Journal of the Malta College of Pharmacy Practice

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Instructions to Authors
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I am a Pharmacist

I am a specialist in medications
I supply medicines and pharmaceuticals to those who need them.
I prepare and compound special dosage forms.
I control the storage and preservation of all medications in my care.

I am a custodian of medical information
My library is a ready store of drug knowledge.
My files contain thousands of specific drug names and tens of thousands of facts about them.
My records include the medication and health history of entire families.
My journals and meetings report advances in pharmacy from around the world.

I am a companion of the physician
I am a partner in the case of every patient who takes any kind of medication.
I a consultant on the merits of different therapeutic agents.
I am the connecting link between physician and patient and the final check on the safety of medicines.

I am a counsellor to the patient
I help the patient understand the proper use of prescription medication.
I assist in the patient's choice of non-prescription drug or in the decision to consult a physician.
I advise the patient on matters of prescription storage and potency

I am a guardian of public health
My pharmacy is a centre for health care information.
I encourage and promote sound personal health practices.
My services are available to all at all times.

This is my calling. This is my pride

Anon

Evolution of JMCPP

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This edition of the Journal of the Malta College of Pharmacy Practice marks it as the first environment friendly paperless edition. The Journal evolved from a humble newsletter called the Chronic*ill*. The first newsletter consisted of a total of 16 pages and included 4 educational articles. The first paragraph of the 'Editorial' read as follows: *'The Malta College of Pharmacy Practice was officially founded on the 31st July 1996. Prior to this date, The College had been providing continuing education courses for one and a half years on a trial basis.'*

The next edition of the newsletter featured a poem by an anonymous author entitled 'I am a pharmacist' which is reproduced on the opposite page of this editorial as it is an elegant description of a pharmacist.

By the summer of 1999 The Chronic*ill* evolved into a Journal with a formidable number of continuing education papers, not much different than it is today. Since then the Journal has gone from strength to strength attracting both local and leading international authors from various disciplines. We have always seen this as very positive since one of our aims has always been to encourage interdisciplinary communication and to enable different professions to understand each other's 'language'. To further commit to this aim the paper edition of the Journal has always been freely distributed to all pharmacists and medical doctors in Malta.

Another of our aims was to encourage our highly capable pharmacists to contribute with papers which were of current relevance to our society. Our objective has always been to respond to the educational needs of pharmacists and other professionals in practice within our healthcare system. We have always welcomed suggestions to improve our Journal and the overall voluntary educational service which we offer.

The website of the Malta College of Pharmacy Practice, www.mcppnet.org, was first available in 2003 and that year the Journal became freely available on the web transforming it into an open access journal; yet another milestone for both the College and the Journal.

The last issue of the Journal as The Chronic*ill* was a special supplement on respiratory disease. Following this issue, in 2005, the Chronic*ill* became The Journal of the Malta College of Pharmacy Practice. The Journal has attracted papers from all areas of practice and has given a voice to different patient groups. The 2008 issues supported the Pharmacy Council by publishing the Code of Ethics for the Pharmaceutical Profession. The 2007 special issue which focused on nutrition remains highly relevant today and has been recently quoted by the Minister of Education. Our last paper edition, a special issue dedicated to gender in health care, aimed at encouraging practioners and researches to integrate gender aspects in their work. This is an area which is being given considerable importance by the European Union as evidenced by the Gendered Innovations project.

We trust that our readers will find the current issue interesting and relevant to their practice.

I would like to take this opportunity to thank the members of the editorial board of the Journal of the Malta College of Pharmacy Practice and the Council of The Malta College of Pharmacy Practice for their commitment and dedication to the College.

Medicines management in the palliative care of cancer patients

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Educational aims

- To provide information on the conventional and off licence use of medicines
- To provide the rationale behind choices of drug treatment of common symptoms
- To update on the precautions to be taken with respect to different medicines and highlight recent drug safety issues
- To empower pharmacists to be more active in the education and support of palliative care patients and their carers

Key words
Palliative care, pain, constipation, nausea and vomiting, oropharyngeal complications

Abstract

Cancer is one of the leading causes of death in Malta. Palliative care is a mainstay in the care of such patients. Commonly encountered symptoms include pain, nausea and vomiting, constipation and oropharyngeal complications. All of these bear an impact on the quality of life of the patient and also of the carers. Drug treatment is an integral part of the management of these symptoms. Patients and their carers may have concerns regarding their medication. The community pharmacist is well positioned and competent to support the needs of these patients as part of their holistic care.

Introduction

Palliative care involves the care of patients with advanced terminal disease, taking a holistic approach to dealing with issues that patients and their relatives encounter in their day-to-day activities.

This paper specifically focuses on palliative care for cancer patients. During 2014, 932 (or 28.5%) of the total number of deaths registered in Malta were due to cancer, with people over the age of 65 years accounting for almost 75% of cancer deaths. Over 80% of these deaths occurred in hospital, just under 10% at their residence and another 6% in care homes.[1] This paper will focus on the control of common symptoms - pain, nausea and vomiting, constipation and oropharyngeal complications. The general principles of such management can be applied to other advanced non-malignant conditions with terminal outcomes, such as neurological disorders. However cancer patients remain the main beneficiaries of such care offered both in hospital as well as the community.

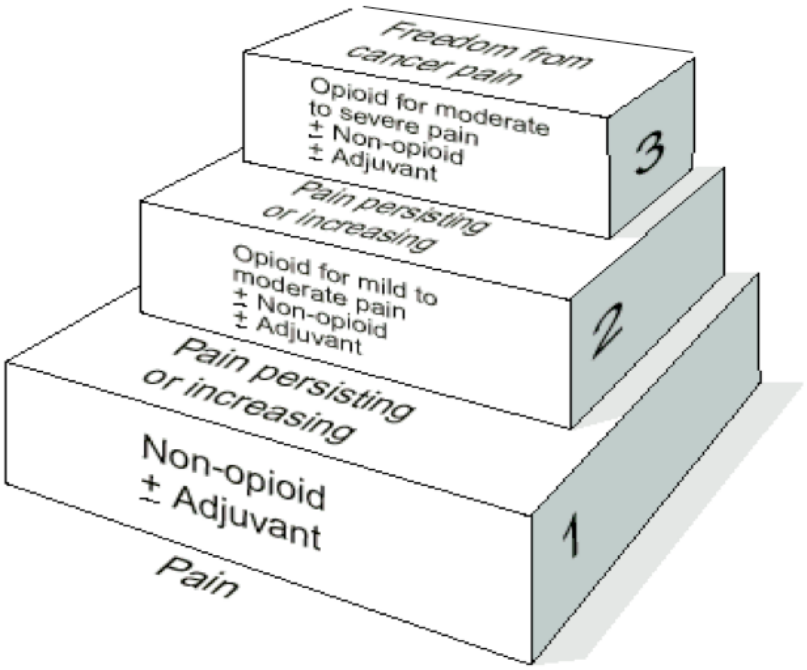
Hospice for terminally ill patients has been established for over 150 years, with the first hospice founded in France back in 1842. During the past 50 years the concept of hospice has developed rapidly to also include care outside the hospital environment.[2]

This article does not focus on the "terminal phase", last few days or hours of life, where an increased level of care is required. During this phase, symptoms such as pain, nausea and constipation change little in prevalence but additional symptoms such as asthenia, dry mouth, confusion and breathlessness may take priority. During this phase the need for drug treatment including the routes by which drugs are administered requires careful evaluation. In such a setting clinical pharmacists' intervention in medicines management goes beyond drug reviews and will require particular expertise with regards to mixing of parenteral medicines and their subsequent stability.

Panel 1: WHO definition of palliative care

"The active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families."

Figure 1: WHO Pain Relief Ladder[4]



Management of cancer pain

Pain is a frequent symptom in patients with cancer, with substantial impact on their quality of life. Despite the availability of opioid analgesics and updated guidelines, under treatment is still frequently encountered.[3] Careful assessment of the patient, including factors that aggravate or relieve the pain, is essential if adequate analgesia is to be achieved. Patients also have concerns with regards to side-effects including dependence and addiction. Such misconceptions can lead to refusal of pain relief and a reduction in patients' quality of life. Palliative patients should have adequate pain relief medication and fear of addiction should not restrict adequate pain relief treatment. Counselling is thus an important component in ensuring effective pain management.

Principles of treatment of cancer pain

The World Health Organization (WHO) pain ladder, originally devised for the treatment of cancer pain, is a well established guideline for the management of patients with chronic pain. The analgesic treatment should start with drugs indicated by the WHO analgesic ladder appropriate for the severity of pain. This guideline recommends the use of conventional analgesics including non-steroidal anti-inflammatory drugs (NSAID's), paracetamol and opioids. Opioids are classified into two categories according to their efficacy (strong and weak opioids). Adjuvant analgesics can be used at any step if indicated (Refer to Figure 1).[4]

Step 1: Mild pain - Non-opioid analgesics such as paracetamol or non-steroidal anti-inflammatory drugs are indicated. To improve outcomes, patients should be advised to take their pain relief medication at regular intervals rather than on an "as required" basis.[4,5,6]

Step 2: Mild to moderate pain - A weak opioid (codeine, tramadol), should be used in combination with a non-opioid analgesic. The prescribing of combinations of weak opioids is not recommended. If a patient is not responding to maximum doses of a weak opioid/ non-opioid combination then it is appropriate to move up to step 3.[4,5,6]

Step 3: Moderate to severe pain - Strong opioid analgesics are required. Once a patient is stabilised on a dose of immediate-release opioid, he/she should be switched to the equivalent dose of a modified-release preparation if possible. An immediate-release formulation should also be prescribed on an "as-required" basis for breakthrough pain episodes. The equivalent dose should be approximately 1/6th of the daily dose.[4,5,6]

Measurement of cancer pain

A number of validated pain assessment scales have been developed to enable the making of consistent, repeated assessments. Complex tools such as the McGill pain questionnaire are generally too time-consuming for daily use and simpler scales such as visual analogue scales (VAS), verbal rating scales (VRS) or numerical rating scales (NRS) are routinely used.

The equivalence of each category in the WHO classification of pain intensity on the numerical rating scale and the relevant pharmacological management is shown in Table 1.[5,6]

Drugs used for analgesia

Non-opioids

Paracetamol remains the main non-opioid used for the treatment of cancer pain. Non-steroidal anti-inflammatory drugs (NSAIDs) may also be prescribed. There is no evidence to support the preference of one NSAID over another. Prescribing of NSAIDs should be based on knowledge of the side-effect profile and previous response to individual drugs. NSAIDs should be used with caution in patients with cardiovascular disease. In the presence of gastro-intestinal (GI) risk factors a proton pump inhibitor should be co-prescribed with all NSAIDs including COX-2 inhibitors. The long-term use of NSAIDs

Table 1: Pharmacological management of cancer pain

Pharmacological management		
Mild	**Mild to moderate**	**Moderate to severe**
Numerical rating scale 1-3	**Numerical rating scale 4-6**	**Numerical rating scale 7-10**
Non-opioids Paracetamol NSAID's Non-selective NSAIDs COX-2 selective inhibitors	**Titration of weak opioid** Codeine Tramadol	**Strong opioids** Morphine Fentanyl
	+/- NSAIDs/paracetamol	
+/- adjuvant analgesic		

including COX-2 inhibitors has to be carefully monitored and reassessed periodically because they can provoke severe toxicity such as GI bleeding, platelet dysfunction and renal failure. COX-2 selective inhibitors may increase the risk of thrombotic cardiovascular adverse reactions and do not protect against renal failure.[5,6,7]

Opioids

The opioids are classified as the weak opioids (e.g. codeine, tramadol) and the strong opioids (e.g. morphine, fentanyl).

Prescribing a high dose of a weak opioid can result in an opioid load comparable to a low dose of a strong opioid (i.e., 100mg of codeine is roughly equivalent to 10mg of oral morphine). Weak opioids can have the same adverse effects as strong opioids, so patient counselling should be the same.

A ceiling analgesic effect is observed with weak opioids. Increasing the dose of a weak opioid beyond the maximum licensed dose will not improve analgesia but expose the patient to more pronounced adverse effects. A maximal ceiling analgesic effect is not observed with strong opioids.[5,6,7]

Panel 2: Codeine, dihydrocodeine and tramadol

Codeine is a pro-drug and has to be metabolised to morphine mainly via CYP2D6 liver enzyme in order to have an analgesic effect.[8,9] Up to 7% of Caucasian populations may have a deficiency in CYP2D6 resulting in an inadequate analgesic effect.[9]

Dihydrocodeine is an active substance. It is also a substrate for CYP2D6, however there is no evidence that inhibition of this enzyme reduces analgesic effect.[8]

Tramadol has clinically relevant serotonergic activity. It should be avoided in patients taking TCA and SSRIs due to the risk of serotonin toxicity. It also lowers seizure threshold.[8]

The range of strong opioids available to prescribers locally is limited, with morphine being the most frequent prescribed opioid for the relief of severe pain. At the initiation of treatment or when changing treatment the patient's dose should be titrated until an adequate maintenance dose is reached. Patients should be prescribed maintenance treatment on a regular basis at the appropriate dose which relieves pain throughout the dosing interval without causing unmanageable adverse effects.

The dose should be titrated with caution in patients with risk factors: impaired renal function, impaired hepatic function, chronic respiratory disease, compromised upper airway, sleep apnoea. Dose increments should be based upon total opioid dose taken in the previous 24 hours. The rapidity of the dose escalation should be related to the severity of the symptoms. Opioid switching can also improve response by at least 50 per cent.

The appropriate formulation should be used for maintenance dose. When tolerated, morphine via the oral route of administration should be advocated as first choice, unless the patient is nil by mouth. Transdermal fentanyl patches are a useful option in patients unable to swallow. Patches are also useful in patients with worsening renal function, intolerable side-effects (e.g. intractable constipation) and patients with poor concordance.

Management of breakthrough pain

Breakthrough pain should be managed using short acting medication (refer to Table 2). Typically "as required" doses are calculated as one sixth of the 24 hour oral regular dose given every 4 hours as needed. Whereas this approach is useful for titration of the background opioid dose it may not be appropriate for breakthrough pain characterised by quick onset and short duration.[10]

Table 2: Causes of breakthrough pain and their management

Causes of breakthrough pain	Management
Incidental to specific activities (e.g. dressing change, physiotherapy)	Potentially managed with short-acting opioids given in anticipation of these events
End of dose failure pain	Potentially managed by increasing the dose of regularly scheduled opioid
Uncontrolled persistent pain	Potentially managed by increasing the dose of regularly scheduled opioid

Management of opioid adverse effects

Opioids have a number of adverse effects. The management of these side-effects is an integral part of palliative care (refer to Table 3). Constipation and nausea are the two most commonly encountered side-effects of opioids. The management of such adverse effect involves the prophylactic use of stimulant laxatives and faecal softeners for the duration of opioid treatment plus possibly anti-emetics for the first few days of opioid treatment.[8, 11]

Table 3: Adverse effects of opioids and their management

Adverse effect	Management
Constipation Very common (≥ 1/10)	Stimulant laxative ± stool softener (titrate stool softener/ laxative as needed to get bowel movement every one to two days) If impacted consider phosphate enema Laxatives only treat constipation and can exacerbate other symptoms of opioid-induced bowel dysfunction; they do not address the cause of the problem. For intractable chronic constipation, consider an alternative opioid e.g. switch to fentanyl Ensure adequate hydration
Nausea Very common (≥ 1/10)	Prochlorperazine 10mg qds PRN PO Metoclopramide 10mg-15mg qds PRN PO Haloperidol 0.5mg-1.0mg tds or qds PRN PO Domperidone 10mg tds PO Change PRN to regular if nausea persists
Pruritus Common (>1%)	Antihistamines e.g. promethazine 10mg-20mg bd to tds PO; Hydroxizine 25mg up to qds PO Consider changing to another opioid
Respiratory depression and sedation Uncommon (<1%)	Naloxone can be used in case of respiratory depression. Administer by iv injection, 0.4 -2.0mg, if no response to be repeated at intervals of 2 to 3minutes to a maximum of 10mg. Further doses may be necessary if respiratory function deteriorates. Consider dose reduction of opioid

Adjuvant analgesia

The choice of a category of drugs, or a specific drug for adjuvant analgesia depends on a number of factors including type of pain (i.e. nociceptive or neuropathic), source of pain, co-morbidities and current medication (refer to Table 4). It is quite common to use low starting doses of adjuvants for neuropathic pain. Adjuvants can have opioid-sparing effects and the dose of the opioid should be carefully reviewed as the adjuvant is titrated.[5,11]

Panel 3: Bisphosphonates

About 50% of patients benefit, typically in one to two weeks, and this may last for 2 to 3 months. In those who respond, continue to treat PRN for as long as there is benefit.

Benefits are seen mainly with intravenous bisphosphonates. Bisphosphonates are poorly absorbed when given orally, and this is reduced further by food. Oral bisphosphonates are contra-indicated in patients with oesophageal abnormalities, strictures and achalasia and inability to stay upright for 60 minutes.[11]

Panel 4: Systemic corticosteroids

Systemic corticosteroids are used off-label for pain relief for pain caused by a tumour in a confined organ or body cavity, for example raised intracranial pressure and bone pain. Dexamethasone is the most frequently used corticosteroid for disease suppression.

Cautions with corticosteroids: Diabetes mellitus, psychotic illness. Although there is only a small increase in risk of peptic ulceration with corticosteroids alone, when given concurrently with NSAIDs the risk increases up to 15 times. Prolonged courses of corticosteroids increase susceptibility to infections and their severity.[11]

Table 4: Indications for adjuvant analgesics

Indication	Treatment
Inflammation	Trial of NSAIDs or corticosteroids
Bone	NSAIDs and titrate analgesic to effect Consider trial of bone-modifying agents (bisphosphonates) For diffuse bone pain consider hormonal therapy or chemotherapy, corticosteroids (and/or systemic administration of radioisotopes) For local bone pain consider non-pharmacological interventions such as radiotherapy and nerve block
Neuropathic pain	Tricyclic antidepressants (Amitriptyline and nortriptyline) Anti-convulsants (carbamazepine, gabapentine, pregabaline) Corticosteroids

Management of nausea and vomiting

Nausea and vomiting are common symptoms experienced by patients who are receiving palliative care. The prevalence of such symptoms tends to increase as disease progresses and is estimated to be up to 70% in patients with advanced cancer.[12]

Pharmacological management is the mainstay in treatment of these symptoms; however good health care strategies such as maintenance of oral hygiene and regularising bowel habit should be ensured. Such measures may also help postpone the need for anti-emetics. Where appropriate any reversible causes of nausea and vomiting should be treated.[13]

Optimal emetic control in the acute phase is essential to prevent nausea and vomiting in the delayed phase. Treatment of nausea and vomiting in palliative care cancer patients depends on the cause of the symptoms and patient's preference.

Principles of antiemetic treatment

Antiemetics are to be selected according to the likely cause of emesis. A combination of two or more antiemetics is needed in over 25% of cases of chronic nausea.[14] Drug combinations may be used as long as the drugs chosen do not act on the same receptor. Drug combinations having the same mode of action increase the risk of side-effects without additional clinical benefit.[11,15]

The emetic risk with intravenous chemotherapy is divided into four categories (high, moderate, low and minimal) based on the Grunberg classification. Antiemetics are commenced before chemotherapy, if indicated. Oral doses are to be administered at least 30 minutes before chemotherapy is initiated. Domperidone is usually started on the evening of chemotherapy. Patients who receive highly emetogenic agents receive ondansetron or Aprepitant and dexamethasone as their pre- and post-chemotherapy schedule. For patients who receive chemotherapy with a moderate risk of causing nausea and vomiting the two-drug combination of a $5HT_3$ antagonist (ondansetron) and dexamethasone is recommended. For chemotherapy that carries a low risk of producing nausea, a single dose of dexamethasone is recommended prior to chemotherapy. No antiemetic agent is routinely recommended before or after low risk chemotherapy to prevent nausea and/or vomiting.

For patients who receive high risk radiation therapy a 5 HT_3 antagonist before each radiation fraction, and at least 24 hours after completing radiation therapy is recommended. Patients should also be given a 5 day course of dexamethasone during fractions 1 to 5 of radiation.

Dexamethasone should be prescribed prophylactically when indicated and not as a treatment for emesis. The risk and benefits of the use of steroids in diabetic patients and in patients who are immunosuppressed are to be carefully considered before prescribing. Dexamethasone should be given no later than 2.00pm to minimise wakefulness in the night.[16,17,18]

Drugs used for the treatment of nausea and vomiting

Various classes of drugs are used to control symptoms of nausea and vomiting (Refer to Table 5). The most commonly used drugs are prokinetic agents (e.g. metoclopramide and domperidone) as well as agents acting principally on the chemoreceptor trigger zone (e.g. haloperidol and domperidone). Drugs with prokinetic action are blocked by anticholinergic drugs (example amitriptyline, hyoscine and ondansetron) and thus such combinations are not recommended.[11,15]

Table 5. Medicines used as antiemetics: indications, side-effects and contra-indications

Class	Examples	Indications
Dopamine antagonists	Haloperidol	Mainly used for drug-induced nausea and vomiting
Histamine/ anticholinergic antagonists	Cyclizine	Mainly used when there is raised intracranial pressure, motion sickness or mechanical bowel obstruction.
Serotonin antagonists	Ondansetron	Prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Prokinetics	Metoclopramide Domperidone	Radiotherapy-induced nausea and vomiting as well as for delayed (but not acute) chemotherapy-induced nausea and vomiting.
NK-1 receptor antagonists	Aprepitant	Chemotherapy induced nausea and vomiting and inhibits both the acute and delayed phases of cisplatin-induced emesis. Augments anti-emetic activity of 5HT3 receptor antagonists and Dexamethasone
Corticosteroids (adjuvant use)	Dexamethasone (off-label use)	Adjuvant in the prevention of nausea and vomiting
Antipsychotics *	Levomepromazine (off-label use)	Levomepromazine by injection can be used in terminally ill patients requiring an anti-emetic and a sedative

*Benzodiazepines may be used in the management of nausea and vomiting due to their anxiolytic action.

Panel 5 Antiemetics: drug safety updates

Domperidone [19]	There is a small increased risk of serious cardiac side effects particularly in the elderly, patients on total daily doses of more than 30 mg, or taking QT-prolonging medicines or potent CYP3A4 inhibitors. The cardiac risk profile of domperidone should be taken into account if there is a clinical need to use this drug.
Metoclopramide [20,21]	A recent EU review has confirmed the well known risks of neurological effects such as short-term extrapyramidal disorders and tardive dyskinesia. The review concluded that these risks outweigh the benefits in long-term or high-dose and recommended changes that include a restriction to the dose and duration of use to help minimise the risk of potentially serious neurological adverse effects.
Ondansetron [22,23,24]	Dose- dependent prolongation of QTc interval and cardiac arrhythmia, including Torsade de Pointes, are known risks with ondansetron. Thus caution must be used if administering ondansetron to patients with such risk factors.

Management of constipation in cancer care

Constipation in advanced cancer is generally a multi-factorial issue. It can be affected by the nutritional status of the patient, weakness, the underlying disease and drugs.

Principles of treatment

The aim of drug management is to restore the amount of water in the faeces and improve rectal evacuation.

Traditionally a combination of a bowel stimulant with a faecal softener is used. The concurrent use of several different laxatives is not recommended. Laxative doses should be titrated every couple of days according to response. If the maximum recommended or tolerated dose is not effective, an alternative preparation is to be used.[25]

Rectal products (suppositories or enemas) are sometimes indicated when oral treatment has failed or in patients with specific conditions such as paralysis, frailty or immobility. Rectal products should be avoided in patients who are neutropenic or thrombocytopenic because of the risk of infection or bleeding.[11]

Drugs used for the constipation

Commonly prescribed laxatives include osmotic laxatives (e.g. lactulose syrup and macrogols) and stimulant laxatives (e.g. senna and bisacodyl). Osmotic laxatives retain water in the gut with a subsequent increase in faecal volume. Stimulant laxatives improve intestinal motility by a direct contact with the submucosal and myenteric plexus causing muscle contraction. They also increase water secretion into the bowel lumen.

Management of oropharyngeal complications

Palliative patients, particularly those receiving chemotherapy and/or head and neck radiation may have various oral complications. Such complications can occur as a direct result of malignancies or as a result of the treatment that the patient might have had. Complications include: mucositis, xerostomia (dry mouth), gum disease and tooth decay.[26]

Elimination of oral disease and implementation of oral care protocols designed to maintain maximum oral health must be components of care before, during and after chemotherapy and radiation therapy. Regular, systematic oral care hygiene, including a combination of tooth brushing using a soft-toothbrush, flossing and one or more bland non-medicated oral rinses and moisturisers are to be used to maintain oral hygiene for all cancer treatment modalities.

Ongoing oral assessment and treatment of complications are essential. Nutritional issues as well as drug administration should also be considered. The alterations of formulations of oral medication (tablet crushing, capsule opening) to assist patients with swallowing difficulties are in most cases unlicensed.

Treatment of oropharyngeal complications

Oral ulceration (mucositis)

Simple mouthwashes e.g. 0.9% saline can be soothing, help maintain oral hygiene and prevent secondary infection. Advising to use at a tepid temperature may be more soothing. Alcohol-based mouth rinses should be avoided.

Protecting the ulcerated area by coating agents are of limited value because they can be difficult to apply and they do not relieve persistent inflammatory pain.

As mucositis severity increases and topical pain management strategies become less effective, it becomes increasingly necessary to depend on systemic analgesics to manage oral radiation mucositis pain. Pain relief in the form of topical analgesics is available in various formulations including gels, sprays and oral rinses. These formulations include anaesthetics and NSAIDs. Benzydamine mouthwash (an NSAID) can be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy) without concomitant chemotherapy. Topical anaesthetics or other agents should be considered to promote oral comfort and provide short-term pain relief.

Antimicrobial lozenges should not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer. [27,28]

Xerostomia (dry mouth)

Saliva helps maintain a healthy balance of bacteria in the mouth. Without saliva pathogenic organisms can colonise the mouth. This can cause sores and mouth infection, including thrush that is caused by an overgrowth of yeast. Saliva also washes away acids and food particles left in the mouth after eating, which means that a lack of saliva can cause gum disease and cavities. Dry mouth may make it difficult to wear dentures.

Chemotherapy and radiation treatments cause dry mouth by damaging the salivary glands. Chemotherapy causes dry mouth by making saliva thicker, which is usually a temporary symptom that clears up about 2 to 8 weeks after treatment ends.

Dry mouth can also be a side-effect of treatment with certain medicines including antidepressants, diuretics and some analgesics. Other causes of dry mouth include mouth infections such as thrush and dehydration.[29]

The underlying cause should be treated, where possible. Unless a main salivary duct is blocked, a saliva stimulant is preferable. Chewing gum is useful. When advising on chewing gum a sugar free brand should be recommended. In addition a low tec brand is more suitable in patients with dentures.

Artificial saliva is a poor substitute for natural saliva. Artificial saliva with a neutral pH is an option for patients who cannot tolerate saliva stimulants. Pilocarpine (a muscarinic agent) is indicated for xerostomia after radiotherapy for head and neck cancer. After radiotherapy, up to 3 drops of 4% eye drops tds (equivalent to 6mg tds) can be administered. This is off-label use of the eye drops, pilocarpine tablets are not available locally.[11]

Oral candidiasis

Oropharyngeal candidiasis is a common oropharyngeal complication in palliative care patients, ranging from 13 to 30%. This may increase during head and neck radiation therapy and in patients who receive concurrent chemotherapy.[30]

Treatment of candidiasis

Topical antifungal agents such as nystatin or clotrimazole can be effective. These can be presented as gels or drops. In order to increase the contact time of the drug with the mucosa, food should not be taken immediately after drugs have been administered.

Patients using dentures should remove the denture before using a topical antifungal agent and should also treat the dentures to avoid repeat colonisation.[11]

For moderate to severe infections and persistent lesions, systemic agents such as fluconazole are preferred. Patients who receive oral antifungals should be asked to avoid eating, drinking or rinsing for at least 30 minutes after use.[11]

Preparations for the topical treatment of oral complications

There are various preparations for the topical treatment of oropharyngeal complications, including the use of off-label and extemporaneously prepared medicines (Table 6).[31]

Table 6: Topical therapies used for oral conditions

Preparation	Therapy	Recommended dose	Precautions
Saline mouthwash	Oral hygiene	Frequent intervals	Made up with warm water
Chlorhexidine 0.2% mouthwash (with alcohol)	Topical antiseptic	10ml rinsed in mouth for one minute twice a day	Alcohol-based mouth rinses should be avoided in mucositis and dry mouth
Chlorhexidine 0.2% alcohol free mouthwash	Topical antiseptic	10ml rinsed in mouth for one minute twice a day	Alcohol free preparation is to be used where there is oral ulceration
Benzydamine 0.15% mouthwash	Topical anti-inflammatory NSAID. Used for the relief of post-radiation mucositis	10-15ml rinsed in mouth every 1.5-3 hours when required. Not usually longer than seven days duration	Only used in patients aged 13 years and older
Benzydamine 0.15% oro-mucosal spray		Four to eight sprays applied to affected area every 1.5-3 hours	None relevant
Orabase	Mucoadhesive	Used as required	None relevant
Hydrocortisone mucoadhesive buccal tablets	Topical corticosteroid	2.5mg tablet dissolved slowly in the mouth four times a day	Increased risk of candidiasis
Beclometasone 50mcg inhaler (unlicensed indication)	Topical corticosteroid	50 – 100mcg twice daily on the oral mucosa	Increased risk of candidiasis
Lidocaine 5% ointment	Local anaesthetic	Rub sparingly and gently on affected area	Avoid prolonged use. Avoid anaesthesia of the pharynx before meals due to risk of choking
Choline salicylate dental gel	Analgesic for mild oral and perioral lesions	Apply gel with gentle massage. Not more often that every 3 hours	Contra-indicated in children under 16 years of age
Artificial saliva Spray Gel	Treatment of dry mouth	To be applied as required	

Administration of medication to patients with swallowing difficulties

Patients or their carers may attempt to modify the medication without seeking advice from a health care professional. Pharmacists are competent to advise and optimise treatment in such situations. Although, in many cases, the modification of drugs (crushing of tablets, opening of capsules) is unlikely to cause harm to the patient evidence supporting this practice is currently limited. Certain medication such as modified release tablets, enteric coated tablets, hormonal and cytotoxic preparations should never be crushed or opened. The tampering with such medication may compromise the safety of the patient or the carer. Formulation tampering is in most cases unlicensed by the manufacturer.

Liquid formulations still remain the first choice alternative for solid dosage forms in patients who retain some ability to swallow. Alternative formulations that avoid the need of swallowing e.g. patches and oro-dispersable formulations are increasingly being made available.

Panel 6: Cytotoxic tablets - do not crush

All health care workers should avoid contact with cytotoxic drugs and hormones (e.g. methotrexate and tamoxifen). There is a risk of cytotoxic powder being aerosolized if cytotoxic tablets are crushed, exposing care workers to hazardous materials.

Conclusion

The pharmacist is in a strategic position to provide holistic care for palliative care patients and their carers. When dispensing and counselling about medicines pharmacists should consider the rationale behind choices of drug treatment. Aspects of patient behaviour which affect concordance should be given appropriate consideration. Pharmacists can support seamless care by improving access to medication, carrying out medication reviews and bridging communication between different health care professionals, patients and their carers.

Acknowledgements

Malta National Mortality Registry, Directorate of Health Information and Research

Oncology Services, Sir Anthony Mamo Oncology Centre

References

1 National Mortality Registry, Malta, Directorate of Health Information and Research (accessed June 2015)

2 Franco DC, Heidi B, Javier R. The development of palliative medicine in Europe. In: Bruera E, Higginson IJ, Ripamonti C, Von Gunter CRC, editors. Textbook of Palliative Care. 1st ed. Florida: CRC Press; 2009.

3 Greco MT *et. al.* Quality of cancer pain management: an update of a systematic review of under treatment of patients with cancer. Journal of Clinical Oncology 2014; 20 32(36): 4149-4154. Accessed January 2015, http://www.ncbi.nlm.gov/pubmed/25403222

4 World Health Organisation. WHO cancer pain relief. Geneva: World Health Organisation; 1996. Accessed January 2015, www.who.int/cancer/palliative/painladder/en/

5 European Society for Medical Oncology. Clinical Practice Guideline 2012, Management of Cancer Pain. Lugano, Switzerland: European Society for Medical Oncology; 2012. Accessed January 2015 www.esmo.org/guidelines/Supportive-Care/Management-of-Cancer-Pain

6 National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, Adult Cancer Pain. Version 2.2014. Pennsylvania, USA: NCCN- National Comprehensive Cancer Network; 2014. Accessed January 2015, www.**nccn**.org/professionals/physician_gls/pdf/**pain**.pdf

7 Dickman A. Pain in palliative care: a review. The Pharmaceutical Journal 2007; 278: 679 – 682.

8 *Electronic Medicines Compendium*. Summary of Product Characteristics for codeine, tramadol, buprenorphine, morphine, fentanyl. UK: Datapharm. Electronic Medicines Compendium. Accessed January 2015, https://www.medicines.org.uk/emc/

9 Persson K et. al. The postoperative pharmacokinetics of codeine. Eur J Clin Pharmacol 1992; 42:663-666.

10 Dickman A. Basics of managing breakthrough cancer pain. The Pharmaceutical Journal 2009; 283: 213-216.

11 Twycross R et. al. Palliative care formulary September 2014. Version 5, 2014. Nottingham: Nottingham University Hospitals; 2014.

12 Harris DG. Nausea and vomiting in advanced cancer. British Medical Bulletin 2010; 96: 175- 185. Accessed April 2015, http://bmb.oxfordjournals.org/content/96/1/175.full

13 Kelly B and Ward K. Nausea and Vomiting in Palliative Care. Nursing Times 2013; 109 (39):16-19. Accessed April 2015, http://www.nursingtimes.net/Journals/2013/09/27/k/t/h/021013-Nausea-and-vomiting-in-palliative-care.pdf

14 Christie Hospital NHS Trust. Guidelines for managing nausea and vomiting. 2006.

15 Chand S. Nausea and vomiting in palliative care. The Pharmaceutical Journal 2014; 292: 240-247. Accessed April 2015, http://www.pharmaceutical-journal.com/learning/learning-article/nausea-and-vomiting-in-palliative-care/11135047.article

16 Kris MG et. al. Consensus recommendations for the prevention of vomiting and nausea following high emetic risk chemotherapy. Support Care Cancer. 2011; 19(Supp 1): S25 – S32.

17 Herrstedt et. al. Acute emesis: moderately emetogenic chemotherapy. Support Care *Cancer* 2011; 19(Supp 1): S15 – S23.

18 Olver I et. al. Guidelines for the control of nausea and vomiting with chemotherapy of low or minimal emetic potential. Support Care Cancer. 2011; 19 (Suppl 1): S33-S36.

19 Medicines and Health Care Products Regulatory Agency, UK. Drug Safety Update volume 7 issue 10, May 2014: A1

20 Medicines and Health Care Products Regulatory Agency, UK. Drug Safety Update volume 7 issue 1, August 2013: S2.

21 Medicines and Health Care Products Regulatory Agency, UK. Press Release by European Medicines Agency recommends changes to the use of metoclopramide-26/07/13.

22 Medicines and Health Care Products Regulatory Agency, UK. Drug Safety Update volume 6 issue 1, August 2012: A2.

23 Medicines and Health Care Products Regulatory Agency, UK. Drug Safety Update volume 6 issue 12, July 2013: A3.

24 Medicines and Health Care Products Regulatory Agency, UK. Drug Safety Update volume 7 issue 1, August 2013: 03.

25 Bunn R et.al. Management of constipation in palliative care. Pharmaceutical Journal 2009; 282:711-714.

26 National Cancer Institute. Oral complications of chemotherapy and head/neck radiation (PDQ) (2014). Accessed May 2015, http://www.cancer.gov/cancertopics/pdq/supportivecare/oralcompliations/HealthProfessional

27 Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. Annals of Oncology 2011; 22 (Suppl 6): vi78 – vi84. Accessed May 2015, http://www.cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/

28 Lalla RV et al. MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy. Cancer 2014

29 Cancer.Net. Navigating Cancer Care 2014. Accessed May 2015, http://www.cancer.net/navigating-cancer-care/side-effects/

30 Davies AN et. al. Oral candidosis in patients with advanced cancer. Oral Oncology 2006; 42: 698 – 702.

31 Thakrar J. Treatment of complex oral lesions. Clinical Pharmacist 2014; 6(6). Accessed June 2015, www.pharmaceutical-journal.com/publication/clinical-pharmacist/treatmentofcomplexorallesions

Key points

- Patients should be treated adequately for pain relief. Chronic pain should be treated with analgesics given at regular intervals and 'as required' medication for break through pain.
- Use of opioids should not be restricted due to fear of addiction to opioids.
- In additional to conventional analgesics, adjuvant medication is sometimes indicated in order to improve pain control. Such medication can have opioid-sparing effects.
- Opioids reduce bowel tone and contractility, predisposing patients to constipation. A combination of a faecal softener plus a stimulant laxative should be prescribed prophylactically on starting treatment with opioids.
- There are various causes of nausea and vomiting in palliative cancer patients and treatment of these symptoms will depend on their cause and the patient's preference.

Questions

1 In 2014 less than a quarter of deaths registered in Malta were due to cancer.

2 Dihydrocodeine is a prodrug which requires hepatic activation before an analgesic effect is achieved.

3 Tramadol is safe to use in patients with epilepsy.

4 Generally patients prescribed an opioid should also be prescribed a stimulant laxative and a faecal softener.

5 Therapeutic use of morphine should be restricted in palliative care patients because drug dependence is a commonly encountered problem in such patients.

6 Domperidone is contraindicated in patients with underlying cardiac conditions.

7 A combination of anti-emetic drugs with the same mode of action is indicated if symptom control is not achieved with a single agent.

8 Patients using dentures should remove the denture before using topical antifungals and should also treat the dentures to avoid repeat colonisation.

9 Alcohol-based mouth rinses should be avoided in patients with oral ulceration.

10 Crushing of tablets containing cytotoxic medication should be avoided.

Over-the-counter weight loss preparations

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Key words
Weight-loss products, citrus arantium, conjugated linoleic acid, garcinia cambogia, guarana, green tea extract, orlistat

Educational aims

- To provide an overview of the main constituents present in commonly used over-the-counter (OTC) weight loss preparations available in Malta to enable a more knowledge based selection
- To increase awareness on the efficacy and safety of weight loss preparations
- To highlight the limitations of data available on such products

Abstract

Obesity has been described as a pandemic as it is estimated to contribute to more than 3 million deaths worldwide.[2] In Malta 28.7% of the population is obese and another 67.6% is classified as overweight.[3, 4] This paper will be provide a summary of systematic reviews and meta-analysis of some common ingredients in weight loss preparations available in local pharmacies.

Introduction

Weight loss is in theory very simple: one needs to use up more calories than one consumes. It is documented that to lose one pound (0.45 kilogram) of body weight there needs to be a negative balance of 3,500 kilocalories (kcal).[1] However, in reality cutting down excess calories or increasing calorie expenditure via exercise might prove to be very difficult. Most community pharmacists can confirm this by the number of clients asking for recommendations on weight loss preparations. As most of the over-the-counter (OTC) weight loss preparations available on the market in Malta are classified as food supplements reliable data is lacking. In this paper the author has consulted systematic reviews and meta-analysis of randomised clinical trials of a few common ingredients in weight loss preparations available in Malta.

Citrus Aurantium

Citrus aurantium or bitter orange has been studied for weight loss as its primary constituent is p-synephrine. P-synephrine which is similar in structure to ephedrine is thought to increase basal metabolic rate and lipolysis as well as acting as a mild appetite suppressant. Unfortunately, most of the data on p-synephrine is clouded by the lack of reproducibility and poorly standardized extracts used. In a review of 23 rigorous studies published in the International Journal of Medical Science it was established that bitter orange extract and p-synephrine increase metabolism and energy expenditure and may contribute to modest weight loss if taken for up to 12 weeks in combination with dietary and exercise regimens. The loss in body weight ranged from 1.04 to 4.63 kg in the study period but the data was for preparations where citrus aurantium was only one of the ingredients.[5] Side-effects commonly associated with ephedrine such as high blood pressure and palpitations are not to be expected with p-synephrine as it has receptor binding specificities. Again, more rigorous studies are required to determine dose and duration to be recommended for significant weight loss.[5]

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is a collection of isomers of linoleic acid, a polyunsaturated omega 6 fatty acid which is commonly found in dietary sources such as egg yolk, animal

fats and a number of oils such as peanut oil and olive oil. Animal studies have suggested that CLA has an effect on body composition and in most species it was found to reduce body fat. This data fuelled research into human studies in the hope that results would be reproducible. In a meta-analysis published in 2007 which included 20 human studies, the authors concluded that CLA causes a limited reduction in fat of about 0.09 kg weekly, around 1 kg every 3 months. This loss was not reproducible in all studies because efficacy is highly dependent on factors such as type of isomer used, dose and duration. It has been recommended that preparations enriched in *c*9, *t*11, and *t*10, *c*12 isomers are preferable. Although CLA is generally safe, its use in patients with chronic conditions such as diabetes should be monitored more closely as CLA has been reported to increase insulin resistance.[6] In another meta-analysis published three years ago, which included only studies with at least 6 months duration, the authors revealed a small significant difference in fat loss favouring CLA over placebo. The loss was of 0.7kg which was thought by the authors to be too small to have a clinically relevant effect on long term body composition. Adverse events reported in this review included constipation and diarrhoea.[7] Therefore although CLA is relatively safe and has a beneficial effect, this may be too low to justify its cost.

Garcinia Cambogia

Garcinia Cambogia is a tropical fruit high in hydroxycitric acid (HCA). There are various claims on how HCA actually causes weight loss, most of which come from animal studies. The most popular is that HCA inhibits the enzyme adenosine triphosphatase-citrate-lyase, which in laymen's terms is the fat producing enzyme. Others report that HCA increases the release or availability of serotonin in the brain, thus leading to appetite suppression. Other theories on its mechanism of action include the inhibition of pancreatic alpha amylase and intestinal alpha glucosidase responsible for carbohydrate metabolism. In a systematic review published in *Journal of Obesity*, the authors concluded that the overall efficacy is minimal to be of clinical relevance when taking into consideration well-designed human studies.[8] It is also still undetermined what the recommended dose should be as it varied significantly from 1 g to 2.8 g daily[8]. Duration of treatment is also uncertain and could be limited by adverse effects such as gastrointestinal disturbances and headaches. In summary, it seems that although some studies have shown that HCA may generate weight loss, this is too minimal for recommending it to the general public and more research is necessary.

Green Tea Extract with or without Caffeine

There are numerous catechins found in green tea extract, the most important of which is believed to be epigallocatechin gallate (EGCG) which is involved in the inhibition of adipocyte differentiation and proliferation, reduced fat absorption, inhibition of catecho-o-methyl transferase, increased energy expenditure and increased utilization of fat.[9] It also has natural caffeine which has been reversibly associated with weight gain probably due to its known thermogenic effects and increase energy expenditure.[10] In a systematic review and meta-analysis which evaluated data from 15 trials it was reported that over a 12-week period those who ingested a median of 588mg daily of green tea catechins (GTCs) with caffeine compared with dose who drank caffeine alone had a statistically significant weight loss of around 1.38kg and an average reduction in waist circumference of 1.93 cm. A statistically significant 0.44 kg weight loss was observed in a group of individuals ingesting GTC with caffeine compared to a caffeine free control group. These results seem to indicate that there is synergism between GTC and caffeine, as studies evaluating GTC administration on its own showed no benefits in weight loss. Safety concerns with GTCs are minimal; although there were some reports of liver dysfunction, these were not sustained when investigated for short-term use.[9] Yet the authors of this meta-analysis stated that despite the significant results, for pharmacologic weight loss products, patients are considered to have failed treatment if they have not achieved a loss of 2 kg after 4 weeks of therapy,[9] which as one can deduce, is well beyond the results provided with GTC and caffeine administration.

Guarana

Guarana is a plant which contains caffeine, theophylline and theobromide and thus has been incorporated as a stimulant into weight loss and nutritional supplements as it enhances athletic performance and reduces mental and physical fatigue.[11] There are no studies which have looked at the isolated effect of guarana however there are studies in combination with yerba mate, Ma Huang (ephedra) and Damiana. In a small study in combination with Ma Huang, it was found that over an eight-week period, subjects had an average weight loss of 4 kg compared to the group receiving placebo, with minimal adverse symptoms reported. In a double-blind randomised trial study investigating a product containing extracts of Yerba Mate, Guarana and Damiana for 45 days, researchers reported a weight loss of 5.1 kg compared with only 0.3 kg in the group given placebo. In a post-marketing research, a small group of 48 patients were followed up for 28 days and self-reported a mean loss of 2.3 kg in body weight.[12] Although the loss in weight was significant the sample size were small and thus it is difficult to extrapolate the data to the general population, yet at least this combination seems to have some potential.

Orlistat

Orlistat is a specific, potent and long-acting inhibitor of gastrointestinal lipases. It forms a covalent bond with around 30% of the active serine site of gastric and pancreatic lipases inactivating them so that they are unavailable to hydrolyse dietary fat into absorbable free fatty acids and monoglycerides.[13] Orlistat was originally marketed as a prescription only medicine (POM) but a few years later the reduced dose was available as an OTC preparation. In 2003 a Cochrane meta-analysis which included eight randomized double blinded trials revealed that the drug was modestly effective in promoting weight loss.[14] An update review published a few years later concluded that orlistat was associated with a weight loss of around 3% more than diet alone in overweight and obese people. Orlistat 120mg administered three times daily contributed to a 2.7 kg weight loss more than diet alone. The period of time over which this loss was observed was not specified. In a 2014 meta-analysis which pooled data from 45 studies reported that patients on orlistat 120mg three times daily had a mean loss of 2.34 kg whereas patients on 60mg or 30mg three times daily had a mean loss of 0.7 kg. This loss was maintained after 18 and 36 months. Adverse events reported with orlistat are directly related to its mode of action and refer to gastrointestinal events.[15] Orlistat was also studied in patients with type-2 diabetes and non-alcoholic fatty liver disease (NAFLD) with good preliminary results of

improvement in glycaemic control, lower cholesterol and blood pressure values.[16] It is suggested that orlistat is only cost effective in those achieving at least 5% weight loss after 3 months[16] and this is the same threshold the company adopts for cessation of treatment.[13]

Conclusion

Most of the products available locally seem to contain different dosages of a number of the above mentioned ingredients, some even combined with other ingredients. It is difficult to say whether combining such ingredients would have an additive or synergistic effect or whether this would mean having more significant adverse events. Most of the studies on individual preparations seem to be flawed in their design and usually come from the company marketing the product which introduces an element of bias. As health care professionals we need to offer the correct advice being mindful that the product may provide minimal benefit

Key points

- To lose one kilogram (kg) in body weight there has to be a deficit of approximately 7,000 kilocalories.[1]
- Most weight loss products available on the market lack rigorous evidence to back up their claims.
- Weight loss products should always be recommended as an adjunct to healthy diet and regular exercise.
- Low-dose orlistat is the only OTC preparation approved by the Food and Drug Administration and the European Medicines Agency available in Malta.
- Extra caution needs to be taken in patients who are overweight or obese and who have additional co-morbidities such as diabetes and cardiovascular events, since most of the products reviewed below have not been investigated in these populations.

References

1 Thomas DM, Martin CK, Lettieri S, BrelauC, Kaiser K, Chruch T, Bouchard C, Heymsfield SB. Can a weight loss of one pound a week be achieved with a 3500-kcal deficit? Comentary on a commonly accepted rule. Int J Obes (Lond) 2013;37:1611-1613

2 World Heart Federation. Obesity: a growing danger. 2010 http://www.worldobesity.org/site_media/uploads/Factsheet_Obesity.pdf Accessed 13 June 2015

3 World Health Organisation. Global Health Observatory Data Repository. 2014. http://apps.who.int/gho/data/view.main.2450C?lang=en Accessed 25 October 2015

4 World Health Organisation. Global Health Observatory Data Repository. 2014 http://apps.who.int/gho/data/node.main.A897C?lang=en Accessed 25/10/2015Stohs SJ, Preuss HG, Shara M.

5 A review of the human clinical studies involving Citrus aurantium (bitter orange) extract and its primary photoalkaloid p-synephrine. Int J Med Sci 2012;9:527-538

6 Whigham LD, Watras AC, Schoeller DA. Efficacy of conjugated linoleic acid for reducing fat mass: a meta-analysis in humans. Am J Clin Nutr 2007;85:1203-1211

7 Onakpoya IJ, Posadzki PP, Watson LK, Davies LA, Ernst E. The efficacy of long-term conjugated linoleic acid (CLA) supplementation on body composition in overweight and obese individuals: a systematic review and meta-analysis of randomized clinical trials. European Journal of Nutrition 2012;51:127-134

8 Onakpoya I, Hung SK, Perry R, Wider B, Ernst E. The use of Garcicia extract (hydroxycitric acid) as a weight loss supplement: A systematic review and Meta- Analysis of Randomised Clinical Trials. *Journal of Obesity* 2011;1-9

9 Phung OJ, Baker WL, Matthews LJ, Lanosa M, Thornes A, Coleman CI. Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis. Am J Clin Nutr 2010;91:73-81

10 Onakpoya I, Terry R, Ernst E. The use of green coffee extract as a weight loss supplement: A systematic review and meta-analysis of randomised clinical trials Gastroenterology Research and Practice. 2011;2011:382582

11 Ruxton CHS, Garder EJ. A review of the efficacy and safety of key ingredients of over-the-counter products for weight management. British Food Journal 2205;107:111-125

12 Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen G, Solomon JL. An herbal supplement containing Ma Huang-Guarana for weight loss: a randomized, double blind trial. Int J Obes Relat Metab Disord 2011;25:316-24

13 Specific Product Characeristics – Orlistat. http://www.medicines.org.uk/emc/medicine/1746 Accessed 12 June 2015

14 Padwal R, Li SK, Lau DC Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2003;(4):CD004094

15 Drew BS, Dixon AF, Dixon JB. Obesity management: Update on Orlistat Vasc Health Risk Manag. 2007 Dec; 3(6): 817–821

16 Dumbrowski SU, Knittle K, Avenell A, Araujo=Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. BMJ 2014;348:g2646

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Hyponatraemia: Is it clinically relevant?

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Educational aims

- To highlight the importance of treating hyponatraemia, even if chronic and not associated with obvious clinical features
- To increase familiarity with the common causes and diagnosis of hyponatraemia
- To update the knowledge on management of hyponatraemia including the use of novel drug therapy

Key words
Hyponatraemia, hypotonic hyponatraemia, Syndrome of inappropriate antidiuresis, demeclocycline, vaptans.

Abstract

Hyponatraemia, defined as a sodium concentration <135mmol/l, is the most common electrolyte imbalance encountered in clinical practice. Symptoms can range from seemingly asymptomatic to severe and even life-threatening. Hyponatraemia is usually managed by clinicians from various fields, leading to a wide variety of approaches to its diagnosis and treatment.

Introduction

Hyponatraemia is the commonest electrolyte imbalance in clinical practice. It is defined as a sodium concentration of less than 135mmol/l. In 2014, Clinical Practice Guidelines[1] on the diagnostic approach and treatment of hyponatraemia were published as a joint venture of 3 major European societies representing specialists with a natural interest in hyponatraemia. The American recommendations on diagnosing, evaluating and treating hyponatraemia[2], published in 2013, are similar in many aspects, but they do differ in others, especially in management. This article reviews the diagnosis and management of hyponatraemia according to the European Clinical practice guidelines, highlighting any discrepancies between the European and American views.

Pathophysiology

Hyponatraemia is primarily a disorder of water balance, with a relative excess of body water compared to total body sodium and potassium content. The major mechanisms responsible for regulating water metabolism are thirst and the pituitary secretion and renal effects of arginine vasopressin (AVP; antidiuretic hormone, ADH). When serum osmolality starts to rise, osmoreceptive neurons located in the anterior hypothalamus detect a decrease in cell stretch which in turn leads to increased thirst and increased release of AVP from the posterior pituitary gland.[3]

In the left atrium, carotid sinus and aortic arch, there are stretch-sensitive receptors (baroreceptors) that sense circulating volume. When the volume decreases, afferent neural impulses decrease and AVP secretion increases[4]. AVP, then, regardless of the stimulus, binds to the AVP V2 receptor subtype in the collecting duct of the kidney and activates the signal transduction cascade resulting in antidiuresis, with urine being more concentrated.

Classification of hyponatraemia

There are three classifications of hyponatraemia based on:

1 Severity;
2 Symptoms;
3 Rate of development.

The first classification is based on the level of serum sodium, with cut-offs below 125mmol/l regarded as profound, levels

between 125 and 129mmol/l moderate and levels above 130mmol/l being mild.

Symptoms can range from seemingly asymptomatic, with subtle clinical findings such as a gait disturbances, falls, mild cognitive deficits[5] and osteoporosis to more severe. In one study, the prevalence of hyponatremia in a group of patients with a verified bone fracture was significantly higher than a control group who had no history of bone fracture[6]. In another study it was found that the occurrence of all forms of hyponatraemia on admission were associated with increased in-hospital mortality and added pressure on the hospital's limited resources. Moderately severe symptoms include confusion, nausea or headache whereas severe symptoms may include vomiting, seizures or coma. Symptoms are very non-specific, so a diagnosis of hyponatraemia should not rely on symptoms alone.

The third classification is based on the time of development, with 48 hours being the cut-off for differentiating acute from chronic. This classification is based on the fact that in the presence of hypotonic hyponatraemia, water shifts from the hypotonic extracellular to the intracellular compartment across an osmotic gradient, causing brain oedema. This is associated with the severe symptoms of hyponatraemia. This seems to occur more frequently when hyponatraemia develops in less than 48 hours because the brain has had too little time to adapt to its hypotonic environment. After 24 to 48 hours, the brain reduces the number of osmotically active particles within its cells, mainly potassium and organic solutes in an attempt to restore brain volume.[8]

Pitfalls in diagnosis

Once biochemical hyponatraemia is confirmed, non-hypotonic hyponatraemia should be excluded. One of the commonest causes is hyperglycaemia. When solutes which are impermeable to the cell membrane are present in excess in the extracellular compartment, an osmotic pressure gradient is created across the cell membranes, leading to osmotic movement of water from the intracellular to the extracellular compartment. This causes dilutional hyponatraemia with a water shift from the intra to the extracellular compartment, so posing no risk of brain oedema.

Pseudohyponatraemia is a laboratory artefact that occurs when an abnormally high concentration of serum lipids or proteins interfere with the accurate measurement of sodium[9].

Differentiating causes of hypotonic hyponatraemia

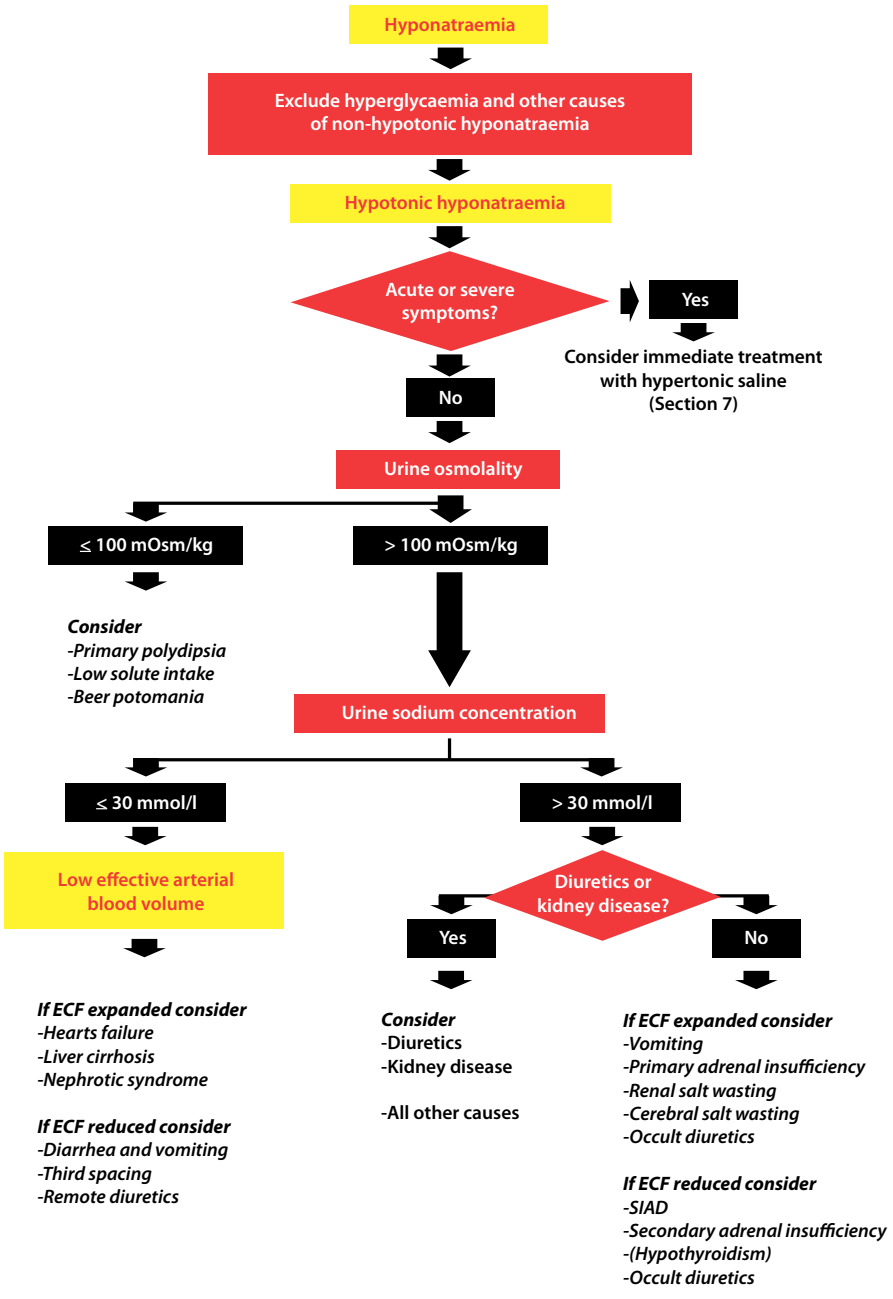
Once hypo-tonic hyponatraemia is confirmed, measurement of a spot urine osmolality and sodium will help diagnose the cause of hyponatraemia (**Figure 1**).

Treatment of hypotonic hyponatraemia

Acute and/or symptomatic hyponatraemia

If hyponatraemia is associated with symptoms, treatment should be initiated immediately and this involves the infusion of 3% hypertonic saline. Hypertonic saline is listed as a high alert medication by the institute for safe medication practice (ISMP)[10]. Such drugs bear a heightened risk of causing significant patient harm when used in error. Preparing this infusion takes time and meticulous

Figure 1: Clinical practice guideline on diagnosis and treatment of hyponatraemia



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attention should be taken to avoid errors when calculating the required amount of sodium chloride. Administration of hypertonic saline should be done in environments where strict clinical and biochemical supervision can be undertaken.

Rate of correction of sodium is of utmost importance and the recommended rate of increase in serum sodium concentration is of a total of 10mmol/l during the first 24 hours and an additional 8mmol/l per day thereafter until sodium concentration reaches 130mmol/l[1]. More rapid correction of serum sodium may lead to osmotic demyelination syndrome (ODS). This is a neurological disease caused by severe damage to the myelin sheath of nerve cells in the brain, which has serious neurological sequele[11]. Patients who are at increased risk of developing ODS include, alcohol abusers, patients with liver disease, use of thiazides or antidepressant medication, serum sodium <105mmol/l and hypokalaemia. In such patients, special caution should be taken in correcting their hyponatraemia.

Chronic hyponatraemia

In this scenario, the focus should be on trying to identify and treat the precipitating factor, rather than treating the hyponatraemia per se.

Chronic hyponatraemia with reduced extracellular fluid volume

In these scenarios, intravenous infusion of 0.9% sodium chloride or any crystalloid should be infused and cause-specific treatment started (Figure 1). In patients with haemodynamic instability, the need for rapid intravenous fluid resuscitation may override the risk of an overly rapid increase in sodium concentration. Cause specific treatment should be initiated as soon as the precipitating factor is identified.

Chronic hyponatraemia with normal extracellular fluid volume

Syndrome of inappropriate antidiuresis (SIAD)

Syndrome of inappropriate antidiuresis is a syndrome in which production of AVP is independent of the stimuli described above. (Figure 1) It results either from an increased release by the pituitary, or an ectopic source or from an increased sensitivity of the collecting duct to vasopressin. **Table 1** defines the diagnostic criteria for diagnosing SIAD. Common causes for SIAD include:

- Malignancies especially lung and gastrointestinal;
- Pulmonary diseases;
- Central nervous system associated diseases;
- Drugs **(Table 2)**;
- Idiopathic.

Treatment includes fluid restriction as first line. Other options for treatment include high solute intake with urea but this should be combined with sweet-tasting substances to mask the bitter taste of urea. Other treatment options include vasopressin receptor antagonists (vaptans) and Demeclocycline.

In the United States[2], vaptan use may be considered in select circumstances, namely, an inability to tolerate fluid restriction or predicted failure of fluid restriction. In normal physiological states, AVP binds to V2 receptors in the collecting duct and an intracellular cascade is activated, resulting in the collecting duct being more permeable to water, thus retaining more water. Vaptans bind to these V2 receptors, blocking the action of AVP, thus rendering the collecting duct less permeable to water. This leads to an increased urine output which is solute-sparing, in contrast to loop diuretics which block sodium transporters, leading to simultaneous electrolyte and water loss. For this reason, the vaptans have been termed *aquaretics*.

In one systematic review, vaptans were found to increase serum sodium concentration modestly, but there was no

Table 2: Drugs associated with SIAD

Psychiatric drugs	Selective serotonin reuptake inhibitors (SSRIs)
	Tricyclic
	Monoamine oxidase inhibitors (MAOIs)
	Antipsychotics
Anticonvulsants	Carbamezapine
	Sodium valproate
	Lamotrigine
Chemotherapy	Vincristine
	Vinblasitne
	Cyclophosphamide
Antidiabetic drugs	Chlorpropamide
	Tolbutamine
Others	Opiates
	Interferon
	Proton pump inhibitors
	Non-steroidal anti-inflammatory drugs (NSAIDS)
	Amiodarone
Vasopressin analogues	Desmopressin
	Oxytocin
	Terlipressin
	Vasopressin

Table 1: Criteria for diagnosis SIAD

Serum osmolality <270mOsm/kg
Inappropriate urine osmolality >100mOsm/kg
Renal sodium >30mmol/l
Euvolaemia
Normal renal, adrenal, and thyroid function

significant reduction in risk of death[12]. Also the risk of rapid increase in sodium was 2.5 times higher than when treated with placebo (relative risk 2.52, 95% CI 1.26-5.06). However there were no reports of osmotic demyelination syndrome. Tolvaptan, one of the vaptans, was studied in patients with autosomal dominant polycystic kidney disease[13] and the tolvapan treatment group was noted to have an elevation of alanine aminotransferase greater than three times the upper limit of normal. But doses administered in these patients were higher than those used in hyponatraemia.

Demeclocycline is a tetracycline derivative and it causes a form of nephrogenic diabetes insipidus, irrespective of the serum AVP level[14]. Treatment must be continued for several days to achieve maximal diuretic effect and dose should not be increased before 3-4 days have passed. Side effects of this drug include azotaemia, photosensitive skin rash and sometimes nephrotoxicity, especially in patients with cirrhosis. Therefore, renal function should be monitored on a regular basis.

Chronic hyponatraemia with expanded extracellular fluid volume

In these conditions, diuretic therapy and dietary sodium restriction form the mainstay of therapy[2]. Fluid restriction may compliment this. Vaptans may be used in a subset of patients in whom hyponatraemia is limiting diuretic use or in whom there are mild symptoms thought to be due to hyponatraemia[2]. The European Guidelines are more cautious in the use of vaptans, and in fact recommend against their use (See Figure 1) [1].

Key points

- Hyponatraemia is associated with a wide range of non-specific clinical symptoms and even if chronic and seemingly asymptomatic, it may be associated with increased morbidity.
- Acute symptomatic hyponatraemia, especially with a serum sodium of less than 125mmol/l, should be managed promptly and under close supervision.
- 3% hypertonic saline may be used in such patients with great care, both in preparation and administration.
- Vaptans may be useful in a selected proportion of patients.

Conclusion

Treatment of acute hyponatraemia can be life-saving in some circumstances, although care should be taken to avoid correcting hyponatraemia too rapidly. Vaptan use may become a cornerstone in the treatment of hyponatraemia in the near future, although more data regarding its safety is awaited.

Reference:

1 Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, Van der Veer S, Van Biesen W, Nagler E. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014: 17:3 G1-G47.

2 Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis , Evaluation, and treatment of Hyponatraemia: Expert Panel Recommendations. AJM. 2013: 07:006

3 Verbalis JG. Disorders of body water homeostasis. Best Practice & Research. Clin Endocrinol Metab. 2003 Dec: 17(4):471-503

4 Robertson GL. Thirst and vasopressin function in normal and disordered states of water balance. J Lab Clin Med.1983; 101: 351-371.

5 Renneboog B, Musch W, Vandemergel X, Manto M, Decaux G. Mild chronic hyponatraemia is associated with falls, unsteadiness and attention deficits. AJM. 2006; 119: 71.el-71.e8.

6 Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM. 2008; 101: 583–588.

7 Wald R, Jaber BL, Price LL, Upadhyay A & Madias NE. Impact of hospital associated hyponatraemia on selected outcomes. Arch Intern Med. 2010; 170:294-302

8 Adrogue HJ, Madias NE. Hyponatraemia. NEJM. 2000; 342: 1581-1589.

9 Turchin A, Seifter JL, Seely EW. Clinical problem-solving. Mind the gap. NEJM. 2003; 349: 1465-1469.

10 ISMP list of high alert medications in acute care setting [Internet]. Horsham: Institute for Safe Medication Practices (ISMP); c2015 [updated 2015; cited 2015 Nov 13]. Available from: http://www.ismp.org/Tools/institutionalhighAlert.asp

11 Cluitmans FH, Meinders AE. Management of severe hyponatremia: rapid or slow correction? AJM. 1990; 88: 161–166.

12 Rozen-Zvi B, Yahav D, Gheorghiade M, Korzets A, Leibovici L & Gafter U. Vasopressin receptor antagonists for the treatment of hyponatraemia: systematic review and meta-analysis. AJKD. 2010; 56: 325-337.

13 Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. NEJM. 2012; 367: 2407-2418.

14 DousaTP, Wilson DM. Effect of demethylchorotetracycline on cellular action of antidiuretic hormone in vitro. Kidney Int. 1974; 5: 279-284.

Heart failure in the paediatric age group

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Educational aims

- To have a better understanding of heart failure in children
- To be familiar with the main causes of heart failure in children
- To be updated on the treatment of heart failure in this age group

Key words

Heart failure, Diuretic, Child, Heart Failure/therapy, Angiotensin-Converting Enzyme Inhibitors, Preschool, Cardiac Surgical Procedures, Infant.

Abstract

Heart failure is uncommon in childhood but its recognition is naturally important. Causes vary, but the commonest are congenital heart disease as well as infections/cardiomyopathy. The main presentation is shortness of breath on exertion and in babies, this may manifest as the inability to complete a feed, along with an elevated respiratory rate. The most commonly used drugs are diuretics, and angiotensin converting enzyme inhibitors, as well as calorific supplementation. The vast majority of patients with heart failure are infants with congenital heart disease and fortunately, treatment for these patients is excellent with very high survival rates.

Introduction

The main presentation is shortness of breath on exertion. In babies, this may manifest as the inability to complete a feed, along with an elevated respiratory rate.[4]

Congenital heart failure

Congenital heart disease leading to heart failure in infancy is usually due to a left to right shunt inside the heart. This may be caused by a hole between the two ventricles (ventricular septal defect - VSD), or a persistently patent arterial duct between the aorta and the pulmonary artery (patent ductus arteriousus – PDA). Since the pressures on the left side (all chambers: atria, ventricles and aorta) exceed those on the right side, blood shunts from left to right, flooding the lungs with an excessive volume of blood, hence the breathlessness. Even at rest, these individuals have a high respiratory rate. Lower limb oedema is not relevant and not found in this age group.

Because of the physiological way in which pressure in the lungs fall after birth, large shunts manifest as above, in heart failure, at about six weeks of age. Treatment of heart failure is usually surgical, at this age, but medications are very useful in these babies to stabilize and relieve symptoms until then.[5]

Management

Heart failure is initially treated with a diuretic to decrease preload by promoting natriuresis, and to provide relief of volume overload symptoms such as pulmonary and peripheral oedema. Loop diuretics are used first, usually furosemide. Bumetanide is a more potent diuretic and is usually reserved for more severe or furosemide-resistant fluid overload. Furosemide is generally supplemented with spironolactone, an aldosterone antagonist which reduces urinary potassium loss, making it particularly suitable for use in conjunction with furosemide. In children up to 12 years, furosemide is usually prescribed in syrup form at a dose of 0.5 - 2 mg, 12 -hourly or 8-hourly, depending on the patient's age. Spironolactone, is generally prescribed, also in syrup form at a dose of 1 - 2 mg /kg/ day in neonates and up to 3 mg/kg/day in infants and children up to 12 years; the daily dose is given in 1 - 2 divided doses.[6]

If this is insufficient to control heart failure, such that, for example, the baby is

not thriving well due to the shortness of breath, an angiotensin converting enzyme inhibitor is added to the treatment. Captopril is usually the drug of choice and this is generally combined with the loop diuretic alone.[7]

Additional helpful treatment includes calorific supplementation of feeds and if feeds cannot be taken, babies can be helped by nasogastric tube feeding. Naturally, once surgery is over, all medications are tailed off. A pharmacological issue that often arises is that some of these medications may not be imported and may be therefore need to be extemporaneously prepared by the hospital pharmacy.[6]

Heart failure in older children

Children may also present in heart failure acutely at an older age, and the commonest cause is viral myocarditis. For example, presentation may be a few days after a coryzal illness. Treatment is as outlined above but the only medication which improves long term prognosis is an angiotensin converting enzyme inhibitor. If not tolerated, e.g. if a dry persistent cough develops, an angiotensin receptor blocker may be used. A third of these children recover completely and their medications are stopped. A third recover partially and may remain on an angiotensin converting enzyme inhibitor. A third will never recover at all, developing dilated cardiomyopathy, and may remain on treatment until organ replacement is arranged. This assumes they survive the disease and its complications until a donor is found.[8]

A rarer presentation is that of de-novo dilated cardiomyopathy which may be familial. Treatment is also as outlined above.[9]

Conclusion

All in all, the vast majority of patients with heart failure are infants with congenital heart disease and fortunately, treatment for these patients is available and is excellent with very high survival rates.[1]

Key points

- Heart failure is uncommon in childhood but recognition is important.
- Commonest causes are congenital heart disease and cardiomyopathy.
- Presentation is tachypnoea and shortness of breath on exertion and poor feeding in babies.
- The most commonly used drugs are diuretics and angiotensin converting enzyme inhibitors.
- Calorific supplementation and nasogastric tube feeding may also be required.

References

1 Rossano JW, Shaddy RE. Heart failure in children: etiology and treatment. J Pediatr. 2014;165:228-33

2 Bajcetic M, Uzelac TV, Jovanovic I. Heart failure pharmacotherapy: differences between adult and paediatric patients. Curr Med Chem. 2014;21:3108-20.

3 Bergmann KR, Kharbanda A, Haveman L. Myocarditis And Pericarditis In The Pediatric Patient: Validated Management Strategies. Pediatr Emerg Med Pract. 2015;12:1-22.

4 Barata IA. Cardiac emergencies. Emerg Med Clin North Am. 2013;31:677-704

5 Kantor PF, Lougheed J, Dancea A, McGillion M, Barbosa N, Chan C, Dillenburg R, Atallah J, Buchholz H, Chant-Gambacort C, Conway J, Gardin L, George K, Greenway S, Human DG, Jeewa A, Price JF, Ross RD, Roche SL, Ryerson L, Soni R, Wilson J, Wong K; Children's Heart Failure Study Group. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. Can J Cardiol. 2013;29:1535-52.

6 Horrox, F. Manual of Neonatal and Paediatric Congenital Heart Disease. New York: Wiley; 2002.

7 Strobel AM, Lu le N. The Critically Ill Infant with Congenital Heart Disease. Emerg Med Clin North Am. 2015;33:501-18

8 Miller JR, Eghtesady P. Ventricular assist device use in congenital heart disease with a comparison to heart transplant. J Comp Eff Res. 2014;3:533-46.

9 Skrzynia C, Berg JS, Willis MS, Jensen BC. Genetics and heart failure: a concise guide for the clinician. Curr Cardiol Rev. 2015;11:10-7.

How will personalised medicine change public health practice?

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Educational aims

- To increase awareness about the growing applications of personalised medicine
- To appreciate the tensions between public health practice and personalised medicine
- To gain an understanding of the manner in which personalised medicine can act as a bridge between public health practice and clinical medicine

Key words
Personalised medicine, public health practice, public health genomics, prevention, screening.

Abstract

Personalised medicine is challenging core elements of public health practice to bring about a paradigm shift. Traditional public health activities such as prevention, screening programmes, infectious diseases control, financing and planning of health systems will all be affected by developments in genomics. There is a need to move away from the traditional high-risk versus population approach debate and to engage with concepts of population stratification and public health genomics. Public health through its activities of surveillance, needs assessment, education and policy advocacy has a critical role to play in shaping the entry of personalised medicine into health systems.

Introduction

This article explores how personalised medicine is challenging core elements of public health practice to bring about a paradigm shift in the organisation of public health services and health care systems.

Personalised medicine is defined as "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis and treatment of disease".[1] Personalised medicine is increasingly being used to develop custom-tailored individualised treatments in the field of oncology and rare diseases but also raises hopes of successful treatments for common illnesses such as cardiovascular disease, diabetes and mental disorders. A closely related approach known as 'stratified medicine' allows decisions to be made for sub groups of people depending on their genetic risk profile. Such concepts are increasingly being portrayed as the future for clinical diagnostic and therapeutic medicine.[2] However some authors have raised ethical issues[3] and others have called for personalised medicine to move away from focussing on targeted treatment for specific organ disease and to embrace personalised medicine as the holistic treatment of the whole person.[4,5] The fact that personalised medicine and stratified medicine have emerged from a focus on the genetic material of individuals or sub groups of people sharing the same characteristics may mistakenly lead one to assume that they bear no relevance to public health practice. Indeed, the World Health Organisation defines public health as "all organised measures (whether public or private) to prevent disease, promote health and prolong life among the population as a whole. Its activities aim to provide conditions in which people can be healthy and focus on entire populations, not on individual patients or diseases". Should public health practice be concerned with personalised medicine when the scope of activities for public health is typically at population level, while personalised medicine deals with individuals? Some public health pioneers recognised the importance of engaging with genetics and genomics early on.[6] Now, as genomics starts to develop a role in common chronic illness prevention and treatment, there is a need for contributions from public health to become more visible.[7] Public health practice will not

be able to ignore the impact of genomics and will need to take into account the concepts of population stratification.[8]

Discussion

Prevention strategies

The debate on the merits of the individual high-risk versus population-based approaches that characterised preventive epidemiology in the second half of the 20th century[9] has returned in full force, fuelled by the advances being made in genetics and genomics. It has been proposed that the traditional one-size-fits-all approach to disease prevention, diagnosis, and treatment would be progressively replaced by a more individualized and tailor-made approach.[10]

Tobacco prevention and control strategies provide an interesting example. In no other policy area has public health been so effective in advocating for an approach that is based on strong regulation with measures that aim to protect the whole population such as taxation and smoke free public places. Genetic and neuroscience research continues to enhance our understanding of addiction and tobacco dependence yet it is not known how best to integrate genetic information about a complex phenomenon like smoking into traditional public health population-based approaches. An empirical study of stakeholder perspectives found that whilst public health approaches remain the preferred vehicle for tackling tobacco, individualised treatment programmes through pharmacogenomics were viewed as useful complementary mechanisms to support individuals provided that sufficient evidence about their effectiveness becomes available.[11] Unsurprisingly, this study found that clinicians were far more open to the possibility of using genetic information to underpin tobacco prevention and control strategies than public health practitioners.

The way in which knowledge of genetic predisposition can affect attitudes to prevention is an important factor for public health strategies. A study amongst persons with Type 2 diabetes found that persons felt less responsible for their Type 2 diabetes if they received information about their genetic predisposition and this information also affected attitudes towards prevention.[12] This is relatively unexplored territory and has important implications for all persons involved in preventive work.

Screening programmes

The genetic basis for public health screening programmes is associated with neonatal screening. Developments in the genomics field are expected to shape the future of other screening programmes in areas such as cancer and familial hypercholesterolaemia.[13]

Cancer screening programmes are an important, if somewhat controversial, area of public health practice. While population-based programmes are commonly available in many countries for breast, cervical and colorectal cancer, the developments taking place in the area of genomics could allow screening for cancers not previously feasible. One such example is ovarian cancer, where genetic testing for germline mutations associated with higher risk is becoming increasingly affordable and offers an opportunity to identify higher risk women irrespective of known family history. Screening for familial breast cancer in younger women than those traditionally targeted in population based screening programmes is another key development. There is some evidence to indicate that women would be ready to participate in such screening programmes.[14] Stratified screening based on genetic testing is a new approach to prevention. Various organisational issues would need to be considered before it could be introduced. Potential issues that arise and would need to be addressed include how the offer of screening would be made, making sure consent is adequately informed, how individuals' risk would be assessed, the age at which risk estimation should occur, and the potential use of genetic data for other purposes.[15] Inter-country differences in the genetic profiles could also provide an explanation for the varying success rates between population based screening programmes and would need to be taken into account when determining the feasibility of establishing stratified screening programmes.

Infectious diseases

The 2009 influenza pandemic exhibited a wide spectrum of disease ranging from very mild to fatal. Traditional factors such as age, comorbidities and being immunocompromised failed to explain the variations observed. Several lines of evidence suggest that different populations have disparate degrees of susceptibility and that host variation in key genes associated with the appropriate immune response could play an important role in determining the outcome of infection. Genomics applied to infectious disease epidemiology, prevention and control has important implications to identify which populations or subgroups may be at highest risk of severe infection and target limited amount of countermeasures or vaccine to those at highest risk.[16]

Funding innovative treatment

The use of genotyping to predict outcomes and determine the most appropriate candidates for treatment has been well established in the field of oncology. More recently expensive treatment for hepatitis C can be carefully planned through the use of genotype testing to predict outcomes.[17] Such applications are important in the management of health systems that have to deal with competing demands on highly limited resources for the financing of innovative therapies. There is a need for public health tools such as health technology assessment to be adapted for evaluations on effectiveness of personalised medicine early on in the development stage.[18] Finer targeting of treatment for persons who truly demonstrate a capacity to benefit may radically alter fundamental public health concepts such as 'numbers needed to treat'. The call for new methods of financing personalised medicines requires strong public health stewardship.[19]

Conclusion

Balancing the aspirations for personalised medicine with public health approaches in fiscally constrained health systems will not be an easy task but could be facilitated through a strong medicine – public health partnership.[20] The extent to which genomics will change public health practice depends on the willingness of the public health community to embrace genomics. The areas of practice within the public health impact pyramid developed by Frieden[21] provide an alternative manner of envisioning the positioning of public health genomics[13] that goes beyond the dichotomous high-risk versus population approach which is unhelpful to take

forward the relationship between public health and personalised medicine. The scope of public health practice is sufficiently wide such that within it, it is possible to identify sectors such as screening, where public health genomics is already challenging and modifying the population-based approach. In other sectors such as tobacco control, personalised medicine at present does not realistically present feasible options to overturn established models of prevention and control. Public health practitioners have an important role to play at multiple levels in influencing the development and uptake of personalised medicine. The need to ensure that public health genomics and personalised medicine finds its way into public health teaching, research and practice cannot be underestimated if public health is to evolve to meet the needs and challenges facing society in the 21st century. Equally public health through its activities of surveillance, needs assessment, education and policy advocacy has a critical role to play in shaping the entry of personalised medicine into health systems such that the basic values of equity, utility and efficiency, underpinning welfare-based health systems, prevail. Indeed it is possible that the introduction of personalised medicine into health systems may become the bridge across the often separate worlds of medicine and public health.

Key points

- Personalised medicine is challenging core elements of public health practice.
- Prevention, screening and infectious diseases activities may need to take population stratification into account.
- Public health is not antagonistic to personalised medicine but has an important role to play in shaping the entry of personalised medicine into health systems.
- Personalised medicine may become the bridge between the specialities of medicine and public health.

References

1 US National Library of Medicine National Institute of Health. Definition of Personalized Medicine. 2015; Available at: http://ghr.nlm.nih.gov/glossary=personalizedmedicine. Accessed 31/07/15, 2015.

2 Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med 2010;363(4):301-304.

3 Vollmann J. 5 Personalised medicine: priority setting and opportunity costs in European public health care systems. The Voices and Rooms of European Bioethics 2015:43.

4 Patel V. Rethinking personalised medicine. The Lancet 2015;385(9980):1826-1827.

5 Varmus H. Ten years on—the human genome and medicine. N Engl J Med 2010;362(21):2028-2029.

6 Brand A, Brand H, in den Bäumen, Tobias Schulte. The impact of genetics and genomics on public health. European Journal of Human Genetics 2008;16(1):5-13.

7 McGrath BB. Advancing the post-genomic era agenda: contributions from public health. Public Health Genomics 2012;15(3-4):125-131.

8 Zimmern RL, Khoury MJ. The impact of genomics on public health practice: the case for change. Public Health Genomics 2012;15(3-4):118-124.

9 Rose GA, Khaw K, Marmot M. Rose's strategy of preventive medicine: the complete original text. : Oxford University Press; 2008.

10 Budin-Ljosne I, Harris JR. Ask not what personalized medicine can do for you--ask what you can do for personalized medicine. Public Health Genomics 2015;18(3):131-138.

11 Dingel MJ, Hicks AD, Robinson ME, Koenig BA. Integrating genetic studies of nicotine addiction into public health practice: stakeholder views on challenges, barriers and opportunities. Public Health Genomics 2012;15(1):46-55.

12 Davies LE, Thirlaway K. The influence of genetic explanations of type 2 diabetes on patients' attitudes to prevention, treatment and personal responsibility for health. Public Health Genomics 2013;16(5):199-207.

13 Bowen MS, Kolor K, Dotson WD, Ned RM, Khoury MJ. Public health action in genomics is now needed beyond newborn screening. Public Health Genomics 2012;15(6):327-334.

14 Meisel SF, Side L, Fraser L, Gessler S, Wardle J, Lanceley A. Population-based, risk-stratified genetic testing for ovarian cancer risk: a focus group study. Public Health Genomics 2013;16(4):184-191.

15 Dent T, Jbilou J, Rafi I, Segnan N, Tornberg S, Chowdhury S, et al. Stratified cancer screening: the practicalities of implementation. Public Health Genomics 2013;16(3):94-99.

16 Keynan Y, Malik S, Fowke KR. The role of polymorphisms in host immune genes in determining the severity of respiratory illness caused by pandemic H1N1 influenza. Public Health Genomics 2013;16(1-2):9-16.

17 Zhang L, Gwinn M, Hu DJ. Viral hepatitis C gets personal--the value of human genomics to public health. Public Health Genomics 2013;16(4):192-197.

18 Lal JA, Schulte In den Baumen T, Morre SA, Brand A. Public health and valorization of genome-based technologies: a new model. J Transl Med 2011 Dec 5;9:207-5876-9-207.

19 Horne R, Bell JI, Montgomery JR, Ravn MO, Tooke JE. A new social contract for medical innovation. Lancet 2015 Mar 28;385(9974):1153-1154.

20 Khoury MJ, Gwinn M, Burke W, Bowen S, Zimmern R. Will genomics widen or help heal the schism between medicine and public health? Am J Prev Med 2007;33(4):310-317.

21 Frieden TR. A framework for public health action: the health impact pyramid. Am J Public Health 2010;100(4):590-595.

Medication wastage: the current situation

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Educational aims

- To provide an insight into the current situation regarding medication wastage both at a national level and internationally
- To have increased awareness on the extent of medication wastage and its financial implication
- To understand the need for policy and guidelines in relation to medication wastage

Key words
Delphi, medication, medication wastage, systematic review, unused medication.

Abstract

Reducing any wastage, including that of medication, is an important priority objective at both a national and European level due to the direct and indirect consequeces of wastage. Following an in-depth study, medication wastage has been defined in the Maltese context. This provides a common ground on which to base local policy to address the issue. The extent of medication wastage has been studied and documented in various countries. Yet to date there is still a lack of policy guidance in relation to medication wastage. This paper highlights the available literature in relation to medication wastage and urges the need to further explore and implement wastage reduction strategies.

Introduction

Reducing any wastage has become an important priority objective at both a national and European level.[1] There are several direct and indirect consequences of medication wastage, mainly the economic implications for both the individual and society arising from costs of unused medications, expenses required to dispose of unused medication, costs related to wasted time spent on the supply based activities of prescribing and dispensing as well as environmental implications associated with wastage disposal.[2-4]

Definition of medication wastage

A systematic review of the published literature carried out in 2010,[5] identifying forty-three papers found that only one study defined medication wastage[6] or related terms. This was defined as *"any drug product, either dispensed by a prescription or purchased over the counter (OTC) that is never fully consumed. Medication wastage may be due to poor compliance of patients, excessive and irrational prescribing, or the lack of control of the sales of prescription medications in the community pharmacy."*
A standard definition was later formulated mainly in the Maltese context by applying the Delphi technique amongst a wide range of panel of experts.[7] Medication wastage was defined as:

"Medication wastage refers to any medication which expires or remains unused throughout the whole medicines supply chain. Medication wastage also refers to the unnecessary or inappropriate consumption of medications by patients, or the unjustified non-adherence to treatment guidelines by healthcare professionals. Medication wastage poses a financial burden on patients themselves and the state's economy and requires adequate education of all people concerned."

Medication wastage: The international scenario

The extent of medication wastage has been studied and documented amongst various countries with quantities ranging from 65 unused medication items gathered from 73 households that had at least one oral medication stored[8] to 20,304 medication packages collected from 100 community pharmacies.[9] Tablets and capsules topped the list in terms of wasted formulation , probably since this is the most commonly used.[10-16] Cardiovascular[2,14,17-23] and central nervous

system[4,9,13,24-26] medication were the most commonly wasted followed by medication acting on the gastro-intestinal[27,28] and respiratory system.[29,30] The most commonly wasted medication were from the 'analgesics' category.[4,8,9,11,14,15,18,22,23,24,25,26,29,31,32,33,34]

Amongst studies, cost of medication wastage was estimated as ranging from approximately 66 euro[8] to over 770,000 euro.[35, 36] A study assigned and supported by the Department of Health in England in 2009 explored the scale and cost of medication wastage. The study concluded that direct costs of unused prescription medication to the National Health Service (NHS) amounted to £300 million annually.[37] A very recent report from NHS England, 'Polypharmacy and Medicines Optimisation' also noted that much dispensed medication remains unused or wasted, and these issues are likely to become more prominent as medication regimens become more complex.[38]

Medication wastage: The Maltese scenario

The information available about the extent of medication wastage in Malta can be gleamed through press reports and statements from politicians.

In April 2012, the Times of Malta reported that the Health Minister of the time voiced his concerns about medication wastage, particularly unused medication and *"urged people to act responsibly and to keep in mind that although medicines were given to them free of charge, they were an investment by the government"*.[39] The newspaper added that *"80 different types of medicine worth around €10,000"* had been returned to government pharmacies by members of the public during a three month period with the Health Minister stating that *"this was likely to be only the tip of the iceberg, since many people kept unused medicine at home"*. These medications were not purchased through community pharmacies but dispensed to the public for free through the National Health System (NHS). The Health Minister stated that many people are afraid that if they do not collect the free medication that they are entitled to, they will lose their entitlement. At the time, the shadow Health Minister had commented about the shortage of medication on the NHS formulary leading to wastage: *"On the other hand, about 632 different medicines were out of stock in 2011. In simple words: shortages lead to hoarding, and hoarding leads to unused medicine"*.[40]

Later on that year, in July 2012, the Times of Malta reported that *"just over €29,500 worth of medicines was retrieved from pharmacies in Gozo last month after serious doubts arose as to the ambience in the contractor's carriage of the medicines"*.[41] The newspaper also reported that *"in June there had been €893.32 worth of expired or damaged medicines retrieved, as well as 439.72 worth of medicines for redistribution to other pharmacies"*. In June 2013 The Times of Malta issued another report revealing a total of 455,000 euro worth of expired medication found at the Oncology and Dermatology Hospital in Malta.[42]

The Malta Pharmacy Owners Business section, in January 2014, proposed a reimbursement system for free medications whereby patients pay for the free medications they are entitled to and are then reimbursed, with a pre-credited card for patients who are unable to pay.[43] The Chamber also contemplated a medication charge which should stipulate the maximum refundable amount on each medication. The Health Minister of the time was not in agreement with a reimbursement system.

In April 2014 The Times of Malta issued findings of a survey study carried out by WasteServ, which is the company responsible for waste management on the Maltese islands, which concluded that only a tenth of the Maltese population dispose of expired medication and syringes correctly, by bringing these to the civic amenity sites which cater for the disposal of expired medication amongst other things. WasteServ also added that EU will be sought to launch a nationwide awareness campaign regarding the civic amenity sites and about hazardous waste.[44] Later on in September 2014, The Times of Malta reported three tonnes of medications being disposed in civic amenity sites.[45]

Laws, directives and policies relating to medication wastage

The EU directive '2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste states that 'waste' refers to *"any substance or object which the holder discards or intends or is required to discard"*.[46] The focus of this directive is on management strategies related to issues such as disposal and recycling, with lack of guidance focusing specifically on medication. The Medicines Act of Malta enacted by the Parliament of Malta prohibits the sale of expired or damaged medication, but provides little guidance on the handling of medication wastage and no guidance at all on minimising wastage.[47]

The Environment and Development Planning Act, under the force of the Malta Environment and Planning Authority, issued waste regulations in 2011.[48] Whilst 'healthcare waste' includes medication, this Act provides detail only on the maximum amount and duration of storage of wastage.

Following the accession of Malta into the EU a National Waste Management Plan strategy was prepared stipulating a number of implementation aspects to be addressed but with no consideration to medication.[49]

Factors associated with or contributing to wastage

A number of factors have been attributed to medication wastage, mainly 'medication changed',[2,4,23,24,25,26,32,50,51,52] 'patient death',[2,4,23,26,27,52,53] 'resolution of patient's condition' [24,25,27,32,51,53] and 'expired medication'.[23,24,25,27,52,53] A panel of experts in Malta, identified 61 potential factors which they attributed to medication wastage. The cause leading to medication wastage which achieved the highest level of consensus (96% consensus) was that *"patients are afraid that their medication will be unavailable when they need it"* and therefore they overstock.[7]

Interventions to reduce wastage

A systematic review identified only two studies which reported wastage as a research outcome measure following intervention, both describing community pharmacy instalment dispensing as a potential solution to reduce medication wastage. However, there were no direct measures of reduction in wastage; therefore, reduction in costs in these studies cannot be equated to reduction in medication wastage.[5]

In 2011 the UK Department of Health roundtable event hosted by the King's fund recruited patients, healthcare professionals, the NHS and industry to consider the findings of the afore-mentioned research and to identify measures that might be taken to help minimise wastage, optimise medication taking and improve health outcomes. Following this, the Department of Health Medicines Pharmacy and Industry group UK issued the report 'Making best use of medicines' and stated that *"wastage of medications involves a wide range of different stakeholders who all have a contribution to make to reducing its occurrence and improving quality of care"*.[54] These stakeholders include

manufacturers and suppliers of medications; healthcare professionals, including pharmacists, doctors and nurses, as well as patients and the public. The report also highlighted the fact that costs related to medication wastage are not just financial but should also take into consideration the price a patient has to pay if medications are not used appropriately at the detriment of improved health outcomes. Through the roundtable event a number of initiatives to improve use of medications emerged. The group concluded that not only should the group participants take ownership of the outcomes and benefits of this study, but they should also engage in future discussions. The group also concluded that patients should be encouraged to become more involved with their medication. The group also acknowledged the fact that issues raised during this discussion should become part of the education of healthcare professionals and the implications of these issues need to be considered by the Department of Health in future discussions relating to community pharmacy contractual framework. The group ultimately supported the initiative of a communications campaign to raise awareness of the issues discussed and alter people's behaviour and concluded that any intervention should be carefully planned before being implemented.

Conclusion

This paper clearly highlights that vast resources are consumed by wastage, with a negative consequence on the economy. Moreover, medication wastage continues to compromise public health in terms of safety and the environment. There is therefore an urgent need to further explore and implement wastage reduction strategies.

Key points

- The extent and cost of medication wastage have been documented locally and internationally.
- A standard definition of medication wastage was formulated mainly in the Maltese context by applying the Delphi technique.
- A number of reasons have been attributed as the causative factors giving rise to medication wastage, mainly 'medication changed', 'patient death', 'resolution of patient's condition', 'expired medication'and overstocking due to fear of medication unavailaibility.
- There is a paucity of studies reporting medication wastage as a research outcome measure following intervention to reduce medication wastage.
- There is a lack of policy guidance in relation to medication wastage.

Disposal of Medicines in Malta

The general public can dispose of their expired medicines at one of the Civic Amenity sites of WasteServ Malta Limited which are located at Maghtab, Mriehel, Hal Far, Luqa, Ta' Qali and Gozo. Further information may be obtained from WasteServ Malta Ltd on the Freephone (8007 2200).

References

1 European Commission. Waste. 2015; Available from: http://ec.europa.eu/environment/waste/; Accessed 3rd October 2015.
2 Langley C, Marriott J, Mackridge A, Daniszewski R. An analysis of returned medicines in primary care. Pharm World Sci. 2005;27(4):296–299.
3 Castensson S, Ekedahl A. Pharmaceutical waste: the patient role. Germany: Springer; 2010. P. 179-200. (Kummerer K, Hempel M, editors. Green and Sustainable Pharmacy; 1st ed.)
4 James TH, Helms ML, Braund R. Analysis of Medications Returned to Community Pharmacies. Ann Pharmacother. 2009;43:1631-1635.
5 West LM, Diack L, Cordina M, *et al*. A systematic review of the literature on 'medication wastage': causative factors and effect of interventions. Int J Clin Pharm 2014; 36(5): 873-881.
6 Abou-Auda HS. An economic assessment of the extent of medication use and wastage among families in Saudi Arabia and Arabian Gulf countries. Clin Ther. 2003;25(4):1276-1292.
7 West LM, Diack L, Cordina M, *et al*. Applying the Delphi technique to define 'medication wastage'. Eur J Hosp Pharm 2015;22(5):274-279.
8 Kiyingi KS, Lauwo JAK. Drugs in the home: danger and waste. World Health Forum. 1993;14(4):381–384.
9 Ekedahl A, Wergeman L, Rydberg T. Unused drugs in Sweden measured by returns to pharmacies. JSAP. 2003;20(1):26-31.
10 David BM, Carwardine E, Longmore RB, McDonald C, Page MA. Some results of a campaign for the collection of unused medicines in Perth. AJP. 1979;60:350-353.
11 Garey KW, Johle ML, Behrman K, Neuhauser MM. Economic consequences of unused medications in Houston, Texas. Ann Pharmacoth. 2004;38(7-8):1165–1168.
12 Harris DW, Karandikar DS, Spencer MG, Leach RH, Bower AC, Mander GA. Returned-medicines campaign in Birmingham, 1977. Lancet, 1979;1(8116):599-601.
13 Longmore R, McDonald C, Sunderland B, Kailis S, Marshall C. Examination of a sample from a Medidump campaign in Perth, Western Australia. AJP. 1990;9(5):145-149.
14 Longmore RB, Sunderland VB, Sansom LN. Analysis of a "Medidump" campaign in Australia. IJPP. 1995;3(3):186–191.
15 Subratty AH, Hassed Nathire ME. A survey on home generated medical waste in Mauritius. Int J Environ Health Res. 2005;15(1):45-52.
16 Wongpoowarak P, Wanakamanee U, Panpongtham K, Trisdikoon P, Wongpoowarak W, Ngorsuraches S. Unused medications at home – reasons and costs. IJPP. 2004;12:141–148.
17 Al Siyabi KH, Al Riyami K. Value and types of medicines returned by patients to Sultan Qaboos University Hospital pharmacy, Oman. Sultan Qaboos Univ Med J. 2007;7(2):109-115.
18 Boivin M. The cost of medication waste. Can Pharmaceut J. 1997;130(4):33-39.
19 Grant P. Return of waste medicines to a community pharmacy. Prescriber, 2001;12(4):29–38.
20 Halloran TN, Frewen DB, Frost, BR. An evaluation of the cost of drug wastage in a South Australian community - a pilot study. Aust J Hosp Pharm. 1978;8(3):84-86.
21 Guirguis K. Medications collected for disposal by outreach pharmacists in Australia. Pharm World Sci. 2010;32(1):52-58.
22 Henderson S. Hospital pharmacy: survey of unwanted medicines. PJ. 1984;232:603-5.
23 Mackridge AJ, Marriott JF. Returned medicines: waste or a wasted opportunity? J Pub Health. 2007;29(3):258–262.
24 Braund R, Chuah F, Gilbert R, Gn G, Soh A, Yin Tan L, et al. Identification of the reasons for medication returns. NZFP. 2008;35:248–252.
25 Braund R, Gn G, Matthews R. Investigating unused medications in New Zealand. Pharm World Sci. 2009;3(6):664-669.
26 Hawksworth GM, Wright DJ, Chrystyn H. A detailed analysis of the day to day unwanted medicinal

products returned to community pharmacies for disposal. JSAP. 1996;13(4):215-222.
27 Coma A, Modamio P, Lastra CF, Bouvy ML, Marino EL. Returned Medicines in community pharmacies of Barcelona, Spain. Pharm World Sci. 2008;30(3):272-277.
28 Sweileh WM, Ansam F, Sawalha AF, Zyoud SH, Al-Jabi SW, Bani Shamseh FF et al. Storage, utilization and cost of drug products in Palestinian households. Int J Clin Pharmacol Ther. 2010;48(1):59-67.
29 Abahussain EA, Ball DE. Disposal of unwanted medicines from households in Kuwait. Pharm World Sci. 2007;29(4):368-373.
30 Isacson D, Olofsson C. Drugs up in smoke: a study of caseated drugs in Sweden. Pharm World Sci. 1999;21(2):96–9.
31 Braund R, Yuen Y, Jung J. Identification and quantification of medication returned to Otago pharmacies. NZFP. 2007;34(4):258–262.
32 Morgan TM. The economic impact of wasted prescription medication in an outpatient population of older adults. J Fam Pract. 2001;50:779–781.
33 Pervanas HC, Cooper MR, Robert L. Description of a medication disposal event in a managed care setting. J Pharm Technol. 2010;26:264-270.
34 Wasserfallen JB, Bourgeois R, Bula C, Yersin B, Buclin T. Composition and cost of drugs stored at home by elderly patients. Ann Pharmacother. 2003;37(5):731-737.
35 Zargarzadeh AH, Tavakoli N, Hassanzadeh A. A survey on the extent of medication storage and wastage in urban Iranian households. Clin Ther. 2005;27(6):970–8.
36 European Central Bank. Euro foreign exchange reference rates. 2012; Available from: http://www.ecb.int/stats/exchange/eurofxref/html/index.en.html; Accessed 15 January 2012.
37 York Health Economics Consortium, School of Pharmacy University of London. Evaluation of the scale, causes and costs of waste medicines, 2010; http://eprints.pharmacy.ac.uk/2605/1/Evaluation_of_NHS_Medicines_Waste__web_publication_version.pdf; Accessed 8 February 2011.
38 Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation. Making it safe and sound. The King's Fund, 2013; http://www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/polypharmacy-and-medicines-optimisation-kingsfund-nov13.pdf; Accessed 16 March 2014.
39 Times of Malta. Returned unused medicines are 'tip of the iceberg'. 2012; Available from: http://www.timesofmalta.com/articles/view/20120404/local/returned-unused-medicines-are-tip-of-the-iceberg.414136; Accessed 19 April 2013.
40 Maltatoday. Destruction of 'wrongly stored' unused medicines at taxpayers expense. 2012; Available from: http://www.maltatoday.com.mt/news/national/17453/destruction-of-wrongly-stored-unused-medicines-at-taxpayers-expense-20120414#.VFZjcTd0zIU; Accessed 2 November 2014.
41 Times of Malta. *Gozo medicine is retrieved*. 2012; Available from: http://www.timesofmalta.com/articles/view/20120706/local/Gozo-medicine-is-retrieved.427366; Accessed 2 November 2014.
42 Calleja, C. 'Shame' of health waste. Times of Malta. 2013; Available from: http://www.timesofmalta.com/articles/view/20130612/local/-Shame-of-health-waste.473472; Accessed 25 October 2013.
43 Dalli, M. Malta Chamber proposes 'reimbursement system' for free medicines. 2014; Available from: http://www.maltatoday.com.mt/news/national/33211/malta-chamber-proposes-reimbursement-system-for-free-medicines-20140117#.VEv85TccTIU; Accessed 25 October 2014.
44 Times of Malta. 42% of people never use a civic amenity site – WasteServ. 2014; Available from: http://www.timesofmalta.com/articles/view/20140425/local/42-of-people-never-use-a-civic-amenity-site-wasteserv.516377; Accessed 25 October 2014.
45 Micallef, K. Use of civic amenity sites is now at an all-time high. The Times of Malta. 2014; Available from: http://www.timesofmalta.com/articles/view/20140908/local/Use-of-civic-amenity-sites-is-now-at-an-all-time-high.534800; Accessed 25 October 2014.
46 Directive 2008/98/EC. Directive 2008/98/EC of the European parliament and of the Council of 19 November 2008, *Official Journal of the European Union*. 2008; Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:312:0003:0030:en:PDF; Accessed 23 November 2014.
47 Malta Government Gazette. *Medicines Act*. 2003; Available from: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lp&itemid=16547&l=1; Accessed 19 November 2014.
48 Environment and Development Planning Act Cap. 504. *The waste regulations*. 2011; Available from: http://www.mepa.org.mt/LpDocumentDetails?syskey=1358; Accessed 26 October 2014.
49 Ministry for Resources and Rural Affairs. *A solid waste management strategy for the Maltese islands*. 2009; Available from: https://www.google.com.mt/?gws_rd=ssl#q=A+solid+waste+management+strategy+for+the+Maltese+islands; Accessed 26 October 2014.
50 Abahussain EA, Ball DE, Matowe WC. Practice and opinion towards disposal of unused medication in Kuwait. Med Princ Pract. 2006;15(5):352–357.
51 Braund R, Peake BM, Shieffelbien L. Disposal practices for unused medications in New Zealand. Environ Int. 2009;35(6):952–955.
52 Cook H. Why so many drugs go to waste. PiP. 1996;6(8):268–70.
53 Ekedahl ABE. Reasons why medicines are returned to Swedish pharmacies unused. Pharm World Sci. 2006;28(6):352–358.
54 Department of Health Medicines Pharmacy and Industry Group. Making best use of medicines. 2011; Available from: https://www.gov.uk/government/publications/making-best-use-of-medicines-report-of-a-department-of-health-roundtable-event-hosted-by-the-king-s-fund; Accessed 2 November 2014.