

Original Research Article

Pharmaceutical Care Network Europe (PCNE) Drug-Related Problems

Classification Version 9.1: First Implementation in Sudan

Abstract

Background: clinical pharmacy services are an emerging specialty in Sudan. Many tools exist to document drug-related problems (DRP), such as the Pharmaceutical Care Network Europe (PCNE) classification. However, none has been attempted and published in Sudan.

Objectives: The study aimed to identify the DRP and its characteristics in real hospital setting using non-modified version of PCNE.

Method: Prospective study of clinical pharmacists' interventions during the routine care work of reviewing patients over a period from December 2020 to February 2021 at the wards of National Cancer Institute, University of Gezira, Sudan. Main outcome measure Using non-modified PCNE version 9.1 to identify the number, types, causes of the DRP, clinical pharmacists' interventions, acceptance, and outcomes.

Results: Five minutes (range, 3-15 minutes) was the median time spent for evaluation and intervention by the clinical pharmacists, a total of 51 DRP were discovered among 40 patients with an average of 1.3 DRP per patient, an adverse drug event (possibly) occurring (29.4%) was the main problem, no or incomplete drug treatment (27.5%) was the main causes, above one-third of the clinical pharmacists' interventions were proposed to the prescriber, these interventions were accepted in 96% and fully implemented among

72.5% of the cases. At the end of the process, the majority of DRP (72.5%) were totally solved.

Conclusion: non-modified PCNE version 9.1 provides a suitable tool for the DRP process for Sudanese clinical pharmacists during routine work in the oncology setting. It hence can be considered as an optimal tool for further quality and policymaking.

Keywords: Drug related problems, PCNE classification, Clinical Pharmacy Services, Sudan.

UNDEER PEER REVIEW

Introduction

Improvement of patients' safety and prevention of drug-related problems (DRPs) are ultimate goals of healthcare systems worldwide [1], this because the DRPs are associated with many undesirable consequences, including substantial mortality, morbidity, emergency department visits, hospitalization, and long-term care admissions. Besides that, DRPs can increase the cost to the patients, families, and the healthcare systems [2,3].

According to the Pharmaceutical Care Network Europe (PCNE), "a DRP is defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" [4]. There were different DRP classification systems published in the literature, sharing many similarities and differences. Some of these classifications are updated and modified regularly [5]. The PCNE classification is commonly used and has several positive features, 1) it comprises a systematic DRP classification with detailed domains and subdomains, which permits each type of DRP to be coded, 2) a DRP can be differentiated by its type, cause, then a pharmacist intervention, acceptance of the intervention by the physician, and the status of the DRP, 3) the DRP and each category are clearly defined. 4) the tool has been validated and regularly updated through various studies in different pharmacy settings and has been translated into different languages [6]. In May 2020, PCNE version 9.1 was released, and English, traditional Chinese, Turkish, and German versions are available on the PCNE official website. Clinical pharmacist-led services have important roles in identifying and resolving DRP, which improves medication safety in different settings and for a variety of diseases [1,7-9].

Clinical pharmacy education introduced in Sudan as a subject for the undergraduate curriculum started from batch one at Faculty of Pharmacy, University of Gezira, formally graduated in 2000. Then the postgraduate clinical pharmacy education was started in 2004 as a master program at the Faculty of Pharmacy, University of Khartoum in collaboration with Bath University, United Kingdom, by running the training of postgraduate students. Besides this in 2005, the General Directorate of Pharmacy at the Federal Ministry of Health sent the first batch of pharmacists to Malaysia for a master's degree in clinical pharmacy. Thereafter, several universities started master's in clinical pharmacy programs [10]. Currently, Ph.D. in clinical pharmacy by research is also available in Gezira University and some Sudanese universities.

In Sudan, pharmacists are taking on a new role as clinical pharmacists in hospitals. Pharmacists must transition from traditional duties within the pharmacy to new roles on the wards, where they will have direct interaction with patients and other healthcare professionals. However, clinical pharmacy services in hospitals are still considered to be in their preliminary stages of development [11]. In an attempt to improve, upgrade the quality, and to document the clinical pharmacists' daily practice, we conducted the first study to be a reference for other clinical pharmacists toward using a uniform DRP classification system across the country.

Methodology

Classification System

PCNE classification system is well structured and regularly updated and validated. We chose the PCNE version 9.1, since it is the last updated version and

contains most of the required aspects described in a late review of classification systems. To our knowledge, the version has neither been used in the real world either (community or hospital settings), nor any previous PCNE version utilized by Sudanese clinical pharmacists. The V.9.1 starts with general information about the patient, then classifies DRP according to problem types, causes, planned interventions, acceptance to proposed interventions, and status of the DRP (outcome of the intervention). DRP in the problem domains is defined as "the expected or unexpected event or circumstance that is, or might be wrong, in therapy with drugs". And while each problem has a cause, DRP in the cause domain is defined as "the action (or lack of action) that leads up to the occurrence of a potential or real problem". On that basis, the classification has with respective codes: three primary domains for different problems (P1-P3), nine primary domains for causes C1-C9, five primary domains for interventions (I0-I4), three primary domains for interventions acceptance (A1-A3), and four primary domains for the status of DRP (O0-O3).

Detailed classifications were in subdomains under the primary domains: 6 subdomains for different problems, 38 subdomains for causes, 17 subdomains for types of interventions, 10 subdomains for acceptance, and 7 subdomains for the status of the DRP [12]. In real-world settings, one problem (P) may be due to several causes (C), leading to more than one intervention (I) or acceptance (A), but leads to only one status of the DRP (O).

Study Area and Design

We performed a prospective hospital-based study during the period of three months from December 2020 to February 2021. The clinical pharmacists screened the

medication of 668 patients during multidisciplinary (MD) ward rounds in the National Cancer Institute, University of Gezira, a tertiary hospital in Sudan. Admitted adult patients taking at least one medication were eligible for this study.

Data Collection

Data were collected by two clinical pharmacists at the hospital, and several training sessions were performed before the commencement of the study to reduce variability. Clinical pharmacists collected data from patients' medical files and during MD team rounds. The DRPs were evaluated by reviewing all administration sheets, laboratory tests, and medication orders. We identified DRP based on assessing the indication, drug regimen, safety, contraindication, availability, and cost appropriateness. Clinical pharmacists rely on local, national, and international treatment guidelines to support evidence-based clinical decision-making.

When DRPs were identified, the involved physician and other MD team members were contacted by the clinical pharmacist, who detected the specific DRP and appropriate interventions.

Data Analysis

Analysis was performed with the Statistical package for social science (SPSS) software version 25 (SPSS Inc., Chicago, IL, USA) and Microsoft Excel. Continuous variables were expressed using median and range, whereas data were expressed as frequency and percentage for categorical variables.

Ethics Statement

Permission to use the PCNE V.9.1 was obtained from PCNE-DRP Group by contacting them through their official website. Additionally, ethical approval (HS-ERC-33-21) was obtained from the Health-Sector Ethical Review Committee, University of

Gezira. Written informed consents for participation were collected from all included patients in this study. All collected checklists were coded to ensure confidentiality throughout the study.

Results

Out of 668 patient files, 40 patients (6%) had DRPs were enrolled in this study. The median age of the patients was 50 years (range, 16-80 years), with 42.5% of them were sixty years and above. The majority of the participants were female 23 (57.5%). Median number of medications taken by the patients was four medications (range, 1-9 medications). The descriptive characteristics of patients are shown in Table 1.

Table 1 Distribution of socio-demographic characteristics among the study sample (n=40)

Demographic and clinical data	Number (Frequency %)
Age group (years)	
16-39	10 (25.0)
40-59	13 (32.5)
≥60	17 (42.5)
Gender	
Male	17 (42.5)
Female	23 (57.5)
Number of medications	
<5	28 (55.0)
≥5	18 (45.0)

A total of 51 DRP were discovered with an average of 1.3 DRP per patient. The majority of DRP were discovered by the clinical pharmacists (39, 76.5%), followed by those discovered by the physician (11, 21.5%), and only (1, 2%) discovered by the patients. While, the median time spent for evaluation and intervention by the clinical pharmacists was 5 minutes (range, 3-15 minutes). Our data revealed that most of DRPs were manifest (80.4%).

Table 2 shows drugs or drug' groups that cause the DRP in our study, in which opioid (27.5%), antibiotics (25.5%), and the anti-malaria quinine (13.7%) were the most frequent medications associated with DRP. Noteworthy, most of the DRPs associated with opioid use were due to incomplete drug treatment despite existing indications. While in the case of quinine, prescriptions were mainly due to the improper frequency of the drug.

Table 2 Drug Groups or Drugs Associated with Drug-related Problems (n=51)

Drug	Number (Frequency %)
Opioid	14 (27.5)
Antibiotic	13 (25.5)
Quinine	7 (13.7)
Spirolactone	2 (3.9)
Lactulose	2 (3.9)
Furosemide	2 (3.9)
Potassium chloride	2 (3.9)
Paracetamol	1 (2)
Tranexamic acid	1 (2)
Fluconazole	1 (2)
Omeprazole	1 (2)
Human Albumin	1 (2)
Phenytoin	1 (2)
Other	3 (5.9)
Total	51 (100)

As shown in Table 3 the most common DRPs were an adverse drug event (possibly) occurring (29.4%), the effect of drug treatment not optimal (29.4%), and the unnecessary drug treatment was 23.5%.

On analysis of DRP causes, we recorded a single cause for each problem, and the study showed that the top three DRP were due to; no or incomplete drug treatment (27.5%), inappropriate drug according to guidelines/formulary (19.6%), and drug dose of a single active ingredient too high (13.7%). These identified DRP led to interventions proposed to the prescriber, discussed with the prescriber in 39.2% and 29.4% of the cases, respectively, and patient counseling (13.7%). These interventions were accepted in

96% and fully implemented among 72.5% of the cases. However, 17.6% of the intervention was accepted but not implemented. While interestingly, only 2% of the intervention was not accepted. At the end of the process, the main outcome of the interventions was that most DRPs (72.5%) were totally solved, and 7.8% of DRP were either partially solved or lack of cooperation of the prescriber.

Table 3 Classification of Drug-related Problems According to PCNE Classification for Drug related problems V 9.1

Drug related problems (DRP) classification	Number (Frequency %)
Potential or manifest problems (n= 51)	
P1.1- No effect of drug treatment despite correct use	1 (2.0)
P1.2- Effect of drug treatment not optimal	15 (29.4)
P1.3- Untreated symptoms or indication	8 (15.7)
P2.1- Adverse drug event (possibly) occurring	15 (29.4)
P3.1- Unnecessary drug-treatment	12 (23.5)
P3.2- Unclear problem/complaint. Further clarification necessary (please use as escape only)	0 (0.0)
DRP causes (n= 51)	
C1.1- Inappropriate drug according to guidelines/formulary	10 (19.6)
C1.2- No indication for drug	4 (7.8)
C1.3- Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	3 (5.9)
C1.4- Inappropriate duplication of therapeutic group or active ingredient	0 (0.0)
C1.5- No or incomplete drug treatment in spite of existing indication	14 (27.5)
C1.6- Too many different drugs/active ingredients prescribed for indication	0 (0.0)
C2.1- Inappropriate drug form/formulation (for this patient)	1 (2.0)
C3.1- Drug dose too low	3 (5.9)
C3.2- Drug dose of a single active ingredient too high	7 (13.7)
C3.3- Dosage regimen not frequent enough	6 (11.8)
C3.4- Dosage regimen too frequent	0 (0.0)
C3. 5- Dose timing instructions wrong, unclear, or missing	0 (0.0)
C4.1- Duration of treatment too short	0 (0.0)
C4.2- Duration of treatment too long	0 (0.0)
C5.1- Prescribed drug not available	1 (2.0)
C5.2- Necessary information not provided or incorrect advice provided	0 (0.0)
C5.3- Wrong drug, strength or dosage advised	0 (0.0)
C5.4- Wrong drug or strength dispensed	0 (0.0)
C6.1- Inappropriate timing of administration or dosing intervals by a health professional	0 (0.0)
C6.2- Drug under-administered by a health professional	0 (0.0)
C6.3- Drug over-administered by a health professional	0 (0.0)

C6.4- Drug not administered at all by a health professional	0 (0.0)
C6.5- Wrong drug administered by a health professional	0 (0.0)
C6.6- Drug administered via wrong route by a health professional	0 (0.0)
C7.1- Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason	1(2.0)
C7.2- Patient uses/takes more drug than prescribed	0 (0.0)
C7.3- Patient abuses drug (unregulated overuse)	0 (0.0)
C7.4- Patient decides to use unnecessary drug	0 (0.0)
C7.5- Patient takes food that interacts	0 (0.0)
C7.6- Patient stores drug inappropriately	0 (0.0)
C7.7- Inappropriate timing or dosing intervals	0 (0.0)
C7.8- Patient unintentionally administers/uses the drug in a wrong way	0 (0.0)
C7.9- Patient physically unable to use drug/form as directed	0 (0.0)
C7.10- Patient unable to understand instructions properly	1(2.0)
C8.1- Medication reconciliation problem	0 (0.0)
C9.1- No or inappropriate outcome monitoring (incl. TDM)	0 (0.0)
C9.2- Other cause; specify	0 (0.0)
C9.3- No obvious cause	0 (0.0)
Planned interventions (n= 51)	
I0- No intervention	0 (0.0)
I1.1- Prescriber informed only	4 (7.8)
I1.2- Prescriber asked for information	7 (13.7)
I1.3- Intervention proposed to prescriber	20 (39.2)
I1.4- Intervention discussed with prescriber	15 (29.4)
I2.1- Patient (drug) counselling	2 (3.9)
I2.2- Written information provided (only)	0 (0.0)
I2.3- Patient referred to prescriber	0 (0.0)
I2.4- Spoken to family member/caregiver	1 (2.0)
I3.1- Drug changed to	1 (2.0)
I3.2- Dosage changed to	0 (0.0)
I3.3- Formulation changed to	0 (0.0)
I3.4- Instructions for use changed to	0 (0.0)
I3.5- Drug paused or stopped	1 (2.0)
I3.6- Drug started	0 (0.0)
I4.1- Other intervention (specify)	0 (0.0)
I4.2- Side effect reported to authorities	0 (0.0)
Acceptance of the intervention proposals (n= 51)	
A1.1- Intervention accepted and fully implemented	37 (72.5)
A 1.2- Intervention accepted and partially implemented	1(2.0)
A1.3- Intervention accepted but not implemented	9 (17.6)
A1.4- Intervention accepted, implementation unknown	2 (3.9)
A2.1- Intervention not accepted, not feasible	1 (2.0)
A2.2- Intervention not accepted: no agreement	1 (2.0)
A2.3- Intervention not accepted: other reason (specify)	0 (0.0)
A2.4- Intervention not accepted: unknown reason	0 (0.0)

A3.1- Intervention proposed, acceptance unknown	0 (0.0)
A3.2- Intervention not proposed	0 (0.0)
Outcome of intervention (n= 51)	
O0- Problem status unknown	2 (3.9)
O1- Problem totally solved	37 (72.5)
O2- Problem Partially solved	4 (7.8)
O3.1- Lack of cooperation of patient	1 (2.0)
O3.2- Lack of cooperation of prescriber	4 (7.8)
O3.3- Intervention not effective	2 (3.9)
O3.4- No need or possibility to solve problem	1 (2.0)

Discussion

The current study highlights and explores the feasibility and suitability of using PCNE V9.1 by clinical pharmacists during routine daily work at oncology settings from the perspective of a developing nation with limited resources looking forward to upgrading clinical pharmacy services. Using such classification will optimize the record-keeping and open the road for policymakers to uniformly analyze the strengths and weaknesses of such emerging pharmacy specialty. To the best of our knowledge, this is the first study to investigate the characteristics of DRP, clinical pharmacist intervention, and status of DRP among admitted cancer patients in a systematic way that reduces the chances of missing any DRP. Thus, improving health outcomes in this subgroup of patients known to have higher chances for DRP due to the complex nature of management by using a combination of chemotherapeutic agents and supportive treatment [13].

The process of DRP is considered a cornerstone in pharmaceutical care and has even been labeled as "the heart and soul of the practice of pharmaceutical care" [5]. The role of pharmacists in detecting, resolving, and preventing DRP has been well documented for a variety of diseases in different settings. For instance, Oliveira et al.

conducted a systematic review to evaluate clinical pharmacy services among 4,771 oncology and hematology patients, and it was found that pharmacists performed more than 3,000 therapeutic interventions and approximately 1,500 DRP identification [14].

PCNE V 9.1 without modification was used in this study, in which the clinical pharmacists discovered the majority of DRP. While the median time spent for evaluation and intervention by the clinical pharmacists was 5 minutes. A total of 51 DRP were detected (7.6% of the patients' files), with an average of 1.3 DRP per patient; this is lower when compared with previous studies [15,16]. A study conducted in Morocco found that 450 DRP were recognized (12.7% of the prescriptions) [17]. Another study conducted in Turkey found that the clinical pharmacist discovered 105 DRP (1.94 per patient) [16]. In a retrospective study conducted in China, on the other hand, of the 291,944 medications orders reviewed, 3548 DRP (rate 1.2%) were identified, with the mean number of DRP per patient being 0.3 [18].

The present study showed that the most common DRPs were an adverse drug event (possibly) occurring, the effect of drug treatment not optimal, and unnecessary drug treatment. This is in line with a study conducted in Turkey that revealed that the most identified DRP were related to adverse drug events and treatment effectiveness-related issues¹⁹. While in Morocco study medication-related problems were represented by untreated indications (31.3%), overdosing (17.1%), and DDI (12.4%) [17]. On the other hand, the adverse drug event (possibly) occurring, followed by the effect of drug treatment not optimal, was the major identified DRP in the study conducted in China [18]. Opioids are commonly prescribed in cancer patients to relieve cancer pain. In the

current study, opioids represented the most frequent drugs that cause DRP (27.5%), which is inconsistent with other studies about DRP in oncology clinics [20].

Our study demonstrated that the top three DRP were due to; no or incomplete drug treatment, inappropriate drug according to guidelines/formulary, and drug dose of a single active ingredient too high. This finding is strikingly different from that found in a study done by Kucuk et al., which showed that the top three causes of DRP were drug selection, drug use/process, and dose selection [19]. Whereas, a study conducted by Qu et al. in China found that dose selection was the major cause of DRPs followed by drug selection and dosage form [18].

This study found that the acceptance rate of the pharmacist's proposed interventions in the management of DRP was 96%. This is similar to a study conducted in a hospital out-patient clinic in Turkey [19]. Moreover, Moukafih et al. reported a 98% acceptance rate for pharmaceutical interventions conducted in the medical oncology department in Morocco [17]. High rates of clinical pharmacist interventions acceptance show that the medical staff recognizes the pharmacist as a reliable source of information about drugs. On analysis of DRP status (outcomes), our study showed that around 72.5% of the identified problems were totally solved, which is lower than those reported in Chinese (93.6%) and Turkish (90.9%) studies in hospitalized oncology patients.

The current study has some limitations. Firstly, it was a single-institution study with relatively small sample size, so the DRP patterns cannot be generalized to other hospitals. Secondly, the research was performed by two clinical pharmacists due to the low recruitment of clinical pharmacists by the Ministry of Health for each hospital. Thirdly, the drug data were only collected during the admission period, which may lead

to missing information about over-the-counter medications and potential DRP. Despite these limitations, this is the first research to evaluate DRP and assess the impact of pharmacists' interventions in DRP among hospitalized cancer patients in Sudan. Further multicenter studies with a larger population and clinical pharmacists in different specialties are required.

Conclusion

In this study, non-modified PCNE version 9.1 provides a suitable tool for DRP identification, classification, clinical pharmacist intervention, and status for Sudanese clinic pharmacists in an oncology setting during their routine work. Hence, it can be considered an optimal tool for documentation of clinical pharmacy services for further appraising, quality upgrading, and policymaking issues.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References

1. Ali MAS, Khedr EMH, Ahmed FAH, Mohamed NNE. Clinical pharmacist interventions in managing drug-related problems in hospitalized patients with neurological diseases. *Int J Clin Pharm* 2018;40(5):1257-64.
2. Yismaw MB, Adam H, Engidawork E. Identification and resolution of drug-related problems among childhood cancer patients in Ethiopia. *J Oncol* 2020;2020.
3. Feyissa Mechessa D, Dessalegn D, Melaku T. Drug-related problem and its predictors among pediatric patients with infectious diseases admitted to Jimma University Medical Center, Southwest Ethiopia: Prospective observational study. *SAGE Open Med* 2020;8:2050312120970734.
4. Puumalainen E, Airaksinen M, Jalava SE, Chen TF, Dimitrow M. Comparison of drug-related problem risk assessment tools for older adults: a systematic review. *Eur J Clin Pharmacol* 2020;76(3):337-48.
5. Westerlund T. Pharmaceutical Care and the Role of Drug-Related Problems. *The Pharmacist Guide to Implementing Pharmaceutical Care*: Springer; 2019. p. 11-22.
6. Koubaity M, Lelubre M, Sansterre G, Amighi K, De Vriese C. Adaptation and validation of PCNE drug-related problem classification v6. 2 in French-speaking Belgian community pharmacies. *Int J Clin Pharm* 2019;41(1):244-50.
7. Drovandi A, Robertson K, Tucker M, Robinson N, Perks S, Kairuz T. A systematic review of clinical pharmacist interventions in paediatric hospital patients. *Eur J Pediatr* 2018;177(8):1139-48.

8. Kheir N, Awaisu A, Sharfi A, Kida M, Adam A. Drug-related problems identified by pharmacists conducting medication use reviews at a primary health center in Qatar. *Int J Clin Pharm* 2014;36(4):702-6.
9. Hsu W-T, Shen L-J, Lee C-M. Drug-related problems vary with medication category and treatment duration in Taiwanese heart failure outpatients receiving case management. *J Formos Med Assoc* 2016;115(5):335-42.
10. Salim AMA, Elhada AHA, Elgizoli B. Exploring clinical pharmacists' perception of their impact on healthcare in Khartoum State, Sudan. *J Res Pharm Pract* 2016;5(4):272-8.
11. Elsadig H, Weiss M, Scott J, Laaksonen R. Exploring the challenges for clinical pharmacists in Sudan. *Int J Clin Pharm* 2017;39(5):1047-54.
12. Schindler E, Richling I, Rose O. Pharmaceutical Care Network Europe (PCNE) drug-related problem classification version 9.00: German translation and validation. *Int J Clin Pharm* 2021;43(3):726-30.
13. Faqeer N, Mustafa N, Abd Al-jalil N, Qur'an T. Impact of clinical pharmacists in an inpatient medical oncology service: A prospective study at a comprehensive cancer center in Jordan. *J Oncol Pharm Pract* 2020:1078155220943277.
14. Oliveira CS, Silva MP, Miranda ÍK, Calumby RT, de Araújo-Calumby RF. Impact of clinical pharmacy in oncology and hematology centers: A systematic review. *J Oncol Pharm Pract* 2021;27(3):679-92.
15. Shah S, Dowell J, Greene S. Evaluation of clinical pharmacy services in a hematology/oncology outpatient setting. *Ann Pharmacother* 2006;40(9):1527-33.

16. Kucuk E, Bayraktar-Ekincioglu A, Erman M, Kilickap S. Drug-related problems with targeted/immunotherapies at an oncology outpatient clinic. *J Oncol Pharm Pract* 2020;26(3):595-602.
17. Moukafih B, Abahssain H, Mrabti H, Errihani H, Rahali Y, Taoufik J, et al. Impact of clinical pharmacy services in a hematology/oncology ward in Morocco. *J Oncol Pharm Pract* 2021;27(2):305-11.
18. Su Y-J, Yan Y-D, Wang W-J, Xu T, Gu Z-C, Bai Y-R, et al. Drug-related problems among hospitalized cancer pain patients: an investigative single-arm intervention trial. *Ann Palliat Med* 2021 Feb;10(2):2008-2017
19. Umar RM, Sule A-R, Fulden YP. Significance of a clinical pharmacist-led comprehensive medication management program for hospitalized oncology patients. *Int J Clin Pharm* 2020;42(2):652-61.
20. Bennett M, Paice JA, Wallace M. Pain and opioids in cancer care: benefits, risks, and alternatives. *American Society of Clinical Oncology Educational Book*. 2017;37:705-13.