Drug utilization review of tramadol hydrochloride in a regional hospital in South Africa; findings and implications

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ABSTRACT

Background: Drug utilization reviews (DURs) can be used to promote rational prescribing and ensure compliance with standard treatment guidelines. In recent years, the use of tramadol hydrochloride (HCl) for pain has increased significantly across countries. We sought to determine prescribing patterns and use of tramadol in a Regional Hospital in South Africa to provide future guidance in view of increasing concerns with the prescribing of tramadol. **Method:** A prospective, quantitative and descriptive study was conducted over two months. Outpatient and inpatient prescriptions and ward requisitions where tramadol HCl was prescribed or ordered were identified, which included outpatients collecting antiretroviral (ARV) treatment. These were reviewed and evaluated to determine the level of compliance to the Standard Treatment Guidelines and Essential Medicines List (STGs/EML) for South Africa as a measure of the quality of prescribing. Quantities issued to the inpatient wards and expenditure incurred by the pharmacy departments were assessed to determine overall usage and total costs. **Results:** In total, 415 tramadol HCl prescriptions were collected over a 2-month period. Compliance was 70.1% to the STGs/EML. The outpatient pharmacy department had the highest compliance at 76.4% while the ARV pharmacy compliance was 29.1%. Most prescriptions dispensed at the outpatient pharmacy were from the Surgical Outpatient Department (140; 33.7%) and the Orthopaedic Outpatient Department (108; 26.0%). The outpatient pharmacy had the highest tramadol HCl consumption and expenditure at \$4,874.13 (R72,054.28), while the inpatient pharmacy's expenditure was \$2,526.63 (R37,351.20), and the ARV pharmacy \$590.13 (R8,722.75). The hospital's tramadol HCl expenditure increased when compared to previous financial years, from \$10,576.04 (R156,326.00) in 2014-2015 to \$39,584.00 (R585,088.80) in 2016-2017. **Conclusion:** This study highlights the need for the implementation of monitoring and evaluation tools to enhance rational prescribing and use of tramadol HCl. These are being implemented and will be evaluated in future projects.

Key words: Tramadol; drug utilization review; guidelines; EML; hospital; South Africa

1. Introduction

Tramadol HCl is a centrally-acting synthetic analgesic compound which acts by inhibiting the reuptake of norepinephrine and serotonin (1), which has a unique dual-action analgesic ability, producing its analgesia by affecting the nociceptive process and the central pain modulation (2-4). Its analgesic properties can be improved by combining it with non-opioid analgesics (2). Initially, tramadol HCl was perceived to have a lower side-effect profile compared to other opioids and a lower dependency compared with morphine (5-8). As a result, tramadol HCL has been widely used

in lower- and middle-income countries especially as it is often the only analgesic available for patients with moderate to severe pain, there are concerns with the use of opioids and non-steroidal anti-inflammatory drugs (NSAIDs) in these patients, as well as being relatively inexpensive despite not being on the World Health Organisation's (WHO) essential medicine list (EML) (6, 8, 9). However, tramadol HCl has the ability to induce psychic and physical dependence of the morphine type leading to concerns about the risk of tramadol dependence and abuse potential especially at supratherapeutic doses (5, 8, 10). In addition, there are concerns including major drug interactions with an appreciable number of medicines as well as the potential for seizures, hallucinations, hypertension and respiratory depression, leading to calls for its prescribing to be carefully monitored (10-17).

Overall, tramadol HCl is seen as a weak opioid analgesic which has been on the market for many years (4, 18-21). Its properties and characteristics have been extensively researched for the treatment of many types of pain, including moderate to moderately severe, acute and chronic pain (5, 8, 14, 18, 19, 22, 23). Recent Cochrane reviews and other systematic analyses have demonstrated its effectiveness in neuropathic pain, chronic low back pain, cancer pain, osteoarthritis and post-operative pain, although there were concerns in patients with rheumatoid arthritis (2, 3, 22, 24-27). There are issues though with the actual level of clinical benefit seen versus other treatments for pain and its adverse effects profile including most commonly nausea, vomiting, dizziness and constipation (5, 8, 9, 23). As a result, patients do discontinue treatment. Research has also shown that tramadol HCl monotherapy does not always offer adequate pain relief in patients with cancer (2, 21).

Despite concerns, the use of tramadol has increased appreciably in recent years with more than 18 million prescriptions now written annually in the US alone (19, 28) and, as mentioned, appreciable use in LMICs (6). However in Australia, for instance, the significant increase in the use of opioids during the past two decades resulted in an increase in opioid-related hospitalisation as well as deaths due to accidental poisoning (29). In addition in a number of African and Middle Eastern countries, data have shown an increase in the prevalence of tramadol misuse, contrary to previously reported lower tendencies towards misuse of tramadol as compared to other opioids (8, 20). Due to the increase in tramadol HCl consumption including the growing abuse of tramadol, the WHO Expert Committee on Drug Dependence has supported a move to critically review the status quo of tramadol HCl and encouraged countries to introduce further controls if needed to reduce abuse (20, 21). However, to date tramadol has not been scheduled by the Expert Committee (6). Clinics have also been established across countries, including South Africa, to address patients' addiction to tramadol (30).

Tramadol HCl was listed as a Step 2 level in the WHO guidelines for the management of cancer-related pain; however, this is no longer the case with recommendations generally for opioids as well as non-opioids for persistent or increasing mild to moderate pain (31). Tramadol HCl has also been listed in the Standard Treatment Guidelines and Essential Medicines List (STG/EML) for Primary Health Care (PHC) in South Africa (32, 33). In the latter, tramadol HCl is indicated for the management of pain in opportunistic infection treatment in adults as well as for chronic non-cancer pain and chronic cancer pain (33). In the STGs/EML for Hospital Level (Adults) in South Africa, tramadol is indicated for peri-operative, post-operative, Zoster, renal calculi and opiate withdrawal (34).

We believe concerns with the potential overuse of tramadol HCl, as well as its side-effect profile and precautions with an appreciable number of medicines, justifies the need for regular drug utilization reviews (DUR) involving a detailed review of the prescriptions of a patient prior to, during, and after dispensing of tramadol, covering all dispensing phases, to ensure positive patient outcomes (14, 18, 35, 36). DURs promote the rational use of medicines and combat wasteful expenditure (36, 37). Lack of control measures and implementation thereof to limit the overuse and abuse of tramadol HCl by both prescribers and patients has made the situation worse. While tramadol HCl use is not internationally controlled, it is the responsibility of individual countries to exert their own control measures (8). The maximum daily dose of tramadol HCl in the South African STG EML must not exceed 400mg administered at a dose of 50-100mg 4-6 hourly, which is in line with the recommendation of the WHO's Expert Committee on Drug Dependence (20). This indicates that the dose must be in the range of 100mg to a maximum of 400mg daily, with overdosing known for instance to cause acute liver failure (28). DURs are also important where the

costs of medicines consume an appreciable proportion of the overall health care budget. Consequently, any activity that seeks to enhance health system efficiency is of benefit especially in countries striving for universal healthcare (38).

In view of these concerns, a DUR of tramadol HCl was conducted at a regional hospital in South Africa. The aim was to determine the prescribing patterns, use and expenditure on tramadol HCl in this hospital. The findings are anticipated to provide guidance in this and other settings in South Africa for the future especially among public hospitals. This could include highlighting potential additional control measures to curb abuse and overuse of tramadol HCl if needed.

2. Methodology

2.1 Study setting and design

The study was conducted in a regional hospital situated in the KwaZulu–Natal (KZN) province of South Africa. The chosen hospital has 900 beds and caters mainly for the rural community from two of the districts in the province. The hospital serves as a referral hospital to a population of approximately 1.4 million people.

This was a prospective, quantitative and descriptive study. At the time of the study, the hospital was dispensing prescriptions to approximately 1,000 patients per month. With a 95% confidence interval, 5% margin of error and 50% response distribution, a sample size of 415 prescriptions for tramadol HCl was calculated. These prescriptions were collected over a two-month period (September and October 2016) from patient files in the outpatient (OP) pharmacy and the antiretroviral pharmacy. In addition, ward requisitions and electronic stock control systems for in-hospital prescriptions were reviewed to determine inpatient usage.

The principal outcome measure was compliance with either the PHC STGs/EML or the Hospital Level (Adult) STGs/EML (33, 34). Consequently, compliance with the diagnosis for tramadol HCl was determined based on the categories obtained from both these guidelines. The use of the PHC STGs/EML was seen as necessary because some patients might have been initiated on tramadol HCl by the medical officer at the PHC level and were reporting for a review at the hospital. Consequently, the diagnosis might comply with the PHC STGs/EML but not necessarily with the Hospital Level (Adult) version of the STGs/EML. Furthermore, the PHC STGs/EML clearly states that tramadol HCl may be used for pain control. It gives a clear description of pain and the medicine treatment steps, and recommends the addition of tramadol HCl for moderate pain which may not be well controlled with paracetamol and ibuprofen. However, the Hospital Level (Adult) version of the STGs/EML does not recommend tramadol HCl usage for chronic cancer pain management whilst the PHC STGs/EML recommends tramadol HCl as a Step 2 weak opioid analgesic. Adherence to guidelines is seen as a better marker for the quality of prescribing than for instance WHO/INRUD criteria (39, 40).

2.2 Data collection

Data were collected by the pharmacy staff, who received training prior to the data collection, to ensure standardisation of the data collection process. Three data collection tools were used to record the required data as well as a scanner. Approximately 10 prescriptions for tramadol were sampled per day, scanned and filed electronically in a computer for analysis. Records of supplies to the wards were printed from the Cost Man® Electronic Stock Control system and filed after being verified against the ward Schedule 5 requisition. The quantity and cost of tramadol HCl supplied from the Provincial Pharmaceutical Supply Depot (PPSD) were obtained from the pharmacy store's electronic system, Plankmed®.

2.3 Data analysis

Statistical analysis was performed on Statistical Analysis System (SAS) (SAS Institute Inc, Carey NC, USA), Release 9.4, running under Microsoft Windows for a personal computer. The total expenditure was calculated to determine the cost of tramadol HCl using monthly expenditure reports.

Expenditure was initially collected in South African Rand and subsequently converted to US\$ for comparative purposes. The conversion rate was 1 Rand = US\$0.0676295 (15 Nov 2019; <https://www.xe.com/currencyconverter/>).

2.4 Ethical considerations

Ethical clearance was obtained from Sefako Makgatho University Research Ethics Committee (SMUREC/H/115/2016:PG). A letter of approval was obtained from the Chief Executive Officer of the institution and from the Provincial Department of Health research unit. Confidentiality of the prescriptions was maintained by using a unique patient identifier and not any personal details.

3. Results

3.1 Sample population

A total sample of 415 prescriptions for tramadol HCl were reviewed, comprising 259 females (62.4%) and 156 males (37.6%). Patients' ages ranged from 18 to 81 years. The majority (360; 86.7%) of prescriptions were from the outpatient department (OPD) clinics (Table 1). More than half of the prescriptions were from the Surgical Outpatients Department (SOPD) (140; 33.7%) and the Orthopaedic Outpatients Department (OOPD) (108; 26.0%). Fifty-five (13.3%) of the 415 prescriptions were from the antiretroviral pharmacy (outpatients), catering for HIV positive patients.

Table 1: Prescriptions for tramadol HCl per hospital department

Hospital department	Number (%) of prescriptions (n=415)
Surgical outpatients' departments (SOPD)	140 (33.7%)
Orthopaedic outpatients' departments (OOPD)	108 (26.0%)
Medical outpatients' departments (MOPD)	54 (13.0%)
Emergency department (ED)	31 (7.5%)
Gynaecology outpatients' departments (GOPD)	25 (6.0%)
Occupational health services (OHS)	1 (0.24%)
No information	1 (0.24%)
Sub-total for outpatient (OP) pharmacy	360 (86.7%)
Antiretroviral pharmacy (outpatients)	55 (13.3%)
TOTAL	415 (100%)

A total of 1,501 items were prescribed on the 415 prescriptions evaluated giving an average of 3.6 medicines per prescription), which means tramadol HCl was co-prescribed with an additional 1,086 items. Of the 1,501 items reviewed, 415 (27.6%) were for tramadol HCl, 517 (34.4%) were adjuvant analgesics and 569 (37.9%) were for other medicines.

3.2 Compliance with provincial formulary prescriber levels

All 360 OPD prescriptions were evaluated for compliance with prescriber levels as per the KZN provincial formulary. According to the KZN provincial formulary, tramadol HCl is a level 1B item, which means it should be initiated by a medical officer (41). In the event where an intern medical officer prescribes tramadol HCl, the prescription must be counter-signed by a senior medical officer or it must have been initiated by a senior medical officer before the prescription can be initiated by an intern medical officer. Non-compliance with the KZN formulary is seen when a prescription is initiated first by anyone other than the senior medical officer, for example a nurse or intern medical officer.

Intern medical officers prescribed 92 (25.8%) of the 360 prescriptions evaluated from the OP pharmacy, and such prescriptions were not compliant in terms of the prescriber levels according to the formulary. Nearly two thirds (62.6%) were written by medical officers (prescriber Level 2), 0.3% by medical registrars (Level 3) and 11.2% by specialist medical officers (Level 4). The prescriber level in three (0.8%) of the prescriptions could not be identified because the prescriber's registration number was not recorded on these prescriptions. This could be because when doctors prescribe tramadol HCl outside of their prescriber level then according to the guidance in the EML/STGs, the pharmacy has to return the prescription for a counter signature. However, in busy facilities this can be overlooked. Both these challenges should be addressed by the pharmacy and therapeutic committee (PTC) in its deliberations. At the antiretroviral pharmacy, all 55 prescriptions were written by Level 2 medical officers, i.e. they do not need to be countersigned.

3.2 Categories of conditions treated

The number of conditions for which tramadol HCL was prescribed on the 360 prescriptions evaluated, were considerable. As a result, these were categorised into the different classes of pain obtained from the Hospital Level (Adult) STGs/EML and the PHC STGs/EML (33, 34).

A wide range of conditions in which tramadol HCL can be used to manage pain are listed under chronic non-cancer pain in the PHC STGs/EML as compared to the Hospital Level (Adult) version STGs/EML (33, 34). Consequently, to evaluate for compliance of the conditions treated, it was necessary to apply both guidelines in order to determine the appropriate category of pain for each condition. The electronic mobile application, which contains both guidelines, was used for this purpose (32).

The categories of pain used in the compliance evaluation process were zoster, chronic non-cancer pain, acute non-surgical pain, chronic cancer pain, post-operative pain and renal calculi. Applying these categories made it possible to evaluate the prescriptions for diagnosis compliance with the STGs/EML (Table 2). Of the 415 prescriptions evaluated, half of the conditions were categorised as chronic non-cancer pain (131; 31.6%), followed by acute non-surgical pain (80; 19.3%). Nearly a third (124; 29.9%) of the conditions treated could not be classified as any of the pain categories. More detailed information on the conditions treated with tramadol HCL, and whether the treatment was compliant to the STGs/EML or not, is available in Supplement A and Supplement B.

Table 2: Compliance of prescriptions for tramadol HCL according to pain categories as specified in the STGs/EML

Pain category	Outpatient pharmacy (n=360)		Antiretroviral pharmacy (n=55)		Total
	Number (%)	Compliant with STGs/EML	Number (%)	Compliant with STGs/EML	Number (%)
Chronic non-cancer pain	117 (32.5%)	Yes	14 (25.5%)	Yes	131 (31.6%)
Acute non-surgical pain	78 (21.7%)	Yes	2 (3.6%)	Yes	80 (19.3%)
Post-operation	53 (14.7%)	Yes	0	-	53 (13.8%)
Cancer	18 (5.0%)	Yes	1 (1.8%)	Yes	19 (4.6%)
Renal Calculi	6 (1.7%)	Yes	0	-	6 (1.5%)
Zoster	2 (0.6%)	Yes	0	-	2 (0.5%)
Not classifiable	86 (23.9%)	No	38 (69.1%)	No	124 (29.9%)
Total	360	274 of 360 (76.1%)	55	17 of 55 (30.9%)	415

NB: STGs/EML: Standard Treatment Guidelines and Essential Medicines List for South Africa; Detailed information available in Supplement A and Supplement B

3.3 Compliance of adjuvant analgesics with the STGs/EML

Table 3 shows the different adjuvant analgesics prescribed alongside tramadol HCL in the 415 prescriptions. Most of these prescriptions contained paracetamol (345; 83.1%), followed by a non-steroidal anti-inflammatory drug (61; 14.5%) and amitriptyline (56; 13.5%). The least prescribed category was the opioids (2; 0.5%).

Additional to the analgesics, other medicines prescribed included anti-hypertensives (81; 19.5%), supplements (91; 21.9%), antivirals (70; 16.8%), antibiotics (52; 12.5%), anti-inflammatories (29; 7.0%), wound dressing treatments (14; 3.4%), anti-diabetic medicines (8; 1.9%), anti-convulsants (8; 1.9%), anti-cancer medicines (3; 0.7%), and other medicines (101; 24.4%).

Furthermore, each individual analgesic prescribed for the management of pain was evaluated for compliance with the STGs/EML. A brief summary of the recommendations as stipulated in the guidelines is available as Supplement C. Compliance was considered by determining whether the diagnosis and the dosage were compliant with the guidelines. The dosage interval was not evaluated in our study as pain medication is often recommended to be taken when necessary, especially in patients with acute mild pain. The frequency of medication also depends on the pain intensity, although for chronic pain and cancer pain maintaining the frequency as recommended by

the guidelines is important. The duration of treatment was not specified in the guidelines; consequently, this was also not taken into account when determining compliance to the STGs/EML (Table 3).

Paracetamol was the most commonly prescribed analgesic (345; 83.1%) as it can be prescribed for mild pain but also as an adjuvant to tramadol HCl for moderate pain management. It is a first line analgesic unless contraindicated. The dosage was 100% compliant while 94.5% compliant with respect to conditions treated. Amitriptyline was 96.4% diagnosis- and 100% dose compliant, ibuprofen was 95.4% diagnosis- and 90.2% dosage compliant, and carbamazepine was found to be 100% compliant with respect to both diagnosis and dosage.

Table 3: Therapeutic category of adjuvant analgesics and compliance with STGs/EML (n=415)

Pharmacological class	No (%) of prescriptions (n=415)	Analgesic	No (%) of prescriptions (n=415)	Diagnosis for number (%) of prescriptions (n=415)			Dosage for number (%) of prescriptions (n=415)		
				Compliant with STGs/EML	Non-compliant	No information	Compliant with STGs/EML	Non-compliant	No information
Aniline analgesics	345 (83.1%)	Paracetamol	345 (83.1%)	326 (94.5%)	11 (3.2%)	8 (2.3%)	345 (100%)	-	-
Non-steroidal anti-inflammatory drugs (NSAIDs)	61 (14.5%)	Ibuprofen	41 (9.9%)	39 (95.1%)	-	2 (4.8%)	37 (90.2%)	4 (9.7%)	-
		Naproxen	17 (4.1%)	15 (88.2%)	-	2 (11.7%)	16 (94.1%)	1 (5.8%)	-
		Diclofenac	2 (0.5%)	2 (100%)	-	-	2 (100%)	-	-
		Indomethacin	1 (0.2%)	1 (100%)	-	-	1 (100%)	-	-
Tricyclic anti-depressants	13.49%	Amitriptyline	56 (13.5%)	54 (96.4%)	1(0.24%)	1 (0.24%)	56 (100%)	-	-
Non-narcotic analgesic	14 (3.3%)	Carbamazepine	13 (3.1%)	13 (100%)	-	-	13 (100%)	-	-
		Gabapentin	1 (0.24%)	-	1 (100%)	-	-	1 (100%)	-
Opioids	2 (0.5%)	Codeine phosphate	1 (0.24%)	-	1 (100%)	-	-	1 (100%)	-
		Morphine sulphate	1 (0.24%)	1 (100%)	-	-	1 (100%)	-	-
Anticonvulsants	1 (0.24%)	Pregabalin	1 (0.24%)	-	1 (100%)	-	-	1 (100%)	-

STGs/EML: Standard Treatment Guidelines and Essential Medicines List for South Africa

3.4 Compliance of diagnosis, dosage, and the dosage interval of tramadol HCl with the STGs/EML

The aspects of compliance such as the diagnosis, dosage, dosage interval have been equally weighted to arrive at a conclusion as to whether the prescription was compliant or not. Tramadol HCl is the basis of this study; consequently, all aspects of compliance to the guidelines were evaluated.

Compliance was found to be 76.1% (274) regarding the conditions treated. Non-compliance (23.9%; 86) was due to over prescribing or because some conditions (diagnosis) were not indicated in the STGs/EML. Compliance at the antiretroviral pharmacy was low at 30.9% because some prescriptions had no direct indication for tramadol HCl and most had no indication at all (Table 2).

The overall dosage compliance was 99.8%. Only one prescription contained a dose of 200mg as a single dose. The dosage interval was found to be non-compliant in 95.4% of prescriptions. The primary reason for non-compliance was that 80.7% of the prescriptions had a dosage interval of 8-hourly whereas the guidelines recommend 4-6 hourly, which is interpreted as 4-6 times a day (Table 4).

Table 4: Tramadol HCl dosage and dosage interval compliance with the STGs/EML

Dose and dosage interval	Compliant with STGs/EML		No (%) of prescriptions
	Dosage	Dosage interval	
50mg 8 hourly	Yes	No	299 (72.9%)
50mg 12 hourly	Yes	No	68 (16.6%)
50mg 6 hourly	Yes	Yes	14 (3.4%)
100mg 8 hourly	Yes	No	13 (3.2%)
100mg 5 hourly	Yes	Yes	5 (1.3%)
100mg 12 hourly	Yes	No	4 (0.9%)
50mg when necessary	Yes	No	3 (0.7%)
50mg daily	Yes	No	3 (0.7%)
200mg daily	No	No	1 (0.24%)
No information	-	-	5 (1.2%)
Total number (%) of prescriptions	414 (99.8%)	19 (4.6%)	415 (100%)

STGs/EML: Standard Treatment Guidelines and Essential Medicines List for South Africa

3.6 Inpatient consumption

A total of 26 100 tramadol HCL tablets were issued to the wards for inpatient use over the period of two months. The breakdown for each ward is shown in Table 5, with more than half (51.5%) of the total consumption among the surgical wards.

Table 5: Inpatient consumption of tramadol HCl

Inpatient ward	Number (%) of tablets
Surgical wards	13 450 (51.5%)
Orthopaedic wards	7 400 (28.3%)
Medical wards	3 860 (14.8%)
Obstetrics and Gynaecology	1 050 (4.0%)
Burns ward	340 (1.4%)
Total	26 100 (100%)

3.7 Expenditure on tramadol HCl

The expense incurred on tramadol HCl over the 2-month study period by the inpatient pharmacy was \$2, 526.63 (R37 351.20), outpatient pharmacy \$4, 874.13 (R72 054.28) and antiretroviral pharmacy \$590.13 (R8 722.75). Table 6 presents the hospital expenditure for tramadol HCl per financial year, showing an appreciable increase from 2014-2016 to 2016-2017.

Table 6: Tramadol HCl hospital expenditure per financial year

Financial year		Expenditure	
		US\$	ZAR
2014-2015		\$ 10 576.04	R 156 326.00
2015-2016		\$ 34 258.79	R 505 602.00
2016-2017		\$ 39 584.00	R 585 088.80
Pharmacy expenditure for 2016-2017	Outpatient pharmacy (34%)	\$ 13 571.23	R 200 288.50
	Inpatient pharmacy (24%)	\$ 140 519.10	R 140 519.10
	Antiretroviral pharmacy (5%)	\$ 2 010.07	R 29 669.90

4. Discussion

Chronic non-cancer pain (32.7%) followed by acute non-surgical pain (21.8%), post-operative pain (14.8%) and cancer pain (5.0%) were the principal indications for tramadol use in this regional hospital in South Africa. Overall, there was a reasonable level of compliance with the STGs/EML for South Africa, Hospital Level (Adults) and the PHC Level. Compliance to guidelines for the use of tramadol HCL as per the pain categories was greatest in the outpatient pharmacy at 76.1% whereas antiretroviral pharmacy compliance was only 30.9%. Overall dosage compliance was 99.8%. All prescriptions reviewed at the antiretroviral pharmacy were written by level 2 medical officers; however, it was noted that most prescriptions had no specific indication for tramadol HCl and were therefore non-compliant. Consequently, this is an area to address in the future, especially with concerns with tramadol.

Of all the wards, the surgical wards had the highest prescribing of tramadol HCl tablets at 51.5% (Table 5) as patients were suffering from cancer, post-operation pain, stab wounds and, in some instances, the wards are treated as a step-down facility for terminally-ill patients who are constantly in pain. This is consistent with the pattern seen when evaluating the OPD clinics.

When assessing the prescriptions from the OPD clinics, it was noted that the SOPD at 33.7% had the most tramadol HCl prescriptions, followed by the OOPD at 26.0%. This prescribing pattern may be due to the nature of the conditions of the patients who visit these departments, which ranged from those with cancer, post-operation and chronic pain to post-motor vehicle accident victims. For prescribers at the SOPD, it was often difficult to prescribe anything else apart from paracetamol and tramadol HCl as most of their patients suffer from epigastric pain or have such related illnesses.

Overall, our findings were encouraging as previous reviews have shown low compliance with STGs/EML for infections and diabetes in Kwa-Zulu-Natal (42-44). However, these reviews did not include the duration of therapy as this was not specified and assumed to be at the discretion of the prescriber assessing the patient.

When evaluating for compliance in adjuvant therapy, the results were found to be consistent with that of tramadol HCl except for the dosage interval. Paracetamol, amitriptyline, carbamazepine and diclofenac were all 100% dosage compliant while the diagnosis compliance varied from 94.5% for paracetamol, 96.4% for amitriptyline, and up to 100% for both carbamazepine and diclofenac. Having said this, there needs to be care when tramadol HCl is co-prescribed with antidepressants and patients with bipolar disorders (14).

There were two situations that could have attributed to and promoted the overuse of tramadol HCl. These are the non-availability of some NSAIDs such as naproxen, and the restriction of others due to their side-effect profiles including indomethacin. In such cases where the first-line agents are not available, prescribers or the pharmacist recommend the next available analgesic in line as it is difficult to send a patient home without medication. This could be tramadol, which will be investigated further in future research projects to help improve the quality of prescribing in this regional hospital.

As seen, expenditure on tramadol has almost doubled in recent years (Table 6), with the highest expenditure in the OP pharmacy department. We will be looking at this further to see if savings can be made in the future without compromising care. We will also point out to the authorities some of the inconsistencies with for instance PHC STGs/EML recommending tramadol HCl as a Step 2 weak opioid analgesic but not in the Hospital Level (Adult) STGs/EML (33, 34). This can cause problems as seen in Namibia with inconsistencies between national guidelines (45).

We are aware of a number of limitations with this study. It was conducted at only one regional hospital and data was collected over a short period of time which means that the results cannot be generalised. Furthermore, regarding the inpatient wards, only the quantity issued to wards was determined and assessed and no level of medication compliance was investigated in the inpatient setting. However, we believe our findings are robust with concerns identified that need to be addressed in this hospital in addition to further research on the use of tramadol HCl across public hospitals in South Africa in view of continued concerns with tramadol HCl. Proposed activities also include investigating issues of stock control practices especially if poor stock control leads to higher prescribing of tramadol where there are limited other alternatives. In addition, looking to introduce measures to enhance proper quantification and forecasting of medicine stocks as well as train pharmacy stock controllers in supply chain management, which are all part of recent developments in South Africa (38).

5. Conclusion and next steps

Encouragingly, the prescribing of tramadol HCl was found to be appropriate in most cases in this regional hospital based on the dose, diagnosis and interval indicated in the STGs/EML for South Africa. This is in contrast to other disease areas in this region.

However, a number of areas were identified that need addressing. These include prescribers not writing the diagnosis on the prescription, which is particularly important for medicines such as tramadol, and addressing the fact that some prescriptions had no clear information on them. The latter is particularly important to be able to evaluate prescribing compliance with guidelines. The number of prescriptions written by intern medical officers was also a concern that needs to be addressed. This can potentially be addressed through greater implementation and monitoring of prescriptions and protocols by the PTC as part of quality improvement practices in the hospital to improve rational prescribing. We are aware of the growing role of PTCs in South Africa as part of government initiatives to improve the use of medicines in hospitals, and such activities can be part of this (46, 47).

Concurrent with greater monitoring of prescribing practices and restrictions, there is a need to review why there has been a significant increase in the use of tramadol HCl in this hospital in recent years with associated increase in expenditure. Addressing these issues with pertinent interventions should help to optimize the use of tramadol HCl in this and other hospitals in South Africa in line with the recent WHO guidance. Alongside this, the hospital management needs to introduce better systems to restrict and control tramadol HCl utilization so that patients do not become dependent. Hospital management is also encouraged to introduce drug monitoring and evaluation tools via the PTC to assess prescribing and dispensing patterns on a monthly basis as seen in other settings in South Africa and wider. The findings should be regularly presented to the PTC for implementation to improve drug utilization practices. We will be following up these suggestions in the future and reporting on them.

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Supplementary data

Supplement A: Compliance of diagnosis per pain classification category as per STGs/EML (n=360)

Pain category	Zoster (n)	Chronic non-cancer pain (n)	Acute non-surgical pain (n)	Chronic cancer pain (n)	Post-operation pain (n)	Renal calculi (n)
Condition compliant per STGs/EML	Multiple abscess query herpes (1)	Arthritis (24)	Lower abdominal pains (6)	Cervical cancer (6)	Amputation (4)	UTI, Spine problem (1)
	Herpes, back pains (1)	Body pains (38)	Gastritis (5)	Follicular cancer (2)	c-spine injury & fusion (1)	UTI query MAO infection (1)
		Wound pain (22)	Arthralgia (1)	Anal cancer (2)	Post operation pains (17)	UTI (1)
		Chronic pains (2)	Trauma (33)	Vulvar cancer (2)	Below knee slab (1)	Obstructive uropathy (1)
		Diabetes, hypertension (4)	Breast pains (1)	Lymphoma (1)	Cuff repair (2)	Orchitis (1)
		Chronic pancreatitis (1)	Acute body pains (15)	Squamous cell carcinoma (1)	Hernia repair (1)	Left renal cyst (1)
		Peptic Ulcer Disease (9)	Hernia (2)	Cancer (not specified) (2)	Left ankle equinus correction (1)	
		Degenerative spine (1)	Painful haemorrhoids (1)	Prostate cancer (1)	Mitral valve replacement (2)	
		Grade 2 Posterior tibialis tender dysfunction (1)	Sam muscle soft tissue (1)	Breast lump (1)	Left patella implant replacement (1)	
		Para infection with focal myelitis (1)	Post chest stab query keloids (1)		Post femur nailing (1)	
		Joint pain (1)	Chest stab (3)		Post debridement (1)	
		Pelvic inflammatory disease (1)	Knee pain and swelling (1)		Post acetabular (1)	
		Lupus anti- coagulant syndrome (1)	Headache (6)		Post right bi-malleolus (2)	
		Spondylitis (4)	Recurrent fonticuli's in neural region (1)		Fracture (15)	
		Vascular disease (1)	Dislocation shoulder (1)		Surgical review previous left BKA (1)	
		Post trauma pains (5)			Tibia plateau with ring fixator (1)	
		Cardiac failure (1)			Post reduction left ankle (1)	
Total; n (%)	2/360; 0.6%	117/360; 32.7%	78/360; 21.8%	18/360; 5.1%	53/360; 14.8%	6/360; 1.7%
A total of 360 prescriptions were evaluated, of which 86 (23.9%) conditions were found not fitting to any of these classes thus termed non-compliant (see Supplement B)						

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Supplement B: Conditions for which tramadol HCL was prescribed, not in compliance with STGs/EML

Condition	Frequency	Reasons no indication
Warts	6	Not indicated in the standard treatment guidelines
Haemorrhoids	5	Not indicated in the standard treatment guidelines
Deep vein thrombosis	4	Not indicated in the standard treatment guidelines
Tuberculosis	3	Not indicated in the standard treatment guidelines
Recurrent tonsillitis	3	Not indicated in the standard treatment guidelines, paracetamol can be used for pain and fever
Abscess	3	Not indicated in the standard treatment guidelines
Mass in the abdomen	2	Not indicated in the standard treatment guidelines, often caused by constipation and over use
Brain tumour	2	Contraindicated as it involves a brain injury
Epilepsy	2	Not recommended in the standard treatment guidelines
Lipoma	2	Condition often regarded as painless and tramadol is not indicated in the guidelines
Mass in the abdomen	2	Not indicated in the standard treatment guidelines, often caused by constipation and over use
Toe and leg cellulitis	2	Not indicated in the standard treatment guidelines and over use of tramadol
Hypothyroidism	2	Only thyroxine is indicated in the guidelines
Blurred vision	1	Not indicated in the standard treatment guidelines and condition not usually painful
Odynophagia	1	Treatment depends on the underlying condition
Nipple discharge	1	Not indicated in the standard treatment guidelines
Sinusitis	1	Not indicated in the standard treatment guidelines
Hypertension	1	Not indicated in the standard treatment guidelines
Abnormal bleeding	1	Not indicated in the standard treatment guidelines
Hypertension and chronic obstructive pulmonary disease	1	Not indicated in the standard treatment guidelines and tramadol causes respiratory depression
Ingrown rib	1	Not indicated in the standard treatment guidelines
Peri-anal mass	1	Not indicated in the standard treatment guidelines
Retained placenta	1	Not indicated in the standard treatment guidelines
Swelling and laceration on the head	1	Contraindicated as it involves a brain injury
Motor Vehicle Accident	1	Not a condition but an incident
Chronic serous otitis media (CSOM) and asthma	1	Not indicated in the standard treatment guidelines and tramadol causes respiratory depression
Bleeding oesophagus	1	Not indicated in the standard treatment guidelines
Hepatitis associated antigen	1	Not a condition therefore not indicated
Hyperthyroidism	1	Not indicated in the standard treatment guidelines
Cyst on the face	1	Not indicated in the standard treatment guidelines
Dry cough	1	Not indicated in the standard treatment guidelines and over use
Valgus deformity and leg length discrepancy	1	Not indicated in the standard treatment guidelines and over use of tramadol
Chronic atrial fibrillation	1	Not indicated in the standard treatment guidelines
Lip laceration	1	Not indicated in the standard treatment guidelines, over use of tramadol
Psoriasis	1	Not indicated in the standard treatment guidelines, over use of tramadol
Cholecystitis	1	Not indicated in the standard treatment guidelines, over use of tramadol
Fibroadenoma	1	Not indicated in the standard treatment guidelines, over use of tramadol
Sebaceous cyst	1	Not indicated in the standard treatment guidelines, over use of tramadol
Critical care medicine	1	Not indicated in the standard treatment guidelines
Sub-total	64	
Condition not clear	13	
No diagnosis/ indication specified	8	
Total	86	

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Supplement C: Recommendations on the suggested treatment approaches as stipulated by the STGs/EML

Class	Analgesic	Dose and dosage interval	Maximum dose
Analgesic for chronic non-cancer pain			
Mild/ moderate pain	Paracetamol	1g 4-6 hourly	4 doses in 24 hours, 15mg/kg/dose, 4g in 24 hours
	Ibuprofen	400mg 8 hourly	2400mg per day, nurses prescribe a max of 1200mg
Severe pain	Tramadol (combined treatment is suggested)	50-100mg 6 hourly	400mg per day
	Add morphine syrup	10-15mg 4 hourly	0.2mg/kg 4 hourly
	Change to morphine long acting oral once stable	10 & 30mg 12 hourly	60mg 12 hourly
Chronic cancer pain This follows the same as above and there is no maximum dose for morphine for cancer or terminally ill patients.			
Chronic neuropathic pain	Amitriptyline	10mg at night	75mg at night
	If not well managed add or replace with Carbamazepine (refer if unresponsive)	100-200mg 12 hourly	600mg 12 hourly
Acute non-surgical pain Analgesic treatment is that of acute postoperative pain, that is postoperative pain in the recovery room. Those already on opioids for chronic pain must be monitored for respiratory and cardiovascular depression.			
Zoster	Paracetamol	1g 4-6 hourly	4 doses in 24 hours, 15mg/kg/dose, 4g in 24 hours
	Tramadol	50-100mg 6 hourly	400mg per day
	Amitriptyline	25mg at night	75mg at night
Perioperative analgesics	Paracetamol	1g 4-6 hourly	4 doses in 24 hours, 15mg/kg/dose, 4g in 24 hours
	Add Tramadol	50-100mg 6 hourly	400mg per day
	Add NSAID e.g. ibuprofen	400mg 8 hourly	2400mg a day
Postoperative pain			
Post-operative analgesia in the recovery room			
Mild pain	Paracetamol	1g 4-6 hourly	4 doses in 24 hours, 15mg/kg/dose, 4g in 24 hours
	NSAID e.g. Ibuprofen	400mg 8 hourly	2400mg per day, nurses prescribe a max of 1200mg
Moderate pain	Tramadol	50-100mg 6 hourly	400mg per day
	Paracetamol	1g 4-6 hourly	4 doses in 24 hours, 15mg/kg/dose, 4g in 24 hours
	NSAID e.g. Ibuprofen	400mg 8 hourly	2400mg per day, nurses prescribe a max of 1200mg
Severe pain	Tramadol	50-100mg 6 hourly	400mg per day
	Morphine	IM 0.1-0.2mg/kg 4 hourly	0.1-0.2mg/ kg 4 hourly

Class	Analgesic	Dose and dosage interval	Maximum dose
	Morphine	1mg bolus every 6-10 minutes	
Opiate withdrawal	Diazepam	5-20 mg / day in divided doses	
	Paracetamol	1g 4-6 hourly	4 doses in 24 hours, 15mg/kg/dose, 4g in 24 hours
	NSAID e.g. Ibuprofen	400mg 8 hourly	2400mg per day, nurses prescribe a max of 1200mg
	Methadone (in case of unavailability tramadol 200mg 12 hourly for 2 weeks)	5-10mg 2-4 hourly	30mg per 24 hours
Pain control			
Mild pain; non-opioid treatment, non-inflammatory pain	Paracetamol	10-15mg/kg/dose for children 1g 6 hourly when required	4g per day
Associated with trauma or inflammation	NSAIDS e.g. Ibuprofen	400mg 6-8 hourly	2400mg per day and nurses may only prescribe 1200mg
Moderate – if no relief to paracetamol	NSAIDS e.g. Ibuprofen if no relief, add tramadol	50mg 4-6 hourly	400mg daily
Severe pain	Tramadol Add paracetamol Or morphine IM 10-15mg	50mg 4-6 hourly 1g 6 hourly when IM 10-15mg 4-5 hourly	400mg daily 4g per day
Cancer pain			
Step 1a	Paracetamol	1g 6 hourly	4g per day
Step 1b	NSAIDS e.g. Ibuprofen	400mg 6-8 hourly	2400mg per day and nurses may only prescribe 1200mg
Step 2	Tramadol	50mg 4-6 hourly	400mg daily
Step 3	To Paracetamol and or . Ibuprofen add morphine	5-10mg 4 hourly	No maximum dose – dose is titrated upwards

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