prominent difference between the two groups. These findings are in agreement with available literature and the findings of *Anderson et al* who demonstrated that in their group of patients requiring laparotomy, three out of ten presented with a perforated duodenal ulcer while the four patients excluded for being *H. Pylori* positive had also presented with duodenal ulcers. This may suggest that methamphetamine, or at least general substance use, is associated with duodenal ulcers within the study population. However, it should be noted that the population described by *Anderson et al* was notably different to our study population, with a higher median age and proportion of female patients. Furthermore, *H. Pylori* was not excluded during our audit.

While the one patient with a Forrest 1a ulcer who also required endoscopic intervention was indeed a Tik user, it would be hazardous to associate Tik with more severe disease or the need for intervention as he was only one patient.

UGIB

An upper-gastrointestinal bleed (UGIB) was significantly associated with substance use. While a source for an UGIB was confirmed in the four substance users with ulcers, it was also suggested in the remaining six having either pangastritis +/- duodenitis as possible causes of a bleed. Not routinely described in the referenced literature, this provides new insights into the manner in which substance users may present to an endoscopy unit. An UGIB is generally associated with increased cost with an increased need for in-hospital monitoring, endoscopy and transfusion requirements, as was demonstrated among all patients presenting with UGIB.

As a result, the use of illicit substances should be investigated in all patients presenting with an UGIB as they represent a high risk group for complicated disease. A lower threshold for endoscopy among substance users may also be warranted. Routine testing of *H. pylori* in substance users may also be warranted to help with early identification and management of those with an additional risk of developing ulcerative disease and complications, as well as providing further insights into this association.

Inpatient and emergency endoscopy

Substance use was shown to have a higher likelihood of requiring inpatient and emergency endoscopy, representing a significant level of disease and cost. This may also be related to the manner in which substance users present, with an UGIB normally qualifying a patient for emergency,

or at least urgent endoscopy. Substance users also did not present with epigastric pain, the most common presentation in the study population. This may relate to altered health-seeking behaviours among substance users, with patients not presenting in the early stages of the disease and rather presenting in an emergent or urgent fashion after the development of complicated peptic ulcer disease.

Demographics and risk factors

When compared to non-users, substance users showed a significant difference in age, as well as gender. This trend is in keeping with those described by the SACENDU among methamphetamine users requiring admission, with a mean age of 30 and 71% male majority (3). It is however in contrast to the findings of *Anderson et al* where the median age of patients using methamphetamines was 54, with 70% females (15). The Eastern Cooperative Group (ECOG) score is a standardised method of reporting the functional baseline of a patient and was lower in the substance user group, suggesting that the substance users in our study population may represent a more functional and generally healthier population group.

Smoking was significantly more prominent among substance users when compared to non users. With the majority of Tik in South Africa also being smoked, it is perhaps not surprising that cigarette smoking was so prevalent among substance users. The prevalence of smoking among South African adults has been reported as 17%, with an increased prevalence in males vs females (29.2% vs 7.35). We have demonstrated a higher prevalence in both users and non-users among patients requiring OGD (23). While smoking is often reported as a risk factor for peptic ulcer disease, it has also been found that it is only a risk factor in association with *H. pylori* and may not be an independent risk factor for ulcer formation (16-18).

Alcohol was significantly more prevalent among substance users. When compared to national reported rates of 28.5%, the rates of alcohol usage are higher in both substance users, as well as non users (27).

Prevalence and type of substance use

The ten substance users made up 5.75% of the overall study population, with Tik users accounting for 4% of the study population. This is notably higher than the global prevalence of amphetamine-like stimulants of 0.6% reported by the UNODC (1). However, the UNODC reports on general population rates, while this study reports on patients requiring endoscopy, representing two very different populations. It may be suggested that substance users display poor health-seeking behaviours and the prevalence at a population level is higher. On the contrary, it may also be suggested that if substance use is ultimately determined to be a major risk for gastrointestinal diseases, they may be represented at a higher proportion in patients requiring endoscopy than at the population level. This is beyond the scope of this study but warrants further investigation.

With 70% of the substance users reporting Tik use, this is far higher than the rates reported among the SACENDU group at 42% (3). This further implies that Tik users may be more prevalent among patients requiring endoscopy, even when compared to all patients being admitted for substance use disorders. The notion that most substance users will use more than one substance is supported by our findings with only two using Tik in isolation. Overall, the above findings support the perceived

notion that the endoscopy unit at MPDH sees a large number of substance users, with Tik representing a significant proportion of substance users.

Management

PPI and eradication was the most prevalent management strategy in both groups. However, it may be debated whether all patients with positive endoscopy findings do in fact require eradication. *Anderson et al* demonstrated that only three out of seven patients they identified with perforated duodenal ulcers were *H. Pylori* positive, while four were either negative or untested. Local data suggests *H. Pylori* prevalence of just under 70% [Tanih et al; Levin]. This may suggest that *H.Pylori* eradication is not indicated in over 34-50% of patients with positive findings on endoscopy. With increasing rates of antibiotic resistance also emerging, targeted testing of *H. pylori* using a Rapid Urease Test (RUT) or similar accessible testing modality could guide the use of eradication therapy in this unit, potentially reducing cost as well as antibiotic resistance.

Limitations

As a result of the following, it is acknowledged that this audit will not be representative of the pattern of disease and substance use in the community overall and will only be representative of patients attending MPDH and requiring OGD during the study period.

Sample Size

While this study may represent one of the larger sample groups for a study investigating this pathology, it remains a relatively small sample size of substance users and limits the ability to correct for any confounding factors. This was limited by the Covid pandemic shortening the sample period, as well as by patients not being fully consented for study inclusion by the attending clinician. This is unfortunately one of the drawbacks of conducting research in a busy unit with clinicians that are already pressed for time.

Confounding factors and polysubstance use

Although the initial aims of this audit had been to provide further insights into methamphetamine users specifically, the low number of patients using methamphetamine in isolation unfortunately limited our ability to correct for polysubstance use that was prevalent among the substance users. The inability to test for *H. pylori* was a major limiter and did not allow for assessment of association or to exclude it as a confounding factor. Future studies should look to perform a RUT or biopsy to exclude *H.pylori* as an underlying cause or confounder. Substance use was also inconsistently recorded in referral and clinical notes and it may be suggested that substance use be added to the standardised OGD referral form, or at least included in the clinical reports of patients undergoing OGD.

Stigma

Drug use has an inherent associated stigma and it was suggested that patients may be unwilling to disclose their use, especially in the outpatient setting with mild symptoms. However, our findings were that patients were willing to engage in the study and disclose their pattern of substance use.

Variability in clinician reporting

Inconsistent reporting and diagnoses were possible considering the variability in endoscopic skills of personnel performing OGD and the lack of a review process to verify the findings. This may be considered in future studies to exclude inter-observer variability.

Conclusions

This study has potentially provided new insights into a common, yet under-researched subject which is highly prevalent in our local setting. It has further provided new data and a better understanding of the demographics and pattern of disease at MPDH. Trends were noted when comparing substance users to non-users, but a larger sample size and long-term monitoring is likely needed to allow for correction of confounding factors.

Of particular interest was the high rate of duodenal ulcers, as well as UGIB among methamphetamine users when compared to non-users. Substance users also tended to require admission and require urgent or emergent endoscopy. While methamphetamine was used in the majority of substance users, further dedicated research is required to identify the isolated effect of methamphetamine on the upper gastrointestinal tract and the mechanism behind it.

The underlying pathophysiology of the effects of substance use, especially methamphetamine, on the gastrointestinal tract remain poorly understood. By providing a better understanding of the pathology they present with, it is hoped that future research looking into the pathophysiology will be facilitated and encouraged by this study.

Appendices

Appendix A - Informed Consent Form for submission of data to database

An audit of patients undergoing gastroscopy at Mitchells Plain District Hospital

We are currently creating a database of all patients requiring gastroscopy at MPDH. As part of this, we are looking at the risk factors and substance use that might contribute to the types of conditions we see. In order to conduct this audit, we ask for your participation by answering a questionnaire. Additional information will be obtained from your hospital records by the researchers. All information obtained will be kept anonymous and will be stored in a confidential registered database that only the researchers have access to.

Your participation is entirely voluntary and if you do not wish to complete the questionnaire this will in no way affect the treatment you receive. If you agree to take part, you may at any time change your mind and your information will be removed from the database. Please inform the day theatre staff if you do not wish to take part.

Information in the database will only be accessible to researchers and studies that have met the relevant ethical clearance. This database may be utilised for future research and has been reviewed and approved by the University of Cape Town's Human Research Ethics Committee (REF031/2015). Their details are as follows if you wish to contact them directly:

UCT Faculty of Health Sciences Human Research Ethics Admin Office
Human Research Ethics Committee
E 53, Room 46, Old Main Building, Groote Schuur Hospital, Observatory
Office Contacts: 021 406 6492; 021 404 7682; 021 406 6626
Email: hrec-enquiries@uct.ac.za

Please inform the day theatre staff if you have any concerns or require clarification. Your participation is greatly appreciated. If there are further concerns or questions, please do not hesitate to contact the researchers.

Regards

Tomé Mendes
Surgical Registrar
083 527 7078
tome@mendes.co.za

Ferhana Gool
Consultant Surgeon
082 464 5903
ferhanagool@hotmail.com

Patient details if no sticker available

Patient Signature:_____Date:

Witness name and signature:

Appendix B – Patient questionnaire

MPDH Gastroscopy Audit - Patient questionnaire

To be completed by attending clinician/day theatre staff

1. Patient sticker/details
   Surname:
   Folder number:
   DOB:

2. Informed consent obtained - Y / N
3. Contact number:
4. Date:

5. Medication used:
   Aspirin: Y / N If yes: 150mg daily / Analgesic use
   Warfarin: Y / N Dose if known:

6. Patient adhering to previous management
   a. Lifestyle modification Y / N / N/A
   b. Medication Y / N / N/A
   c. Decreased substance use Y / N / N/A

7. Substance use:

Substance	Daily	Weekly	Monthly	Recently stopped (< 2 months)	Never used or stopped for one year	Not willing to disclose/ Unclear
Smoking						
NSAIDs						
Grandpa						
Alcohol						
Tik						
Mandrax						
Cannabis						

8. Do you wish to receive any further information or guidance with substance use? Y / N
9. Other concerns/comments of relevance:

Interviewer:

Signature:

Appendix C – Current MPDH OGD referral form

MITCHELLS PLAIN HOSPITAL
Gastroscopy Referral Letter

Referring Department:	**Phone:**
Referring Doctor: (Please print)	**Date:**_____

Patients Name / Sticker:

Age:

Gender: **M** **F**

Presenting complaint:

dysphagia		dyspepsia		odynophagia	
epigastric pain		vomiting		haematemesis	
melaena stools		weight loss		Other…	

Background History:

Hypertension		Ischaemic HD		Asthma	
Diabetes Mellitus		Epilepsy		HIV	
Arthritis		Other…			

Allergies:

Medication:

NSAIDs	
Aspirin	
WARFARIN*	

*INR must be < 1.5

Trial of H2 receptor blocker / antacids? **yes** **no**

Smoker: **yes** **no** **Alcohol:** **yes** **no**

Previous gastroscopy: **yes** **no**
If yes - findings:

Clinical findings:

PR exam:

Hb:	
MCV:	

SIGNATURE:_____

Please attach signed and witnessed consent form.

MPH0079

Appendix D - MPDH OGD reporting form

MITCHELLS PLAIN HOSPITAL

UPPER GASTRO-INTESTINAL

Attach sticker or complete by hand

Name: .....

Folder number: .....

Date of Birth: .....

DATE_____

WARD_____

REFERRING DR/CLINIC_____

SCOPE USED_____ PREMEDICATION_____

ENDOSCOPY INDICATION AND PROVISIONALDIAGNOSIS

_____

_____

PREVIOUS INVESTIGATIONS (BARIUM STUDIES, ENDOSCOPIES, ETC)

_____

_____

FINDINGS

OESOPHAGUS_____

_____

_____

O.G. JUCTION_____

_____

_____

STOMACH: BODY_____

_____

ANTRUM_____

_____

POLYRUS_____

_____

DUODENUM_____

_____

BIOPSY TAKEN	YES	NO
CYTOLOGY SENT	YES	NO

OVERALL IMPRESSION:

RAPID UEASE TEST	YES	NO

SUGGESTED MANAGEMENT:

NAME AND SIGNATURE_____

* M P H Q 0 7 8 *

Appendix E - Summary of all substance users

	Age	Gender	Comorbidities	Risk Factors				Scope #	Location	Urgency	Indication	Findings					Management	
				NSAIDS	Alcohol	Smoking	Drugs*					Oesophagus	OGJ	Stomach	Duodenum	Forrest	Medication	Follow-up
1	59	Male	None	No	Yes	Yes	TC	1	Out	Emergency	UGIB Hb 6.3	Candida		Multiple F3 ulcers at fundus	F3 ulcer at D1	3	PPI,eradicate, Lifestyle Transfused 2 x RBC	Repeat scope
2	31	Male	Previous gastritis	No	No	Yes	C	1	Out	Routine	Pain		HH		Ulcer	3	PPI and eradicate Lifestyle	Nil
3	42	Female	Schizophrenia	No	Yes	Yes	T	1	In	Emergency	UGIB, Anaemia Hb 10.3		HH	Pangastritis	Duodenitis		PPI and eradicate	Nil
4	46	Male	None	Grand-Pa Aspirin	Yes	Yes	C	1	In	Urgent	UGIB, Melaena, vomiting Hb 8.8			Two ulcers (Incisura)	Normal	3	PPI and eradicate Fluconazole Transfused 2 x RBC	Repeat scope
5	39	Male	None	No	No	Yes	TMH	1	In	Emergency	UGIB Hb 13.3			Pangastritis	Normal		PPI and eradicate	Nil
6	37	Male	None	No	Yes	Yes	TM	1 And 2**	In	Emergency and Urgent**	UGIB, Melaena, Hb 6.1	Oesophagitis	HH	Food	Bleeding ulcer	1a 3**	Chronic PPI and eradicate Lifestyle Transfused 2 x RBC	Repeat scope
7	35	Male	None	No	No	No	C	1	In	Urgent	UGIB, vomiting Hb 16.9		HH	Pangastritis	Duodenitis		PPI and eradicate	Nil
8	28	Male	Previous GSW and laparotomy	Grand-Pa	Yes	Yes	TMC	1	in	Urgent	UGIB, vomiting Hb 14.2	Oesophagitis		Pangastritis and residual food	Normal		PPI and eradicate Lifestyle	Nil
9	21	Male	6 weeks post perforated gastric ulcer	No	Yes	Yes	TC	1	Out	Routine	Follow-up			Pangastritis and scar/healing	Normal		PPI	Nil
10	50	Male	Diabetes	No	No	Yes	TMC	1	In	Emergency	UGIB Hb 13.4			Haemorrhagic pangastritis	Normal		PPI and eradicate	Nil
**	35	Male	None	Grand-Pa	No	Yes	T	3	In	Urgent	UGIB Hb 7.9	Candida		Ulcer and GOO and Food	**Not seen****	3	Fluconazole Transfused 2 x RBC	Repeat scope

* T - Tik; C - Cannabis; M - Mandrax; H - Heroin

**Excluded due to incomplete or repeat endoscopy

Appendix F - Forrest Classification of Peptic Ulcers and ECOG Score Summary

Forrest Classification of Peptic Ulcers	
Forrest 1 - actively bleeding ulcer 1a 1b	 Spurting/arterial bleed Oozing bleed
Forrest 2 - Evidence of recent bleed 2a 2b 2c	 Non-bleeding visible vessel Adherent clot Hematin spot in ulcer base
Forrest 3	Clean ulcer base

Eastern Cooperative Oncology Group Score	
0	Fully active with no performance restrictions
1	Restriction in strenuous physical activity but fully ambulant and able to carry out light work
2	Ambulant > 50% of waking hours and capable of self care but unable to carry out any work activities
3	Confined to chair or bed >50% of the day and only capable of limited self care
4	Confined to chair or bed most/all of the day and unable to carry out self care

Appendix G – Table demonstrating urgency and presenting complaints for all gastroscopies performed, compared between users and non users

	Combined n=174	Non-users n=164	%	Substance Users n=10	%	p-value
Urgency						
Elective	96	94	57%	2	20%	0.1127
Urgent	58	55	34%	3	30%	1
Emergency	20	15	9%	5	50%	0.000576
Patient Location						
Inpatient	55	48	29%	7	70%	0.01584
Outpatient	119	116	71%	3	30%	
Presenting Complaint						
Epigastric Pain	82	81	49%	1	10%	
Dyspepsia	62	62	38%	0	0%	
Loss of weight	33	33	20%	0	0%	
Vomiting	33	30	18%	3	30%	
UGIB*	30	**22**	13%	**8**	80%	<0.001
Anaemia	23	21	13%	2	20%	0.8762
Dysphagia	12	12	7%	0	0%	
Melaena	18	16	10%	2	20%	
Reflux	15	15	9%	0	0%	

*Upper gastro-intestinal bleed

Appendix H - Summary of endoscopic findings among substance users and non-users

	Combined n=174	Non-users n=164	%	Substance Users n=10	%		Combined n=174	Non-users n=164	%	Substance Users n=10	%	p-value
Cords						**Stomach**						
Normal	**146**	137	84%	9	90%	Gastritis	**134**	128	78%	6	60%	
Polyp	**1**	1	1%	0	0%	Normal	**22**	21	13%	1	10%	
Inflamed	**1**	1	1%	0	0%	Ulcer	**19**	17	10%	2	20%	0.6293
						Incomplete GOO**	**1**	1	1%	0	0%	
Oesophagus						Polyp	**3**	3	2%	0	0%	
Normal	**131**	123	75%	8	80%	Malignancy	**1**	1	1%	0	0%	
Candida	**21**	20	12%	1	10%	Stomal Ulcer	**1**	1	1%	0	0%	
Oesophagitis	**18**	17	10%	1	10%	Caustic injury	**1**	1	1%	0	0%	
Stricture	**2**	2	1%	0	0%	**Duodenum**						
Varices	**1**	1	1%	0	0%	Normal	**99**	94	57%	5	50%	
Ulcer	**1**	1	1%	0	0%	Duodenitis	**61**	59	36%	2	20%	0.476
OGJ*						Ulcer	**7**	**4**	**2%**	**3**	**30%**	**0.00055573**
Normal	**107**	100	61%	7	70%	Malignancy	**2**	2	1%	0	0%	
Hiatus Hernia	**64**	61	37%	3	30%							
Stricture	**1**	1	1%	0	0%							

*Oesophagogastric junction
**Gastric Outlet Obstruction

Appendix J - Summary of utilised literature discussing gastrointestinal implications of methamphetamine

Author	Year	Title	Study Type	Patients	Key findings
Pecha et al	1996	Association of cocaine and methamphetamine use with giant gastroduodenal ulcers	Record review	220	Strong association between the abuse of cocaine and/or methamphetamine with the development of giant gastric and duodenal ulcers (OR 9.66)
Martinez-Aguirre et al	2012	Perforated peptic ulcer: is the form of methamphetamine known as "crystal meth" a new risk factor?	Retrospective review `	42 (25 Users, 17 non)	Methamphetamine users had a significantly lower age, but no statistically significant differences in clinical presentation
Vaghefi and Mostafazadeh	2014	A perforated duodenal ulcer after using of methamphetamin and methadone.	Case Report	1	Perforated duodenal ulcer after using methamphetamine and methadone
Jones et al	2012	A perforated duodenal ulcer presenting as inferior lead ST elevation following amphetamine use	Case Report	1	Perforated duodenal ulcer
Peterman et al	2020	Methamphetamine Granuloma Presenting as a Gastric Mass	Case Report	1	Methamphetamine granuloma
Brannan et al	2004	Methamphetamine-associated shock with intestinal infarction	Case Report	1	Mesenteric infarction in a methamphetamine user presenting with shock
Anderson et al	2018	Nonocclusive mesenteric ischemia in patients with methamphetamine use	Retrospective review	10 (+4)	High rates of duodenal perforation but *H. pylori* a major confounder

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