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Novel opioid detoxification using loperamide and P-glycoprotein inhibitor

Mohamed Al Garhy MD, Jennifer Jean Williams, RN, Sona Mohan, MD, Hana Abu Sharib RN

Opioids were responsible for 76% of substance-related death in 2015 and only one in six people received effective treatment for their substance use disorder globally due to unavailability of services in 2016. Here, Al Garhy et al. describe the characteristics of inpatients receiving loperamide with a P-glycoprotein inhibitor for medically-supported detoxification at Sheikh Khalifa Medical City Hospital and provide preliminary evidence that loperamide and omeprazole, two inexpensive over-the-counter medications, can effectively and safely reduce the full spectrum of opioid withdrawal manifestations in male patients.

Globally, the burden attributable to mental and substance use disorders (MSUDs) increased by 37.6% between 1990 and 2010.¹ Indications are that by 2016, 30.5 million of the world's population had a substance use disorder.² Despite global variation in patterns of use, opioids are conservatively estimated to be the largest contributor to the overall burden of disease expressed as disability adjusted life years (9.2 million, 95% UI 7.1–11.4).¹ By 2013 drugs were the fourth most common cause of death in the Middle East's high-income countries and opioids were among the top five causes of years lived with disability in all six countries.³

Opioid dependence is characterised by a chronic compulsive use/seeking of an opioid medication leading to major adverse consequences in all main aspects of life. Acute withdrawal is anticipated when opioids are abruptly stopped, or their use significantly reduced after being continually used for at least 2–10 days.⁴ Symptoms include central nervous system arousal, autonomic symptoms like nausea and diarrhoea, pain and craving for opioids. Current opioid detoxification approaches include the use of opioid agonists (*eg* methadone), partial agonists (*eg* buprenorphine), non-opioid alternatives (*eg* α 2-adrenergic agonists as clonidine) or symptomatic medications (*eg* loperamide for diarrhoea). The choice of medication used to support withdrawal depends on multiple factors, including patient preference, clinician expertise and experience, type of treatment facility and resource availability. Methadone,

commonly used for opioid withdrawal, is currently only advised for use by clinically skilled and knowledgeable clinicians, given the associated risks.^{5,6} Inherent risks are associated with all pharmacotherapy used to manage withdrawal and dependence. Additional barriers to treatment include cost,^{7,8} insufficient data on patterns of use,⁹ especially in low- and middle-income countries, and integrated national policies, including those related to regulation and availability of established medications to treat opioid withdrawal.¹⁰

Loperamide, an inexpensive over-the-counter phenylpiperidine derivative and μ -opioid receptor agonist, does not readily cross the blood-brain barrier and thus has minimal impact on the central nervous system. Theoretically, as loperamide is a P-glycoprotein substrate, co-administering it with a P-glycoprotein inhibitor such as omeprazole (a proton pump inhibitor), would support breaching this barrier,¹¹ converting it from a peripherally-acting μ opioid receptor to treat diarrhoea to a central-acting opioid agonist that reduces the full spectrum of opioid withdrawal manifestations. Considering both loperamide and omeprazole are well-tolerated, effective, cheap and easy-to-use medications and with no recognised adverse drug interactions, in 2014 the first author initiated the practice of prescribing loperamide (2mg BD) and omeprazole (20mg BD) for seven days, extended to a maximum of 10 days, to support the period of physical opioid withdrawal.

Methods and materials

This retrospective medical record review was conducted in the residential addiction treatment unit of a psychiatric department of a tertiary hospital in the Middle East from 1 January 2015 to 31 December 2016. Given anecdotal reports from patients and clinicians of the effectiveness of the treatment regimen, the aim of this study is to describe the characteristics of patients receiving the treatment and determine safety and effectiveness of the intervention.

Chemical dependency treatment

Patients admitted either voluntarily or by order of the court, receive clinical services from a team led by a consultant psychiatrist. Twenty-four-hour care is provided

by a nursing team and psychiatrists with medical emergency support through the general hospital's emergency and internal medicine teams. Suitability for admission for detoxification is determined by a psychiatrist and is based on a full physical and psychiatric assessment, including drug and alcohol assessment, and mental state examination. Only patients who are medically stable are accepted. Within 24 hours of admission, routine laboratory investigations (complete blood count, fasting blood sugar, kidney and liver functions, HIV, hepatitis B & C) and electrocardiogram are done. All patients are physically examined by a medical internist. Registered nurses administer all medication and monitor vital signs at least every 12 hours for each patient, throughout the admission period. Participation in the withdrawal protocol is voluntary and patients may exit the protocol at any time without providing a reason. In all instances of opioid withdrawal the therapeutic goal is safe and effective detoxification.

Data management and measurement

The hospital's fully computerised electronic health record (EHR) is linked to its billing system and all patients are accounted for electronically. Data related to service contact are automatically logged at the point of service contact (*eg* admission) and an electronic time recording is embedded in the system. Clinical data are entered into the EHR at each patient encounter and a discharge report must be completed by a consultant psychiatrist prior to discharging patients from the service. Applying a computerised algorithm developed for this study, 271 records were initially retrieved from the psychiatric pharmacy's database. Based on the unique identifiers of the psychiatrists attached to the unit, a subset of 156 records was identified related to prescriptions for loperamide and omeprazole for 7–10 days. Excluding all records for diagnoses other than 304.0 and 304.7 as per the International Classification of Diseases, Ninth Revision criteria¹² on admission resulted in 66 reports. A further eight records were excluded as more than seven days had elapsed between last taking an opioid and admission, along with six others as the last date of taking an opioid prior to admission could not be determined. Demographics, medication prescription and length of stay data were imported into the electronic abstraction tool. Further data were abstracted in accordance with a predetermined protocol by one researcher and directly entered as a unique code into the computerised data capturing tool in the order in which they appeared in the record. This abstraction process was replicated by a second researcher on 100% of the records and duplicated variables compared using Microsoft Excel 2016.

Table 1. Clinical characteristics of participants treated with the loperamide-omeprazole protocol

History of opioid use and withdrawal	Episodes n (%)
1 Frequency of substance use per week	
1–3 times	4 (7.7)
4–6 times	1 (1.9)
7 or more times	48 (86.5)
2 Number of opioids used	
1 substance	30 (57.7)
2 or more substances	20 (38.5)
Missing data	2 (3.8)
3 Substance (opioid) used	
Heroin	10 (19.2)
Morphine	3 (5.8)
Tramadol	21 (40.1)
Combination of 2 or more	16 (30.8)
Not reported	3 (5.3)
4 Route	
Intravenous	9 (17.3)
Smoke	1 (1.9)
Nasal	6 (1.5)
Oral	21 (40.4)
Combination of routes	13 (25.0)
Not reported	2 (3.8)
5 Longest duration of use of substance	
≤6 months	2 (3.6)
7 months to 2 years	17 (30.4)
3 years to 5 years	19 (33.9)
>5 years	13 (23.2)
Not reported	5 (8.9)
6 Previous withdrawal symptoms reported	
Yes	49 (94.2)
No	1 (1.8)
Not reported	2 (3.8)
7 Last dose of opioid prior to admission	
0–3 days	40 (76.9)
4–7 days	12 (23.1)

Where discrepancies were found (19 instances), these were corrected by manual rechecking of the individual record by the lead author.

Definitions and endpoints (outcome measures)

Researchers adopted the unit's definition of medication *effectiveness* (treatment achieves the therapeutic

Table 1. Clinical characteristics of participants treated with the loperamide-omeprazole protocol Cont.

History of opioid use and withdrawal	Episodes n (%)
Diagnoses	
8 Main ICD-9 psychiatric diagnosis	
Opioid type dependence (304.0)	40 (76.9)
Combinations of opioid type drug with any other drug dependence (304.7)	12 (23.1)
9 Secondary ICD-9-CM psychiatric diagnosis on admission	
None	41 (75.0)
Alcohol dependence syndrome (303)	4 (7.7)
Benzodiazepine and sedatives	3 (5.8)
Stimulants	1 (1.9)
Cannabis	1 (1.9)
Mood [affective] disorders	2 (3.8)
10 ICD-9-CM medical diagnosis at discharge	
None	40 (76.9)
Endocrine, nutritional & metabolic diseases & immunity disorders (240–279.9)	6 (11.5)
Diseases of the respiratory system (460–519.9)	2 (3.8)
Diseases of the digestive system (520–579.9)	2 (3.8)
Diseases of the skin & subcutaneous tissues (680–709.9)	1 (1.9)
Late effects of motor vehicle accident (E929.0)	1 (1.9)
Suicide and self-inflicted injury (E950–E959)	1 (1.9)

outcome). While not outcome measures of effectiveness in themselves, data were collected on length of hospital stay (LOS) and whether an admission episode was terminated against medical advice (AMA), as these indicate failure to access the next phase of the treatment program and discharge planning. We defined *safety* as the absence of an episode of preventable potential or actual harm, whether the outcome was serious or not. An episode of harm, a serious adverse event (SAE), was defined as a patient event requiring clinical intervention to manage the effects and/or side-effects of either loperamide or omeprazole, referral to a medical or emergency team due to increased acuity, or death during or within 72 hours of stopping the regimen. For a withdrawal episode to be considered successfully completed, three criteria needed to be met: all doses of loperamide and omeprazole were taken as prescribed; no reported requests were made by patient for additional support to manage withdrawal symptoms/discomfort, and no re-emergence of withdrawal manifestations within 72 hours of completing the regimen.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics for Windows, version 20.¹³

Ethics

Ethical approval for this study was granted by the Institutional Review Board of Sheikh Khalifa Medical City, UAE. No patients were contacted for additional information and data in this manuscript are anonymised.

Results

Demographics and clinical characteristics

In the two-year period of this retrospective study, 44 individual patients were admitted for opioid detoxification, accounting for 52 detoxification episodes. In all cases, opioids were obtained and used illicitly. Given that the focus of this study was detoxification events rather than the patients themselves, all results are reported for detoxification episodes and not individual patients. All cases were male, aged 17 to 50 years (mean 26.70, SD±8.96). Clinical characteristics are described in Table 1.

In 48 episodes (85.7%) opioids were used at least daily. Tramadol was the most used substance (n=28, 53.8%) and on 21 occasions (40.1%) was the sole substance. Duration of opioid use ranged from two months to 20 years. In 49 events (94.2%) there were previous withdrawal symptoms. Opioids were used within 24 hours prior to admission in 24 episodes (46.2%). The majority of this population had no comorbid psychiatric or general medical diagnoses.

Measures of safety and effectiveness

Measures of effectiveness and safety are reported in Table 2. The mean length of stay was 18.96 days (SD± 23.063, range 0–105). No serious adverse events were associated with the protocol and no requests for an increase in the doses of loperamide or omeprazole were recorded.

Table 3 compares the length of stay (LOS) and discharge against medical advice for complete and incomplete detoxification events. Mean LOS of incomplete episodes was 4.62 days (SD±7.476, range 0–38 days) while completers stayed a mean of 30.34 days (SD±24.930, range 7–105 days). Nineteen (82.6%) of the 23 events of incomplete detoxification events were terminated when a patient discharged himself against medical advice as opposed to three (10.3%) incomplete detoxification episodes.

Discussion

Demographics

This retrospective EHR review is, to our knowledge, the first to describe co-administering loperamide and omeprazole as an opioid detoxification protocol. Despite indications of the increasing problem of opioid use in

Middle East, there is a paucity of scientific literature on addiction generally and withdrawal specifically within which to position this study. The prevalence of substance use is higher in males, both globally and regionally,^{2,14} and regional opioid use is on the rise.² While exclusively male with a mean age of 26.70 years, subjects were diverse in terms of their substance use histories. However, the majority (53.8%) used tramadol, either alone (40.1%) or in combination, consistent with findings from the UAE.^{15,16} Concern about the risky use of this prescription medication in the Middle East is mounting, with the United Nations Office on Drugs and Crime identifying it as an increasing contributor to admissions to substance abuse treatment services and deaths.²

Females accounted for 24.2% and 31.8% of participants in two opioid detoxification program studies in the USA, respectively,^{17,18} and 39% in Sweden.¹⁹ A study from Saudi Arabia identified that 19 (1.3%) females were admitted with substance-related diagnoses to a psychiatric service, but the nature of substances used were not reported.²⁰ Of the three studies identified from the UAE, two identified only males as users of a national rehabilitation service and one identified a single female with a substance-related diagnosis among 285 randomly selected admissions to a psychiatric service.^{15,16,21} Although an expected finding, the absence of females is of concern in this region with its conservative traditions and stigma associated with opioid use which are likely barriers to accessing medically-supported withdrawal services.

Safety

Both loperamide and omeprazole are recommended to be available in all countries at over-the-counter doses.²² Given that this protocol uses a dose of loperamide that is far below the maximum FDA approved dose,²³ no adverse events were anticipated. Current literature confirms that only excessively high doses can cause serious cardiac side-effects and potential death.^{24–31} This study addressed the safety of loperamide over a short period of time and during the study development no serious adverse events were reported. Despite differences in study design, this finding is comparable with other treatment approaches used for opioid detoxification^{17,18,32,33} and, when considered together with the finding that no instances were reported of additional requests for either medication, suggests that this protocol is not only safe, but also well-tolerated. This potentially places it within reach of those unable to access other medically supervised detoxification programs due to barriers outlined earlier, including inpatient, outpatient and primary

Table 2. Primary and secondary outcomes of admission for opioid detoxification (n=52)

Course of admission	n (%)
11 Length of stay	
Mean length of stay 18.96 days (SD± 23.063, range 0–105)	
0–9 days	27 (51.9)
10–19 days	8 (15.4)
20–29 days	4 (7.7)
≥30 days	13 (25.0)
12 Completed treatment regimen	
Yes	29 (55.8)
No	23 (44.2)
13 Requested increased doses of protocol medication	
Yes	0 (0.0)
No	52 (100.0)
14 Discharged self against medical advice (AMA)	
Yes	22 (42.3)
No	30 (57.7)
15 Serious adverse event: referral to emergency department during admission period	
Yes	0 (0.0)
No	52 (100)
16 Serious adverse event: care transferred to internal medicine department during admission period	
Yes	0 (0.0)
No	52 (100)
17 Serious adverse event: medication discontinued by clinician due to effects or side-effects	
Yes	0 (0.0)
No	52 (100)
18 Serious adverse event: death up to within 72 hours after discharge	
Yes	0 (0.0)
No	52 (100)

health care settings. Applying this protocol as maintenance treatment needs further evaluation due to safety concerns associated with prolonged use of loperamide as well as the possibility of medication consumption without supervision owing to its easy accessibility.

Effectiveness

The overall retention rate was impressive with only 22 (42.3%) episodes terminated against medical advice. This compares favorably with inpatient medically supervised opioid withdrawal programs from Sweden,

Table 3. Completion of opioid withdrawal protocol

Length of stay in unit in bands of ten days		Completed treatment regimen		Total
Length of stay		no	yes	
0–9 days	N %	22 81.5%	5 18.5%	27 100.0%
10–19 days	N %	0 0.0%	8 100%	8 100%
20–29 days	N %	0 0.0%	4 100%	4 100%
30 or more days	N %	1 7.7%	12 92.3%	13 100%
Total	N %	23 44.2%	29 55.8%	52 100.0%

Discharged against medical advice		Completed treatment regimen		Total
Discharged against medical advice (AMA)		no	yes	
no	N % AMA	4 17.4%	26 89.7%	30
yes	N % AMA	19 82.6%	3 10.3%	22
Total	N	23 100%	29 100%	52

USA and Iran.^{19,34–36} Due to the voluntary nature of participation in the protocol, it is beyond the scope of this study to identify the reasons for early termination of detoxification episodes. Other studies have identified associated factors, including younger age, longer use of opioids and availability of a post-detoxification plan,^{34,36} which may apply here.

While not an end, detoxification serves as a transitional period where opioids are discontinued, and the opportunity created for recovery. The mean length of stay for completed episodes was 30.34 days, almost seven times that of incomplete episodes. When considered alongside our finding that 10.3% of completed episodes were associated with discharge against medical advice as opposed to 82.6%, we can conclude that our protocol is effective.

While efforts were made to counter the limitations inherent in the design of this study, the small number of events, absence of females, and not using objective scales to measure withdrawal symptoms, limit the generalisability of our results.

Conclusion

Opioids were responsible for 76% of substance-related death in 2015² and only one in six people received effective treatment for their substance use disorder globally due to unavailability of services in 2016. This retrospective EHR review provides preliminary evidence of the safety and effectiveness of an opioid withdrawal protocol using cheap, readily-available over the counter medications. Given existing barriers to other established protocols in certain parts of the world, it offers a potentially financially, socially and culturally more acceptable option than other regimens. Further studies with more robust designs that evaluate the loperamide P-Glycoprotein modulator complex are necessary to confirm the results of this study.

Declaration of interests

No conflicts of interest were declared.

Dr Al Garhy is a Consultant Psychiatrist, Ms Williams is a Mental Health and Research Nurse, Dr Mohan is a Psychiatric Specialist, Ms Hana Abu Sharib is an Informat-ics Nurse, all at Sheikh Khalifa Medical City, UAE.

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