Journal of the Malta College of Pharmacy Practice

Issue 23 2017
ISSN 1811-9514

Malta College of Pharmacy Practice

www.mcppnet.org

Journal of the Malta College of Pharmacy Practice

Issue 23 2017

ISSN 1811-9514

The Official Publication of
the Malta College of Pharmacy Practice
c/o Department of Clinical Pharmacology
and Therapeutics,
University of Malta, Msida
Email: info@mcppnet.org
www.mcppnet.org

Instructions to Authors
Before submitting an article to The Journal of the Malta College of Pharmacy Practice, please read and carefully follow the instructions to authors which are found at www.mcppnet.org

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

What do patients want from their pharmacist?

Maria Cordina B. Pharm (Hons) *Melit.* PhD (QUB)

Editor

Email: president@mcppnet.org

I recently attended a conference where a 'representative' patient was asked to talk about what patients want from the pharmacist. The reply was a very touching and honest one. One which I felt should be shared with the readers of our Journal.

Patients who come to the pharmacy for medication are people who are unwell. In some cases it may be mild but in others their condition may be very serious and having a significantly negative impact on their lives and those of their loved ones. Sometimes it may not be the patients themselves, but their carers who interact with the pharmacist, and they too could be passing through a difficult time. Hence the primary requirement was for the pharmacist to be kind and approachable and not just a person who is an 'expert' and instructs on the use of medication. The pharmacist needs to put the patient at ease, and address their fears and concerns. Some patients who are going through very difficult times may be scared and anxious and need understanding and reassurance.

Having a pharmacist who can communicate effectively was seen a priority. Developing a professional relationship, earning the patients' trust and showing respect towards the patient and their situations would go a long way to supporting the patient and working together to achieve the desired health outcomes.

'I would like the pharmacist to know my name, I want to feel that she/he knows me and understands what I am going through. I want the pharmacist to smile, to listen to me, to talk to me in a language that I can understand. I would like the pharmacist to tell me "please make sure that you take your medication" in a way that he /she really means it. Above all I want the pharmacist to really care for me and demonstrate that care. Concluding our encounter with a personal approach such as "do your best to get better and come back if you need more assistance" would be really appreciated.'

I have reported the above paragraph in the individuals own words which I believe are very meaningful. The patient wants to be treated as a person first and foremost and wants to feel cared for. Patients want to build a relationship with the pharmacist, and would like the pharmacist to be receptive to this. While they want to be given general advice about their health and about their medication, discuss problems with their medication and be supported in the taking of their medication they want to do this in the right environment, both psychological and physical environment, which needs to be created by the pharmacist.

What patient is highlighting can only be achieved when pharmacists make the full transition from product focus to patient focus. While this may have been achieved in some situations, in others it is still lacking and we need to strive harder towards this goal. Treating the patient as a person who needs our care, support and expertise will enable us to better deliver the necessary pharmaceutical care to the individual.

The European added value of health system cooperation to ensure access to innovative medicines and technologies

The contribution made by the Maltese Presidency of the Council of the European Union January-June 2017 to strengthen health system cooperation

Natasha Azzopardi Muscat
MD, Msc Public Health, Msc Health Services Management, PhD, FFPH, DLSHTM

Directorate for Health Information and Research, 95 G'Mangia Hill PTA 1313 G'Mangia, Malta
Department of Health Services Management, Faculty of Health Sciences, University of Malta
c/o/ Mater Dei Hospital MSD 2090 Msida, Malta
President European Public Health Association (EUPHA)
Email: Natasha.azzopardi-muscat@um.edu.mt @natasha_azzmus

Educational aims

- To increase awareness about the role played by the Maltese Presidency of the Council of the European Union
- To appreciate the potential of increased cooperation between health systems as a mechanism to address critical health system challenges
- To gain an understanding of the state of play in regional country cooperation to improve access to innovative medicines and technologies

Key words
Health systems, European Union, International Cooperation, Health technology, joint procurement

Abstract
Between January and June 2017, Malta held the Presidency of the Council of the European Union (EU). One of its thematic priorities was Structured Cooperation between health systems. Evidence for strengthened cooperation in the areas of procurement of health technologies and delivery of highly specialised services was presented and discussed in a series of meetings. Council Conclusions were elaborated and an ambitious cooperation declaration between Southern European countries in the area of access to innovative medicines was signed. This article describes the rationale for these linked activities as a means to support European health systems in addressing critical challenges that cannot be tackled by Member States acting alone. These cooperation initiatives are important in the light of the evolving debate on the Future of Europe and the role that health policy should play in the European Union post 2020. Malta, as a small Member State with an open market, is often exposed earlier and more harshly to the impacts of market and environmental changes on its health system. It can therefore play an important role in scanning the horizon for potential impacts and proposing appropriate policy responses at European level.

Introduction
In January 2017, for the first time in history, Malta took up the Presidency of the Council of the EU. As is customary, Malta presented its thematic priorities for discussion and debate. In the health sector, one of the two main priorities presented was that of 'Structured Cooperation between Health Systems'.[1] This was defined as *"Voluntary and organized cross-border activity between health care sector actors (e.g. governments, health agencies, providers, professional bodies, funders, educational institutions and others)"*.[2] Article 168(7) of the Treaty of the EU makes it clear that when it comes to health systems, Member States are in the driving seat and Union action shall complement the efforts of Member States.[3] Traditionally, there have been serious tensions between Member States and the EU on issues related to health systems at EU level.[4] The Maltese Presidency by proposing a voluntary approach, took into consideration the existing tensions whilst attempting to propose a solution that would allow those Member States who wish to do more together to do so in an effective manner with continuity, structure and support from the European institutions. This multi speed Europe approach is one of the options put forward for consideration on the Future of Europe White Paper by the Juncker's European Commission as Europe deliberates on its future post 2020 and post Brexit.[5]

Rationale
The Maltese Presidency chose to focus upon improving health systems cooperation with a view to finding ways to enhance access to innovative medicines, technologies and highly specialised services for European citizens. In its approach, the Presidency sought to emphasise the word voluntary when talking about structured cooperation since following the experience of the patients' rights and cross-border directive, the need to promote the idea of moving away from a one size fits all approach in the health sector was acknowledged. Increasing cross-border health system cooperation was proposed as one of the solutions that can be used to address commonly experienced challenges arising due to circumstances beyond the control of national policy more effectively. The rationale considered that cooperation with other health systems may lead to enhanced efficiency thereby contributing towards the health system sustainability objective.

The Maltese health system is well placed to steer this discussion at a European level for the following reasons. Cross border cooperation is an intrinsic characteristic of the Maltese health system with long-standing practical experience in both structured patient mobility (e.g. patients travelling overseas for treatment of rare diseases) and structured professional mobility (for specialist training purposes).[6] Secondly the Maltese health system with its small market characteristics has been faced with challenges in securing affordable access to innovative medicines for cancer and rare diseases, but this issue is now mainstream on the European (global) policy agenda and therefore a window of opportunity for concrete action is available.

Process

In order to construct an informed debate, the Maltese Presidency commissioned the production of two policy briefs by the European Observatory on Health Systems and Policies to answer the following questions:

- **How can structured cooperation between countries address health workforce challenges related to highly specialized health care?**[2]
- **How can voluntary cross-border collaboration in public procurement improve access to health technologies in Europe?**[7]

The Presidency, through the Ministry for Health, organised a series of meetings where the above topics were discussed. These included a workshop on Structured Cooperation between Health Systems, an informal meeting for Directors of Pharmaceutical Policy, the meeting of Competent Authorities for Pricing and Reimbursement of Medicines and the Pharma Round Table of Health Minister with Industry. These items were also on the agenda of the Informal Health Ministers meeting as well as the EPSCO Council where Council Conclusions were presented for adoption. Under the Maltese Presidency, eight EU Member States (Cyprus, Greece, Ireland, Italy, Malta, Romania, Portugal, Spain) signed up to the Valletta declaration.[8] In this declaration, these Member States agreed to cooperate to be in a position to better guarantee patient access to innovative medicines and therapies whilst ensuring health system sustainability. In order to achieve this objective, the Member States agreed to establish a technical committee to explore voluntary cooperation in areas including; sharing information, identifying best practices, horizon scanning, price negotiations and joint procurement. The values of trust, loyalty, solidarity and transparency were underlined as being key to the success of this initiative.

Discussion

Health systems are currently facing a 'perfect storm' with multiple challenges producing a strong force that is challenging the status quo and traditional way of funding and organising health services. Changes in information technology (IT), changes in citizen and patient expectations, the new medicines and technology pipeline, genetic therapies, changes in payment systems and changes in provider configurations are some of the key issues that are coinciding to produce a serious effect on access and sustainability of European health systems. Furthermore, the nature of developments in medicine and the evolution of the pharmaceutical market means that mechanisms that may have worked in the past to secure access at sustainable prices will no longer continue to produce the desired results. As a consequence, it appears that there is a clear added value for health systems to work more closely together. The following areas emerge specifically as focus areas in which cross border cooperation can be strengthened: collation of data, evidence and knowledge in the post-marketing/ procurement phase, new ways of funding – new financial instruments (bonds system, data for discounts, grouping of countries to enable negotiations for larger populations and increase bargaining power).[7] These considerations are particularly relevant for the areas of rare diseases and personalised health care.

Member States have shown interest in coming together in groups to try and address the issue of access to innovative medicines more cost-effectively. A number of agreements have been signed in past months incuding the BENELUXA, Baltic, Visegrad and during the Maltese Presidency the Valletta group of Southern European countries, including Cyprus, Greece, Italy, Malta, Portugal, Spain joined by Ireland and Romania. The expectation is that by pooling capacities and bargaining power, Member States would be better able to address the market asymmetry between industry and governments, particularly for smaller Member States. This of course will depend upon the willingness of the pharma industry to engage in meaningful dialogue. In this sense, the adoption of terms of reference for a more permanent forum between Member States and industry achieved through the efforts of the Maltese Presidency is an important step in this process.

The adoption of Council Conclusions on Encouraging Member States driven Voluntary Cooperation between Health Systems provides a framework within which several actions can be developed in the coming years.[9] The following are amongst the key priorities identified:

- Better anticipation of the impact of new medicines and technologies on health systems through more coordinated horizon scanning
- An emphasis on the monitoring during the post-marketing phase, to evaluate the outcomes, including the impact, that adoption of innovative health technologies has on patient and on health systems
- Exchange information to increase transparency and improve the leverage of individual Member States' in negotiations with industry

As discussions on the role of the future of Europe unfold, it is important to ensure that the public health objectives and health system dimension remain firmly embedded in the

Key points

- Between January and June 2017 Malta took up the Presidency of the Council of the EU
- Improving health systems voluntary cooperation to enhance access to innovative medicines, technologies and highly specialised services for European citizen was a key priority
- Eight countries signed the Valletta declaration to cooperate to better guarantee patient access to innovative medicines and therapies whilst ensuring health system sustainability
- The adoption of Council Conclusions on *Encouraging Member States driven Voluntary Cooperation between Health Systems* provides a strong legacy for the Maltese Presidency

context of promoting pharmaceutical policy and industry within the European Union. In this way, it will be possible to strike the much-needed balance between promoting the European Union as a hub for innovation and industrial growth alongside assurance of equitable access to this innovation by all European Union citizens irrespective of where they reside.

Conclusion

Developments in the medicines pipeline and changes to the medicines regulatory framework are placing increased pressure on health systems to rethink their approach to ensure sustainable access to innovation. This issue is being dealt with at an international level through several fora. The Maltese Presidency, through its policy proposals and discussions has made an important contribution in taking this agenda forward within the European Union[10] and has left a strong legacy upon which further work can be carried out.[11]

References

1. PROGRAMME OF THE MALTESE PRESIDENCY OF THE COUNCIL OF THE EUROPEAN UNION (1 January 2017 - 30 June 2017) Employment, Social Policy, Health and Consumer Affairs Pg 27. Available at: https://www.eu2017.mt/en/Documents/NationalProgramme_EN.pdf Accessed 20 May 2017.
2. Kroezen M, Buchan J, Dussault G, Glinos I, Wismar M. How can structured cooperation between countries address health workforce challenges related to highly specialized health care? Improving access to services through voluntary cooperation in the EU. Policy Brief No 20. European Observatory on Health Systems and Policies, World Health Organisation 2016. ISSN 1997–8073.
3. Consolidated versions of the Treaty on European Union and the Treaty on the Functioning of the European Union: Charter of Fundamental Rights of the European Union. European Union, Brussels: Official Journal of the European Union C 83. 2010.
4. Greer SL. Uninvited Europeanization: Neofunctionalism and the EU in health policy. J Eur Public Policy. 2006;13(1):134-152.
5. European Commission. WHITE PAPER ON THE FUTURE OF EUROPE. COM(2017)2025 of 1 March 2017. Available at: https://ec.europa.eu/commission/sites/beta-political/files/white_paper_on_the_future_of_europe_en.pdf Accessed 20 May 2017.
6. Azzopardi Muscat N, Grech K, Cachia JM, Xuereb D. Sharing capacities: Malta and the United Kingdom. In: Rosenmoller M, McKee M, Baeten R, editors. Patient Mobility in the European Union Learning from Experience. Copenhagen: World Health Organization; on behalf of the Europe 4 Patients project and the European Observatory on Health Systems and Policies; 2006.
7. Espin J, Rovira J, Calleja A, Azzopardi-Muscat N, Richardson E, Palm W, et al. How can voluntary cross-border collaboration in public procurement improve access to health technologies in Europe? Policy Brief No 21. European Observatory on Health Systems and Policies, World Health Organisation 2016. ISSN 1997–8073
8. EUrACTIV.com Southern EU states present unified front in drug talks 10 may 2017. Available at http://www.euractiv.com/section/health-consumers/news/southern-eu-states-present-unified-front-in-drug-talks/ Accessed 20 May 2017.
9. Council conclusions on Encouraging Member States-driven Voluntary Cooperation between Health Systems. C 206 2017 page(s) 3-7 Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2017:206:0003:0007:EN:PDF Accessed 5 July 2017.
10. Azzopardi-Muscat N, Calleja A, Gauci C, Agius-Muscat H, Mifsud S. Health Priorities of the 2017 Maltese EU Presidency. EUROHEALTH. 2017;23(1):10-12.
11. Fearne C. Malta's EU Presidency ending in Exceptional Health. EURACTIVE 21 June 2017. Available at: https://www.euractiv.com/section/health-consumers/opinion/maltas-eu-presidency-ending-in-rude-health/ Accessed 5 July 2017.

Drug-induced QTc-prolongation: risk management in a community pharmacy

Eline Vandael
Veerle Foulon

Clinical Pharmacology and Pharmacotherapy, KU Leuven, Leuven, Belgium
Email: Eline.Vandae@kuleuven.be; Veerle.Foulon@kuleuven.be

Educational aims

- To summarize basic information about the risk of QTc-prolongation
- To list recommended sources and provide a risk score and an algorithm to deal with the risk of QTc-prolongation in a community pharmacy
- To emphasize the role of a community pharmacist in this risk management

Key words
QTc-prolongation, Torsade de Pointes, risk management, community pharmacy

Abstract

A prolonged QTc-interval can in rare cases lead to ventricular arrhythmias (Torsade de Pointes) and sudden cardiac death. Most cases of QTc-prolongation are associated with medication, as listed in the QT-drug lists of CredibleMeds. Beside QTc-prolonging drugs, other patient-specific risk factors are associated with this risk. Community pharmacists have an important role in the risk management of QTc-prolongation. The aim of this paper is to give an overview of the most important aspects in the risk of QTc-prolongation, to underline the relevance of this risk and to offer tools to help community pharmacists deal with this risk in clinical practice.

Introduction

The risk of QTc-prolongation has become an important issue in medication safety, as in rare cases it can lead to serious adverse events such as Torsade de pointes (TdP) and sudden cardiac death (SCD). In the last decade, several drugs have been removed from the market (e.g. cisapride) or restricted in use (e.g. domperidone, (es)citalopram) because of this risk.[1] At the moment, more than 170 drugs are linked with this risk of QTc-prolongation, as defined in the QT-drug lists of CredibleMeds.[2] Furthermore, a lot of other risk factors (e.g. age, female gender, electrolyte disturbances, cardiovascular and other comorbidities, congenital long QT-syndrome) can increase the risk.[3] Due to possible combinations of these factors with additive effect on the QTc-interval, a complex risk estimation is warranted for each individual patient who receives a QTc-prolonging drug. Community pharmacists play an important role in this risk management, especially in the detection of drug-drug interactions (DDI) with risk of QTc-prolongation.

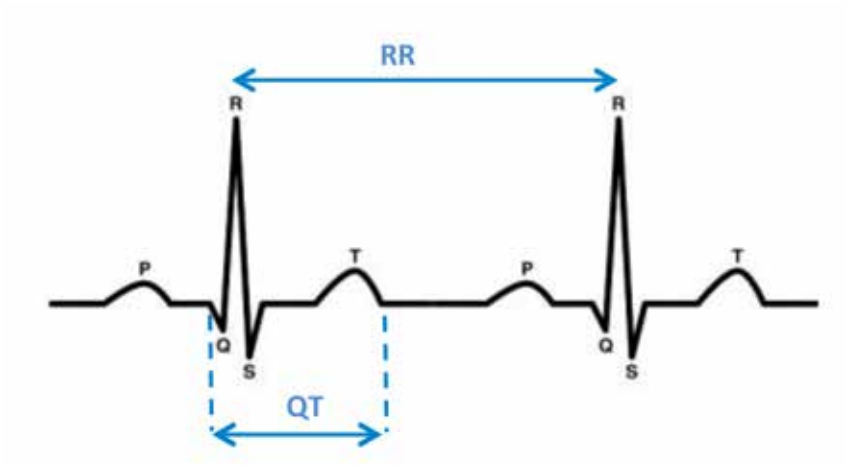
Definition of a prolonged QTc-interval

The QT-interval is an important phase in an electrocardiogram (ECG); it is measured in milliseconds (ms) from the beginning of the QRS-complex until the end of the T-wave (see Figure 1). The QT-interval measures the ventricular depolarization followed by the ventricular repolarization. QT-prolongation is used as a marker for a prolongation of the ventricular repolarization time.[4,5]

Because the QT-interval varies with the heart rate (HR), the corrected QT-interval (QTc-interval) should be used. Various correction formulas are available for this correction.[6] The Bazett formula is the easiest correction and most used in clinical practice. However, this is not an ideal correction; it results in an over-correction of the QT-interval at elevated heart rates and in an under-correction at heart rates below 60 beats per minute (bpm).[4,7] The Fridericia formula has been suggested to replace Bazett.[4]

A QTc-interval higher than 450 ms in adult males and higher than 470 ms in adult females is defined as prolonged. QTc-values higher than 500 ms are strongly prolonged and linked with a 2- to 3-fold higher risk for TdP (4;5;8). A delta QTc (difference in QTc between a baseline and follow-up ECG) higher than 30 ms and certainly higher than 60 ms must also be considered as a risk for TdP.[7]

Figure 1: QT-interval



Torsade de Pointes

The term TdP, referring to the presentation of 'twisting points' on an ECG (see Figure 2), was introduced by the French cardiologist Dessertenne in 1966.[1,4] TdP is a ventricular polymorphic tachycardia, characterized by a change in amplitude and morphology of QRS-complexes, a short-long-short pattern at the start and a HR of 160 to 240 bpm. In most cases, it terminates spontaneously. However, in few cases, it will lead to ventricular fibrillation and SCD. Typical symptoms of TdP are dizziness and syncope. In case of non-spontaneously ending TdP or ventricular fibrillation, immediate cardioversion should be performed. Other treatments for TdP (including prevention of reoccurrence) consist of intravenous magnesium sulfate, repletion of potassium, isoproterenol (ß-receptor agonist) to prevent bradycardia, stopping QTc-prolonging drugs and implanting a pacemaker in case of chronic bradycardia.[4,8,9]

The overall incidence of TdP in a general population was estimated at 50 per million person-years.[10,11] However, these numbers are probably an underestimation, because only a part of the patients reach the hospital alive. Furthermore, TdP-cases are often not recognized or not registered on an ECG. Also the proportion of SCD that are caused by TdP is unclear.[4,12] Approximately one-fifth of the TdP-cases will proceed in ventricular fibrillation of which approximately 85% will be fatal.[11,13]

Besides TdP and sudden cardiac death, QTc-prolongation is also linked with other serious outcomes. Pickham *et al*. reported that patients in critical care units with a prolonged QTc-interval have a longer hospital stay and a 3-times higher overall in-hospital mortality than patients without QTc-prolongation.[14]

Drugs with a risk of QTc-prolongation and TdP

Both cardiac and non-cardiac drugs are linked with QTc-prolongation and TdP. Different therapeutic classes are involved, e.g. antibiotics, antipsychotics, antidepressants, oncolytic agents and antihistamines. Antiarrhythmic drugs like quinidine and sotalol have the highest risk of causing TdP (in 1-5% of the exposed subjects). With non-cardiac drugs, the risk of TdP is considered to be lower (0.01-0.0001%).[1,15] Most frequently, QTc-prolonging drugs inhibit the rapid component of the delayed potassium current by blocking the hERG-channels (regulated by the human ether-a-go-go–related gene (hERG)), which results in a prolongation of the repolarization phase and a prolongation of the QTc-interval.[4,16]

The American organization CredibleMeds ([2]) has created lists of QTc-prolonging drugs, based on the evidence per drug:

- List 1: drugs with a known risk for TdP (substantial evidence for causing TdP) e.g. haloperidol, escitalopram, domperidone, methadone, macrolides, moxi/levo/ciprofloxacine, sotalol
- List 2: drugs with a possible risk for TdP (substantial evidence for QTc-prolongation, but evidence for TdP is lacking) e.g. risperidone, venlafaxine, protein kinase inhibitors, tacrolimus, tamoxifen
- List 3: drugs with a conditional risk for TdP (risk of QTc-prolongation and/or TdP in certain conditions, e.g. overdose, cLQTS, interaction with other drugs) e.g. furosemide, indapamide, trazodone, pantoprazole, metronidazole
- List 4: drugs to be avoided by patients with congenital long QT-syndrome (all drugs in the previous lists and heart stimulants)

The evidence per drug is collected in the medical literature (Pubmed search), the FDA label, summary of approval on the FDA website, cases in the FDA's Adverse Event reporting System and reports to CredibleMeds. Subsequently, this evidence is reviewed by the CredibleMeds review team with the help of the Bradford-Hill criteria, and finally allocated to the different lists. The QT-drug lists are freely available on the website www.crediblemeds.org

Table 1: Risk score for QTc-prolongation, score ≥ 5 defined as high risk

Risk factors for QTc-prolongation	Points
▪ Use of ≥1 potassium-lowering diuretic *	3 points
▪ Use of ≥1 anti-arrhythmic drug	3 points
▪ Age ≥65 years	2 points
▪ Female gender	2 points
▪ Thyroid disturbances	2 points
▪ Cardiovascular comorbidities **	1 point
▪ Diabetes mellitus	1 point
TOTAL RISK SCORE	**Maximum 14 points**

* No points if used in combination with potassium-sparing diuretics

** Including antihypertensive drugs, beta-blocking agents, nitrates, calcium-channel blockers, agents acting on the renin-angiotensin system and lipid-modifying agents

for registered users and are continuously updated based on new information.[2,17]

Other risk factors for QTc-prolongation

Besides QTc-prolonging drugs, a lot of other patient-specific risk factors are mentioned in the literature[1,4,18,19] including:

- Demographic factors (e.g. age ≥65 years, female gender, smoking, alcohol use, over- and underweight)
- History of a prolonged QTc-interval
- Cardiovascular comorbidities (e.g. rhythm disturbances, heart failure, hypertension)
- Other comorbidities (e.g. thyroid disturbances, diabetes, liver- or kidney failure, infections)
- Electrolyte disturbances (e.g. hypokalemia, hypocalcemia, hypomagnesemia)
- Genetic predisposition

To understand the interplay between genetic mutations, the use of QTc-prolonging drugs and other risk factors, the term 'repolarization reserve' was introduced by Roden *et al*. in 1998. This framework explains that there are physiological mechanisms available that maintain the normal cardiac repolarization and that this can vary among patients. These mechanisms are a protection (reserve) against factors that may distort the normal ventricular repolarization. The more risk factors present, the more susceptible a person becomes for developing QTc-prolongation and TdP (reduced reserve). Consequently, multiple risk factors are needed to overcome this barrier. However, one should be aware that one additional factor can suddenly lead to QTc-prolongation and TdP.[4,9,20]

A recent systematic review of Vandael *et al*. summarized and assessed the evidence on different risk factors for QTc-prolongation.[3] Based on this review, a preliminary risk score for QTc-prolongation (the RISQ-PATH score) was developed.[21] This risk score is mainly useful for the hospital setting, as it needs a lot of clinical information, including recent lab results. For community pharmacists, we developed a simplified QT risk score based on the information that is usually available in a community pharmacy (see Table 1).[22] A QT risk score ≥ 5 points is defined as a high risk for QTc-prolongation. Moreover, an algorithm (see Figure 3) was developed to help community pharmacists decide when the prescribing physician should be contacted in case of a QTc-prolonging DDI, taking into account the number of QTc-prolonging drugs, the classification in CredibleMeds and the risk score.[22] In Table 2, some additional recommendations for clinical practice are listed.

Table 2: Additional recommendations for clinical practice

If you need to contact the prescribing physician concerning a QTc-prolonging DDI:

- Specify the type of DDI and the involved QTc-prolonging drugs.
- Specify the other risk factors for QTc-prolongation (see risk score in Table 1).
- Ask if a recent ECG is available.
- Try to propose an alternative drug.

Recommendations to find an alternative drug:

- Focus on the QTc-prolonging drug that is started.
- Try to find an alternative which is not listed in the CredibleMeds lists.
- If such an alternative is not available, a drug of list 3 or 2 of CredibleMeds should be preferred.
- Still no alternative? Ask the physician if it is possible to plan a follow-up ECG and/or if you can warn the patient for the symptoms of TdP.

How to warn a patient for the risk of QTc-prolongation and TdP?

- Underline that it is a very rare risk.
- Mention the most common symptoms of TdP: sudden dizziness, fainting and palpitations.
- Tell the patient that if these symptoms occur, the physician should be contacted as soon as possible.
- Emphasize that the patient can always contact you in case of questions or worry.

An example in clinical practice

Andrew (70 years old) enters the pharmacy with a prescription for levofloxacin (indication: prostate infection). You notice in his medication history that he also takes donepezil for Alzheimer disease. On your screen, an alert for a QTc-prolonging DDI pops open.

STEP 1: Check which drugs are involved in the QTc-prolonging DDI

In this case, levofloxacin and donepezil are linked with a risk of QTc-prolongation. Both drugs are classified in list 1 of CredibleMeds (known risk of TdP).

STEP 2: Check if the patient has other risk factors for QTc-prolongation

Andrew is older than 65 years and he also uses two cardiovascular drugs (perindopril and bumetanide). If we calculate the simplified QT risk score (Table 1), Andrew has a score of 6 points which correlates with a high risk.

STEP 3: Consider if an action is needed

Taking into account that 2 drugs of list 1 are involved in the QTc-prolonging DDI (see algorithm in Figure 3), that Andrew has a high risk score for QTc-prolongation and that it is a new prescription for an antibiotic treatment in which case it is still possible to suggest an alternative, it is in this case recommended to contact the physician.

STEP 4: Consider which physician should be contacted

The best choice is to contact the physician who prescribed the new treatment. It is possible that it was prescribed by a specialist who was not aware of the other medications of Andrew. If the specialist cannot be reached, you can also contact the general practitioner (GP). In this case levofloxacin was prescribed by the GP, so we will contact him.

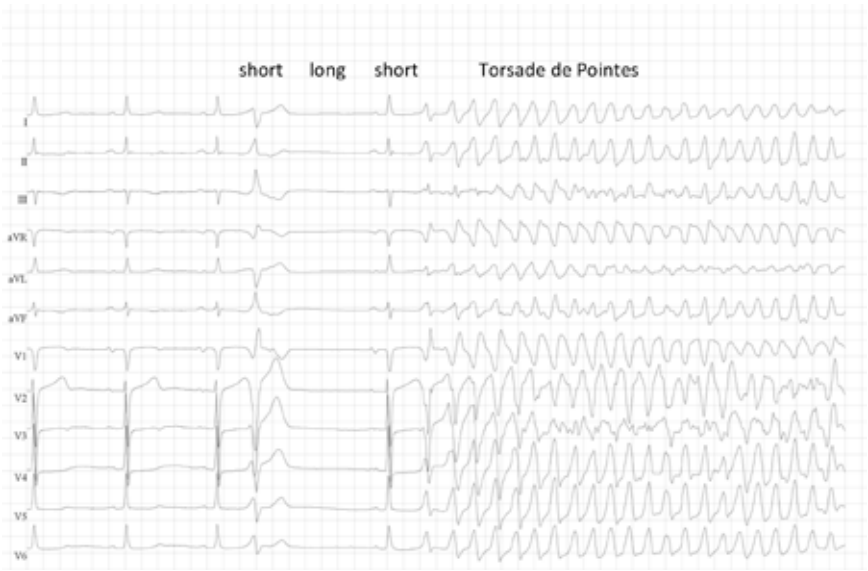
STEP 5: Try to suggest an alternative drug

For a prostate infection, amoxicillin in combination with an enzyme inhibitor is the second-line choice besides levofloxacin and is not included in the lists of Crediblemeds. We can suggest this as an alternative treatment for Andrew.

STEP 6: Contacting the physician

The GP agrees with your suggestion to replace levofloxacin with amoxicillin in combination with clavulanic acid.

Figure 2: An example of a TdP



STEP 7: Explanation to the patient

Carefully explain the potential risk of QTc-prolongation to Andrew. Underline that it concerns a very rare side effect, but that you discussed it with his GP that it is a safer option to use an alternative antibiotic treatment.

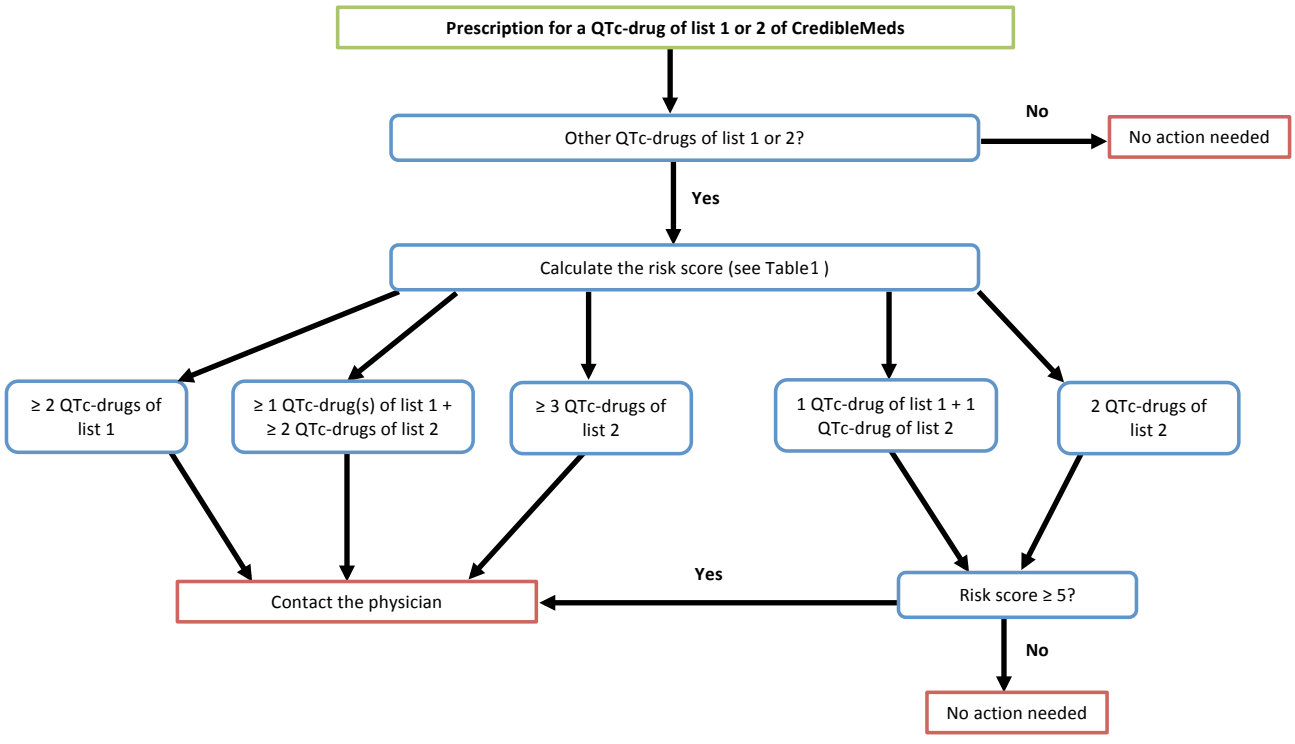
STEP 8: Register in the pharmaceutical file of the patient how you handled the DDI

By registering the performed action in the pharmaceutical file of Andrew, you can always look back how you handled this QTc-prolonging DDI.

Conclusion

Drug-induced QTc-prolongation can in rare cases lead to serious life-threatening outcomes. Pharmacists have an important role in the risk management of QTc-prolongation. They should be cautious for QTc-prolonging DDI, especially if drugs of list 1 of CredibleMeds or other patient-specific risk factors are involved.

Figure 3: Algorithm to handle QTc-prolonging DDI in a community pharmacy



10 multiple choice evaluation questions

1. **Which length of the QTc-interval is correlated with a significant higher risk for TdP?**
   - ☐ A. QTc ≥ 100 ms
   - ☐ B. QTc ≥ 400 ms
   - ☐ C. QTc ≥ 500 ms

2. **A prolonged QTc-interval will always result in TdP.**
   - ☐ A. Correct
   - ☐ B. Not correct

3. **Most of the times, QTc-prolonging drugs will prolong the QTc-interval by:**
   - ☐ A. Blockage of calcium channels
   - ☐ B. Activation of calcium channels
   - ☐ C. Blockage of potassium (hERG) channels
   - ☐ D. Activation of potassium (hERG) channels

4. **Which are typical symptoms of a TdP?**
   A. Dizziness | B. Paresthesia
   C. Chest pain | D. Syncope | E. Palpitations
   - ☐ A. Only symptom e
   - ☐ B. Symptoms b and e
   - ☐ C. Symptoms a, d and e
   - ☐ D. None of the mentioned symptoms

5. **Which of the following drugs have a clear risk for TdP (list 1 CredibleMeds)?**
   A. Erythromycin | B. Ranitidine
   C. Levetiracetam | D. Doxycycline | E. Donepezil
   - ☐ A. Drugs a and e
   - ☐ B. Only drug a
   - ☐ C. Drugs b, d, and e
   - ☐ D. All mentioned drugs

6. **Citalopram is classified in list 1 of CredibleMeds.**
   - ☐ A. Correct
   - ☐ B. Not correct

7. **Which of the following risk factors are all linked with QTc-prolongation?**
   - ☐ A. Age, female gender, dementia, hyperkalemia
   - ☐ B. Age, female gender, diabetes, hypokalemia
   - ☐ C. Age, dementia, diabetes, hypercalcemia
   - ☐ D. Age, female gender, hypocalcemia, gout

8. **The use of diuretics is a risk factor for QTc-prolongation.**
   - ☐ A. Correct
   - ☐ B. Not correct

9. **Hanna (24 years) enters the pharmacy with a prescription for ciprofloxacin 250mg for a bladder infection. You know that she also suffers from a depression and that she is treated with escitalopram 10mg. Besides escitalopram, paracetamol is also included in her medication history. Based on the provided algorithm (see Figure 3), which action will you take?**
   - ☐ A. There is no risk for QTc-prolongation. No action is needed
   - ☐ B. There is an increased risk for QTc-prolongation and you decide to contact the physician.
   - ☐ C. There is increased risk for QTc-prolongation. However, you decide to only warn the patient for the symptoms of TdP.

10. **Thomas (35 years) suffers from a bipolar disorder and, for already 10 years, he is treated with lithium 500mg. Lately, his disorder deteriorated and his psychiatrist decided to additionally start levomepromazine. Thomas does not use other chronic medication. Based on the provided algorithm (see Figure 3), which action will you take?**
   - ☐ A. There is no risk for QTc-prolongation. No action is needed
   - ☐ B. There is an increased risk for QTc-prolongation and you decide to contact the physician.
   - ☐ C. There is increased risk for QTc-prolongation. However, you decide to only warn the patient for the symptoms of TdP.

Answers may be found on page 41

Key points

- A QTc-interval ≥500 ms is severely prolonged and correlated with a 2 to 3 times higher risk of TdP
- Typical symptoms of TdP are sudden dizziness, fainting and palpitations
- More than 160 drugs of different therapeutic classes are currently linked with a risk of QTc-prolongation and listed in the QT-drug lists of CredibleMeds (list 1: known risk of TdP, list 2: possible risk of TdP, list 3: conditional risk of TdP)
- Besides QTc-prolonging drugs, a lot of other patient-specific risk factors should be taken into account in the risk estimation
- The risk score and algorithm proposed in this paper can be used in clinical practice to deal with the risk of QTc-prolongation

Acknowledgements

EV was supported by funding of the Belgian government agency for Innovation by Science and Technology (IWT).

Abbreviations

bpm = beats per minute
DDI = drug-drug interactions
ECG = electrocardiogram
GP = general practitioner
hERG = human ether-a-go-go-related gene
HR = heart rhythm
ms = milliseconds
SCD = sudden cardiac death
TdP = Torsade de Pointes

References

1. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004;350(10):1013-1022.
2. Woosley RL, Romero KA. QTdrugs List, December 2015, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755. Available from: http://www.crediblemeds.org Accessed 9 November 2016.
3. Vandael E, Vandenberk B, Vandenberghe J, Willems R, Foulon V. Risk factors for QTc-prolongation: systematic review of the evidence. Int J Clin Pharm. 2017;39(1):16-25.
4. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol. 2010;55(9):934-947.
5. van Noord C, Eijgelsheim M, Stricker BH. Drug- and non-drug-associated QT interval prolongation. Br J Clin Pharmacol. 2010;70(1):16-23.
6. Malik M. Problems of heart rate correction in assessment of drug-induced QT interval prolongation. J Cardiovasc Electrophysiol. 2001;12(4):411-420.
7. U.S.Department of Health and Human Services. International Conference on Harmonisation (ICH). Guidance for Industry: E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. 2005. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf Accessed 6 February 2017.
8. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. Ther Adv Drug Saf. 2012;3(5):241-253.
9. Thomas SH, Behr ER. Pharmacological treatment of acquired QT prolongation and torsades de pointes. Br J Clin Pharmacol. 2016;81(3):420-427.
10. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. Br J Clin Pharmacol. 1999;47(3):307-313.
11. Warnier M, Rutten F, Souverein P, Hoes A, de Boer A, De Bruin M. Are ECG Monitoring Recommendations before Prescription of QT Prolonging Drugs Applied in Daily Practice? The Example of Haloperidol. Pharmacoepidemiol Drug Saf. 2015;24(7):701-708.
12. Molokhia M, Pathak A, Lapeyre-Mestre M, Caturla L, Montastruc JL, McKeigue P. Case ascertainment and estimated incidence of drug-induced long-QT syndrome: study in Southwest France. Br J Clin Pharmacol. 2008;66(3):386-395.
13. Nielsen J, Graff C, Kanters JK, Toft E, Taylor D, Meyer JM. Assessing QT interval prolongation and its associated risks with antipsychotics. CNS Drugs. 2011;25(6):473-490.
14. Pickham D, Helfenbein E, Shinn JA, Chan G, Funk M, Weinacker A, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: results of the QT in Practice (QTIP) Study. Crit Care Med. 2012;40(2):394-9.
15. De Ponto F, Poluzzi E, Montanaro N. Organising evidence on QT prolongation and occurrence of Torsades de Pointes with non-antiarrhythmic drugs: a call for consensus. Eur J Clin Pharmacol. 2001;57(3):185-209.
16. Rampe D, Brown AM. A history of the role of the hERG channel in cardiac risk assessment. J Pharmacol Toxicol Methods. 2013;68(1):13-22.
17. Woosley RL, Romero K. Assessing cardiovascular drug safety for clinical decision-making. Nat Rev Cardiol. 2013;10(6):330-337.
18. Haugaa KH, Bos JM, Tarrell RF, Morlan BW, Caraballo PJ, Ackerman MJ. Institution-wide QT alert system identifies patients with a high risk of mortality. Mayo Clin Proc. 2013;88(4):315-325.
19. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes. 2013;6(4):479-487.
20. Roden DM. Taking the "idio" out of "idiosyncratic": predicting torsades de pointes. Pacing Clin Electrophysiol. 1998;21(5):1029-34.
21. Vandael E, Vandenberk B, Vandenberghe J, Spriet I, Willems R, Foulon V. Development of a risk score for QTc-prolongation: the RISQ-PATH study. Int J Clin Pharm. 2017; doi: 10.1007/s11096-017-0446-2.
22. Vandael E. The risk of QTc-prolongation and Torsade de Pointes in clinical practice. 2016. KU Leuven. [Not published doctoral thesis]

What should pharmacists keep in mind to communicate with patients more effectively? Some key concepts for everyday use

Afonso Miguel Cavaco
PharmD, MSc, PhD

Associate Professor in Social Pharmacy, Faculty of Pharmacy, University of Lisbon, Portugal
Email: acavaco@ff.ulisboa.pt

Educational aims

- To explain and reinforce the importance of communication skills as underlying abilities to pharmacists' work-life and professional outcomes
- To address the main components of these skills as objective features that can be learned and optimized through education and training
- To promote individual self-reflection on how each practitioner regards the present skills usage and what can improve while communicating with patients and caregivers

Key words
communication skills, interpersonal exchange, non-verbal communication, written information, patient interaction, pharmacy practice

Abstract

Communication skills for pharmacists are commonly described in professional frameworks and guidelines equally important as other current pharmaceutical competencies. However, these abilities usually receive less attention from university syllabuses, while in life long education they are many times discussed in a theoretical level or as a supplement to other skills. The present work aims to discuss several interpersonal skills used in daily practice with variable extension, improving communication and relational aspects needed for optimizing patient care.

Introduction

From the last decades, the World Health Organization (WHO) recognised the essential role of pharmacists in healthcare, particularly concerning the rational use of medicines by patients. Besides the customary pharmaceutical and drug-based knowledge, international guidelines recommend pharmacists' education and training to comprise competencies and skills that enable these professionals, amongst other tasks, to provide the best patient care and education possible.[1] An underlying condition to achieve these and many other professional responsibilities, described by the WHO and the International Pharmacy Federation (FIP), is the capacity to communicate effectively with patients, peers and others.

Pharmacy practice is mainly based on the interaction with those seeking healthcare, which range from people who are unwell to caregivers. It is therefore universally accepted that the pharmacist needs to be highly competent in human communication. Using a very simplified view, competency can be defined as the ability to "know and know how".[2] However, it is not guaranteed that pharmacy curricula are addressing pharmacists' communication competencies in a comprehensive and systematised manner, in a manner equivalent to the traditional pharmaceutical subjects training.[3]

The dominance of the biomedical models deliver a view of the patient in terms of clinical cases, to whom medicines need to be prescribed, dispensed and administered. This context limits healthcare professionals' ability to accept all information emerging from the ill person, thus to truly provide patient-centred, individualised and humanistic care. It also limits patients' autonomy, empowerment and health outcomes.[4] Effective communication, i.e. the one dealing with ALL significant aspects of the patient, plays a central role when delivering the appropriated and essential healthcare. Practitioners must be more sensitive and aware of their professional relationships with patients (and other stakeholders) in the caring process. Pharmacists cannot stay indifferent to a patient's request for professional attention. Possessing the ability to respond and communicate accordingly, is a professional pharmacists' responsibility equivalent to guaranteeing access to good quality medicines to be dispensed.[5] Pharmacists should be able to accept and process the exchange of information with their patients (including emotions), if willing to completely understand

each patient biopsychosocial specificities. Without such an approach, it is very hard to provide or support the best therapeutic solution, guided by ethical principles of confidentiality, mutual respect and trust, therefore establishing a co-responsible and professional rapport.[6]

Improving communication

1. The starting point: mutual trust

While communicating, individuals are assimilating the surrounding environment, taking decisions and acting accordingly. Thus, communicating with others should have a clear purpose and meaning. The dialogue between pharmacists and patients is indispensable to establish an agreement aimed at a "therapy-centred" relationship. In this sense, one basic underlying feature, which should permanently infuse the pharmacist-patient interaction, is mutual trust. This means that for communicating effectively with the patient, both dialoguing persons must believe in their selves as well as in the other. While the patient is looking to prevent or to solve his/her biopsychosocial health issues, the pharmacists cannot ignore the patient's autonomy in the health-related decisions, adapting his/her knowledge and actions to the patients' expectations. Respecting the patient's rights and willingness, and establishing his/her co-responsibility in the treatment process, are the corner stone towards a relationship built on trust and an essential bond to provide patient-centred care. If the pharmacist is not able to recognise the patient's acceptance of the pharmacist's role as a healthcare professional, then effective health communication will be harder or impossible to achieve.

2. The essential elements

Communicare, the Latin root of the word "communication", means to make common or share something. In very simple terms, between communicating humans there occurs the production and transmission, within symbolic systems, of signs. These are stimuli that convey information organised in a message. The meaning of the exchanged signs to each of the communicating subjects depends on the education and cultural background of each. In this sense, it is relevant to the pharmacist to recognize and understand the education and cultural level of the interacting patient, besides the first impressions, and be aware of bias provided by stereotypes. This can be achieved from the very start and throughout the conversation, by paying attention to the verbal content of the exchange, including the lexical (i.e. words or vocabulary used) and syntactical (the arrangement of words and phrases to create sentences), i.e. the "kind" of language used by the patient.

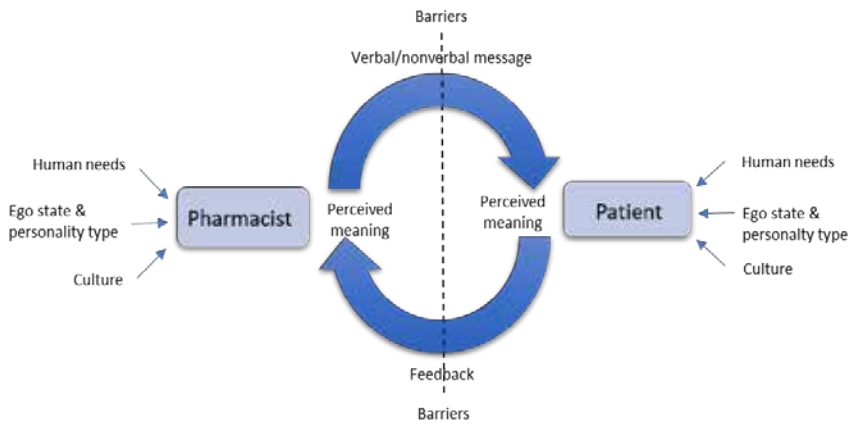
The typical model to represent the process of communication, as proposed by Beardsley *et al.*, is based on 5 main components, as follows (Figure 1):[7]

a. The sender of the message, who produces and transmits the information to be exchanged.
b. The message itself, encompassing the verbal and non-verbal code of a thought or an emotion, and the mean through which propagates, e.g. spoken or written communication, or the facial expression.
c. The receiver of the message, who receives and decodes the information, attaching a meaning to it, per context and background.
d. The feedback message, produced by the receiver and revealing what was understood from the received information, thus implying an inversion of roles.
e. The barriers, i.e. all interferences that limit the extension to which the messages exchanged are understood as initially intended by the sender.

From the previous model, it is possible to notice several important factors contributing to an effective pharmacist-patient communication:

a. **Sender**. As mentioned previously, the pharmacist as the message sender should never forget to adjust the level of language to the recipient, e.g. apparent level of education and age. Should always start with a plain language i.e. simple terms, shortened sentences as possible, with the right verbal construction (subject + verb + object + object complement), to be adjusted along the dialogue. The pharmacist should always be attentive to patient's non-verbal feedback, including incomprehension or distraction signals. When interviewing the patient, pharmacists need to initially ask exploratory open-ended questions and, using a funnelling technique, move down along the interview towards closed-ended and confirmatory questions.
b. **Message**. Besides the verbal content and formulation, the message encompasses paralanguage (e.g. voice tone and speed), as well as non-linguistic features (e.g. gestures and posture). These should be coordinated with the patient's characteristics, e.g. elderly patients usually require a slower speech and shorter body movements. Pharmacists should keep an upright body position, with a gentle lean forward of the torso, parallel shoulders with patient's, while respecting proxemics (i.e. the interpersonal distance) and keeping an open attitude (avoiding arms crossed and hidden hands); all this shows non-

Figure 1: One illustration of pharmacist communication (Rantucci MJ, 2007)



verbal interest and attention. Without staring at the patient, eye contact most of the time (>75%) is crucial to prove interest for patient's situation and exchange. Authentic care is disclosed also by the facial expression, by smiling only when appropriate, thus activating mirror neurons and developing a sense of acceptance and well-being.

c. **Receiver**. The pharmacist, as a message receiver, should focus on the message being sent, moving from a pretend to an active listening attitude. This can be achieved by ignoring other visual and hearing stimuli, mostly focusing on the other's face and voice. When the listening attitude addresses the deciphered underlying emotions, then the pharmacist reaches the level of empathic listening. Empathy, as a central competency for providing patient care, will be detailed next.
d. The **feedback** message is the most important single element necessary to define a true communication episode. If feedback is happening, such as a simple head nodding, then subjects are experiencing a two-way process, avoiding lecturing of the patient. So, breaking communication reciprocity is a clear limitation for providing the right patient care, i.e. pharmacists should make sure there is enough rapport and patient engagement in the dialogue, if willing to achieve an effective communication.
e. Barriers to communication comprehend falling all previously described behaviours, from both pharmacists and patients. Patient's age, gender, schooling, socio-economic status, health beliefs, medication experiences, etc., may raise distortions in how the information exchanged is perceived. Common pharmacist-centred barriers are the low motivation and lack of interest in the patient situation, difficulties of leaving the biomedical attitude (e.g. using pharmaceutical jargon), and worries in establishing a relationship (e.g. time pressures, personality traits, lack of training). Knowing how brief and superficial the contact with patients and pharmacy customers may be, barriers as these needs to be under control for effective communication.

One aspect of the previously described communication elements, which deserve additional consideration, is non-verbal communication. The literature states that 93% of all information exchanged between two speakers is of non-verbal nature, with 55% as body language (e.g. posture and gestures) and 38% concerning voice features.[8] While words are used to exchange mainly information, body language discloses attitudes, sometimes replacing the verbal message. It works as the reflection of one's emotional state, being the most truthful source of evidence; just remember how patients usually manifest discomfort, confusion or fear. One key non-verbal element, necessary to meet most non-verbal responses, is eye contact. [9] Besides being the most common form to initiate interpersonal communication, watching here should be regarded through its Latin root "*atendere*" i.e. giving attention or taking care of all non-spoken exchange. The pharmacist's superficial look, such as not paying attention to someone staring at his/her mouth (searching for words in hearing impairments), looking at the floor (a signal of shyness) or looking in other directions (feeling less interested), works as a barrier to understand the patient and any therapy-related issues. This absence of adequate looking works as a barrier to instil the right level of trust expected in patient care. The pharmacist's gestures, being spontaneous and descriptive, provide an illustration and emphasise the verbal message. Hands also offer tactile communication, which delivers non-verbal messages of adequacy and care, according to haptics location, duration and pressure. Touching the patient runs from the everyday warm welcoming handshake to the instrumental touch, i.e. the deliberate contact for a procedure (e.g. measuring blood pressure or giving an injection), the spontaneous affective touch (e.g. a supporting hug or kiss), and the therapeutic touch (e.g. a firm touch to delivered confidence).[10,11] Finally, the interpersonal distance should not interfere with the intimate sphere (a radius of 45cm) without previous permission or tacit agreement from the patient – a defense reaction or even the patient moving away, can happen.

Personality traits, lack of awareness and/or training in non-verbal communication strategies may work as sources of additional anxiety. When realizing and applying these communication behaviours, the pharmacist should observe the patient's body to improve the exchange. Professionals should keep in mind that communication behaviours are usually reciprocal: thus a "soft" look, an open and sincere stance, reinforces the belief in following the pharmacist's directions and advice.

3. One key relational skill

Most of the previous skills are needed to improve communication and the relationship with patients. However, one critical skill for optimal patient care is empathy. Several empathy definitions exist, a common one being the capacity to place oneself in the position of the other, i.e. to understand and accept without any attempts to stop, modify or block the ideas or the emotional content that the patient might be disclosing. [12] By feeling accepted and secured, the level of detail in the exchange increases, thus enhancing the chances of providing optimal and responsible care. For instance, there is ample evidence to illustrate that a good i.e. empathic relationship between pharmacists and patients improves medication adherence. [6]

Empathic behaviour should be expressed both verbally and non-verbally. While clear spoken or written language supports effective verbal communication, e.g. when the pharmacist is giving treatment directions and information plainly, to reach empathy the pharmacists also needs to dominate the non-verbal characteristics of his/her communication approach. One main feature for reaching empathy and emotional resonance is paralanguage, particularly the voice i.e. how one sounds to the other.[13,14] In this way, the pharmacist should reduce the pitch and decrease the speaking rate if he/she wants to be perceived as an empathic person, amongst the previously mentioned effective communication behaviours.

However, only warm voice does not turn an unwelcoming pharmacist into a caring one. Of course, verbal behaviours need to be preceded by active listening. The empathic pharmacist should "listen with the eyes", i.e. not to miss any hints of emotional disclosure. This is a difficult exercise, therefore listening to all empathic opportunities is harder than e.g. asking good questions. Empathic listening also requires physical proximity (within the accepted interpersonal distance), full attention to what the other is saying, how he/she is expressing him/herself non-verbally, without interruptions and showing respect. Again, this requires attention to one's own body language, avoiding emotional signals of disgust or disapproval. Exchange location

and setting takes great importance too: interruptions and distractions break the construction of the empathic moment; thus, having disruption sources, such as the presence of others who are not part of that interaction, do not help to build the deep understanding required for empathy.

4. Other communication skills

Writing still is a frequent form of pharmacist-patient communication. Graphical signs replace the vocal ones, yet on paper, but so many times via digital resources e.g. text messages, emails, or over the internet (sites, blogs, etc.). In written communication, general education and literacy play an important role. Plain language rules should always apply, such as those mentioned earlier: avoiding jargon and technical terms, using well-structured and short sentences, bullet lists and other features; all these help the readability and usefulness of the written message, including the reader's ability to later remember the most relevant information. Being coherent, i.e. all text segments are related and make a relevant contribution to the overall goal, can be better achieved if the text is thoroughly read, more than once (if possible by another person), before being handed to the patient.

Cautionary labels and pictograms have been widely used and tested. Besides the legal requirements with medication warnings, pictograms for less literate patients, or those with slight cognitive impairment or seeing difficulties, have long received attention from many organizations. For instance, the FIP has a freeware (PictoRX, available at https://www.fip.org/pictograms), which provides means of communicating medication instructions, plus a prescription calendar combining all medicines and working also as storyboard of a medication.

Conclusion

The concepts for effective communication here briefly described are not intended to be an "instrumental" view of communication, warranting for instance the expected medication outcomes, but mostly to illustrate communication skills as unique and concrete tools to provide the best patient care possible. In the present pharmacy verticalized system, pharmacists are usually placed higher than patients in the social ladder, establishing a social differentiation through specific knowledge, and many times exerting power and paternalism over patients. Suitable communication skills should promote a humanised practice, aiming to have a horizontalization of professionals' and patients' roles in healthcare, within a setting of permanent cooperation and patient empowerment.

All the abilities previously mentioned, including individual and social skills, may be innate or informally developed, in variable extension, for most of the readers. Nevertheless, and knowing the relevance of humanistic skills for present professional practice, this paper was aimed at rising or reinforcing readers' awareness of key features (underlined in the text) for effective communication and, accordingly, to contribute to the integration of such skills in pharmacists' practice and continuous education.

Finally, there is one basic feature which is an absolute necessity for effective communication between pharmacists and their patients: the right length or duration of interaction. Although ineffective consultations do occur for apparently long communication episodes, when pharmacists are deprived of enough time to properly listen, ask and talk with patients, pharmacists are unable to address patient's needs from a biopsychosocial point of view. As with any responsible healthcare professional, pharmacists cannot neglect the importance of patient's effective information and exchange, including emotional adequacy. Emotions, which continuously permeate human existence, are even more relevant in ill-health circumstances. The caring and responsible pharmacist can ignore all previous aspects, including the loss of autonomy usually associated to ill-health, as well as the ethical duty of communicating, with full respect for frailer human beings.

Key points

- Pharmacist-patient communication, both orally and written, is core mean by which professionals can use their clinical expertise and benefit patients' health and well-being
- Communication is a complex system comprising several structures and processes, including verbal and non-verbal exchange, thus subject to limitations and undue variations
- Communication features, including emotional resonance or empathy, impacts not only the information interchange, but also patient behaviour e.g. adherence and motivation
- It is core for providing accountable pharmacist care to continuously develop interactional skills and to be able to apply them as required by the patient and the situation

References

1. World Health Organization. The Role of the Pharmacist in the Health Care System - Preparing the future pharmacist: curricular development. Report of a third WHO Consultative Group on the Role of the Pharmacist. 1997. Available from: http://apps.who.int/medicinedocs/pdf/s2214e/s2214e.pdf Acessed 31 July 2017.
2. Bruno A, Bates I, Brock T, Anderson C. Towards a global competency framework. Am J Pharm Educ. 2010;74(3):56.
3. Wallman A, Vaudan C, Sporrong SK. Communications training in pharmacy education, 1995-2010. Am J Pharm Educ. 2013 Mar 12; 77(2): 36.
4. Bensing J. Bridging the gap: The separate worlds of evidence-based medicine and patient-centered medicine. Patient Educ Couns. 2000;39(1):17–25.
5. Ramalho-De-Oliveira D, Shoemaker SJ. Achieving patient centeredness in pharmacy practice: openness and the pharmacist's natural attitude. J Am Pharm Assoc (2003). 2006;46(1):56–64.
6. Lyra DP, Rocha CE, Abriata JP, Gimenes FRE, Machuca M, Pela IR. Influence of Pharmaceutical Care intervention and communication skills on the improvement of pharmacotherapeutic outcomes with elderly Brazilian outpatients. Patient Educ Couns. 2007;68:186–192.
7. Beardsley RS, Kimberlin CL, Tindall W. Principles and elements of interpersonal communication. In: Communication Skills in Pharmacy Practice: A Practical Guide for Students and Practitioners. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 15–30.
8. Birdwhistell RL. Kinesics and Context. Essays on Body Motion Communication. Philadelphia: University of Pennsylvania Press; 1970.
9. Berger BA. Communication Skills for Pharmacists: Building Relationships, Improving Patient Care. 3rd ed. American Pharmacists Association; 2009.
10. Davidhizar R, Giger JN. When touch is not the best approach. J Clin Nurs [Internet]. 1997;6(3):203–206.
11. Hertenstein MJ, Keltner D, App B, Bulleit B a, Jaskolka AR. Touch communicates distinct emotions. Emotion. 2006;6(3):528–533.
12. Halpern J. What is clinical empathy? J Gen Intern Med. 2003;18(8):670–674.
13. Elliott R, Filipovich H, Harrigan L, Gaynor J, Reimschuessel C, Zapadka JK. Measuring response empathy: The development of a multicomponent rating scale. J Couns Psychol. 1982;29(4):379–87.
14. McHenry M, Parker PA, Baile WF, Lenzi R. Voice analysis during bad news discussion in oncology: Reduced pitch, decreased speaking rate, and nonverbal communication of empathy. Support Care Cancer. 2012;20(5):1073–8.

Attention deficit hyperactivity disorder across the lifespan

Nigel Camilleri MD(Melit.), MD(Newcastle), MRCPsych(UK), CCT (UK), DCP (Ire)
Andrea Saliba MD(Melit.), MRCPsych (UK)
Nadine Calleja Stafrace MD

Mental Health Services, Mount Carmel Hospital, Attard, Malta
Email: nigel.a.camilleri@gov.mt
Email: andrea.a.saliba@gov.mt
Email: nadine.calleja-stafrace@gov.mt

Educational aims

- The most up to date research on Attention Deficit Hyperactivity Disorder, in a succinct complete way
- A description of a multimodal assessment for ADHD
- A complete description of treatment methodologies available for people with ADHD
- To answer questions often asked of ADHD and its treatment

Key words
Attention deficit hyperactivity disorder, multimodal assessment, medication, non-pharmaceutical interventions, evidence based

Abstract

This article is a research summary of published and non-published work pertaining to Attention Deficit Hyperactivity Disorders (ADHD). ADHD is one of the most common child mental health disorders and is under-recognised in children (5.29%) and adults (2.5%). ADHD is highly heritable with a multifactorial pattern of inheritance. Siblings and parents of a child with ADHD are 4 to 5 times more likely to have ADHD. Methylphenidate is the first line pharmacological treatment with a combined response (this includes trials of other licensed amphetamines) rate of 95%. All clinicians working in mental health should be aware of this disorder, comfortable diagnosing and treating people with ADHD. Young people with untreated ADHD are 5 times more likely to develop antisocial behaviour, substance abuse and other co morbid psychiatric disorders.

Introduction

The purpose of the review is to cover the epidemiology, aetiology, diagnostic criteria and different managements of Attention Deficit Hyperactivity Disorder (ADHD) with specific reference to practice of ADHD assessment and treatment management in Malta. This review's target audience is for all clinicians to better understand what ADHD is and explain any misconceptions there are related to the medications which are used to manage ADHD and relate this to Malta. The authors will look to answer the questions using evidence based published and unpublished research.

What is ADHD?

ADHD is among the most common neurobehavioural disorders presenting in children and adolescents.[1] It is characterised by persistent symptoms of inattention, hyperactivity and impulsivity according to Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM 5) present in two of three environments (namely home, school, clinic).[2] The onset of the symptoms must have been present before the age of 12 years; this was increased from the previous DSM- IV due to the recognition that adults may also be diagnosed with ADHD, however may not clearly remember their symptomatology in early childhood.[2] This increase in age to diagnosis was thought to create a sudden rise in the prevalence of ADHD diagnosis around the world. ADHD is also classed under the term Hyperkinetic Disorder in the International Classification of Diseases 10th edition (ICD10) with similar characteristics including early onset, disorganized, ill-regulated, excessive activity, recklessness and impulsivity.[3] The main difference between the DSM-5 and ICD-10 diagnostic criteria is that in the former a young person (YP) may be diagnosed with concentration difficulties only, also known as Attention Deficit Disorder (ADD) or hyperactivity and impulsive symptoms but no concentration difficulties or ADHD combined type (attention, hyperactivity and impulsive symptoms). As opposed to the ICD-10 diagnostic criteria where a diagnosis is made only when all three core symptoms are present.[3]

Over the last decade there has been interest in the pragmatic use of social language in children with ADHD, this is the domain that manages conversational contexts. It was reported that as many as 50% of children with ADHD[4] have less

developed pragmatic language skills (receptive and expressive) related to their typically developing peers. They also suffer from a developmental delay in onset of talking.[5,6] As a result, social problems are reported in 52-82% of children with ADHD7; such as having fewer reciprocated friendships,[8] and being more often disliked by their peers.[9] Social problems arise due to symptoms of impulsivity (e.g. interrupting, difficulty waiting their turn), and inattention (e.g. not listening). This means that a child with ADHD has a greater chance of getting into trouble at school and then when called in to explain to the teacher what really happened, struggles to verbalise the experience, as a result may be judged as defiant. Subsequently peer rejection and education failure has been associated with negative long-term outcomes such as substance abuse, delinquency and academic problems.[10]

Is ADHD a valid diagnosis in adults?

ADHD is a common behavioural disorder that is associated with significant adult psychopathology, social and academic impairments and the risk for negative long-term outcomes. There is no doubt that in many cases ADHD symptoms persist into adult life and cause significant clinical impairments. ADHD diagnosed in childhood tracks on through to adulthood, with 4-15% of adults retaining the full diagnosis and 50-66% of YP presenting in partial remission of ADHD symptoms.[11,12,13] The main clinical issue is recognition of the disorder in adults and quantifying the impact on adult mental health.[12]

To date there has been considerable debate on whether ADHD is a disorder solely present in YP or whether there is evidence that ADHD symptoms persist through to adult life. The latter hypothesis, is strongly supported by research,[11] which found that symptoms of ADHD persist in 65% of adults. Furthermore, it is thought that the ADHD symptoms do not resolve in adulthood, but rather adults develop the required social skills to control and mask their ADHD symptoms and adapt to social requirements.[11] On the other hand, Moncrieff has argued that the validity of symptoms in adults do not automatically follow those used to diagnose children and concluded that the rapid growth in interest in adult ADHD could be the result of the drug companies seizing the opportunity to expand on a lucrative market.[14]

Clinical presentation in adults

Adults with ADHD clinically present with more symptoms of poor attention (rather than hyperactivity) and ceaseless mental activity (distracted mind) such as procrastinating to start a job, then trying to multitask and carry out a number of jobs at the same, without ever finishing any of these jobs or finishing them with careless mistakes. Hyperactivity (over activity) is not as prominent symptom in adults, since adults learn to manage their behaviour, on the one hand through learning to adapt to social norms and also due to development (maturity) of the pre-frontal cortex. Mood dysregulation and lability are common symptoms in adults with ADHD. These symptoms lead to low tolerance of frustration, falling out with peers and colleagues, and as a result this effects their self-esteem and can lead to poor performance at the work place.

Adults with ADHD prefer occupations that are exciting and busy and that have an element of risk, such as: sales, stock broking, entrepreneurial ventures. They undergo frequent changes in employment, have poor planning abilities, e.g.: organising finances, handling course work at college, live and work in a messy environment, enjoy reckless driving, have trouble maintaining stability within their relationships and as a result may suffer from social isolation. They may choose to engage in leisure activities that are highly absorbing or stimulating, such as downhill skiing or high-contact sports. Adults with ADHD usually have difficulty organising their homes, such as cooking regular meals, cleaning and managing their children (e.g. packing their lunches, getting them to appointments and school on time).[15]

Newly diagnosed adults with ADHD have presented in adulthood, the commonest precipitant factors for these include: infection (e.g. Rheumatic fever), degenerative disorders (e.g. early onset dementia), acquired brain injury (e.g. punch drunk syndrome) and intoxication (e.g. heavy metal poisoning).

There is, thus, clear evidence that ADHD is evident in adults but the diagnosis of adult ADHD is complex and the diagnostic criteria may be unreliable. Untreated YP with ADHD symptoms who are exposed to high expressed emotion within their families and experience poor social interactions, have a higher risk of developing conduct disorder (anti-social personality traits) symptoms in adulthood.[16,17]

Epidemiology - how common is ADHD?

The worldwide prevalence of ADHD in children 0 - 18 years was reported to be 5.29% in a systematic review and meta-regression analysis conducted by Polanczyk *et al*,[18] with minor differences found between countries around the world. For example in the United Kingdom it was estimated that the prevalence of ADHD is 2.23% of children age 5-15 years.[19] Whilst in the United States of America, the National Health Interview Survey (NHIS) in 2006 estimated the prevalence of ADHD among children age 3-17 is 7%.[20] The possible reasons for the significant difference in prevalence rates between these two countries has been widely debated; the most common reasons for the low prevalence reported in the UK is due to the strict adherence to ICD-10[2] as opposed to the DSM-5 in the USA. Furthermore, Biederman *et al*[19] reported that the USA have higher rates of social deprivation and experiences of trauma as a country when compared to the UK. In addition, one of the reasons apart from the more lax DSM-5 criteria for diagnosing ADHD, is that for parents to get clinician reviews refunded by insurance, a diagnosis needs to be given. It is reported that ADHD is more common in YP living in urban rather than rural communities and there is a link with low socio-economic status. It is believed that ADHD is an under-identified and under treated disorder.[21]

In adulthood, the overall pooled prevalence rate for adult ADHD was 2.5%[22] reported in a robustly conducted meta-analysis. Furthermore, Simon *et al* reported that children do not outgrow the disorder (ADHD) but they outgrow the diagnostic criteria (ICD-10, DSM-5), therefore this means that there may be an underestimation of the true prevalence of this disorder in adults. Some of the reasons for the possible underestimation include: different methodological and diagnostic differences used in the different studies lead to differences in results, symptom recall bias, the use of DSM-5 diagnostic criteria to diagnose adult ADHD[23] which were written for YP, not adults,[12] and the overlap of the symptoms of adult ADHD with other disorders, as well as the adult co-morbid disorders.[12]

ADHD is more prevalent in males than females,[24] however the ratio varies depending on the study design of populations. The reported range varies between 9 males is to 1 female and 2.5 is to 1.[25] Further analysis has gone into why

there is such a discrepancy between males and females, it was hypothesised that it is almost socially accepted for boys to be hyperactive (boisterous), however girls are praised for being more obedient. It is also reported that girls tend to daydream more. However, day dreamers tend to still be quiet in class, therefore not picked up by teachers as having a concentration problem which may be effecting their overall academic potential.

The Evolving Concept of ADHD - is this a disorder created by today's world?

The diagnosis of ADHD in children has been a controversial issue for many years, with some researchers arguing that it does not exist and whilst others presenting evidence of its existence. Similar controversy as expected evolved in reaction to the diagnosis of adults with ADHD.[17] The skepticism about adult ADHD is influenced by the absence of well validated and universally accepted diagnostic criteria so adult ADHD diagnosis is significantly biased by current level of functioning.[22]

The evolution of the concept of ADHD goes back to the early 20th century when Still in 1902 described children with hyperactivity and poor attention as having a "defect of moral control".[26] The first reported use of a stimulant to reduce hyperactivity was by Bradley who used Benzedrine (stimulant) in children as early as 1937.[27] Furthermore DSM-II included the earliest form of ADHD in their criteria, describing it as "hyperkinetic reaction of childhood". This evolution of ADHD as a disorder continued with the latest edition of the DSM-5 broadening the age of onset from "on or before age 7" to "on and before age 12".

Aetiology - Is ADHD a group of behaviours acquired through one environment or is there a genetic linkage?

ADHD is a developmental disorder, which is biologically based but environmentally influenced. There is no one gene which causes ADHD, due to interactions between multiple genes of small effect size.[28] It is understood that ADHD results from an interacting combination of genetic and environmental factors.[29] Genetic studies including twin and adoption studies indicate high heritability of 0.8. Family studies report a 57% prevalence rate in children of ADHD adults, whilst parents and siblings of a child with ADHD have an increased risk of 4 to 5 times being more likely to have ADHD than the general population.[30,31]

ADHD is best viewed as a gene-environment interaction. Currently there are two predominant theoretical models used to explain ADHD with a genetic predisposition. Each based on a distinct neuropsychological deficit: first executive dysfunction underpinned by deficient inhibitory control mechanisms and second, delay aversion, underpinned by behaving impulsively in order to avoid delay. Children with a biological predisposition will manifest the disorder when placed in the correct environment, typically one characterised by chaotic parenting.[32]

The neurobiology of ADHD suggests its association with cognitive processing deficit [24] and the pathophysiology is strongly linked to dopamine and norepinephrine neurotransmitter systems in frontostriatal circuitry based on brain imaging, carried out in neuropsychological and pharmacologic studies.[25] Rutter *et al* indicated that the main problem lies in "behavioural dysregulation, executive deficits in inhibitory control and working memory, and delay aversion".[24]

Neuroimaging studies of children have shown smaller amygdala volumes which were not evident in adults with ADHD.[33] Poor functioning in the striatum, frontal lobes, and posterior periventricular regions are indicated in attention problems.[34] The hypofrontality theory suggests that ADHD is associated with subnormal activation of the prefrontal systems responsible for higher-order motor control.[35]

For complex conditions such as this, biological based phenotypes that lie in the pathway from genes to behaviour may provide insight into the link. Such endophenotypes have aided the clarification

Table 1: ADHD diagnostic criteria[2,3]

Symptoms Groups		
Inattention	**Hyperactivity**	**Impulsivity**
Does not attend	Fidgets	Talks excessively
Fails to finish tasks	Leaves seat in class	Blurts out answers
Cannot organise	Runs/climbs excessively	Cannot await turn
Avoids sustained effort	Cannot play/work quiet-ly	Interrupts others
Loses things	Always "on the go"	Intrudes on others
Forgetful		Blurts out answers
Easily distracted		
Does not listen		

DSM-IV ADHD	ICD-10 HKD
Either or both of following:	All of following
At least six of nine inattentive symp-toms	At least six of eight inattentive symp-toms
At least six of nine hyperactive or impulsive symptoms	At least three of five hyperactive symptoms
	At least one of four impulsive symp-toms

Pervasiveness

Criteria are met in one situation and impairment is present in another Criteria are met in more than one situation

of aetiology at pathophysiology of several conditions in medicine. Neuropsychological impairments, neuroimaging and electrophysiological paradigms for ADHD show potential to move molecular genetics research forward. However, familial or genetic overlaps between these constructs still remain unclear. The identification of an 'endophenotype' to help clarify which 'at risk' subjects will go on to develop ADHD could help reduce this high rate of disability.[32]

Environmental factors also play a role in the development of ADHD, these include severe neglect resulting in attachment disorders.[36] A lot of work and research has come out of the seminal Bucharest studies, these are large scale studies conducted on children raised in very deprived conditions in the Romanian orphanages in the times of Caucescu. The findings reveal that children who suffered from maternal and nutritional deprivation at the ages of 0 to 1 year are likely to have under developed right limbic systems and as a result suffer from emotional dysregulation.[37] Further environmental factors include, obstetric complications[38] although this theory is currently disputed, very low birth weight (<1000g), pre or post-natal insults, exposure to lead poisoning, head trauma[25] and nutritional deficiency were expansively shown to contribute to the development of ADHD.[39]

Proportion of co-morbidity in people suffering from ADHD

If ADHD is under or misdiagnosed or not managed well, the prognosis for YP is poor; this means that there will be negative social, academic and vocational consequences. A large proportion (78%) of YP with ADHD tend to present with at least one co-morbidity, the commonest include mood disorders (40%), substance dependence (35%), anxiety disorders (25%).

Furthermore, co-morbid psychiatric conditions are not uncommon in adults with ADHD. By comparing adults with ADHD with a sample of YP without the childhood psychopathology, the results show high rates of antisocial personality disorders with poorer prognosis,[24] these rates vary from 12%[12] to 23%[13]. Other co-morbidities include a high rate of substance abuse,[12,24] depression,[40] anxiety and bipolar disorder[41] Social impairment, repetitiveness or perseveration, rigidity and inflexibility[42] are also common co-morbidities.

Assessment process - is a one stop shop at a psychiatrist for a Methylphenidate prescription considered good practice?

According to NICE guidelines 2008[43], a diagnosis of ADHD should follow a multimodal approach. Therefore, the diagnosis needs to be made by a multidisciplinary team (MDT) specialised in ADHD. These include a clinical assessment of the YP, the ADHD symptoms in the different domains and settings over the past 6 months, substantiated by using standardised rating scales e.g. Connors',[44] SNAP–IV[45]. The initial assessment is then followed by a developmental (including prenatal, infant and early years) and neuropsychiatric history (ADHD symptoms e.g. DIVA 2.0[46] and assessment of co-morbidities e.g. anxiety, depression, learning disorders, autism spectrum disorders, tics, substance misuse), obtaining a collateral history and assessment of the YP's current mental state. A school or home observation are valuable adjuncts to reviewing the YP in their natural environment. Furthermore, obtaining a family psychiatric history, especially concerning learning problems, attention and behaviour problems, ADHD and tics and enquiring about all first-degree relatives (parents, siblings and offspring) is necessary. A physical examination to rule out medical causes of symptoms (e.g., serious head injury, seizures, heart problems, thyroid problems) or contraindications to medical therapy (e.g., hypertension, glaucoma) and to get baseline recordings of heart rate, blood pressure, weight and height are also required.

There are some controversies around the use of cognitive testing, however, there are centres of excellence such as the Tees Esk and Wear NHS Foundation Trust who recommend the use of a Weschler Intelligence scale for children - WISC V[47] and the administration of the TEACH.[48] The former assesses not only the intelligence quotient of the child, but also gives an indication of the working memory and processing speed of the YP. Lower scores in these domains could give rise to the suspicion of attention problems. Furthermore, the actual assessment process gives the psychologist the time to subjectively observe the level of attention, hyperactivity (ability to sit) and impulsivity (when answering questions) the YP displays in clinic. On the other hand, the TEACH is a computer test, which objectively measures various forms of attention e.g. sustained and joint attention.

The diagnosis of ADHD is then made at a MDT meeting where all the reports of the YP are brought together and discussed. This diagnosis is then made based on the chosen diagnostic criteria and level of functioning of the YP. The diagnosis is presented together with the strengths and weaknesses of the YP and recommendations are given at a feedback session, accompanied by a report to parents or care givers and YP.

Can a diagnosis be made in children under the age of 5?

Published literature suggests that neuropsychological symptoms of ADHD are present from birth, but the disorder is rarely diagnosed at preschool age. The reasons for this is that the brain is still undergoing neural pruning and developing cranio-frontally under the age of 5, therefore most children at the age of 3 will present with little executive function ability (which is derived from the pre-frontal cortex). As a result, the brain would appear to be almost all overactive and with a poor ability to concentrate and make rational decisions over impulsive ones. As a result, an early diagnosis would often result in a number of false positive results, furthermore, side effects from treatment with stimulants in under 5 year olds are as high as 33%, which is much higher than reported in school age children. However, research does report that ADHD symptoms could be identified as early as 15 months in females and 24 months in males.[49] Behavioural correlates to ADHD in preschool age children include difficult temperament and regulatory disturbances e.g. increased irritability, crying, hyperactivity and sleep problems.[50] A higher prevalence of externalising and internalising symptoms,[51] social problems,[52] learning problems[53] in preschool age children are all linked to an increased risk for developing and being given an ADHD diagnosis in later years.

NICE recommends that the first line of treatment for pre-school age children is parent-training and education programmes.[43] These programmes are the same as those recommended for the parents or carers of other children with conduct disorder. Drug treatment is not recommended for preschool children with ADHD.

Management

The combination of a number of interventions may have a role in managing children and adults with ADHD including pharmacological, neuropsychological and environmental interventions.[34] Methylphenidate is suggested as the first line of pharmacological treatments.[34,41] Other common treatments include Atomoxetine, and other amphetamines[34,41] such as Lisdexamfetamine a combination medication containing 25% levoamphetamne and 75% dextroampethamine. The latter is licensed for ADHD and narcolepsy but is also used as a performance enhancer in athletes and cognitive enhancer in students, apart from recreationally used as an aphrodisiac and euphoriant. However, other pharmacological treatments are used but with less supporting evidence, these include: alpha-2 agonists such as Guanfacine, Clonidine, antipsychotics such as Risperidone, Bupropion, Modafinil, and antidepressants with nor-adrenergic effects such as Amitriptyline, Imipramine, and Venlafaxine.[41] Management of ADHD must be delivered by a specialist in ADHD and is often done in combination with parenting groups such as the Incredible Years[53] and other non-pharmacological management; these include a range of psychological therapies e.g. Cognitive Behavioural Therapy (CBT), Behavioural Therapy, Family Therapy. Psychoeducation provided to the YP and parent is of outmost importance to ensure good understanding of the disorder, self-management of the symptoms and compliance to prescribed medication. This involves passing on the appropriate information and advice to parents and YP, informing GP, with school education of the care plan being provided. Special diets, avoidance of food colourings and exercise as well as other therapies such as neurofeedback should be discussed as part of the care plan.

In mild to moderate ADHD diagnosed in school age children, group-based parent training and education programmes are usually the first-line treatment. This may also include psychological treatment such as CBT and/or social skills training. Drug treatment is not indicated as the first-line treatment for all school-age children and YP with ADHD. It should be reserved for those with severe symptoms and impairment or for those with moderate levels of impairment who have refused non-drug interventions, or whose symptoms have not responded sufficiently to parent-training/education programmes or group psychological treatment.[43,54]

Pharmacological management

Stimulants (methylphenidate and amphetamines) - Why should I give my over active child a stimulant?

The use of psychomotor stimulants to treat the symptoms of ADHD has been reported in published literature as far back as 1937 by Bradley.[27] Bradley reported significant improvement in school performance after 1 week treatment of Benzedrine (stimulant) in 14 of 30 children with behaviour problems.[27] Later in 1957, methylphenidate hydrochloride was first used as a treatment for ADHD.[34] The efficacy for methylphenidate and amphetamines measured in Numbers Needed to Treat (NNT) is 4 and the effect size is 1.0, making this medication one of the most efficacious in all medicine.

There is little variety between the efficacy of slow release methylphenidate, with Concerta XL® having a NNT of 1.9 and Equasym XL® a NNT of 5.3, however, the lower NNT of Concerta XL® is thought to be a result of the poorer quality of the study design. The effect size of Atomoxetine is 0.7 with a NNT of 4.2, making it also a very efficacious medication. If a YP is diagnosed correctly with ADHD then the response rate with one of the stimulants is 95% (refer to Table 2[55]).

Methylphenidate is a central nervous system (CNS) stimulant. The mode of therapeutic action in ADHD is not exactly known.[56] However following on from the hypofrontality theory[24] it is understood that this medication stimulates the under developed dorsolateral prefrontal cortex in YP with ADHD, thereby increasing the concentration of the YP who is otherwise over attending to all diverse stimuli and providing negative neuronal feedback from the higher brain centre. This enables the YP in a classroom situation to follow the social norms and remain sitting down, rather than getting out of their place when this is not acceptable. At a neurotransmitter level, Methylphenidate blocks the presynaptic membrane dopamine transporter and thereby inhibits the re-uptake of dopamine and noradrenaline into the presynaptic neuron.[41]

Methylphenidate immediate release (Ritalin®) is a racemic mixture comprised of the d- and l-threo enantiomers.[56] This medication has a half-life of 3 to 4 hours, which means the YP must take at least 3 tablets to cover the school day and afternoon homework period. This medication has an on off effect, just like Paracetamol, and the medication is found to be out of the blood system within a few hours, therefore, there are no long-term side effects on the YP. However, the on off effect does mean that the blood level of Methylphenidate varies throughout the time in which it is effective, causing frustration to the YP who notices their concentration fluctuating throughout usage time.

The extended release form such as Metadate CD® comprises both of an immediate release component (30% of the dose) and an extended release component (70% of the dose)[55] or such as Concerta® which uses osmotic pressure to deliver methylphenidate hydrochloride at a controlled rate.[57] The extended-release form of methylphenidate was initially developed to address the issues of multiple dosing and compliance issues in children and adolescents. It was developed in the early 1980s.[57] Potential advantages for the extended-release methylphenidate might be the improved compliance and adherence to medication and avoidance of multi daily dosing. However, the 30/70% release formulation means that during

Table 2: Behaviours that reflect executive function impairments in adults[55]

Activation: organising, prioritising and initiating work
Focus: focusing, sustaining and shifting attention to tasks
Effort: regulating alertness, sustaining effort and processing speed
Emotion: managing frustration and regulating emotions
Memory: utilising working memory and accessing recall
Action: monitoring and self-regulating of activities

Table 3: Medication efficacy in psychiatry[65]

Medication Efficacy	Numbers Needed to Treat (NNT)	Effect Size (range 0-1)
Methylphenidate	4	1.0
Amfetamine	4	1.0
Atomoxetine	4	0.7
SSRI for depression in adults	10	0.5
Antipsychotics for Schizophrenia in adults	10	0.25

the morning when the YP may need to concentrate the most, is the time when the least concentration of methylphenidate is released into the blood stream, and only reaching its peak blood concentration at 12pm. Immediate release methylphenidate might have some advantages when it is used in older adolescents and adults for targeted situations such as important meetings/ events or exams.

Medikinet retard® and Equasm XL® are medium release preparations with half-lives of 8 hours, the former is released in a 50/50% release formulation, whilst the latter is released in a 30/70% formulation. The advantage of having an 8-hour preparation is that since insomnia and reduced appetite are major side effects of stimulants, not all children are awake for the full 12 hours and also, if Concerta XL® is given at 7am the YP would not develop an appetite till after 7pm, which means that the child would then have a late evening meal and then struggle to fall asleep.

Therapeutic effects of medication include improvements in ADHD symptoms, peer and family relationships, improved learning, self-esteem and social skills. A good response to methylphenidate is predicted in people with higher levels of inattention, restless behaviour and those of a younger age.

Clinical monitoring with medication include: pre-treatment, plotting height and weight on a growth chart, checking hearing clinically, assessing motor coordination and a cardiovascular examination. During treatment: measurement of weight and height, blood pressure and pulse are required.

What are the long-term side effects of taking methylphenidate?

There are no reported long-term side effects with methylphenidate, however, there are recently reported studies for the development of tolerance with very long-term use, therefore 'drug holidays' are recorded so as to reduce this risk. The commonest short-term side effects are sleep deprivation, this is avoided by not taking the medication after 4pm, and appetite suppression. xcv The latter is managed by encouraging the YP to take a good breakfast and then a large evening meal. Methylphenidate does not directly affect the growth potential of the child, however if the child is losing weight then there is a chance that the child will not achieve their potential height. Other common initial side effects include headaches, irritability, tics, tremor, dizziness, over stimulation and blurred vision, most of which disappear after a few weeks of taking the medication. Rare and dangerous side effects include psychosis, seizures, neuroleptic malignant syndrome, mania, palpitations, hypertension and sudden death.[57] There is some research on the potential for drug diversions and misuse, however Methylphenidate does not have a euphoric effect on YP that have ADHD and need this medication for therapeutic purposes.

Non-Stimulants

Atomoxetine increases noradrenaline and may also increase dopamine in the prefrontal cortex. It also blocks noradrenaline re-uptake pumps. Atomoxetine appears to be an efficacious treatment of children and adults with ADHD, and has a half-life of 24 hours so is prescribed as a once daily dose and is not a controlled drug. Its lack of abuse potential may be an advantage. The effect size is smaller (0.7) than that of the stimulants,[58] however in recent findings published by,[59] it was reported that once the controlling for parental reporting, the effect size of Atomoxetine was only 0.3 (which means a mild effect).

There are no long-term adverse effects of Atomoxetine, however the notable immediate effects include sedation and fatigue, a decrease in appetite (however this is less than for stimulants), an increase in heart rate of 6 to 9 beats per minute and an increase in blood pressure of 2 to 4 mmHg. Insomnia, anxiety, agitation, irritability, dizziness, nausea and vomiting are reported, however, these generally subside within 2 weeks of starting medication. Rare but potentially life-threatening side effects include orthostatic hypotension, hypomania, mania, suicidal ideation and very rarely liver failure.

Non-Pharmacological treatment

Non-pharmacological management for ADHD includes behavioural therapy, CBT, family therapy, social skills training, parenting groups, neurofeedback, special diets, avoiding eating food with artificial colouring from ones diet and supplementation with free fatty acids such as omega 3 and 6. This treatment could be used alone or in combination with stimulant medication and must be maintained over an extended period of time for more positive and long lasting results. The results on non-pharmacological studies remain mixed. In the large MTA follow up study[60] there was no difference found between those YP prescribed stimulant medication alone compared to those receiving a combination of medication and psychological treatment.[60] There are some small scale individual studies which demonstrate the benefit of omega 3 and 6 fatty acids,[61] cognitive training,[62] parenting groups[54] and removal of diets containing artificial colouring, however in a large and robust systematic review and meta-analysis, it was found that only in the case of food colouring was there some evidence to show the benefit on the treatment of ADHD symptoms and all the rest showed no difference when compared to placebo effect.[63]

Conclusion

ADHD is a common neurodevelopmental disorder which is possibly under-recognised in mental health settings and in community

both in children (5.29%)[18] and adults (2.5%).[18] ADHD is a highly heritable disorder 0.76 and parents and siblings of a child with ADHD are 4 to 5 times more likely to have ADHD.[30,31] ADHD is easy to treat with 95% of correctly diagnosed patients (children or adults) responding to treatment[11,64] Methylphenidate is suggested as the first line of pharmacological treatments.[34,41] For most patients with ADHD symptoms, these should be safely managed by the use of a single medication, however there is evidence where methylphenidate immediate release has been added to augment the effect of methylphenidate extended release and also that of Atomoxetine, when the clinical response remains inadequate. There is initial good evidence which suggests that stimulants and alpha-2 agonist combinations may have an additive effect, improving effectively and reducing adverse side effects. The evidence for non-pharmacological treatment of ADHD remains mixed,[63] there is some evidence to support the removal of food supplements from the diet of YP with ADHD and combination of psychological treatments and parenting groups with medication could have an added effect.[60] All general psychiatrists should be aware of this disorder and be comfortable with making the diagnosis and treating both children and adults with ADHD.

References

1. WilensT, Spencer TJ. Understanding Attention-Deficit/Hyperactivity Disorder from Childhood to Adulthood. Postgrad Med J. 2010;122(5):97-109.
2. World Health Organization. International Classification of Diseases 10th edition (ICD10). Revision 1. Geneva: World health organization. Division of mental health; 1994.
3. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
4. Cohen NJ, Vallance DD, Barwick M, Im N, Menna R, Horodezky NB, et al. The Interface between ADHD and Language Impairment: An Examination of Language, Achievement, and Cognitive Processing. J Child Psychol Psychiatry. 2000;41:353-362.
5. Hartsough CS, Lambert NM. Medical factors in hyperactive and normal children: Prenatal, developmental, and health history findings. Am J Orthopsychiatry. 1985;31(6):190-201.
6. Berk L, Potts M. Development and functional significance of private speech among attention-deficit hyperactivity disordered and normal boys. J Abnorm Child Psychol. 1991;19(3):357-377.
7. Landau S, Milich R, Diener M. Peer relations of children with attention-deficit hyperactivity disorder. Reading and Writing Quarterly. 1998;14:83-105.
8. Hoza B, Mrug S, Gerdes AC, Hinshaw SP, Bukowski WM, Gold JA, e al. What Aspects of Peer Relationships Are Impaired in Children With Attention-Deficit/Hyperactivity Disorder? J Consult Clin Psychol. 2005;73(3):411-423.
9. Bickett L, Milich R. First Impressions Formed of Boys with Learning Disabilities and Attention Deficit Disorder. J Abnorm Child Psychol. 1990;24:457-470.
10. Greene RW, Biederman J, Faraone SV, Wilens TE, Mick E, Blier HK. Further Validation of Social Impairment as a Predictor of Substance Use Disorders: Findings From a Sample of Siblings of Boys With and Without ADHD. J Clin Child Psychol. 1999;28:349-354.
11. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Pscyhol Med. 2000;36(2):159-165.
12. Mannuzza S, Klein R, Bessler A, Malloy P, LaPadula M. Adult Psychiatric Status of Hyperactive Boys Grown Up. Am J Psychiatry. 1998;155(4):493-498.
13. Weiss G, Hechtman L, Milroy T, Perlman T. Psychiatric status of hyperactive as adults: a control led prospective 15-year follow-up of 63 hyperactive children. J Am Acad Child Psychiatry. 1985;24(2):211-220.
14. Moncrrieff J, Timmi S. Is ADHD a valid diagnosis in adults? No. BMJ. 2010;340(547):736-737.
15. Weiss M, Murray C. Review Assessment and management of attention-deficit hyperactivity disorder in adults. CMAJ. 2003;168(6):665.
16. Golding J, Pembrey M, Jones R; ALSPAC Study Team. ALSPAC–The Avon Longitudinal Study of Parents and Children. Paediatr Perinat Epidemiol. 2001;15(1):74-87.
17. Schepank H. Epidemiology of psychogenic disorders - The Mannheim Study· Results of a Field Survey in the Federal Republic of Germany. Mannheim: Springer Science & Business Media; 2012.
18. Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA. The Worldwide Prevalence of ADHD: A Systematic Reviewand Metaregression Analysis. Am J Psychiatry. 2007;164:942-948.
19. Biederman J, Petty CR, Evans M, Small J, Faraone SV. How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. Psychiatry Res. 2010;177(3):299-304.
20. Bloom Barbara, Cohen Robin A. National Center for Health Statistics. Vital and Health Statistics. Vol. 10. Washington DC: U.S Department of Health and Human Services; 2007.
21. Costello EJ, Angold A, Burns BJ, Stangl DK, Tweed DL, Erkanli A, e al. The Great Smoky Mountains Study of YouthGoals, Design, Methods, and the Prevalence of DSM-III-R Disorders. Arch Gen Psychiatry. 1996;53(12):1129-1136.
22. McGough JJ, Barkley RA. Diagnostic Controversies in Adult Attention Deficit Hyperactivity Disorder. Am J Psychiatry. 2004;161:1948-1956.
23. Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder:meta-analysis. Br J Psychiatry. 2009;194:204-211.
24. Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. J Child Psychol Psychiatry. 2006;47(3/4):276-295.
25. Rappley, MD. Attention Deficit–Hyperactivity Disorder. N Engl J Med. 2005;352:165-173.
26. Still GF. Some Abnormal Psychical Conditions in Children: Excerpts From Three Lectures. J Atten Disord. 2006;10(2):126-136.
27. Bradley C. The behaviour of children receiving Benzedrine. Am J Psychiatry. 1937;94:577-585.
28. Rutter M, Moffitt TE, Caspi A. Gene–environment interplay and psychopathology: multiple varieties but real effects. J Child Psychol Psychiatry. 2005;47:226–261.
29. Nigg J, Nikolas M, Burt A. Measured Gene-by-Environment Interaction in Relation to Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry. 2010;49(9):863-873.
30. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, et al. Molecular Genetics of Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry. 2005;57(11):1313-1323.
31. Faraone SV, Biederman J, Spencer T, Wilens T, Seidman LJ, Mick E, et al. Attention-deficit/ hyperactivity disorder in adults: an overview. Biol Psychiatry. 2000;48(1):9-20.
32. Rutter M. Nature–Nurture Integration. In: Lewis M, Rudolph KD. Handbook of Developmental Psychopathology. US: Springer; 2014: p.45-65.
33. Perlov E, Philipsen A, Tebartz van Elst L, Ebert D, Henning J, Maier S, et al. Hippocampus and amygdala morphology in adults with attention-deficit hyperactivity disorder. J Psychiatry Neurosc. 2008;33(6):509-515.
34. Janakiraman R, Benning T. Attention-deficit hyperactivity disorder in adults. Adv Psychiatr Treat. 2010;16:96-104.
35. Rubia K, Overmeyer S, Taylor E, Brammer M,

Key points

- ADHD is a common neurodevelopmental disorder which is possibly under-recognised in children and adults
- ADHD is easy to treat with 95% of correctly diagnosed patients responding to treatment
- To ensure the accuracy, a diagnosis of ADHD should be made following a multimodal assessment which is carried out by a multidisciplinary team trained in ADHD
- In younger children there is evidence to support that parenting groups and psychological treatment is effective, although the evidence is mixed regarding if combination with medication could have an added effect
- All general psychiatrists should be aware of and comfortable with making the diagnosis of ADHD and treating both children and adults

Williams SC, Simmons A, et al. Hypofrontality in Attention Deficit Hyperactivity Disorder During Higher-Order Motor Control: A Study With Functional MRI. Am J Psychiatry. 1999;156:891-896.
36. Rutter M, Maughan B. School Effectiveness Findings 1979–2002. J Sch Psychol. 2002;40(6):451-475.
37. Schore AN. Dysregulation of the right brain: a fundamental mechanism of traumatic attachment and the psychopathogenesis of posttraumatic stress disorder. Aust N Z J Psychiatry. 2002;36:9–30.
38. Biederman J. Attention-Deficit/Hyperactivity Disorder: A Selective Overview. Biol Psychiatry. 2005;57(11):1215-1220.
39. Freeman MP, Hibbeln JR, Wisner KL, Davis JM, Mischoulon D, Peet M, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry. 2006;67(12):1954-1967.
40. Alpert JE, Maddocks A, Nierenberg AA, O'Sullivan R, Pava JA, Worthington JJ 3rd, et al. Attention deficit hyperactivity disorder in childhood among adults with major depression. Psychiatry Res. 1996;62(3):213-219.
41. National Institute for Clinical Excellence. Attention Deficit Hyperactivity Disoder: Diagnosis and management of ADHD in children, young people and adults, National Clinical Practice Guideline Number 72. national institute for health and clinical excellence . London: The British Psychological Society and the royal college of Psychiatrists; 2009.
42. Kadesjo B, Gillberg C. The comorbidity of ADHD in the general population of Swedish school age children. J Child Psychol Psychiatry. 2001;42(4):487-492.
43. National Institute for Clinical Excellence. Diagnosing and managing attention deficit hyperactivity disorder (ADHD) in children over 3 years, young people and adults. It aims to improve the diagnosis of ADHD as well as the quality of care and support for people with ADHD. Guideline number CG72. ISBN: 978-1-4731-1674-0
44. Conners KC. Conners Manual. 3rd ed. Toronto, Ontario, Canada: Multi-health systems Inc; 2008.
45. Swanson J, Gupta S, Lam A, Shoulson I, Lerner M, Modi N, et al. Development of a New Once-a-Day Formulation of Methylphenidate for the Treatment of Attention-deficit/Hyperactivity Disorder. Arch Gen Psychiatry. 2003;60:204-211.
46. Kooij JS, Francken MH. Diagnostic interview for ADHD in adults (DIVA). The Netherlands: DIVA Foundation; 2010.
47. Wechsler D. Wechsler Intelligence Scale for Children® - Fourth Edition Integrated (WISC® — IV Integrated). WISC-V: 2014. Psychological scoring scale.
48. Camilleri N, Samer M. ADHD: from childhood into adulthood. MMJ. 2013;25(1):2-7.
49. Arnett AB, Macdonald B, Pennington BF. Cognitive and behavioral indicators of ADHD symptoms prior to school age. J Child Psychol Psychiatry. 2013;54(12):1284-1294.
50. Nigg JT, Goldsmith H, Sachek J. Temperament and Attention Deficit Hyperactivity Disorder: The Development of a Multiple Pathway Model. J Clin Child Adolesc Psychol. 2004;33(1):42-53.
51. Larsson H, Dilshad R, Lichtenstein P, Barker ED. Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology. J Child Psychol Psychiatry. 2011;52(9):954–963.
52. DuPaul GJ, McGoey KE, Eckert TL, VanBrakle J. Preschool Children With Attention-Deficit/Hyperactivity Disorder: Impairments in Behavioural, Social, and School Functioning. J Am Acad Child Adolesc Psychiatry. 2001;40(5):508-515.
53. Pennington BF. Nature and nurture. In: Guilford Press The development of psychopathology. New York: Guilford Press; 2002.
54. Webster-Stratton C, Reid MJ, Hammond M. Preventing Conduct Problems, Promoting Social Competence: A Parent and Teacher Training Partnership in Head Start. J Clin Child Psychol. 2001;30(3):283–302.
55. Brown TE. Executive Functions and Attention Deficit Hyperactivity Disorder: Implications of two conflicting views. Int J Disabil Dev Ed. 2006;53(1):35-46.
56. FDA. Concerta®. 2008. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021121s015s017lbl.pdf; Accessed 28 July 2017.
57. FDA. Metadate CD®. 2008. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021259s021lbl.pdf; Accessed 28 July 2017.
58. Michelson D, Adler L, Spencer T, Reimherr FW, West SA, Allen AJ, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry. 2003;53(2):112-120.
59. Sonuga-Barke E. Do psychosocial / non-pharma interventions work?. Controversies in ADHD - Emanuel Miller Lecture and National Conference. London: Royal College of Physicians 2016.
60. Jensen PS, Arnold LE, Swanson JM, Vitiello B, Abikoff HB, Greenhill LL, et al. 3-Year Follow-up of the NIMH MTA Study. J Am Acad Child Adolesc Psychiatry. 2007;46(8):989-1002.
61. Richardson AJ, Montgomery P. The Oxford-Durham Study: A Randomized, Controlled Trial of Dietary Supplementation With Fatty Acids in Children With Developmental Coordination Disorder. Paediatr. 2005;115(5)1360-1366.
62. Johnson MH. Executive function and developmental disorders: the flip side of the coin. Trends Cogn Sci. 2012;16(9):454-457.
63. Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry. 2013;170(3):275-289.
64. Faraone SV, Spencer T, Aleardi M, Pagano C, Biederman J. Meta-analysis of the efficacy of methylphenidate for treating adult attention deficit hyperactivity disorder. J Clin Psychopharmacol. 2004;24(1):24-29.
65. Bolea-Alamañac B, Nutt DJ, Adamou M, Asherson P, Bazire S, Coghill D, et al.Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(3):179-203.

Using antiepileptic drugs in children: recent developments and recommendations

[1]Hana Shabbi, [1]Anne Marie Scerri, [2]Doriette M Soler, [1]Janet Mifsud

[1]Department of Clinical Pharmacology and Therapeutics,
University of Malta Msida MSD2040 Malta
[2]Department of Paediatrics, Mater Dei Hospital, Msida Malta

Educational aims

- To understand the correct use of antiepileptic drugs in different types of epilepsy seizures in children
- To comprehend how an understanding of pharmacokinetics can improve drug therapy in epilepsy
- To recognize how appropriate pharmacological treatment of epilepsy in children can ensure better quality of life and better neurodevelopmental outcomes

Key words
epilepsy, anti-epileptic drugs, paediatrics, pharmacokinetics

Abstract

Epilepsy is one of the most common neurological disorders, with approximately 45 per 100,000 children developing new-onset epilepsy every year. Children are a vulnerable population with unique health needs and a correct diagnosis and thus correct treatment of epilepsy in children, particularly a diagnosis of early onset epilepsy, is important in order to ensure better quality of life, neurodevelopmental outcomes, cognition, education, improved level of function and future employment. Therapy with antiepileptic drugs (AEDs) aims to minimize the frequency of epileptic seizures with minimal side effects. The first generation AEDs (such as phenytoin, carbamazepine and valproic acid) are still widely used, although they are associated with serious side effects and pharmacokinetic problems (narrow therapeutic indices, nonlinear kinetics, and drug-drug interactions due to enzyme inhibition and enzyme induction properties). The novel AEDs (such as lamotrigine, levetiracetam, rufinamide, and zonisamide) have expanded the treatment options of epilepsy, however they are also associated with severe pharmacokinetic shortcomings, especially for paediatric populations.

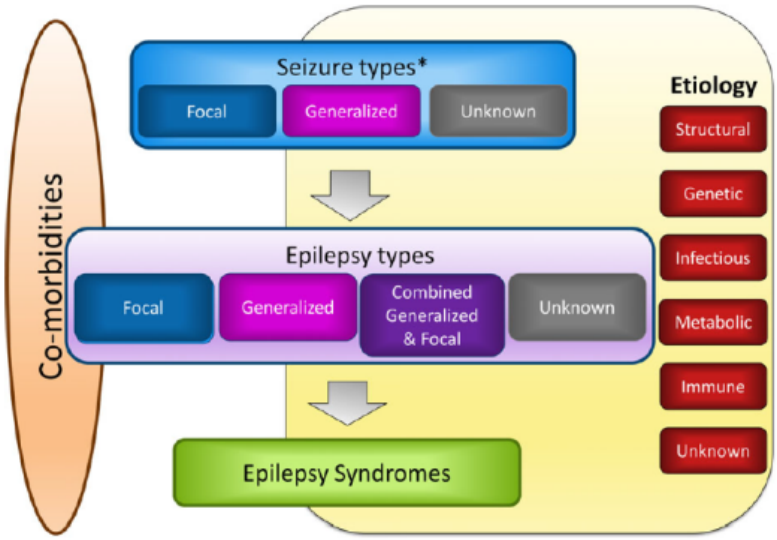
This educational article will discuss how the correct use of these drugs can lead to improved quality of life measures. This paper also provides an overview of ongoing research on the use of population pharmacokinetics in addressing the challenges paediatric populations offer to drug and dose individualisation.

Introduction

Epilepsy is one of the most common neurological disorders, occurring in the range of 0.5-1.0% of the general population.[1] It is a heterogeneous condition and classification of epileptic seizures by the International League Against Epilepsy (ILAE), the most widely adopted scheme, classifies seizures according to seizures symptoms and not underlying aetiology. A revised framework for the Classification of the Epilepsies, designed to work with the classification of seizure types, which considers levels of diagnosis: seizure type, epilepsy type (focal, generalized, combined generalized and focal, unknown) and epilepsy syndrome has just been approved by ILAE[2] (see Figure 1). Most persons with epilepsy first develop the condition in childhood with approximately 45 per 100,000 children per year developing new-onset epilepsy.[3] Between 2% and 4% of all children in Europe develop at least one convulsion associated with a febrile illness before the age of 5 years. The highest incidence of epilepsy is in the first year of life. Neonatal seizures occur in ~1.5% of neonates, febrile seizures in 2-4% of young children, and epilepsy in up to 1% of children and adolescents.[4] The paediatric population poses a challenge to the individualisation of drug therapy and this is even more so in epilepsy.

In Malta, epilepsy is known as a 'Schedule V' condition, meaning that it is one of the medical conditions in which patients can obtain free drug therapy through the Maltese National Health Service (Social Security Act, 2014). At a local level only specifically branded drugs are used in the pharmacological management of epilepsy. In a Maltese study of 220 children with epilepsy by Soler[5] the point prevalence rate of active epilepsy in children up to the age of 15 years in 1999 was 2.22 per 1000 population in females and 2.61 per 1000 in males up to the age of 15 years, with no significant difference between males and females (p=0.25). Similar findings regarding the larger number of boys with epilepsy are found in a number of studies. In Soler's study, 47% of children suffered from generalized seizures which were more common in infants and pre-school children, while 37% had partial seizures. Motor seizures were present in 30% of children while 30% had complex partial seizures with secondary generalization. There was equal prevalence of both generalised and partial seizures in school-aged children. Twenty-three per cent of children (all up to the age of 5 years) also had a history of

Figure 1: New ILAE framework for the classification of the Epilepsies. *Denotes onset of seizure (adapted from Scheffer et al., 2017[2])



febrile seizures (17% simple seizures, 5% complex febrile seizures). In Soler's study, 2% of children had infantile spasms, 30% had major motor seizures, 15% had absence seizures, 37% had partial seizures, 15% had a mixtures of seizure phenotypes, whereas 1% of seizures were unclassified.

Pharmacological therapy with antiepileptic drugs (AEDs)

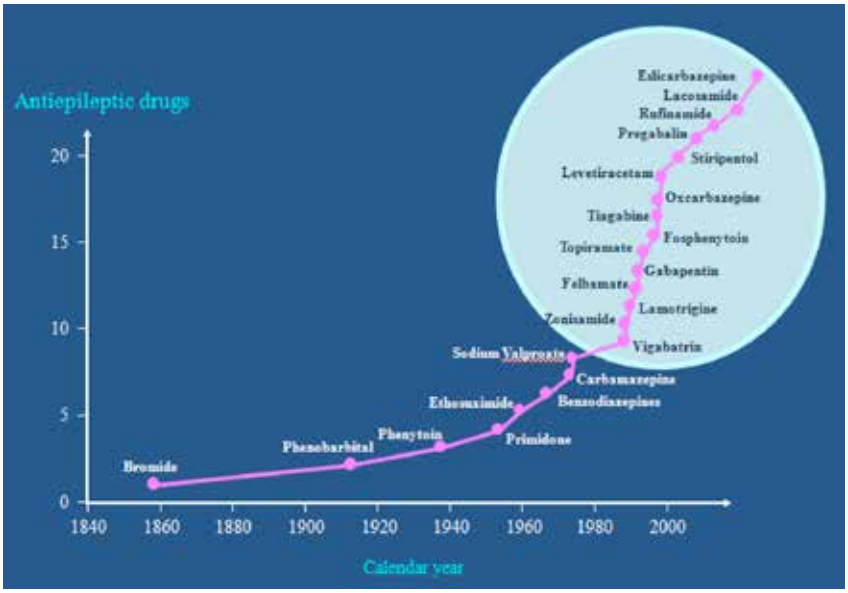
Pharmacological therapy with antiepileptic drugs (AEDs) aims to minimize the frequency of epileptic seizures with minimal side effects.[6] AEDs are used as long term adjunctive therapy or as monotherapy in epilepsy and can result in seizure freedom for around 70% of patients. The target in the treatment of epilepsy is to control seizures with low or no adverse effects. About 20 % of paediatric epilepsy population are not seizure free despite AEDs therapy either as mono or poly therapy.[7] Before 1993, phenobarbital, phenytoin, carbamazepine, valproic acid, ethosuximide, and the benzodiazepines were the only antiepileptic drugs used in the treatment of epilepsy in children. The approval of new generation AEDs expanded the treatment options for epilepsy for children and adults. These new generation AEDs have equal efficacy with better tolerability, pharmacokinetic properties, and side effect profiles compared to the older AEDs.[8]

The first-generation AEDs (phenytoin, phenobarbital, carbamazepine, ethosuximide, primidone, and valproic acid) were mostly developed before the 1960s, and they are still used, although they are associated with serious side effects and problems in the individualisation of drug therapy due to narrow therapeutic indices. They are also associated with numerous drug-drug interactions due to enzyme induction and enzyme inhibition properties and even non-linear kinetics in some case.

In 1990s, second or third generation AEDs were developed (felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin, zonisamide, eslicarbazepine acetate, and lacosamide) in attempts to address the shortcomings of the older AEDs and improve the risk-benefit ratio.[9] Consequently, the treatment options of epilepsy have been expanded, however even this novel therapy is still associated with significant shortcomings, especially for paediatric populations.

Felbamate was approved by FDA to be used in United Stated in 1993. It shows efficacy in Lennox-Gastaut syndrome and partial seizures in children.[10] Aplastic anemia and hepatic failure are life-threatening adverse side effects of felbamate. Gabapentin was approved in 1993 as adjunctive therapy in the treatment of partial seizures with or without secondary generalization as adjunctive therapy in patients 3 years and older. It is also effective in some children with refractory partial seizures and in controlling seizures associated with benign childhood epilepsy with centrotemporal spikes.[11] Lamotrigine (LTG) was approved in the USA in 1994 for the treatment of focal seizures, then in 1998 it was approved to be used as adjunctive treatment of Lennox-Gastaut syndrome. LTG is now considered as first line drug for focal seizures and generalized tonic-clonic seizures. Oxcarbazepine was approved in 2000 for the treatment of partial-onset epilepsy as monotherapy or polytherapy in patients aged 4 years or older.

Figure 2: Development of Antiepileptic drugs. Adapted from Brodie, 2010[8]



It shows equal efficacy to phenytoin with better tolerability in a randomized study in children.[12] Levetircetam was approved in 1999 for the treatment of partial-onset seizures in adults as adjunctive therapy. It shows high efficacy and tolerability in refractory mixed seizure in children.[13] Tiagabine was approved in 1997 for the treatment of partial seizures in patients 12 years of age and older as adjunctive therapy. Topiramate was approved 1997 as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures, partial-onset seizures, and seizures associated with Lennox-Gastaut syndrome in patients older than 2 years. Vigabatrin was initially licensed in 1989 however due to its visual toxicity it was eventually with withdrawn.[14] Zonisamide was approved in 2000 for the treatment of partial-onset seizures.

Local practice for the treatment of epilepsy in Malta follows the Guidelines issued by the UK's National Institute of Clinical Excellence (NICE)[15] (see Table 1). NICE guidelines also recommend that patients who do not respond to adjunctive drugs after an adequate trial of first line AED has been unsuccessful are referred to tertiary centres for evaluation in adjunction to consideration of further pharmacotherapy. An adequate trial of AED is one in which an AED (preferably one recommended by the guidelines) has been used at a therapeutic dose (preferably confirmed by means of therapeutic monitoring of serum blood levels), for sufficient duration of time, in a patient who has been adherent to drug therapy. If this trial has not been sufficient to provide seizure control, another drug may be added. If the first drug attempted has not been well-tolerated by the patient, one may change initial monotherapy to another drug which is better tolerated. In some circumstances, one may need to seek the optimum balance between, seizure control, drug efficacy, safety, tolerability and patient quality of life. NICE guidelines recommend that in the case of adults, AED therapy is initiated on the recommendation of a specialist, but in the case of children, NICE guidelines recommend that AED therapy should be initiated by a specialist directly, in the context of communication, discussion and explanation to the patient and their carers/family, as appropriate. The decision with regard to which AED to use as initial therapy depends on the nature of the presenting epilepsy syndrome or type of seizure if the diagnosis of an epilepsy syndrome is unclear. Usually, AED therapy is initiated after a second seizure. It is initiated after the first seizure if there is an associated neurological deficit, there is clear evidence of epileptic activity on electroencephalography, the risk of further seizures is deemed to be unacceptable or there is a structural brain lesion on cerebral radiographic imaging.[15]

Pharmacokinetics of AEDs

Understanding differences in the pharmacokinetics (PK) and /or pharmacodynamics (PD) between children and adults and also between children of different ages is important in the individualisation of drug therapy in epilepsy. Pharmacokinetic processes (absorption, distribution, metabolism, and elimination) and pharmacodynamic effects are affected by developmental changes in childhood.[16] For example, pH of intra-gastric fluid is higher in neonates than in adults and this can cause a decrease in the bioavailability of weak acidic AEDs such as phenytoin and phenobarbital and subsequently higher doses is needed.[17] Additionally, the delayed gastric emptying time in neonates slows the absorption of some drugs. Many studies have shown that the metabolizing enzyme capacity is changed during childhood and maturation of the enzyme systems occur at different rates. Thus, total drug clearance is highest in neonates, and declines with age reaching adult values in adolescence.

This is also the case for AEDs since many studies have indicated that the apparent oral clearance of AEDs is higher in children compared with adults.[18] Moreover, Perucca pointed out that the data available indicates that clearance of novel AEDs in children is increased by 20-170%, depending on the drug and patient's characteristics. Furthermore, the distribution of drugs in children is influenced by the changes in the body composition which is depending also on the age. For instance, the increase in body water:body fat ratio in neonates and infants leads to an increase in the volume of distribution for hydrophilic AEDs such as phenobarbital. [17]

The influence of such developmental changes in childhood on PK of a drug is

Table 1: Drugs used in the management of more common epilepsies (adapted from 2013 NICE guidelines for the management of epilepsy)[15]

TYPE OF SEIZURE	AED RECOMMENDED BY NICE GUIDELINES	TYPE OF THERAPY (INITIAL THERAPY OR ADJUNCTIVE THERAPY)
Focal	Lamotrigine, Carbamazepine	Initial monotherapy
Refractory focal	Carbamazepine, Clobazam, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Sodium valproate, Topiramate	Adjunctive
Generalised tonic-clonic	Valproate, Lamotrigine, Carbamazepine, Oxcarbazepine	Initial monotherapy
Refractory generalised tonic-clonic	Lamotrigine, Levetiracetam, Sodium valproate, Topiramate	Adjunctive
Absence	Ethosuximide, Sodium valproate, Lamotrigine	Initial monotherapy
Myoclonic	Sodium valproate, Levetiracetam, Topiramate	Initial monotherapy
Tonic or atonic	Sodium valproate	Initial monotherapy
Refractory tonic or atonic	Lamotrigine	Adjunctive
Infantile spasms	Vigabatrin or (if not due to tuberous sclerosis) add steroid	Initial therapy
Idiopathic generalised epilepsy	Sodium valproate, Lamotrigine, Topiramate	Initial therapy
Refractory idiopathic generalised epilepsy	Sodium valproate, Lamotrigine, Levetiracetam, Topiramate	Adjunctive therapy
Juvenile myoclonic epilepsy	Sodium valproate	Initial monotherapy

investigated using plasma drug concentration time profiles, which require measurements of drug concentrations from biological matrixes. Thus, these age-related PK and PD differences are rarely reported in the literature, since for ethical reasons, children are rarely included in clinical trials. Investigators usually have access only to a small number and volumes of blood samples which makes interpretation and modelling of the pharmacokinetics more difficult.[16]

In addition, it is estimated that between 50 and 90% of medicinal products used in paediatric population have never been specifically evaluated for use in that group. The absence of suitable authorised medicinal products to treat conditions in children is due to the fact that pharmaceutical companies do not perform the necessary research and development to adapt medicinal products to the needs of the paediatric population. The use of off-label and unauthorised products with the associated risks on inefficacy and/or adverse reactions is the only alternative solution for the physician to treat paediatric patients.[18] The current use of many AEDs in children is off-label and is based on the safety and efficacy derived from adult trials and from smaller uncontrolled studies in children that provide early pharmacokinetic data.[19] Most paediatric epileptologists have, to date used, ad hoc reasoning in the design of dosage regimens for AEDs in children. This may cause therapeutic failure and occurrence of severe adverse effects.

Pharmacokinetics of the new antiepileptic drugs

Thus the availability of these new AEDs in the last decades promised an increase in the efficacy of pharmacological treatment for many types of epileptic seizures in children, with reduced adverse effects and less need for therapeutic drug monitoring. Yet various shortfalls were also seen with some of these novel AEDs especially due to some of their pharmacokinetic properties. Pharmacokinetics is the study of the time course of a drug in the body, basically the liberation, absorption, distribution, metabolism and elimination of the drug. The pharmacokinetics of a drug vary from one patient to another due to several factors such as genetic factors, age, concomitant treatment, physiological and pathophysiological conditions such as pregnancy and impaired function of the liver and the kidneys.[20] This pharmacokinetics variability results in altered dosage requirements. Thus an inclusive understanding of pharmacokinetic properties of AEDs and the factors which contribute to their pharmacokinetic variability is essential for the correct use of AEDs in clinical practice.[21]

Felbamate shows linear kinetics in children and adults during mono or polytherapy.[22] The metabolism of felbamate is enhanced by enzyme-inducing AEDs such as phenobarbital, phenytoin, primidone and carbamazepine. Gabapentin's bioavailability decreases with increasing dosage, possibly because of saturation of the transporter system.[23] Lamotrigine (LTG) clearance in infants below the age of 2 months is lower than in older infants. Lamotrigine clearance is influenced by enzyme inducing and enzyme inhibiting AEDs. Enzyme inducing increases LTG clearance in children to 1.8ml/min/kg whereas; enzyme inhibiting decreases LTG clearance to 0.67 ml/min/kg.[24] Levetiracetam is mostly eliminated unchanged in the urine (66%) and 27% as inactive metabolites.[25] Oxcarbazepine is a prodrug and is metabolised to the two equipotent pharmacologically active enantiomers of a monohydroxy derivative (MHD).[26] Enzyme inducing AEDs (phenytoin, Phenobarbital and carbamazepine) enhance the metabolism of MHD and decrease its serum concentrations. Tiagabine is displaced by valproic acid from its serum protein binding sites.[26] Co-administration of enzyme-inducing AEDs decreases topiramate half-life to 12h, increase topiramate clearance and subsequently its serum concentrations decreased to 50%.[27] The half-life of zonisamide is 50-70 h during monotherapy, and it is reduced to 25-35 hrs with co-administration with enzyme inducing AEDs. Clearance of zonisamide is higher in children compared to adults, and children require higher doses to achieve the serum concentrations as that in adults.[18]

Thus, overall, new AEDs are negligibly bound to plasma proteins, except tiagabine which is over 95% bound to plasma proteins. The clearance of the new AEDs has also been found to be higher in children than in adults and thus dosage adjustment is required in paediatric population, which is not only weight-based. Gabapentin and vigabatrin are eliminated primarily through renal excretion and therefore, show low drug-drug interaction potential. On the other hand, the hepatic metabolism of several of the new AEDs such as lamotrigine, topiramate, oxcarbazepine, tiagabine, and felbamate is accelerated by enzyme inducing enzymes, including some of the traditional AEDs. Moreover, the metabolism of lamotrigine is inhibited by valproic acid.

AED use in Malta

In a study carried out by Scerri[28] valproate was found to be the most commonly prescribed conventional AED (65%) in the paediatric population in Malta. This was followed by carbamazepine (24%). Lamotrigine was also the most commonly prescribed of the newer AEDs (16%) in Soler's study and in 19.7% of cases in Scerri's study. It may be that the use of lamotrigine and levetiracetam (both newer AEDs) may have increased in comparison to carbamazepine use, possibly because of the efficacy, safety and tolerability profile of newer AEDs and the relative lack of drug interactions.

In Soler's study[5], the main type of AED therapy was monotherapy (in 70% of cases i.e. 144 children), while 21% were on poly-drug therapy. The findings of predominant AED monotherapy were also described by Dörks *et al* in their 2013 German study[29] and Nicholas *et al* in their 2012 UK study[30] which revealed that more patients were on monotherapy compared to poly-drug therapy in the study populations concerned. It is significant that in the studies in which AED monotherapy was the main type of therapy as well as the studies reporting a dominant use of multiple drugs, a common AED in all the studies in which the main AED used was reported, was valproate. This could be because valproate has been used for a long time and clinicians have good experience with it, but also because it has good efficacy and generic effects on multiple types of seizures. It is important to evaluate the role of drugs and their efficacy in the context of different genetic and environmental risk factors in populations, which may lead to a differential resistance to AEDs between different populations, especially in the context of specific genetic polymorphisms in different populations which alter a drug's pharmacodynamic properties.

However, the use of monotherapy versus poly-drug therapy has a number of implications for patient management. The use of more than one AED could result in reduced quality of life, loss of function and impaired productivity. Poly-drug therapy is also associated with increased adverse drug reactions, worsening of mental function and aggressive behaviour in some patients, which can be a key variable in their adverse health-related quality of life scores. Poly-drug therapy may also be associated with a complex dosing regimen which may also lead to poor adherence to AED therapy. It also increases the risk of drug toxicity.

In Soler's local study[5], mean age at onset of epilepsy was of 5.3 years. In her study,

Soler also confirms that onset of epilepsy had commonly occurred by the time the child was 2 years old. These findings are important because age of onset of epilepsy has implications on prognosis for development. Persons with early onset epilepsy and longer duration of the condition perform poorly in neuropsychological tests carried out in adulthood, showing more generalised, far-reaching and intrusive deficits in comparison to persons diagnosed with epilepsy over the age of 11 years, even when adjusting for confounders such as seizure frequency.[31] These findings emphasise the need for early diagnosis and optimal management of seizure disorders, especially in persons who are diagnosed earlier in life, so as to maximise their functional potential at a neurocognitive level, especially since drug efficacy studies reveal that 30% to 40% of persons with epilepsy remain uncontrolled despite pharmacotherapy.[32]

Epilepsy affects multiple domains in a patient's life, including work and employment, relationships, family and care providers. It is associated with organic, psychiatric and psychological morbidity, stigma, social isolation, cognitive difficulties, dependence on others and difficulties related to employment.[33] Epilepsy is also associated with decreased life expectancy and increased mortality, with increased risk of suicide and accidental injury, and a general decrease in quality of life, especially in patients with active epilepsy who experience frequent seizures. Increased patient self-efficacy is associated with improved quality of life.[34] Support groups and social services may help empower patients with epilepsy, but these services may be under-utilised due to lack of awareness of their existence or due to stigma.[35] In a 2006 survey of 907 patients between the ages of 18 and 65 years, antiepileptic drug (AED) monotherapy was associated with better quality of life than poly-drug therapy for the treatment of epilepsy.[36]

Hermann *et al.*[31] described that cognitive impairment exists at baseline, prior to the initiation of AED therapy and that these impairments can be altered for better or for worse by AEDs. In a study by Meador et al, 2005[36] using the Medical College of Georgia Delayed Paragraph Recall test, lamotrigine and gabapentin were not found to produce deterioration in recall, unlike carbamazepine, phenytoin and topiramate, which produced a 10% to 20% reduction in number of items recalled. A decrease in recall can have a profound impact on the well-being of a child sitting in a classroom, or an office worker, carrying out activities that rely on focus, attention and memory, with a decrease in quality of life as a result of impaired performance and achievement. This also shows us how complex the selection of AEDs can be, since one must consider multiple factors including formulation, concurrent drug therapies and comorbidities, dosage regimen, adherence to therapy, adverse effect profile and frequency, efficacy and likelihood of cognitive effects.

The European task force for drug development in children (TEDDY) was developed as part of the 6th European Framework for Research and Development between 2005 and 2010, with the cooperation of eleven countries seeking to develop new drug therapies to treat a variety of illnesses.[37] TEDDY recommended research on 21 Antiepileptic drugs, including pharmacoepidemiological studies to determine which drugs were to be prioritised in research endeavours. The Scottish Intercollegiate Guideline Development Network (SIGN)[38] (guideline 70) suggests the use of carbamazepine, sodium valproate, lamotrigine and oxcarbazepine as first line AEDs in the management of partial and secondary generalised seizures. Sodium valproate and lamotrigine are used as first-line drugs in the management primary generalised seizures, as well as in the case of doubt about the type of seizure or seizure syndrome. Level 1 evidence suggests that phenytoin, carbamazepine, sodium valproate, lamotrigine and oxcarbazepine have similar efficacy when used in the management of generalised tonic-clonic. The newer AEDs, lamotrigine and oxcarbazepine have a better safety and tolerability profile. Sodium valproate and lamotrigine are also used in the management of absence seizures and myoclonic seizures. Lamotrigine can worsen myoclonic seizures in some cases. Ethosuximide has been used for absence seizures in children for a very long time. Due to improved safety and tolerability profiles – especially with regard to fewer effects on cognition and behaviour, as well as the lack of interactions with other drugs, lamotrigine use may prove to be particularly advantageous in treating adolescents, young women and elderly persons with epilepsy.

Pharmacokinetic modelling and population pharmacokinetics of antiepileptic drugs

Pharmacokinetic modelling is a powerful tool to study how demographic parameters, pathophysiological conditions, genetic factors and other sources of variability influence the dose-concentration relationship in such populations.[16] The population PK approach allows the analysis of data from unbalanced designs and also from studies that are usually excluded from pharmacokinetic analysis, such as concentration data obtained from paediatric and elderly patients. Thus, population pharmacokinetic analysis plays an important role in individualization drug therapy in paediatric epilepsy. In traditional pharmacokinetic studies, the subjects are usually healthy volunteers or highly selected patients and the mean plasma concentration-time profile is the main focus of interest. Pharmacokinetic modelling is thus useful in the determination of pharmacokinetic parameters in a specific patient population. This type of prediction of pharmacokinetic parameters is of great importance in order to individualize dosing regimen in a specific population such as paediatric epileptic population since epilepsy is a chronic neurological condition and developmental changes occur from childhood to adulthood. Many variables influence plasma drug concentrations of AEDs, and thus the pharmacokinetics of these drugs, especially in children. However, satisfactory pharmacokinetic models which allow accurate predictions of drug plasma concentrations still lack especially in paediatric populations and little published research has been found in this area. Most paediatric epileptiologists use ad hoc reasoning in the design of dosage regimens for AEDs in paediatric epilepsy. Pharmacokinetic software packages, such as Adapt® and NONMEM® are useful in the determination of pharmacokinetic parameters and can be very useful in a chronic neurological condition such as epilepsy.[39]

Conclusion

Epilepsy is a common neurological condition and research initiatives are being promoted at an international level, in order to address issues of drug development in epilepsy. This is a move in accordance with the WHO's 2013 report on 'Priority Medicines for Europe and the World', which emphasises the importance of addressing chronic non-communicable diseases which are characterised by high morbidity and mortality.[40] This same document includes children among 'special groups' whose needs need to be addressed and in whom the management of illnesses needs to be prioritised. Children are a vulnerable population with unique health needs – physical, psychological and social. Their physiology is different from that of adults. Hence even the way their body is able to handle drugs differs from that of an adult. Parents play an important role in the healthcare management of young children

who are dependent. As children grow into adolescence they meet unique healthcare challenges, such as possible difficulties in adherence to therapy, especially when they begin to take control themselves over certain aspects of their healthcare such a taking their own medication on their own.

Population pharmacokinetics also play an important role in improving the therapeutic outcomes for paediatric populations with epilepsy, by contributing to the individualization of drug therapy and development of personalised medicine. It will thus lead to improved therapeutic outcomes and reduced adverse events in these patients.

References

1. Sander JW, Hart YM. Epilepsy: Questions and Answers. Merit, 1999.
2. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-521.
3. Wirrell, EC, Grossardt BR., Wong-Kisiel, LC, Nickels, KC. Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted Country, Minnesota from 1980 to 2004: a population-based study. Epilepsy Res. 2011;95(1-2):110-118.
4. Berg, AT, Jallon, P, Preux, PM. The epidemiology of seizure disorders in infancy and childhood: definitions and classifications. Handb Clin Neurol. 2013;111:391-398.
5. Soler D. Epilepsy in Maltese Children [dissertation]. Msida: University of Malta. 2000.
6. Gidal BE, Garnett WR. Epilepsy. In: Pharmacotherapy: a Pathophysiologic Approach. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM (Eds.). New York: McGraw-Hill; 2005. p.1023-1048.
7. Wirrell EC. Predicting pharmacoresistance in pediatric epilepsy. Epilepsia. 2013;54 (Suppl 2):19-22.
8. Brodie MJ. Antiepileptic drug therapy the story so far. Seizure. 2010; 19(10):650-655.
9. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser, TA, Johannessen, SI, et al. Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-1276.
10. Carmant L, Holmes GL, Sawyer S, Rifai N, Anderson J, Mikati MA. Efficacy of felbamate in therapy for partial epilepsy in children. J Pediatr. 1994;125(3):481-486.
11. Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Perucca E, Tomson T. Progress report on new antiepileptic drugs: a summary of the Seventh Eilat Conference (EILAT VII). Epilepsy Res. 2004;61(1-3):1-48.
12. Guerreiro MM, Vigonius U, Pohlmann H, de Manreza ML, Fejerman N, Antoniuk SA, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res. 1997;27(3):205-213.
13. Bourgeois BFD, Holder DL, Valencia I. Open label assessment of levetiracetam efficacy and adverse effects in a pediatric population. Epilepsia. 2001;42(Suppl 7):253–254.
14. Hammoudi DS, Lee SS, Madison A, Mirabella G, Buncic JR, Logan WJ, et al. Reduced visual function associated with infantile spasms in children on vigabatrin therapy. Invest Ophthalmol Vis Sci. 2005;46(2):514-520.
15. National Institute of Clinical Excellence. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. London: National Institute of Clinical Excellence. c2014. Available from: http://www.nice.org.uk/guidance/cg137 Accessed 14 October 2014.
16. De Cock RFW, Piana C, Krekels EHJ, Danhof M, Allegaert K, Knibbe CAJ. The role of population PK-PD modelling in paediatric clinical research. Eur J Clin Pharmacol. 2011;67(Suppl 1):S5-S16.
17. Anderson GD, Lym AM. Optimizing paediatric dosing: a developmental pharmacological approach. Pharmacother. 2009;29(6):680-690.
18. Perucca, E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age. Clin Pharmacokinet. 2006;45(4):351-363.
19. Rosati A, De Masi S, Guerrini R. Antiepileptic Drug Treatment in Children with Epilepsy. CNS Drug 2015;29(10):847-863.
20. Ette EI, Williams PJ. Population Pharmacokinetics I: Background, Concepts, and Models. Ann Pharmacother. 2004;38(10):1702-1706.
21. Perucca E. The clinical pharmacokinetics of the new antiepileptic drugs. Epilepsia. 1999;40(Suppl. 9):S7–S13.
22. Banfield CR, Zhu GR, Jen JF, Jensen PK, Schumaker RC, Perhach JL, et al. The effect of age on the apparent clearance of felbamate: a retrospective analysis using nonlinear mixed-effects modelling. Ther Drug Monit. 1996;18(1):19-29.
23. Ouellet D, Bockbrader HN, Wesche DL, Shapiro DY, Garofalo E. Population pharmacokinetics of gabapentin in infants and children. Epilepsy Res. 2001;47(3):229-241.
24. Battino D, Croci D, Granata T, Mamoli D, Messina S, Perucca E. Single-dose pharmacokinetics of lamotrigine in children: influence of age and co-medication. Ther Drug Monit. 2001;23(3):217-222.
25. Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet. 2004;43(11):707–724.
26. May TW, Korn-Merker E, Rambeck B. Clinical pharmacokinetics of oxcarbazepine. Clin Pharmacokinet. 2003;42(12):1023-1042.
26. Patsalos PN, Elyas AA, Ratnaraj N, Iley J. Concentration-dependent displacement of tiagabine by valproic acid. Epilepsia. 2002;43(suppl. 8):43.
27. Britzi M, Perucca E, Soback S, Levy RH, Fattore C, Crema F, et al. Pharmacokinetic and metabolic investigation of topiramate disposition in healthy subjects in the absence and in the presence of enzyme induction by carbamazepine. Epilepsia. 2005;46(3):378-384.
28. Scerri AM. Pharmacoepidemiology of epilepsy in a paediatric neurology clinic. University of Malta MSc Thesis; 2014.
29. Dörks M, Langner I, Timmer A, Garbe E. Treatment of Paediatric Epilepsy in Germany: Antiepileptic Drug Utilization in Children and Adolescents with a focus on new antiepileptic drugs. Epilepsy Res. 2013;103:45-53.
30. Nicholas JM, Ridsdale L, Richardson MP, Ashworth M, Guilliford MC. Trends in Antiepileptic Drug Utilisation in UK Primary Care 1993-2008: Cohort Study Using the General Practice Research Database. Seizure. 2012;21:466-470.
31. Hermann B, Seidenberg M, Bell B, Rutecki P, Sheth R, Ruggles K, et al. The neurodevelopmental impact of childhood-onset temporal lobe epilepsy on brain structure and function. Epilepsia. 2002;43(9):1062-71.
32. Griffin S, Tranel D. Age of seizure onset, functional reorganization, and neuropsychological outcome in temporal lobectomy. J Clin Exp Neuropsychol. 2007;29(1):13-24.
33. Räty LKA, Wilde Larsson BM. Quality of life in young adults with uncomplicated epilepsy. Epilepsy Behav. 2007;10:142-147.
34. Jacoby A, Baker GA. Quality-of-life trajectories in epilepsy: A review of the literature. Epilepsy Behav. 2008;12:557-71.
35. Chung K, Liu Y, Ivey SL, Huang D, Chung C, Guo W, et al. Quality of life in epilepsy (QOLIE): Insights about epilepsy and support groups from people with epilepsy (San Francisco Bay Area, USA). Epilepsy Behav. 2012;24:256-263.
36. Haag A, Strzelczyk A, Bauer S, Kühne S, Hamer HM, Rosenbow F. Quality of Life and Employment Status are Correlated with Antiepileptic Monotherapy versus Polytherapy, not with 'Newer' versus 'Classic' Drugs: Results of the 'Compliant 2006' Survey in 907 Patients. Epilepsy Behav. 2010;19:618-22.
37. Ceci A, Giaquinto C, Aboulker JP, Baiardi P, Bonifazi F, Della Pasqua O, et al. The Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence. Paediatr Drugs. 2009;11(1):18-21.
38. Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults. Edinburgh: Scottish Intercollegiate Guidelines Network. 2014. Available from: http://www.sign.ac.uk/pdf/sign70.pdf Accessed 18 October 2014.
39. Vučićević K , Miljković B, Pokrajac M, Prostran M, Martinović Z, Grabnar I. The influence of drug-drug interaction and patients' characteristics on valproic acid's clearance in adults with epilepsy using nonlinear mixed effects modelling. Eur J Pharm Sci. 2009; 38(5):512-518.
40. Kaplan W, Wirtz V, Mantel-Teeuwisse A, Stolk P, Duthe B, Laing R. Priority Medicines for Europe and the World 2013 Update. World Health Organisation. 2013. Available from: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1 Accessed 28 July 2017

Key points

- Epilepsy is one of the most common neurological disorders, with approximately 45 per 100,000 children developing new-onset epilepsy every year
- Children are a vulnerable population with unique health needs whose physiology is different from that of adults and thus handle drugs differently from adults
- The novel antiepileptic drugs have expanded the treatment options of epilepsy, however, they are also associated with pharmacokinetic shortcomings, especially for paediatric populations
- The correct use of these drugs can lead to improved quality of life measures
- The use of population pharmacokinetics addresses the challenges paediatric populations offer to drug and dose individualisation

Childhood obesity: a priority area of the Maltese Presidency of the Council of the European Union

[1]Charmaine Gauci MD, MSc, PhD, FRSPH, FFPH
[2]Antoinette Calleja PhD

[1]Superintendent of Public Health, Coordinator of Presidency childhood obesity priority area.
[2]Director Department for Policy in Health International Affairs and Policy Development, Chairperson Presidency, Ministry for Health

Key words
childhood obesity, Council of the European Union

Abstract

The magnitude of childhood obesity has reached alarming levels. Approximately, 40% of the global population suffers from overweight or obesity. The EU Action Plan on Childhood Obesity 2014-2020 has an overarching goal to halt the rise in overweight and obesity in children and young people by 2020. Notwithstanding the various actions at both EU and national levels, the problem of overweight and obesity remains high. Urgent action needs to be stepped up. Towards this end the Maltese Presidency of the Council of the European Union placed childhood obesity as one of its priority areas. During its Presidency, a midterm evaluation on the EU Action Plan on Childhood Obesity 2014-2020 was carried out in order to derive with a status update on the extent of implementation by each Member State in the eight policy areas identified within the said Action Plan. The presidency output also focused on the development of food procurement guidelines in schools in order to facilitate the procurement of food for health. To this effect, the presidency produced a technical report elaborating on public procurement guidelines of food for health within school settings. This provides a useful tool for member states when issuing procurement tenders for food in schools. Progressive and targeted public procurement of food for health can reward food business operators who provide nutritionally balanced meals and food products, prompting innovation, food reformulation and social responsibility to achieve better diets and positively impact public health. In addition, with a view to stepping actions to end the childhood obesity epidemic health ministers adopted Council Conclusions on halting the rise in childhood overweight and obesity. The Council Conclusions call upon Member States to integrate in their national action plans and strategies cross-sectoral measures, enabling environments that encourage healthy diets and adequate health-enhancing physical activity amongst others.

The scale and consequences of childhood obesity demand bold and urgent actions. Collaborative actions between European Member States and intersectoral concerted actions at national level are required to tackle the burden of childhood obesity.

Educational aims

- The prevalence of obesity in Europe has more than tripled in many Member States since the 1980s, with consequent increase in the rate of associated non-communicable disease
- Notwithstanding the various actions at both EU and national levels, the problem of overweight and obesity remains high and urgent action needs to be stepped up
- The EU Action Plan on Childhood Obesity 2014-2020, provides a basis for Member States to develop their policies on tackling childhood obesity
- Progressive and targeted public procurement of food for health can reward food business operators who provide nutritionally balanced meals and food products, prompting innovation, food reformulation and social responsibility to achieve better diets and positively impact public health
- Collaborative actions between European Member States and actions at national level are required to tackle the burden of childhood obesity
- Actions to address the obesogenic environment, initiatives at critical points in the life-course and the treatment of children who are already obese are urgently needed. No single intervention can halt the rise of the ever increasing obesity epidemic

Introduction

The magnitude of childhood obesity at global, European and national levels has reached alarming levels. Approximately, 40% of the global population suffers from overweight or obesity.[1] According to the World Health Organisation (WHO) (2014) some 44 million (6.7%) of the world's under five years old are overweight or obese.[2] If current trends continue the number of overweight or obese infants and young children globally will increase to 70 million by 2025. According to estimates from the WHO's Childhood Obesity Surveillance Initiative, around 1 in 3 children in the EU aged 6-9 years old were overweight or obese in 2014.[3]

The prevalence of obesity in Europe has more than tripled in many Member States since the 1980s, with consequent increase in the rate of associated non-communicable disease (NCD). Non-communicable diseases kill 40 million people each year, equivalent to 70% of all deaths globally.[4]

According to estimates from the "Global Status Report on Non-Communicable Diseases 2010"[5] around 2.8 million deaths per year in the EU are due to causes associated with overweight and obesity. Obesity is a major public health concern. It is a known fact that childhood obesity has physical and psychological health consequences that can lead to behavioural and emotional difficulties and reduce educational attainment.[6,7] Childhood obesity is a strong predictor of adult obesity which in turn leads to various health, and socio-economic consequences.[7] It causes a considerable economic burden on society through increased healthcare costs of treating associated diseases (direct costs) and costs associated with lost productivity due to absenteeism and premature death (indirect costs). At present, it is estimated that around 7% of national health budgets across the EU are spent on diseases linked to obesity each year. Substantial indirect costs are also incurred from lost productivity arising from work absences due to health problems and premature death.

Actions at European Level

The EU momentum for tackling the rising incidence of obesity was further increased with the 2003 Council conclusions on healthy lifestyles when the European Commission was invited to study ways to promote better nutrition and healthier lifestyles within the EU. This resulted in the publication of the green paper on "Promoting healthy diets and physical activity - A European dimension for the prevention of overweight, obesity and chronic diseases"[8] and the establishment of the European Platform for Action on Diet, Physical Activity and Health in 2005. The Strategy on Nutrition, Overweight and Obesity-related health issues[9] was adopted in 2007 and evaluated in 2012. The evaluation among other things argued for the introduction of more intrusive measures to address the problem. The EU Action Plan on Childhood Obesity 2014-2020[10] launched during the Hellenic EU presidency of the Council has an overarching goal to halt the rise in overweight and obesity in children and young people (0-18 years) by 2020.

To achieve this goal, the Plan sets out eight priority areas for various stakeholders in order to:

1. Support a healthy start in life
2. Promote healthier environments, especially in schools and pre-schools
3. Make the healthy option the easier option
4. Restrict marketing and advertising to children
5. Inform and empower families
6. Encourage physical activity
7. Monitor and evaluate
8. Increase research

In addition to the above, EU Member States actively participate and support WHO initiatives including the adoption of the Vienna Ministerial declaration on Nutrition and Non-communicable diseases (NCDs)[11] in the context of the Health 2020 and the adoption on the Food and Nutrition Action Plan for the European Region.[12]

Local situation

Overweight and obesity is a major public health challenge affecting Maltese schoolchildren across all ages. Over the past 10 years, Malta has been actively participating in the Childhood Obesity Surveillance Initiative (COSI) established by the WHO Regional Office for Europe. This involves the routine measurement of height and weight among primary school children aged 6-9 years generating data in overweight and obesity prevalence and trends whilst enabling inter-country comparisons across the European Region. On the basis of the last report (2017) an increasing trend in obesity in both boys and girls has been depicted. However, the rate of increase in obesity for the period 2010 to 2013 was at a slower rate than for the period 2008 to 2010.[13] There was declining trend in overweight rate for both boys and girls from 2010 to 2013. Looking at the total overweight and obese over same period, there was a declining trend for boys though constant for girls.

In the Health Behaviour school aged children study (HBSC), 2014[13] Malta again ranked the highest who self-report on overweight and obesity - 32% and 38% of 11-year olds respectively; 33% and 36% of 13-year olds respectively and 26% and 43% of 15-year-old girls and boys respectively using WHO cut off values. This is above the HBSC average for all ages. When compared to 2010 rates, we have seen a decrease in rates for 11-year-old and 13-year-old boys but an increase for 15-year-old boys and for girls at all ages.

A nationwide study conducted during 2016 measuring all schoolchildren (age 4.7-17 years) showed that approximately 40% of school aged children are overweight or obese.[14]

Actions at Local Level

Malta launched its National Strategy for the Prevention and Control of NCDs[15] in April 2010, the Healthy Weight for life Strategy in 2012[16] and the Food and Nutrition Policy and Action Plan in 2014.[17] These set a clear direction for intersectoral collaboration and an integrated whole of government and whole of society approach to tackle risk factors, prevention, reduce the chronic diseases burden, curb and reverse the growing population of overweight and obese children and adults. In February 2015, the Whole of School Approach to lifestyle: nutrition and physical activity[18,19] was launched as a joint co-operation between health and education sectors.

Need for action

Notwithstanding the various actions at both EU and national levels, the problem of overweight and obesity remains high and urgent action needs to be stepped up. Towards this end the Maltese Presidency of the Council of the European Union has put childhood obesity as a priority area for its Presidency.

On the 22nd and 23rd February 2017, the Maltese Presidency brought together leading experts on childhood obesity, public health experts from across the EU, representatives

from the European Commission and WHO to jointly explore ways in halting the rise in childhood obesity. Towards this end the focus was on two main areas namely, evaluation of the mid-term EU action plan (2014-2020) on childhood obesity[20] and development of procurement guidelines for healthy food in schools.

Midterm evaluation of the European Union Action Plan on Childhood Obesity

The EU Action Plan on Childhood Obesity 2014-2020, provides a basis for Member States to develop their policies on tackling childhood obesity. Although defining national health policy remains within the exclusive competence of Member States, there is EU added value in joint voluntary collaboration in this respect. A case in point is the direct relevance of obesity and various factors that are linked to the internal market and which could be effectively addressed through EU Action.

DG SANTE in collaboration with the Maltese EU Presidency of the council subcontracted Ephort Consortium to carry out a midterm evaluation on the EU Action Plan on Childhood Obesity 2014-2020[10] in order to derive with a status update on the extent of implementation by each Member State in the eight policy areas identified within the said Action Plan. According to this review, it transpires that the areas with most action by the majority of member states included actions, which support a healthy start in life, promoting healthier environments, and actions to encourage physical activity. New actions for curbing obesity by member states was identified in the area of food product improvement. On the other hand, fewer actions were observed in the areas concerning labelling and taxation, regultion of marketing, informing and empowering families.

Public Procurement of Food for Health: Technical report on the school setting

At an estimated €82 billion, the European social food service market is sizeable in both reach and force. Public procurement is a process by which public authorities purchase goods. Procurement of healthy food will benefit health in various ways. Progressive and targeted public procurement of food for health can reward food business operators who provide nutritionally balanced meals and food products, prompting innovation, food reformulation and social responsibility to achieve better diets and positively impact public health.

In fact, success stories are already visible, with articles about the health benefits of better school food provision via procurement beginning to emerge in the scientific literature.[21] Another favourable trend is that schools have been quick to apply the EU green public procurement criteria.[22] The same forward-thinking and flexibility should be expected and promoted for public procurement of healthy food. While the EU legal framework offers substantial scope for health-sensitive public procurement of food, authorities face a number of challenges. In schools, a major obstacle is the translation of school food standards into adequate procurement technical language. In order to ensure the smooth implementation of public procurement of healthy food, it is important to set clear technical specifications on the foods and food services to be procured.

One of the deliverables steered by the Maltese Presidency of the Council of the EU was the production of a technical report elaborating on public procurement guidelines of food for health within school settings.[23] This report was compiled by representatives from the Maltese Presidency, DG SANTE and the Joint Research Centre with the support of Member States. The report includes specifications and other considerations for key food groups and nutrients as well as specifications regarding food preparation and the catering service in general. This report provides a strong justification for action and supports Member States in the real-life tasks necessary to effectively translate national school food policies into healthy school food environments. In doing so, it also raises awareness on the importance of promoting healthy diets for the benefit of children and schools, and for health systems and the economy. After all, schools are not just places to learn about mathematics, history, science and languages but also places where children should be given the opportunity to thrive by developing good eating and lifestyle habits that can last a lifetime.

Stepping up political action to end Childhood obesity

The need for stepping up actions to end the childhood obesity epidemic was further given high profile during the Maltese Presidency when two important related documents were endorsed at the political level by health Ministers.

On the 16th of June, during the Employment, Social Policy, Health and Consumer Affairs (EPSCO) Council meeting health ministers adopted Conclusions on halting the rise in childhood overweight and obesity. The Council calls upon Member States to integrate in their national action plans and strategies cross-sectoral measures adopting a life course approach. It calls for policies that create enabling environments in educational settings for children and childcare centres to encourage healthy diets and adequate health-enhancing physical activity. Measures to promote physical activity in recreational facilities and accessible services for leisure time physical activity. The Council also calls for the reduction of advertisement and sponsorship of sugary and fatty foods which are targeted at children and adolescents.

On the 26-27 June health Ministers in the European Region of the World Health Organisation with populations of less than one million met in Malta to participate in the fourth high-level meeting of the small countries initiative. Ministers acknowledged that childhood obesity as an important public health challenge of the 21st century and have thus agreed to join forces to launch comprehensive initiatives to create conditions that foster health and well-being for all children. Towards this end, Ministers adopted the *Malta Statement on ending childhood obesity, promoting healthy weight and well-being throughout the life-course*. The Malta Statement was presented during the 67th WHO Regional Committee for Europe to be held in September 2017.

Conclusion

The scale and consequences of childhood obesity demand bold and urgent actions. Collaborative actions between European Member States and intersectoral concerted actions at national level are required to tackle the burden of childhood obesity. Actions addressing the multitude of influences surrounding our environment at the various critical points the life-course are needed. Indeed, no single intervention can halt the rise of the ever-increasing obesity epidemic.

References

1. NCD Risk Factor Collaboration. 2014.
2. World Health Organization. World Health Statistics Report. 2014. Available from: http://apps.who.int/iris/bitstream/10665/112738/1/9789240692671_eng.pdf Accessed 29 July 2017.
3. World Health Organization. European Childhood Obesity Surveillance Initiative, COSI, round 2014.
4. World Health Organization. Noncommunicable diseases, fact sheet. 2017. Available from: http://www.who.int/mediacentre/factsheets/fs355/en/ Accessed 29 July 2017.
5. World Health Organization. Global Status Report on Non-Communicable Diseases 2010. Available from: http://www.who.int/nmh/publications/ncd_report2010/en/ Accessed 29 July 2017.
6. Lobstein T, Jackson-Leach R. Estimated burden of paediatric obesity and co-morbidities in Europe. Part 2. Numbers of children with indicators of obesity-related disease. Int J Pediatr Obes. 2006;1:33–41.
7. Pizzi MA, Vroman K. Childhood obesity: effects on children's participation, mental health, and psychosocial development. Occup Ther Health Care. 2013;27:99–112.
8. Commission of the European Communities. Green paper on Promoting healthy diets and physical activity - A European dimension for the prevention of overweight, obesity and chronic diseases. 2005. Available from: http://ec.europa.eu/health/ph_determinants/life_style/nutrition/documents/nutrition_gp_en.pdf Accessed 29 July 2017.
9. Commission of the European Communities. A Strategy for Europe on Nutrition, Overweight and Obesity related health issues. 2007. Available from: http://ec.europa.eu/health/archive/ph_determinants/life_style/nutrition/documents/nutrition_wp_en.pdf Accessed 29 July 2017.
10. EU Action Plan on Childhood Obesity 2014-2020. Available from: http://ec.europa.eu/health//sites/health/files/nutrition_physical_activity/docs/childhoodobesity_actionplan_2014_2020_en.pdf. Accessed 29 July 2017.
11. Vienna Declaration on Nutrition and Noncommunicable Diseases in the Context of Health 2020, 5 July 2013, WHO European Ministerial Conference on Nutrition and Noncommunicable Diseases in the Context of Health 2020 Vienna, 4–5 July 2013.
12. World Health Organization. Regional Office for Europe. European Food and Nutrition Action Plan 2015-2020. Available from: http://www.euro.who.int/__data/assets/pdf_file/0008/253727/64wd14e_FoodNutAP_140426.pdf Accessed 29 July 2017.
13. Unpublished data. Communication with Dr V. Farrugia Sant Angelo.
14. Health Behaviour Study in School Children, 2014.
15. Grech V, Aquilina S, Camilleri E, Camilleri K, Busuttil ML, Sant'Angelo VF, e al. The Malta Childhood National Body Mass Index Study - A Population Study. J Pediatr Gastroenterol Nutr. 2016 Oct 4. [Epub ahead of print]
16. Ministry for Health. Non Communicable Disease Strategy. 2010. Available from: https://health.gov.mt/en/health-promotion/Noncommunicable-Disease-Prevention-and-Control-Unit/Pages/Noncommunicable-disease-strategy.aspx Accessed 29 July 2017.
17. Ministry for Health. Healthy Weight for Life Strategy. 2012. Available from: https://extranet.who.int/nutrition/gina/sites/default/files/MLT%202012%20A%20Healthy%20Weight%20for%20Life.pdf Accessed 29 July 2017.
18. Ministry for Health. Food and Nutrition Policy and Action Plan. 2014. Available from: https://health.gov.mt/en/Documents/National-Health-Strategies/FNAP_EN.pdf Accessed 29 July 2017.
19. Ministry for Education. A Whole School Approach to a healthy lifestyle: healthy eating and physical activity. 2015. Available from: https://education.gov.mt/en/resources/News/Documents/Healthy%20Eating%20and%20Physical%20Activity%20Policy.pdf Accessed 29 July 2017.
20. Op.cit ref.no.11.
21. Hetherington MM. Nutrition in the early years: laying the foundations for healthy eating. Nutr Bull. 2016;41(4):310–313.
22. European Commission. Green public procurement. Available from: http://ec.europa.eu/environment/gpp/index_en.htm Accessed 29 July 2017.
23. Ministry for Health. Public procurement of food for health. Technical report on the school setting. 2017. Available from: https://ec.europa.eu/jrc/sites/jrcsh/files/public-procurement-food-health-technical-report.pdf Accessed 29 July 2017.

Systematic Review: a cornerstone to promote the uptake of research findings for evidence-based practice

Patricia Vella Bonanno
B. Pharm (Hons.), MSc (Clinical Pharmacy) (QUB), PhD (RGU), Post-Grad Cert (EBMgt)

Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, United Kingdom.
Email: patricia.vella-bonanno@strath.ac.uk

Educational aims

- To inform of the benefits of using systematic review to support evidence-based practice, decision making and policy
- To outline the advantages of systematic review over traditional literature review
- To describe the methodology of systematic review and explain its applicability to different areas
- To explain some of the difficulties encountered with the conduct of systematic review
- To motivate the increased adoption and use of systematic review

Key words
systematic review, traditional literature review, evidence-based practice, decision making; uptake

Abstract

Review of existing research findings from the literature is essential to inform evidence-based practice, decision making, academia and policy. In the medical field, systematic review is considered as standard practice, while in other fields there are different levels of uptake. As compared to traditional literature review, the methodology of systematic review adopts a number of steps and is systematic and transparent. This leads to increased rigour, less bias and allows reproducibility and update. There are still a number of difficulties with the conduct of systematic reviews. The utilisation of systematic review to support different areas of practice is highly recommendable.

Introduction

There is increasing interest in 'evidence-based health care'. Decisions made by healthcare professionals, providers, managers, purchasers and policy makers are consistently required to critically consider the research evidence to ensure best practice, achieve maximal benefit/risk and maintain optimal utilisation of resources.[1] Reviews of existing research accumulate findings from existing literature and have the potential to inform evidence-based practice, decision making and academia. The quality of the information used is critical to its value[2,3] and systematic review can enhance the use of evidence by producing reliable knowledge through systematic accumulation, assimilation and presentation of findings from a range of studies.[4] Moreover the way that the voluminous information is analysed, synthesised and presented through systematic review allows it to be assimilated quickly and increases its access to practitioners and its use by them.[5]

The developments in the utilisation of systematic review

Systematic review has been extensively developed and improved as an important technique in the evidence-based approach particularly in certain fields such as medicine, social policy, healthcare and education where knowledge of the value of an intervention is critical.[6,7] A 'standard' approach to systematic review was developed initially in the field of medicine by the Cochrane Collaboration in the early 1990s and this is still contemporary.[8] This was followed by other consortia such as the Campbell Collaboration which was founded in 1999 and the Evidence for Policy and Practice Information and Co-ordinating Centre.[9] In other areas such as management and organisation studies the adoption of systematic reviews has been more slow and divergent.[4,7,10]

In the medical field adoption of systematic review is the standard practice, particularly in the evaluation of medical interventions.[5,6,7] In education systematic review methodology was mainly promoted due to changes in policy towards evidence-based practice and the introduction of benchmarking and performance indicators to support achievement of targets.[9] In the area of management and organisational research a number of leaders in the field such as Briner and Denyer[4] and Denyer and Tranfield[10] support the basic principles

associated with systematic review as compared to traditional literature review. However, there is general concern that systematic reviews as conducted in fields such as medicine are not adequate for management and organisation studies. A number of authors are against the simple and direct transfer of systematic review as specified by the Cochrane Collaboration to management research and argue that certain fields have distinctive features which require developments in systematic review which are specific, tailored and 'fit' for the particular purposes, forms and applications relevant to the field.[4,7,10]

The advantages of systematic review over traditional literature review

Systematic review has improved its methodology over traditional literature review to make it systematic, rigorous, minimise the level of bias and increase replicability. It is distinct from the traditional literature review as it is guided by specific principles. A comparison between systematic reviews and traditional literature reviews and listing of the advantages of systematic reviews is summarised in Table 1.

Systematic review addresses a clear specific question, usually derived from a specific problem or objective. It utilises transparent methods and draws conclusions about the available knowledge related to the question addressed. Systematic review has improved its methodology to make it explicit, standardised, replicable and updateable.[1,5,11] This standardisation allows someone from outside the review team to replicate the study method and to be able to update the systematic review.[4,5]

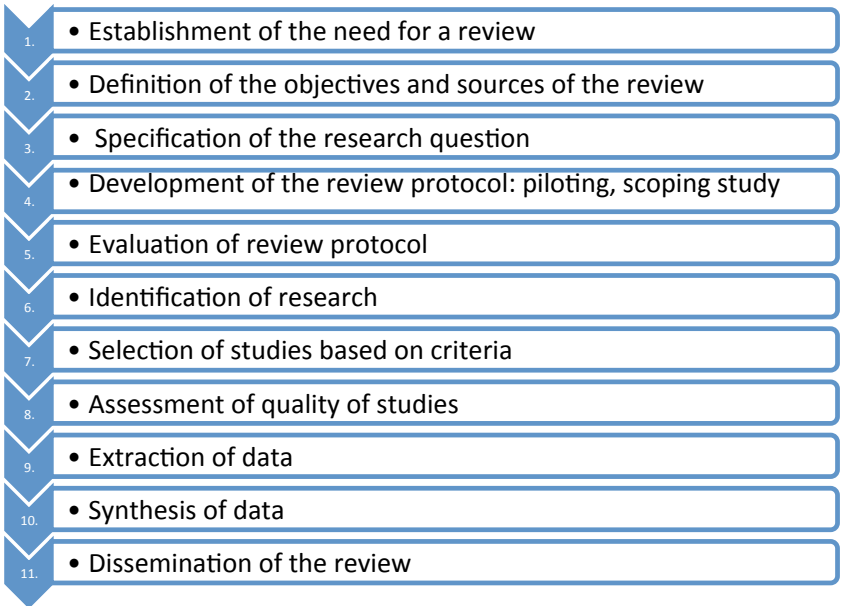
In contrast, traditional literature reviews are usually not systematic. They are less focused and more wide-ranging in scope. They are also less explicit about the inclusion and exclusion criteria.[2] In traditional review, there is no validation and the decision for inclusion and interpretation lies with the author, leading to a high risk of author bias. Traditional reviews have informal and subjective methods to collect and interpret information and do not address the possibility of 'cherry picking'.[10] There are no specific criteria for judging of quality of articles. Authors are sometimes influenced by different aspects such as the rating factors of the journal in which the study is published, the number of citations, the rejection rate or the name of the author of the research.[4] Information from traditional literature reviews is generally represented in quite broad and confident statements which can be biased, particularly by the orientation of the authors. Similarly, the existence of a relationship between phenomena is often presented dogmatically and then simply followed by a list of authors or references to renowned organisations. Such reviews do not quantify the proportion of previous literature supporting certain information, how many

Table 1: Comparison between systematic review and traditional literature review

Elements of review	Systematic review (SR)	Traditional literature review	Advantages of systematic review
Authorship	Involves a team of researchers and ideally also users	Usually involves one researcher	Improves validity, reduces bias
Review question	Focused and specific on a single defined question. Usually in PICO format	May describe an overview or general discussion	Provides focused answer, Pre-set, Clearly defined
Protocol	A peer reviewed protocol	No protocol	Avoids reporting bias. Reproducible
Background	Summaries of available literature provided		
Objectives	Clear objectives identified	May be identified or not	Focused answer
Inclusion and exclusion criteria	Stated before review is conducted	Usually do not describe why studies are included/excluded	Addresses selection bias
Search strategy	Comprehensive, Systematic, Pre-defined databases, To locate all published and unpublished studies	Not explicitly stated, Not systematic, Do not usually attempt to locate all relevant literature	Addresses selection bias, Can be updated
Selection and evaluation of articles	Clear and explicit. Evaluation of study methods and quality	Evaluation of study quality may or not be included, Could be subjective	Explicit. Reproducible by anyone using similar methods
Evaluation of evidence	Clear and specific; Overall assessment of strength of evidence by outcome	Not explicit; Subjective or absent	Study quality and confidence of evidence reported
Results and data synthesis	Clear summaries of studies related to quality and source of evidence; Can be quantitative	Qualitative summary; May be influenced by reviewers' perspectives	Combines evidence Identifies gaps; Reports validity of findings
Conclusion and presentation	Based on set and pre-defined outcome measures	Based on summary of the findings of the studies	Relates to research question; Quality of review evaluated

Adapted from: Bettany-Saltikov[15], Briner & Denyer[4], Denyer &Tranfield[10], Perry & Hammond[9], Petticrew[23], Sriganesh *et al*[3] and Vishnu *et al*[25]

Figure 1: Summary of the process of systematic review



Adapted from: Boell & Cezec-Kecmanovic[12]

studies, consistency of information, the negative studies, the study designs of the studies referenced and the justification of these designs.[4]

The methodology of systematic reviews

The methodology of systematic review covers a number of steps. These steps are summarised in Figure 1. The steps consist of the planning: including framing a question, criteria and a protocol for the review; identification, selection and critical appraisal of primary research including the assessment of the quality of the studies; the extract and analysis of data from the studies that are included in the review and the synthesis of the evidence and interpretation and reporting of best evidence.[2,5,8,10,12,13] Authors in management research Briner and Denyer[4] show a broad consensus about the steps involved in systematic review as specified by the Cochrane Collaboration,[8] however they stress that the stages are not 'linear' and in practice may involve a series of smaller steps. The process may vary considerably across reviews as it is very dependent on the review question.[4]

The review question

Systematic reviews should identify and be set to answer a clear specific well-formulated and answerable review question.[4,10] User involvement in the setting of the research question supports the uptake of the evidence by practitioners in the field. The review question guides setting of the protocol, the design of research strategy including inclusion and exclusion criteria and pre-set the databases to be used. In the medical field review questions are set specific, focused and are concerned with the effectiveness of an intervention.[2] Generally, in social sciences research questions are much wider, with unclear boundaries and are subject to evolve. In management research, it is difficult to find a precise review question.[2,7,12] It is recommended to find an advisory group of experts and potential users of the review to help formulate and adapt the research question to ensure that the question is answerable and that it is adequate to address the needs of practitioners.[4]

The protocol

A protocol should be set which clearly details each step of the review before the search is actually conducted, in order to minimise bias.[14] The protocol enables third parties to challenge the review method, to be criticised and to be revised or improved in future reviews.[4]

Search strategy

Systematic reviews offer a strong search strategy which is designed in advance and in relation to the research question which is explicit, documented, ensures transparency and minimises biases.[5] Systematic searches identify key words and mesh terms. Moreover, there are pre-specified relevance and quality and eligibility criteria for the selection and inclusion of studies and to make such criteria transparent to readers.[2,10] In systematic reviews researchers make extensive efforts to locate all studies that fit the set criteria including those that show negative and contradictory findings and in order to eliminate biases such as publication bias and author 'cherry picking'. In traditional reviews studies which show positive findings tend to be published and those with negative findings are put away – 'file-drawer problem'.[4]

Evaluation of the effectiveness of interventions

The systematic review evaluates the effectiveness of an intervention and considers PICO criteria (Patient group/s with the condition, Intervention, action or activity under consideration, Comparison or alternative to the intervention and Outcomes).[15] Social sciences adopt versions of the PICO framework. SPICE considers the Setting or context, Perspective of the stakeholder asking the question, the Intervention or phenomenon of interest, Comparison and Evaluation of the success.[4]

Utilisaton of reviewers

Systematic reviews include two or more reviewers for interpretation and evaluation of the evidence and there need to be mechanisms to solve disagreement between reviewers. The Campbell Collaboration recommends that in social science a number of tasks of systematic review are conducted by a review advisory group to enhance the iterative, critical and collaborative process expected in this kind of field.[4,7,11]

Appraisal of articles

Reviewers need to apply the inclusion and exclusion criteria to each paper or study to check whether they are relevant to the review. Information can be provided from the abstract or from full papers as needed particularly to find details of the method. The studies are critically appraised in line with the quality criteria devised as part of the systematic review protocol. The criteria

for evaluation are listed in a checklist which is used consistently by all the reviewers. The reviewers would answer each of the specific questions contained in the checklist and thus there will be an overall quality score or rating or category.[4]

Specificity about sources of information

In systematic review, the authors are required to specify the source of the data and how it was processed. Popular sources for health literature include Medline, PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL) database, Exerpta Medica dataBASE (EMBASE) and other databases, Cochrane controlled clinical trials register, literature in foreign languages, 'grey-literature', references cited in primary sources, other unpublished sources known to experts in the specialty and raw data from published trials.[5,8,16,17]

Description of the sources of information and the process

Systematic review gives an overall picture of the quality and amount of evidence in relation to the review question. This includes a systematic and stratified synthesis and presentation of the numbers, characteristics and quality of the studies reviewed and the findings of the included studies. Searches and acquisition of data need to be clearly described so that there can be tracking back of the reasons why certain study designs and attributes are judged to reflect the required quality of studies. It provides an audit trail of the reviewers' decisions, procedures and conclusions.[4,7,10] The PRISMA Statement guides authors to systematically report the exercise of systematic reviews including the number of records identified, screened, assessed, excluded and those finally included.[18,19] In a number of instances reviewers may find that there is less evidence on a given topic and then the information is inconsistent and less robust than widely believed. Finding an absence of evidence is important information. Scoping studies, which are a type of literature review used to map relevant literature in the field of interest, can be conducted to ensure that the search studies are effective and that the studies picked are relevant.[4]

Inclusion and exclusion criteria for research

Systematic reviews apply criteria for quality of research to be included in relation to the review question in advance.[4] Quality assessment addresses the study's internal validity, its design and how it related to the research question.[7] Each study in a medical systematic review is assigned weight and evaluated in terms of its methodological quality considering the extent to which the design is likely to have prevented systematic error (bias), precision (which is a measure of the likelihood of random errors) and external validity which concerns the extent to which the results are generalisable or applicable to a particular target population.[5,7]

Table 2: The 'hierarchy of evidence'

1. Systematic reviews and meta-analyses
2. Randomised controlled trials with definitive results
3. Randomised controlled trials with non-definitive results
4. Cohort studies
5. Case-control studies
6. Cross-sectional surveys
7. Case reports

Adapted from: Greenhalgh[5] and Petticrew & Roberts[20]

The 'hierarchy of evidence'

In the field of medicine the 'hierarchy of evidence' which lists a range of study designs ranked in the order of increasing internal validity is used to critically evaluate studies (Refer to Table 2). This hierarchy places systematic reviews and meta-analyses first and randomised controlled trials with definitive results second.[5,7,20] In contrast the concept of hierarchy of evidence is often problematic to appraise evidence in certain other fields. Leading authors in management and organisational studies insist that reviews cannot be restricted to certain research designs but require identification of the best available evidence from a variety of sources to answer the research question. Rather than supporting a specific classification these authors resist privileging one method over another and insist that the design decision should prioritise that the review is 'fit for purpose'.[4,7] In fields where there is concern over the incompatibility problem in the hierarchy of evidence a switch to the matrix-analytical approach for conceptualising the strength and weaknesses of methodologies is preferred.[20,21] Different quality checklists and tools have been adopted to critically appraise different types of studies, particularly qualitative studies. Qualitative research is not a unified field and in spite of many proposals for quality criteria, there is lack of consensus over the evaluation of such studies.[22]

Synthesis and presentation of the information

Systematic reviews should summarise all existing information in a thorough and unbiased manner.[10] Reviews should present meaningful information and ideally a conclusion about the outcome.[4] Where possible they should compare results of different studies to establish generalisability of findings and consistency of results. Moreover, reasons for heterogeneity (inconsistency of results across studies) can be identified and new hypotheses can be generated across particular subgroups.[5]

Systematic reviews pull together the results of the review in a structured and organised way and summarise the evidence related to the review question. Systematic reviews report what is known and what is not known about the question addressed and ideally result in mapping of the field.[4] Where there are studies that provide consistent results, systematic reviews might be expected to provide solid and dependable evidence that is robust and potential for generalisation and possibly transfer across different contexts. Use of tables helps the presentation and generalisation of results.[7,10] There are numerous established methods for synthesis of research which can be grouped into four categories: aggregative, integrative, interpretation and explanation. Statistical methods (meta-analysis) may be used in some systematic reviews as a method for aggregation which quantitatively analyses, combines or summarises the findings from studies using statistical techniques. This increases the precision of the overall result.[5,19] In the field of management there is less standardisation and the most common approach for presentation of results remains narrative synthesis and the applicability of other methods of synthesis remains limited.[4] Where reviews identify knowledge

gaps or incongruent findings then this calls for further research.[10] Generalisation is not sought in terms of association among variables but considers the application of generative mechanisms over time. The output of systematic review in management serves as guide and refers to what works, why and how the relation works.[7]

Difficulties with conducting systematic reviews

Despite the advantages of systematic reviews over the traditional literature review and the advances and increased utilisation of this review methodology, there are still a number of difficulties with systematic reviews.

Different levels of acceptability of systematic review in different areas

There are different levels of application, acceptability, experience and use of systematic review in different fields. In medical research, systematic research is considered as the expected norm. The lack of exposure and experience of management researchers and management practitioners with systematic reviews and the priority for the adoption of cutting edge practices may limit the acceptability and use of this type of research in this field.[4] Petticrew[23] explains that there is common misconception that systematic reviews are only capable of summarising the results of randomised controlled trials and cannot be used for other study designs. This creates concern in researchers who do not come from the medical field. Systematic reviews of non – randomised studies and of qualitative studies are common and guidelines for carrying out systematic review do not exclude qualitative studies.[23]

Applicability of systematic review across different fields

As discussed above, systematic review as applied to medical research is not considered to be directly transferable to management and organisational research. The use of systematic review for management research presents more challenges. Systematic review requires the formulation of the research question before a literature review is undertaken to identify gaps in the search and this limits the type of research questions which could be addressed by management and social sciences.[12] Another concern is limited consensus regarding what counts as evidence, what constitutes good quality of evidence and on the classification of the evidence. It is important that the approach adopted is made clear and that there is justification for all decisions taken.[2,4,24]

Difficulties concerning the methodology of systematic review

There are various difficulties with the methodology of systematic reviews. The explicit and methodological requirements of a systematic review in relation to the question present limits which impact the outcomes of the review. The limits encountered should be made clear.[4] Keywords used need to be carefully selected to ensure that they generate the information being sought through the research question.[16] Although there is more than one reviewer, assessment can still be subjective. Systematic reviews in the field of management and organisation are likely to encounter difficulties when appraising the quality of sources of information such as lack of sufficient detail and not allowing assessment of quality of the source articles. Also in this sector, there are variations in methods and analyses amongst articles.[7,10] Research synthesis may end up in 'summing up' of qualitative studies and rather than resulting in evidence of the effectiveness of an intervention it more likely gives and understanding of a process.[7]

Resource requirement for systematic review

Systematic reviews are laborious and resource intensive. They require considerably more work than traditional reviews.[12,16] They are also considered to be bureaucratic.[2] Systematic reviews may take a long time (a number of months) and they require regular follow up to keep the review up-to-date.[25] They require a number of reviewers who need to have expertise, critical appraisal skills and pay attention to detail.[4,7,11]

Quality of systematic reviews

Systematic reviews vary in quality. As with any type of research they may be done well or badly. The quality of systematic reviews can be judged for example by using critical appraisal checklists based on a validated index of the quality of review articles. Aspects determining quality include precautions to minimise biases and errors, assessment of validity, appropriateness of the different steps with respect to the review question, how comprehensive the search was, level of detail and appropriateness of the presentation.[4,18,26]

Availability of primary research

There may be difficulties with the amount, quality and accessibility of the primary research. Moreover, the evidence may be dispersed.[24] Previous systematic reviews which address a similar type of question or which present previous gaps in knowledge in a particular field may be a good starting point for a systematic review, however no such systematic reviews may be found. If there are no or very limited trials, if the question/intervention is too complex to be tested by trials or if most trials are of poor quality and are excluded, it will not be possible to conduct a systematic review and to answer the review question and the results of the review remain inconclusive. There may not be enough good primary studies to obtain the required information about a particular question. Alternatively, if a large number of articles are found it may be difficult to comprehensively compile the studies.[25]

Elimination of biases

Although systematic reviews include explicit inclusion and exclusion criteria this does not necessarily eliminate all bias. By including only randomised controlled

Key points

- Systematic review is of benefit to inform and improve evidence-based practice, decision making and academia.
- Systematic review is increasingly utilised in the field of medicine and other fields.
- Systematic review has a number of advantages over traditional literature reviews particularly in increased replicability and reduction of bias.
- The methodology of systematic review is guided by specific principles which make it more rigorous and transparent.
- There are still a number of difficulties with the conduct of systematic reviews.
- The uptake of systematic review to strengthen practice and decision making is encouraged.

trials there can be the introduction of an 'intervention-selection' bias.[24] Alternatively, if a review does not include all studies (non English, grey literature, and early literature) there can be distortion of the final picture.[4] Inclusion of unpublished literature may be considered to reduce the rigour of the research and introduce bias through the introduction of weak evidence.[24] Over the period 1994 to 2014 the number of bibliographic databases searched in individual systematic reviews has increased from a mean of 1.62 to a mean of 3.73.[17]

Conclusion

Systematic reviews have the potential to inform different areas of practice by presenting the best available evidence so that this can be integrated with judgement and experience to support practitioners and scholars make better decisions. There are significant advantages of systematic review over the traditional literature review. While systematic review is an expected standard in the evaluation of medical interventions, in the field of management and organisational practice the use and adoption of the results of systematic reviews may be more difficult and there may be limited level of uptake by decision makers. The systematic review methodology used in the medical science can and should be adopted and adapted to fit management research. Motivation to use systematic review may be increased by explaining the benefits of this type of review. Moreover, reviews should be framed to address the specific question, problem and context that are relevant to practitioners. By augmenting the methodological rigour of the research, the legitimacy and quality of the resultant evidence from systematic reviews and the relevance and sensitivity to practitioners and policy-makers, systematic review gives a reliable basis for practice and decision making.

References

1. Sheldon TA, Guyatt G, Haines A. Criteria for the implementation of research evidence in policy and practice. In: Haines A, Donald A, editors. Getting Research Findings into Practice. London: BMJ Publishing Group; 1998.
2. Bryman A, Bell E. Business Research Methods. Oxford, New York: Oxford University Press; 2011.
3. Sriganesh K, Shanthanna H, Busse JW. A brief overview of systematic reviews and meta-analysis. Indian J Anaesth. 2016;60:689-694.
4. Briner RB, Denyer D. Systematic review and evidence synthesis as a practice and scholarship tool. In: Rousseau DM, editor. The Oxford Handbook of Evidence-based Management. Third Edition. Oxford: Oxford University Press; 2012. p. 328-374.
5. Greenhalgh T. How to read a paper. Second Edition. London: BMJ Publishing House; 2001.
6. Centre for Reviews and Dissemination. Systematic reviews, CRD's guidance for undertaking reviews in health care. York: York Publishing Services Ltd; 2009.
7. Tranfield D, Denyer D, Smart P. Towards a methodology for developing evidence-informed management knowledge by means of Systematic review. Brit J Manage. 2003;14:207-222.
8. Higgins J, Green S. (Eds.) Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration, Cochrane Library and John Wiley & Sons. Ltd; 2011. Available from http://handbook.cochrane.org/ Accessed 28 July 2017
9. Perry A, Hammond N. Systematic reviews: the experience of a PhD student. Psychology Learn Teach. 2002;2(1):32-35.
10. Denyer D, Tranfield D. Producing a systematic review. In: Buchanan DA, Bryman Aeditors. The SAGE Handbook of Organizational Research Methods. Los Angeles, London, New Delhi, Singapore, Washington: SAGE Publications Ltd; 2009. p. 671 – 689.
11. Campbell S, Schryer-Roy A. Systematic Review Chapter 9. In: Research Matters editor. 2008. Available from: www.research-matters.net. Accessed 28 July 2017.
12. Boell SK, Cezec-Kecmanovic D. Are systematic reviews better, less biased and of higher quality? European Conference on Information Systems (ECIS 2011) 2011: Paper 223. Avalable from: http://aisel.aisnet.org/ecis2011/233. Accessed 28 July 2017.
13. Khan KS, Kunz R, KleijnenJ, Antes G. Five steps to conducting a systematic review. J R Soc Med. 2003;96:118–121.
14. Bettany-Saltikov J. Learning how to undertake a systematic review: part 2. Nurs Stand. 2010;24(51):47-56.
15. Bettany-Saltikov J. Learning how to undertake a systematic review: part 1. Nurs Stand. 2010;24(50):47-55.
16. Cronin P, Ryan F, Coughlan M. Undertaking a literature review: a step-by-step approach. Br J Nurs. 2008;17(1):38-43.
17. Lam MT, McDiarmid M. Increasing number of databases searched in systematic reviews and meta-analyses between 1994 and 2014. J Med Libr Assoc. 2016;104(4): 284-289.
18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et. al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7). e1000100. doi: 10.1371/journal.pmed.1000100.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7). e1000097.
20. Petticrew M, Roberts H. Evidence, hierarchies, and typologies: horses for courses. J Epidemiol Community Health. 2003;57:527-529.
21. Walach H, Loef M. Using a matrix-analytical approach to synthesizing evidence solved incompatibility problem in the hierarchy of evidence. J Clin Epidemiol. 2015;68:1251-1260.
22. Dixon-Woods S, Shaw RL, Agarwal S, Smith JA. The problem of appraising qualitative research. Qual Saf Health Care. 2004;13:223-225.
23. Petticrew, M. Systematic reviews from astronomy to zoology: myths and misconceptions. BMJ. 2001;322:98-101.
24. Petticrew M, Roberts H. Systematic reviews-do they 'work' in informing decision-making around health inequalities? Health Econ Policy Law. 2008;3:197-211.
25. Vishnu R, Anice G, Preethy D. Undertaking systematic reviews in nursing. Int J Nurs Educ. 2015;7(4):104-109.
26. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. J Clin Epidemiol. 1991;44(11):1271-1278.

Legal aspects of dispensing and prescription retention procedures according to the laws of Malta

Valerie Vella
B.Pharm (Hons), MSc(Aberdeen), RPharmS

Email: valvel77@gmail.com

The aim of this brief overview is to highlight the situation regarding retention of dispensed prescriptions according to Maltese law.

Single use /fully dispensed prescriptions

According to the Laws of Malta[1,2]- a fully dispensed prescription should be signed by the pharmacist (including registration number) and dated. This documentation needs to be retained, for a period of no less than three months from the date of dispensing, in a manner where easy retrieval is possible. The law also specifies that disposal of such prescriptions after the three months have elapsed should be done in a way that patient's confidentiality is protected.[1,2]

Repeat/Partially filled prescriptions

With regards to repeat or partially filled prescriptions the law[3] states that the managing pharmacist is duty bound to keep written or electronic records of medicinals sold against such prescriptions. The dispensing pharmacist is obliged to endorse the prescription with the pharmacy stamp and with the word "dispensed", together with the date on which it was dispensed, the amount given, the signature and the registration number.[3]

Prescription for controlled drugs

The subsidiary legislation 101.02 which deals with internal control of dangerous drugs clearly states that on dispensing a controlled prescription, Part C needs to be filled accordingly and retained by the pharmacist. The managing pharmacist is then obliged, on the first day of the month, to send all the prescriptions for controlled drugs dispensed the previous month to the Superintendent of Public Health. Details of controlled prescriptions need to be recorded into the respective register and this register must be retained for a period of not less than two years from the date of the last entry in the register.[4,5]

In 2014 a communication was issued by the Malta Chamber of Pharmacists (Malta Chamber of Pharmacists 2014, letter, 21 April) advising pharmacists to retain prescriptions and records for a minimum of five years in view of professional indemnity policy requirements.

References

1. SUBSIDIARY LEGISLATION 458.16 PHARMACY LICENCE REGULATIONS 5th October, 2007. Available at http://www.justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=11256&l=1 Accessed 2nd August 2017.
2. LEGAL NOTICE 305 of 2013MEDICINES ACT(CAP. 458)Pharmacy Licence (Amendment) Regulations, 2013. Available at http://justiceservices.gov.mt/DownloadDocument.aspx?app=lp&itemid=25547&l=1Accessed 2nd August 2017
3. LEGAL NOTICE 303 of 2013MEDICINES ACT(CAP. 458)Prescription and DispensingRequirements (Amendment)Rules, 2013. Available at http://justiceservices.gov.mt/DownloadDocument.aspx?app=lp&itemid=25545&l=1 Accessed 2nd August 2017
4. SUBSIDIARY LEGISLATION 101.02INTERNAL CONTROL OF DANGEROUS DRUGS RULES. Available at http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=9261 Accessed 2nd August 2017
5. SUBSIDIARY LEGISLATION 31.18DRUGS (CONTROL) REGULATIONS. Available at http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=9056 Accessed 2nd August 2017

Answers to page 11: 1c, 2b,3c,4c,5a,6a,7b,8a,9b,10c