Can a relationship between medicines consumption and gender be determined in Malta?

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Educational aims

- To attempt to review the relationship between females and males in medicine use in Malta
- To highlight lacunae in available data related to medicines use in Malta in terms of gender amd otherwise.
- To pinpoint limitations of current date for the purpose of provided better care

Key words
Gender, medicine consumption, NHS entitlement, Malta

Abstract

For many years, females were under represented in clinical trials and only recently has there been a significant increase in the number and proportion of women who participate in such studies. Major issues about gender differences in the field of medicines revolve around medicines used in cardiovascular and respiratory disease, oncology, liver diseases, and osteoporosis. Various international studies have shown that overall rates of medicine use are significantly higher in males than in females. These studies also found that patterns of medicine use, abuse and/or dependence differ by age group, gender and medicine used. In this paper, an attempt will be made to identify patterns of medicine use between men and women in Malta in some disease areas. Limitations will be highlighted.

Introduction

It has been only since early 1980's, that medical research began to actively consider gender issues.[1] Gender differences have, in fact, been identified in the initiation of medicines, escalation of use, addiction and relapse following abstinence for drug abuse.[2] Gender differences have also been found in terms of disease prevention, clinical signs of disease, therapeutic approach, and prognosis, psychological and social impact.[3] For example, overall rates of medicine consumption have been found to be significantly higher in males than in females.[4]

Such differences could be due to physiological differences between sexes, which affect the pharmacokinetics and the pharmacodynamics of drugs. Pharmacokinetics involves the rate and extent of drug movement through the body, including absorption, distribution, metabolism, and excretion. Females have a tendency for lower body weights and slower gastrointestinal tract movements, which indicates a need to prolong time intervals, between meals and medication.[5]

Several physiologic differences between men and women may account for variations in pharmacokinetics, which can affect the dosages of medications with narrow therapeutic indices.[5] For example, drug clearance tends to be slower in women, and medications with a narrow therapeutic index and a higher potential for toxicity, such as digoxin, need to have their dose titrated for the specific patient.[6]

Pharmacodynamics is the study of drug mechanism of action, including the physiologic and biochemical effects on the body, and the relationship between drug concentration and the rate and extent of pharmacologic response.[6] Therefore, in any

Table 1 Adaptation of differences in medicine effects between women and men[6]

Medicine	Advice
Aspirin	Higher dosages in women recommended for secondary prevention after a cardiovascular event due to poorer platelet inhibition
Atenolol	Monitor blood pressure and heart rate since as less effective in women
Digoxin	Women require a lower dosage due to association with high mortality risk
Morphine	Men require a higher dosage than women since the response is less in men
Paroxetine	More effective in women suffering from depression
Amitriptyline	Choose alternative with improved effectiveness in women

given blood concentration, a drug may invoke variations in response, including differences in effectiveness or safety.[6] Some differences in medication effects between men and women, and subsequent recommendations are listed in Table 1.

Women are 50 to 75 percent more likely than men to experience an adverse drug reaction.[7] These differences may be caused by increased polypharmacy, increased drug bioavailability, and greater sensitivity to medication.[8]

Access to medicines in Malta

Malta does not have a reimbursement system. Patients are entitled to receive free medicines depending on a number of set criteria. Access to free medicines under NHS is regulated by Schedule V scheme which lists the chronic medical conditions for which patients in Malta are entitled to free medicines. [9]

In 2012, legislative changes were made to the Social Security Act Cap 318 Article 23 and the Fifth Schedule of the same Act resulting in an increase in the number of listed Schedule V medical conditions, from 38 to 79. [9] In 2014 two further conditions, fibromyalgia and encephalomyelitis were added to this list. Patients suffering from a chronic medical condition which is listed under the second part of the Fifth Schedule of the Social Security Act are entitled to free medication for that specific disease and entitlement is based solely upon the presence of disease irrespective of means, income or age. [9]

Additionally patients with limited means are generally entitled to the Schedule II (Pink Card). Pink card holders are entitled to a limited number of medicinal products.[9]

Moreover, some medicines available under NHS are regulated with an additional protocol and the necessary approvals are made on an interim basis for the necessary follow-up to take place. These medicines are usually regulated due to the costs.[9]

In Malta there is no national drug consumption data. Information is highly fragmented and not collected in a manner conducive to determine drug consumption. A limited number of protocol regulated medicines will be presented in this paper. This however is far from the actual picture

Consumption of medicine data through free entitlement

In this paper, disaggregated gender data for the consumption of medicine through free entitlement in Malta, is described. Data was provided by the Central Procurement Supplies Unit (CPSU)[10] and the Medicines Entitlement databases (Schedule V and protocol-regulated databases). In Malta, CPSU is responsible for the management of all procurement processes related to the supplies, services and works across the Ministry for Health in line with Government Public Procurement Regulations.[11] Analysis of such data theoretically should provide the possibility of extrapolating information about possible differences between genders in use of medicines indicated for some conditions.

In calendar year 2013, approximately, seventy eight Million Euros were spent on medicines and medical materials/surgical devices in Malta. This data retrieved from the CPSU[10], provides information on the medicines, borderline substances listed on the published Government Formulary List and on other items procured. The Government Formulary List[12] includes approximately 1300 introduced items. There are also medicines which are not listed and which are procured through the Exceptional Medicines Treatment Policy to target urgent clinical cases or gaps within the Government Formulary, until there is the formal introduction for this medicine in the formulary, as regulated by through Legal notice LN 58/2009.[13]. The equipment and, medical/surgical devices are not included in the government formulary list.[12]

Gender differences in protocol regulated anti-asthmatic drug consumption in Malta

Asthma is usually treated with drugs which reduce inflammation and provide bronchodilation.[14] Prevalence of asthma is higher in males than in females before adolescence, however the trend changes after puberty.[15] The higher prevalence of asthma in boys has been proposed to be due to the airways in males developing more slowly, as compared to lung volume and thus males are more prone to indoor allergens.[16] Various asthma studies have in fact shown differences in anti-asthmatic drug use due to gender and age.[17] Some studies also indicate that responses to anti-asthmatic drugs differ between sexes.[15]

In Malta, in March 2014, the data from CPSU and the protocol-regulated entitlement database indicated that there were 254 (67.7%) female patients on budesonide inhalers,with 8 patients under 16 years. On the other hand, there were 121 (32.3%) males on these inhalers, with 4 patients being under 16 years old. The other inhaled steroids are not included in this database since they do not have a protocol and therefore no data is available to perform analysis on. There are however 11 females and 17 males on omalizumab. This medicines is administered as an injectable for subcutaneous use for patients 12 years of age and older

indicated for patients with moderate to severe persistent allergic periannual asthma. This data does not provide much information and since it is so limited a full picture related to medication consumption for asthma cannot be seen.

Gender differences in drugs used for schizophrenia use in Malta

Various studies have shown that there are gender differences in risk of developing schizophrenia. Women are more likely to be diagnosed as compared to men.[6] Studies have also shown that women respond differently to certain classes of drugs used in schizophrenia, since there is an enhanced effect with respect to the medicines used in the females (Table 1). In Malta, however, entitlement data for March 2014 indicates that the number of patients on clozapine, which is a controlled medication due to potential for agranulocytosis which necessitates that it is used with caution, was found to be the same for both sexes - 90 females and 90 males respectively.

The use of other antipsychotics could not be estimated since none of theses medicines are regulated by a protocol. In addition, until 2012, most of the central nervous system conditions were included under the only listed mental health condition on the Schedule V Act[9], that is, schizophrenia once again presenting a highly inaccurate picture..

Gender differences in drugs used for blood disorders and cardiovascular disease in Malta

Deferasirox, an iron chelator used in the management of thalassemia is the current oral preparation used in Malta. Prior to 2011 this treatment was only available as an injectable, presenting challenges with adherence to therapy. The valid approvals in 2014 indicate that there are 11 males and 8 females on oral treatment. It has been repeatedly reported that female patients with thalassemia major survive longer than males. This difference has been attributed to a lower rate of cardiac disease in females.[18-21] It has also been suggested that females have a better compliance with treatment than males and, therefore, accumulate less iron in crucial organs such as the heart and the liver. [18-21] This latter hypothesis is however not supported in Malta because there is no difference in the ferritin levels of male and female thalassemia patients.

Gender differences, may also be observed in the treatment for cardiovascular disease.[22] Certain conditions present differently in males and in females. These include myocardial infarction, where in men, the predominant symptom is usually chest pain, women present with chest pain, shortness of breath, nausea, indigestion and fatigue[23]. Gender and ethnic variables in medication use in these conditions are still being debated.[22]

Table 2 gives an overview of the number of patients on angiotensin II receptor blockers and statins. Statistical analysis of these patients using a student t-test concluded that there is no statistically significant difference between the two gender groups ($p>0.05$). The Pearson Correlation was found to be 0.97. This, once again, is not as expected, throwing substantial doubt on the quality of the data available.

Key points

- Physiological differences between sexes, affect the pharmacokinetics and the pharmacodynamics of drugs.
- Women are 50 to 75 percent more likely than men to experience an adverse drug reactions.
- In Malta data regarding medicine consumption in general or according to gender is exceptionally difficult to determine.
- Gender approach to medicines is not taken into consideration within the NHS
- Differences in gender and medicine use have not resulted as being significant in Malta. However, this may be due to the poor quality of data available and the current local entitlement/prescribing system.

Conclusion

The information presented in this paper highlights the limitations of the inferences that can be drawn from the data available. It is difficult to obtain information on prevalence of chronic diseases and even harder to obtain information about drug consumption. The latter has to be obtained through entitlement data, for protocol regulated drugs ,which as demonstrated, does not provide reliable information in terms of consumption. At best the Schedule V entitlement data may only be used in conjunction with CPSU data as a loose indicator of total national consumption of medicines according to the entitled condition. Due to these limitations it is even more difficult to obtain gender specific data.

Malta requires a national drug consumption database. In addition an integrated Information Technology system with the appropriate focus would assist in providing better data which would enhance patient management. This would also enable gender specific information to be generated, enabling improved resource management and patient care.

Table 2: Drugs used for cardiovascular conditions (valid approvals as available in March 2014)

Medicine	Females	Males
Angiotensin II Receptor Blocker	9869	7438
Statin (simvastatin)*	6607	7227
Fluvastatin	2849	2970
Rosuvastatin	30	44

** Valid permits as they had been issued for a considerable number of years. Item no longer requires a permit*

References

1. Anderson T. Gender Differences in Drug Use and Abuse in Drug Use and Gender. Chicago, US: University of Illinois; 1980.
2. Becker J. Gender differences in dopaminergic function in striatum and nucleus accumbens. Pharmacology Biochemistry and Behavior. 1999; 64:803–812.
3. Annual Estimates of the Population by Selected Age Groups and Sex for the United States. IN: U.S. Census Bureau Population Estimates by Demographic Characteristics. US: Population Division, U.S. Census Bureau; 2005.
4. Burden of disease in DALYs by cause, sex, and mortality stratum in WHO regions, estimates for 2002. IN: The World Health Report 2004: Changing History. Geneva, Switzerland: The World Health Organization, 2004.
5. Schwartz J. The influence of sex on pharmacokinetics. Clin Pharmacokinet. 2004; 43(11):732
6. Whitley H, Lindsey W. Sex-Based Differences in Drug Activity. Am Fam Physician. 2009;80(11):1254-1258.
7. Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol. 2001;2(6):349–351.
8. Drici M, Clément N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. Drug Saf. 2001;24(8):575–585.
9. Part of the Fifth Schedule in Social Security Act Cap. 318. Laws of Malta. 2014
10. Central Procurement Supplies Unit 2014. [Internet] Available from: https://ehealth.gov.mt/HealthPortal/health_institutions/cpsu/overview.aspx. Accessed 31st March 2014
11. The Government Formulary List 2014. [Internet] Available from: https://ehealth.gov.mt/HealthPortal/chief_medical_officer/pharm_pol_mon/med_within_ghs/gov_form_list.aspx12 Accessed 31st March 2014
12. Public Procurement Regulations in Laws of Malta: Legal Notice 296. 2010.
13. Medicines Act in Laws of Malta: Legal Notice 58. 2009.
14. Pocket Guide for Asthma Management and Prevention. IN: A pocket guide for physicians and nurses. US: Global Initiative for Asthma (GINA); 2012. Available at http:// ginasthma.org. Accessed 14th March 2014
15. Adult asthma data (2008): prevalence tables and maps. Centers for Disease Control and Prevention. [Internet] Available from: http://www.cdc.gov/asthma/brfss/2010/lifetime/tableL1.htm. Accessed 14th March 2014
16. Legato M *et al*. Principles of Gender-Specific Medicine. London: Academic Press;2010. 38
17. Trends in asthma morbidity and mortality [Internet]. American Lung Association 2010. Available from: http://www.lungusa.org/finding-cures/our-research/trend-reports/asthma-trend-report.pdf. Accessed 14th march 2014
18. Marsella M. Cardiac iron and cardiac disease in males and females with transfusion-dependent thalassemia major: a T2* magnetic resonance imaging study. Haematologica 2011; 96(4): 515–520.
19. Yiannoutsos C., *et al*. Cardiac related death in thalassaemia major: time trend and risk factors in a large Greek Unit. Eur J Haematol. 2009; 82(5):381-7.
20. Telfer P.*et al*. Survival of medically treated thalassemia patients in Cyprus. Trends and risk factors over the period 1980–2004. Haematologica 2006;91 (9):1187–92.
21. Borgna-Pignatti C, *et al*. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 2004;89(10):1187–93.
22. Stramba-Badiale M., Priori S. Gender-specific prescription for cardiovascular diseases? European Heart Journal 2005;26:1571-1572.