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Rational and Irrational Drug Use: Factors, Impacts and Strategies to Combat Irrational Drug Use: A Narrative Review

Zahra Hassan AL Qamariat

Senior Clinical Pharmacist, First Health Cluster in Eastern Province, Dammam Medical Complex, Saudi Arabia

***Corresponding author:** Zahra Hassan AL Qamariat, Senior Clinical Pharmacist, First Health Cluster in Eastern Province, Dammam Medical Complex, Saudi Arabia, Email: study.zalqamariat@gmail.com*

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Abstract

Misuse of drugs is a serious health problem all around the world. Rational drug use can be characterized as follows: patients receive drugs that meet their clinical needs, at doses that meet their requirements, promptly and at the lowest cost to themselves and their region. Drug abuse, polypharmacy, and misuse are the most prominent drug use problems today. Misuse of drugs can occur for a variety of reasons at different levels, including recommended mistakes and over-the- counter medications. Inappropriate use of income can lead to real negative benefits and financial results. There are many irrational drug mixtures available. Appropriate rational use of medicines will increase personal satisfaction and lead to better local health services. A list of essential medicines recommended by the World Health Organization (WHO) can assist the countries around the globe in rationalizing the distribution and purchasing of medicines, thus decreasing the costs to healthcare systems. Irrational drug use has been a subject of concern for years as it affects the health system and patients badly. Irrational use of drugs can result from several factors such as patient, prescriber, dispenser, health system, supply system, or regulations. Thus, diverse strategies have been used to promote rational drug use and also to tackle irrational use. Thereby the concept of rational and irrational drug use and factors that lead to either result should be identified and monitored.

1. Introduction

Medication is an essential key in healthcare delivery. The purposes of its use like disease cure or prevention, symptom relive and pain palliation can be achieved when it is used properly. Thus, rational drug use (RDU) has been addressed since 300 B.C. by the Greek physician Herophilus as he said 'Medicines are nothing in themselves, but are the very hands of God if employed with reason and prudence'. However, it is estimated by the World health organization (WHO) that more than half of drugs are used irrationally. Several factors can result in irrational drug use (IRDU). The practice may occur at any point of drug use such as prescribing, dispensing, selling, or administration. This issue has been negatively impacting health system safety and the economy and can be a leading cause of mortality in some circumstances. For this reason, different strategies have been involved to promote rational or combat IRDU (Ofori-Asenso and Agyeman, 2016).

Even though drugs are one of the important components of health care system, and play an essential and important role in saving the lives of people, still usage of drugs is a complicated and sensitive issue that involves the patient, the prescriber/physician and the dispenser as a whole. Doctors prescribe drugs regularly. In order to optimize the benefit of drugs to the patient for a particular condition, they should be selected appropriately in correct doses for right time period. But this can only happen in an ideal world where ideal doctors are trained ideally. But in real world, situation is quite different as the existing situation highlighted by WHO is horrendous. WHO has developed the indicators to assess the practice of RDU in health systems. According to an estimate of WHO over a half of all the drugs are prescribed, sold or dispensed inappropriately and almost half of the all the patients around the world don't take their medicines correctly. All these practices are the leading cause of wastage

of limited sources as well as health hazards on an international level (Chaturvedi et al., 2012).

Drug misuse is a serious global health problem with serious implications for patients, managers, and healthcare networks. Several variables can increase inappropriate drug use at different stages of the drug use cycle. Understanding these elements is essential for changing population behavior, addressing regulatory and health gaps, and implementing appropriate interventions. The key elements that contribute to drug abuse are likely to change over time, and strategists need to be fully informed of the latest developments. Inappropriate use and over-the- counter offerings will not only improve health problems but can also be associated with well-articulated antagonistic potentials, including drug side effects, significant costs, and complications. Although, the act of injustice/ misuse of drugs is incorrect and misleading. Changing the act of waiver and disapproval requires a complementary update of the proposed health care system to make clinical considerations available to individuals and educate the public and clinicians in advance on the rational use of drugs. This study aimed to identify the causes and factors that influence RDU consistency (Erku et al., 2021).

Prescriptions play an important role in medical care and, when used correctly, can help cure infections, reduce symptoms, and reduce patient suffering. Nonetheless, inappropriate drug use remains a serious problem faced by most healthcare professionals around the world. The WHO estimates that most drugs are poorly approved, distributed, or marketed". Also, about half of patients neglect the correct medication. The problem of IRDU is known to be more serious in non- industrialized countries with poor health conditions, where components of routine drug testing are usually underdeveloped or occasionally absent. Improving RDU requires compelling strategies of equally effective collaborative efforts on the part of healthcare providers, patients, and entire networks. To encourage synergistic efforts towards a trend towards IRDU, there must be sufficient agreement by all partners on the relevant aspects of drug use. Addressing the problem of IRDU is seen as fundamental not only to improve health care and patient safety but also to ensure the ideal use of goods. "This is because 25–70% of total health spending in agricultural countries is spent on medicines, while about 10% of health needs in most high-wage countries are met by prescription". In this article, we focus on summarizing key ideas about drug use to provide clear and concise data to educate healthcare providers, patients, politicians, and society at large (Mamo and Alemu, 2020).

The availability of a limited number of 'essential drugs' has been improved by essential drug programs running in many developing countries. According to a report by the WHO, about 67% of people still do not have access to essential medicines. All around the world, governments have, over the years, developed policies and issued orders for drug price controls from time to time, to meet the demands of medicines at low prices. Government, universities, and professional organizations play a vital role in improving student undergraduate, postgraduate, and ongoing medical education in therapeutics, medicine information issues, and clinical pharmacology. The teaching of pharmacotherapy related to current problems can be an effective strategy in this regard. In order to improve the care quality, the right drugs should be given to patients. It has been observed that IRDU occurs all around the world especially in developing countries; however, this practice has not been so common in developed countries. So, there is a dire need of paying attention to this issue especially in developing countries (Laing, 1990). Rational use of medicines is seen as one of the most important standards for the delivery of quality and effective healthcare (Sabir, 2018).

The current epidemic of COVID-19 is an unprecedented challenge for Governments and the general public of all the countries. Doctors and researchers are eager to find a solution. When standard drugs such as chloroquine, ritonavir, lopinavir, and hydroxychloroquine do not work as well as expected, then testing of the active ingredients of herbal medicine is an effective method that should not be ignored. Although the mortality and morbidity rate of COVID-19 is terrifying and it is understandable to observe the usage of drugs with unproven benefits and other traditional methods of treatments, but there is a dire need to enforce the rules to use these drugs after evidence of their effectiveness (Yang, 2020).

2. Objectives

The objectives of this review are as follows:

1. Understand RDU and IRDU
2. Illustrate and appraise factors causing IRDU
3. A clinical perspective of misuse of drugs
4. Summary of impacts of IRDU
5. Introduce and summarize strategies used to promote RDU and combat IRDU
6. Discuss the effect of self-medication on irrational use of drugs
7. Identify how COVID 19 pandemic has affected IRDU
8. Controlling of self-medication in the era of COVID 19

3. Method

Literature was searched using Pub Med and Google scholar. Selected papers were reviewed for creating the objectives of this narrative review.

4. Discussion

4.1 Understanding RDU and IRDU

RDU is a core element to provide effective, safe, and quality healthcare. In 1985, WHO summoned a conference of experts in Nairobi on the "Rational use of drugs" in which experts defined it as a situation that can be achieved when 'Patients received medications appropriate to their clinical needs, in doses that meet their individual requirements, for an adequate time period, and at the lowest cost to them and their community' (World Health Organization, 2001).

This definition addressed about five rights which are the prescription of the right drug at the right time by the right route at the right dose for the right patient. If the prescribing process follows the necessary steps, then the requirements of the five rights can be fulfilled. These steps are as follows: (1) defining the problems of the patients (known as diagnosis); (2) defining safe and effective treatments (non-drug and drug treatment); (3) choosing correct drugs, their dosage, and time period; (4) writing a comprehensible prescription; (5) guiding patients correctly regarding their disease condition and drug dosage and lastly (6) planning to assess the process of treatment (Chaturvedi et al., 2012).

The World Bank (WB) has also characterized RDU as incorporating two key standards: drug use, as indicated by logical evidence of resistance, well-being, and resilience; and economically reasonable use of drugs following the requirements of the given healthcare facility.

WHO's definition of RDU differs from the World Bank (WB) definition in two aspects. First in which the WB requires drug prescribing based on scientific data. Then, WB recommends the use of drugs concerning the country's financial capacity while WHO encourages the use of drugs with the lowest possible cost (Ofori-Asenso and Agyeman, 2016). Both WHO and WB definitions generally take a clinically useful point of view; however, RDU can also be viewed from the perspective of the client or patient. What is clinically rational can be seen by the patient as irrational, and vice versa (Brahma wt al., 2012). Therefore, it is of fundamental importance that both clinical and client / patient views are viewed as a holistic understanding of the rational use of prescriptions. RDU requires an appropriate combination of all these factors. In this article, we have mainly focused on the clinical perspective of misuse of drugs.

From the medical therapeutic perspective, the IRDU can occur at any of the four stages of the medication use cycle; diagnosis or follow-up, prescribing, dispensing, and patient adherence. Inappropriate diagnosis or follow-up to patient status or effect of treatment course will end with irrational prescribing (IRP). Although prescribing may be perceived as a routine activity, it is a complex process that needs skillful prescribers in different aspects like knowledge, communication, application of therapeutic principles, and the ability to deal with risks and uncertainty. The WHO has listed essential cores for rational prescribing (RP). These cores can be summarized as making an appropriate decision to prescribe a drug that is safe and cost-effective with minimal harm or toxicity to a specific patient. This needs to be accompanied by monitoring for the drug effects and relevant information given to the patient regarding the drug and medical condition (Ofori-Asenso and Agyeman, 2016).

There is an ongoing debate about whether RDU should be characterized as a widespread idea or whether it should be modified to suit the individual's environment. It has been observed that developing countries face multiple challenges and fluctuations in health status capacities as they have limited sources and inadequate infrastructure to handle the drug supply process efficiently (Almarsdóttir and Traulsen, 2005). The case of EML (essential medicine lists), defined as a minimum list of drugs that meet the health needs of the population can be taken as an example. Even developed countries are facing a rise in healthcare budget so the idea of EML medicine is highly essential and applicable in both developed and developing countries (Laing et al., 2003).

IRP is classified into five categories: under-prescribing, over-prescribing, incorrect prescribing, extravagant prescribing, and multiple prescribing. Under-prescribing results when either the required drug is not prescribed or prescribed with low dose or for insufficient duration course. On the other hand, over-prescribing is when a drug is prescribed with no relevant indication to patient conditions or a required drug is prescribed for the prolonged treatment course duration. This may include, for example, giving a long antibiotic treatment of 21 days to a patient that needs a course of just 7 days or prescribing an antibiotic in viral infection (Alam et al., 2019). While incorrect prescribing can be an instance of selection of a drug based on the wrong diagnosis. It can be also due to prescribing a drug that interferes with co-existing patients' conditions or current therapy. The extravagant prescribing occurs as a result of selecting an expensive drug in the availability of lower-cost with comparable safety and efficacy alternative. Also, it can be a result of treating the patient's symptoms without determining and dealing with underlying causes. Finally, multiple prescribing occurs when the prescriber uses many drugs at the time fewer numbers would provide the required effect (Ofori-Asenso and Agyeman, 2016).

Prescribing is normally followed by dispensing; a process that involves preparation and labeling of drugs and translation of a prescription instruction for a selected patient (Almarsdóttir and Traulsen, 2005). It is usually performed by a trained pharmacist or technician but it might be carried out by a trained prescriber. However, dispensing by prescriber may affect the therapy cost and safety. For example, in Zimbabwe doctors' dispensing resulted in more costly and less RP. Thus, an additional independent dispenser is important to assess prescription appropriateness through interpretation and evaluation. A pharmacist is uniquely qualified for this stage of dispensing. During the interpretation and evaluation phase, the pharmacist assesses prescription appropriateness in terms of drug indication, dose, route, dosage form, strength, and duration. Also, pharmacist checks and assesses the availability of suitable and equally safe, effective and lower-cost alternative. Additionally, the pharmacist ensures the drug's safety and rules out any contraindication or interactions with other drugs or patient conditions. Thus, all dispensing phases are applied to ensure RDU (Ofori-Asenso and Agyeman, 2016).

Moreover, pharmacist practice has expanded to be no longer a supplier or dispenser only. Nevertheless, pharmacist responsibilities have grown to meet RDU through interacting with and educating prescribers and other health workers. Also, pharmacist plays a major role in improving patient medication compliance via counseling, one of medicine use cycle stages where RDU needs to be enforced (World Health Organization, 2004).

4.2 Essential medicine concept and rational use

The proclamation of Alma-Ata during the 1978 International Conference on Primary Health Care confirms that health is a fundamental human

right and that the attainment of the highest standard of living is the most important social goal in the world. The Alma Ata Declaration outlines eight key components of primary health care and one of them is the provision of essential medicines. Medication is an important part of health care and modern health care cannot be imagined without the availability of the necessary medications. Not only do they save lives and improve the health of patients, but they also prevent diseases and epidemics too. Medicine is undoubtedly one of mankind's greatest weapons against illness and disease. Access to treatment is also a basic human right (Karet al., 2010).

4.2.1 Essential medicine concept

The concept of essential medicines was introduced by the WHO in 1977. Essential medicines are those that meet the basic health care needs of the people. They are selected based on the importance of public health, comparative cost-effectiveness, and proof of efficiency and safety. Essential medicines are intended to be available within an operating healthcare system at all times at reasonable prices, in sufficient amounts, in proper dosage forms, with guaranteed quality and sufficient information, and at a price that the community and the individual can pay for. The execution of the concept of essential medicines is anticipated to be adaptable and flexible to various different situations; exactly which drugs are considered as essential remains the responsibility at the national level. Knowledge regarding essential medicine has shown that the selection of a limited number of essential medicines carefully leads to a higher level of care, better medication management (including better quality of prescribed medications), and modest use of available health resources. The WHO established the first list of essential medicines in 1977 and since then the list has been updated after every two years. The list of essential medicines is limited to safe and cost-effective medicines, while large numbers of drugs having doubtful effects and value are available in the open pharmaceutical market. The WHO model list serves as a guide for the development of nationally and institutionally important drug lists. The concept of essential medicines has been accepted all around the globe as a great tool for promoting quality of health and its impact is significant as the essential medicines have proved themselves as one of the most reasonable elements in healthcare systems (Obuaku-Igwe, 2015).

4.2.2 Selection of list of essential medicines

The process of drug selection is important. The list of essential drugs forced from authority will not reflect the need for individuals or be accepted by them. It is therefore of the utmost importance that the process be transparent and consultative, criteria for selection be explicit, drug selection be linked standard clinical guidelines based on pieces of evidence, medicine lists, and clinical guidelines be split into levels of care, and regularly updated and reviewed. A review of medicine lists and clinical guidelines should be done at least after every two years, and their use and impact should be considered (Mustafa and Kowalski, 2010). The process of making a list of essential drugs is as follows:

- Establish a transparent process for developing and reviewing a list of essential medicines, providing a voice for key stakeholders, but ensuring a scientific and evidence-based approach.
- Standard clinical guidelines implementation and involvement of both primary care providers and specialists.
- Garner support from senior doctors, educational institutions, community health workers, trade unions, non-governmental organizations, and members of the community.
- Making a list of essential medicines available (essential medicines, clinical guidelines, and prescriptions) in all health facilities/health care providers in both electronic and printed formats.
- Consider introducing a new or updated list with the participation of relevant government officials with ample publicity.
- To clarify a particular legal or administrative authority list of essential medicines for training, procurement, public information, and refunds.
- Establish a management or budget "safety valve" for the supply and limited use of unregistered medicines.
- Regular improvement of the list to reflect medical advances and changes in antimicrobial resistance patterns and costs, and measures to address the importance of public health (World Health Organization, 2006).

4.2.3 Utilization of essential medicine list

The concept of essential medicines has also been embraced by many international organizations, including the Office of the United Nations High Commissioner for Refugees (UNHCR), and the United Nations Children's Fund (UNICEF), as well as non-governmental and foreign non-profit organizations. Many of these agencies base their drug delivery program on the Model list. The list of essential medicines also directs the supply and procurement of medicines in the public sector, reimbursement schemes, drug donations, and local drug production, and, in addition, is widely used as tools of knowledge and education by health professionals. Health insurance schemes are also increasingly using a national list of essential medicines for recommendation purposes. The model list provides the basis for further advancement (addition and removal of new drugs), the dosage form, and strength depending on the available evidence and national priority (World Health Organization, 2007).

4.2.4 Essential medicine lists followed by rational use

Selection of essential medicines is only one step in improving the quality of health care; it should be followed by proper use of these selected essential medicines. Each person should get the correct medicine, for the right amount of time, with accurate information and the right treatment, and at the lowest cost. As mentioned earlier, all around the world, more than 50% of all drugs are prescribed, dispensed, or sold inappropriately, while 50% of patients don't take the medicines correctly. The situation is frightening. Unfortunately, due to misuse, effective drugs of yesterday do not work today. This can be explained through the example of antimicrobials. Therefore, in addition to gaining advanced access to

essential medicines (availability and accessibility); it is equally essential to use medication properly, known as rational use (Kar et al., 2010).

4.3 Examples of IRDU

4.3.1 Polypharmacy

Polypharmacy occurs with any of the two scenarios. First by prescribing more than one medication to treat one condition. Second by prescribing more than one medication of the same chemical class or with a similar mechanism of action to treat different conditions. In addition to these scenarios, a patient may contribute to polypharmacy by self-medication, visiting different clinics, or using of over the counter (OTC) alternative medicines that in many cases physician is unaware of. Polypharmacy is often prevalent in the elderly and commonly in populations with chronic conditions. One reason of polypharmacy is combination therapy for the purpose of enhancing one of the main medicine's effect. For example, the use of benzodiazepine as adjunctive to antidepressant in early stage of depression treatment for anxiety or sleeplessness alleviation is justifiable. However, prolonged use of benzodiazepine after antidepressant effect is reached is irrational and may cause dependence. The second reason is stuck titration which may be caused by adding one drug with a high dose while reducing the dose of another drug. At a period of this, the patient may deteriorate due to receiving allow concentration of both drugs so the physician may increase the reduced drug dose to the initial dose and do not think of the newly added drug dose. Thus, due to no improvement third drug may be added. Also, the patient may improve and combination is continued with no further assessment. Another reason is sloppy diagnosis like treating agitation in intensive care with haloperidol in the constipated patient rather than treating constipation as a possible cause of patient agitation. The fourth cause is 'blind adherence to specifications listed in the Physicians' Desk Reference'. An example that explains this is when maximum dose is recommended in references and there is a suggestion that some patients could require higher safe doses. Some physicians might choose to add another drug instead of increasing the dose and this may be common with antihypertensive medications. The fifth reason is poor knowledge about drug pharmacological action or classes like using a combination of angiotensin-converting enzyme inhibitor with angiotensin receptor blocker. A similar example is an unjustified combination of antibacterial. One of the reasons for polypharmacy can be also through educational activity sponsored by the drug company as the company may promote its product by using a less expert speaker to give combination suggestions with the product that has notable studied yet. Finally, physicians thinking of adding more drugs would accelerate treatment response without evidence may be a source of polypharmacy (Kingsbury and Simpson, 2001).

4.3.2 No utilization of therapeutic guideline

When no therapeutic guideline is implanted in an institution or there is unjustifiable deviation and non-adherence to the institutional guideline, then the drug may be used irrationally. A Simple example is when a guideline recommends the use of oral rehydration solution for acute diarrhea in children and the physician prescribes antibacterial instead. In this instance, prescriber underused effective drug and abused other when it is not needed. Also, using of metronidazole in combination with carbapenems or piperacillin-tazobactam to empirically cover anaerobic bacteria in aspiration pneumonia is an example of guideline non- adherence and reason for polypharmacy that creates IRDU. Moreover, using prolong or shorter duration of antimicrobial than guideline recommendation may be considered as IRDU. Lastly, the use of ineffective or no recommended drug such as multivitamins can be an example of guideline deviation and IRDU (Reddenna, 2014).

4.3.3 Excessive use of injections

Exaggerated use of injections may be because prescriber or patient usually think they are more potent than oral forms. However, many medications are with oral bioavailability similar to their injectable form and proven to be effective and safe. This IRDU may be a source of resources wastage. Also, excessive injection use may be a risk for infection (Reddenna, 2014).

4.3.4 Self-medication

Self-medication is another example of IRDU that can be acted even by prescribers themselves.

4.3.4.1 Self-medication in COVID-19

According to the WHO, self-medication is the utilization and selection of drug to treat known symptoms or diseases without consulting a physician. It includes the use or reuse of formerly prescribed or unused medicines, the direct purchase of prescription drugs without physician's consultation, and irrational usage of OTC (over-the-counter drug). Self-medication is observed all around the world affecting not only developing but developed countries also. Various studies have shown that self-medication is the most widespread practice, with a worldwide prevalence of 32.5 to 81.5% (Kassie et al., 2018).The most commonly prescribed medications are antidiarrheals, antitussives, antipyretics, analgesics, vitamin and calcium supplements, sedatives, anabolic steroids, certain antibiotics, and homeopathic and herbal remedies. Up till September 21, 2020, almost 30,905,162 confirmed cases of COVID-19 have been reported, and, till now, there are no antiretroviral drugs or drugs available to treat or prevent this infection. This situation has increased the impact of social media regarding misinformation about medicine, which has led to social confusion and increased fear and use of self-medication, including home remedies, with no guaranteed efficacy and safety (Erku et al., 2021).

Between 7 January, 2020 and 1st June, 2020, an increase in public interest in online information regarding self-medication during the COVID-19 epidemic is reflected in Google's search trend on self-medication. Self-medication suggestions for COVID-19 can come from family, friends, neighbors, past prescriptions, pharmacists, and the media. In developing countries, usage of chloroquine and hydroxychloroquine as self-medication for COVID-19 has been reported. Afterward, in

accordance with the therapeutic safety profile of patients of COVID- 19, the U.S. FDA (Food and Drug Administration) announced that the use of chloroquine and hydroxychloroquine is dangerous for mild to moderate COVID-19 (Chauhan et al., 2020). Likewise, for the treatment of COVID-19, researchers of United Kingdom have announced dexamethasone as a 'life-saving drug', still, the UK Health Minister stressed that this drug should only be used in those patients which are critically ill and should not be used as self-medication in mild to moderate cases as this drug has inherent safety problems (Onchonga, 2020).

In some countries, for COVID-19 treatment, Vermectin is being used as OTC (over the counter drug) and people are self-medicating and self-dosing themselves. That is why, the WHO has issued a number of cautions when treating COVID-19 using the self-medication, including herbal remedies, irrational use of antimicrobials, and other over the counter drugs. All over the world and especially in countries like Pakistan and China, herbal remedies are being used to treat COVID-19 (Yang, 2020). Such herbal products/drugs are easily available to common people without a prescription and are used as self-medication in order to avoid hospital admissions and visits, but their use in COVID-19 has no evidence-based support. In China, for the treatment of COVID-19, three pharmaceutical products that have been patented are recommended (Jinhua Qinggan granules and Lianhuaqingwen tablets for treatment of mild conditions, and Xuebijing for treatment of critical conditions). But, before being used to treat COVID-19, their potential efficacy and safety need to be confirmed by the results of randomized controlled clinical trials. Likewise, there was a demand for and use of an herbal plant known as Sanna Makki, by local people in Pakistan because of its effectiveness in treating the symptoms of COVID-19 (Malik et al., 2020).

Self-medication is considered to be part of a process of comprehensive self-care, which encourages people to engage in activities related to improving health, treating disease, preventing disease, and restoring health after disease or injury (Hughes, 2001).Self-medication (SM) helps reduce the economic burden on people, third-party government agencies, the health care system, and insurance companies. But, the negative and undesirable effects of self-medication cannot be underestimated, as self-medication can lead to wrong diagnosis, polypharmacy, side effects, antibiotic resistance, drug interactions, and additional drug costs. Policymakers of healthcare prefer to promote the policies and law by allowing the use of prescription drugs, however, the challenges linked with self-medication in the general public cannot be disregarded. That is why improved public education and awareness about the rational and safe use of drugs is essential to overcome the challenges of self-medication (Atif et al., 2020).

4.4 Factors lead to realization of RDU (Shivhare et al., 2010)

4.4.1 Drug explosion

Availability of a high number of medications for specific indication may complicate planning treatment regimen. In old times, the "one drug, one disease" phenomenon was employed while treating the disease but nowadays, the practice of Non-evidence based use of drugs as an alternative to well-known and classical medicines in spite of the clinical uncertainty of new drug and the most disappointing fact is that it is not due to continuing education or lack of information. A few alternative drugs have been studied so far and considered safe for consumption but the effects of the majority of alternative drugs have not been studied that is why many among these medicines pose harmful effects on the patient. As a prescriber or the patient, it has become difficult to choose medicine or treatment available for a particular disease especially when the prescriber does not know that which option would work for a particular patient. This has led to an increase in the irrational use of drugs tremendously (Figueras, 2011).

4.4.2 The emergence of antimicrobial resistance

Due to misuse of the antimicrobials high rate of resistance have been developed worldwide. Resistance of microbes against the antimicrobial which was once used to kill them is a part of the natural process of evolution but in the last few decades, the social organization of animal and human health has catered to the acceleration of antimicrobial resistance. Several factors especially social and political forces that include patient's expectations, healthcare systems' financing, unexpected changes in research, and the development of the pharmaceutical industry have contributed towards the flourishment of antimicrobial resistance. Antimicrobial resistance is one of the crucial health challenges of our era. Global action plan of world health organization (WHO) remarked that drug resistance "threatens the very core of modern medicine and the sustainability of an effective, global public health response to the enduring threat from infectious diseases". IRDU is one of the leading factors of the emergence of antimicrobial resistance. Growing qualitative studies regarding antimicrobial resistance around the globe have escalated the understanding of causes of excess antimicrobial use that include poor hygiene, limited access to healthcare, absence of alternatives to antibiotics, and poor sanitation infrastructure (Dixon et al., 2021).

Due to this, considerable interventions, policies, and research have been accelerated to optimize the use of antimicrobials/antibiotics. In recent decades, LMICs (low and middle-income countries) have witnessed a considerable increase in antibiotic usage. Several countries have formulated national action plans on antimicrobial resistance by following the guidance of global plan action. These action plans aim to reduce the irrational usage of antimicrobials and use various approaches that focus on restriction, correction, and surveillance of antimicrobials. Recent approaches to combat antimicrobial resistance have focused on two main strategies: one is to restrict the access of antimicrobials to the people and another is to change the practices of individual prescribers (Broom et al., 2020). It is essential to work on strategies to reduce antimicrobials use and prevent resistance.

4.4.3 Open information access

Improve awareness about new drugs, their uses, and adverse effects. Nowadays, people have 24/7 access to an internet connection and there

is excess information available on the internet regarding every disease. Due to this open access to increasingly relevant therapeutic guidelines and clinical research, self-medication practices and irrational use of drugs have been tremendously increased (Mamo and Alemu, 2020).

4.4.4 Costly treatment

Affect patient and government budget. Due to IRDU, resistant pathogens have emerged against many diseases such as in 90% of countries falciparum malaria resistance to chloroquine has been evolved. Cases of NCDs (Non-communicable diseases) have increased but 80% of its cost burden can be reduced with proper drug use. Similarly, tuberculosis resistant against primary drugs and shigellosis resistant against ampicillin/trimethoprim has also emerged. Due to this, doctors have to use second-line drugs for the treatment of these diseases which are very expensive. According to an estimation, the USA has to spend 4000-5000 US dollars annually in order to combat antibiotic resistance. Similarly, adverse drug effects are estimated to cost up to 5.6 million US dollars per hospital annually in the USA. With rational use of medicine, this cost can be reduced to half (Kshirsagar, 2016).

4.4.5 Consumer Protection Act (CPA)

Consumer protection is not a new or modern issue. In order to protect the consumer in every organized society, the government makes efforts to regulate economic activities. It is the only major and more complex problem today. Food and drug administration (FDA) which is a part of the health department plays a vital role in the context of the role of government in protecting consumers while considering the topic of drugs. Before "new drugs" are introduced in the market, the regulatory authority tests and examines them, and then these drugs are introduced in the market. These regulatory controls help in the reduction of IRDU and RDU (Liefmann-Keil, 1974).

4.5 Hazardous impacts of IRDU

The impact of IRDU can be enormously harmful in different aspects. First, it can affect the quality of treatment and care in various ways. For example, when oral rehydration solution is underused for pediatric acute diarrhea, then dehydration may not be corrected and thus mortality rate may increase. Another example is if an antibiotic is not given before surgery which indicates preoperational infection prophylaxis, then the risk of postsurgical infection may rise. On the other hand, IRP of antimicrobial can be a risk for treatment failure due to the emergence of resistance. This may also lead to another result of IRDU that is adverse drug reaction like renal impair mentor exacerbate the patient condition or cause iatrogenic disease. Consequently, this will prolong hospitalization or lead to mortality. Together with these consequences antimicrobial resistance will limit the choices of treatment and increase pressure on expensive antimicrobial resulting in resources and money wastage. Misuse of prescriptions increases the risk of antagonistic drug reactions (AR), especially in geriatric patients or in unfortunate people who may have impaired physiological abilities. For example, in a participatory review of seasonal people in Australia, the presence of comorbidities was a strong indicator of re-confirmation of adverse reactions, especially in people with locally-controlled comorbidities. The cost implications for ADRs can also be significant. For example, in Germany, it is estimated that ADRs are worth more than 430 million euros per year, while in the UK the cost of crisis positions arising from ADRs is estimated at 2 billion pounds per year (Pirmohamed et al., 2004).

According to winner of Nobel Prize, Laureate Joshua Lederberg, "the future of humanity and microbes will evolve as episodes...of our wits versus their genes". Lederberg indicated that bad human behavior, such as the misuse of antibiotics, is one of the key factors in the global response to antimicrobial resistance. (Lederberg, 2000). For example, studies have shown that diagnostic antibiotics that have therapeutic effects contribute to development of antibiotic resistance by promoting genetic modifications, including changes in mutagenesis and genetic expression. The emergence of antimicrobial resistance is seen not only as a threat to advancement in health but it can draw the whole mankind back to pre-antibiotic era, when many people suffered and died from chronic bacterial infections (Ventola, 2015).

The IRDU generally increases financial waste through spending on nonessential medicines like multivitamins instead of preserving resources for more vital medicines or vaccines. Affecting health system financial resources by IRDU will also limit the availability of essential tools in practice such as diagnostic tools which in turn may be a risk factor for further irrational prescribing and drug use. Moreover, irrational use of injections form of drugs can be a source of infection transmission as well as budget wasting when an oral form of the drug or its alternative with same efficacy and safety available. Lastly, IRDU by overprescribing may influence patient dependency on medication (Shivhare et al., 2010; Sabir, 2018; Chordia, 2019).

4.6 Factors for IRDU

There are many factors that contribute towards irrational usage of drugs, major forces for these factors can be classified as those derived from the workplace, prescribers, patients, supply system that includes industry regulation, influences, drug misinformation and information, and an amalgam of all these factors.

Patient and prescriber are the two main personnel contributing to IRDU.

4.6.1 Prescriber

One factor for IRP is knowledge gap due to poor baseline knowledge and medical background, lack of continuing education, inaccessible informational resources, inadequate training, and/or weak supervisory. For instance, insufficient knowledge and poor training in disease diagnosis and management may result in IRP leading to IRDU. Also, consultant or supervisor with non-updated information and outdated prescribing practice can poorly influence their junior or peers' knowledge and attitude resulting in IRP (Ofori-Asenso and Agyeman, 2016). Moreover,

if pharmacy staff lack the required knowledge, skills, and confidence to interpret prescriptions, review, and appraise scientific and medical references to advise prescribers on appropriate disease management and drug dosing, then the knowledge gap will be worsen and IRP will be escalated. Another factor is inefficient work environment and facilities such as insufficient manpower resulting in heavy workload that may negatively affect prescriber performance towards RP. Also, lack of required or some advanced diagnostic or monitoring tools is another example in which physicians may fail to make a precise diagnoses and consequently polypharmacy and IRDU can occur (Ofori-Asenso and Agyeman, 2016; Mohamadloo, et al.,2017). The third factor is an overestimation of patient demands or expectations by prescribers usually to a keep good patient relationship or to avoid pressure. For instance, a UK survey showed that 55% of general practitioners (GPs) prescribed unnecessary antibiotics due to patients' pressure (Mohamadloo, et al., 2017). The fourth factor for IRP is pharmaceutical industry promotion. It has been shown that prescriber's attitude is highly influenced by pharmaceutical company representative information. A systemic review indicated that a higher rate of unnecessary and expensive medicines prescribing is due to exposure to medical representative information. Also, one-to-one contact between sales representative and physician is an opportunity for building a relationship that influences physician prescribing in favor for company products. A study in 1992 revealed that pharmaceutical company sponsors physician trips to attend symposia will tremendously impact their prescribing patterns later. The influence of pharmaceutical companies also extends to 'authors of Clinical Practice Guideline (CPGs)'. One study stated that about 87% of CPGs authors interact with the pharmaceutical industry, 58% were supported financially for their research and 38% worked for a pharmaceutical company before (Chaturvedi, 2012). Thus, CPGs may be a bias source of information that may mislead prescriber decisions and be a cause of IRDU. Moreover, a defective health system with unorganized drug regulatory authority and poor supply are factors for IRDU. The absence of regulation and policy to control the availability of safe, effective, affordable drugs and ban availability of doubtable ones in the country's market or health institutions will fail to support RDU. Unreliable supply systems with expired and medicine shortages will affect prescriber decision for an appropriate treatment plan or lead to inconsistent prescribing for chronic condition management resulting in IRDU. Finally, a fee-for-service payment system can influence physician prescribing to IRP. It was shown that GPs with this payment system work for the benefit of their economic and self-interest and utilize huge health resources and services (Mohamadloo, et al., 2017).

4.6.2 Patient

Patient beliefs are one of the factors that influence drug use badly. For example, when the community believes misfortunes and witchcraft are the cause of illness then there would be members who would not seek medical consultation and not take required medicines. Another one is high social status people who dislike being with the low social status in health centers may also not seek medical assessment or select and use medications on their own. Another example of patient beliefs is that low social status in Uganda believes in sharing and taking under-dose of drugs. Also, some communities may believe that injections are more effective than oral form and thus overuse injections irrationally. Moreover, a patient may fear being stigmatized especially with sexually transmitted diseases and so practice self-medication leading to IRDU. Along with beliefs, low educational level is another contributing factor. Due to ignorance, these patients would follow peers' advice or community myths resulting in IRDU. This may be influenced by the prescriber or dispenser during the communication process if no appropriate information is provided to the patient and no educational tools are given. The result of this will be poor drug compliance. Another factor is difficult to access to health care or unaffordable service which can contribute to self-medication practicing. The final factor is the media advertisements which make patients familiar with many drugs and may either enforce prescriber for polypharmacy or self-medicate themselves particularly if no health regulation bands access to the drug without prescription (Celiket al., 2013; Twinomujuni, 2016).

4.7 Strategies used to promote RDU and combat IRDU

In rational use of medicine (RUM), there is a concept of 3M which denotes Medicines Mean Money. Therefore, RMU means less income and profit for those dealing with medication; doctors, and sellers. For better health care, physicians/doctors have accountability and wide scope too in promoting the rational use of drugs. Educational strategies for consumers and health care workers have been proved to be an effective model of promoting rational drug usage. One of the educational strategies is to train medical students of different years on how to use medicines rationally. The concept and benefit of RDU should be part of the syllabus. Accordingly, WHO sets core interventions to promote RDU. A manual of the WHO, "Guide to Good Prescribing: a Practical Manual" is a very helpful guide for both undergraduate and postgraduate students is an appreciated step in this venture (Kar, et al., 2010)

Medical professionals should keep themselves up to date by attending meetings, conferences, and other programs to keep up with the technology. These programs should not be funded by the pharmaceutical industry, as there is often a conflict of interest. They should consult independent publications or drug information agencies for drug-related information, but not from representatives of medical. One of the good sources of information is the hospital formulary. The first choice during the treatment of a patient should be essential medicines. Lastly, they should take good care of their patients and clients by spending some time with them elucidating the proper use of prescribed medications. In the prescription of drug therapy, the patients should be considered as partners (Kassie, et al., 2018).

For the elimination of IRDU, it is advisable to measure it first by frequently monitoring prescribing practices, dispensing, and patient use. Measurement may be done in terms of types of IRDU so the strategy is selected to target problem, the amount of IRDU so the size of the problem is identified and effect of the strategy is monitored, and finally reasons of IRDU occurrence so an appropriate strategy can be selected. The Second International Conference on Improving the Use of Medicines (ICIUM) held

in Thailand in 2004 was concluded with three recommendations: first, countries need to implement long term national medicines programs that cover both public as well as private healthcare sectors, second, to monitor impacts of interventions, third, to involve communities.

The following strategies have been recommended by the WHO for the promotion of RDU and elimination of IRDU. These strategies are classified under three classes; educational, managerial, and regulatory strategies (Rabbie, et al., 2020).

4.7.1 A mandated multi-disciplinary national body to coordinate medicine use policy

Pharmaceutical regulations and legislations are developed and implemented by the national regulatory authority in both the public and private sectors. However, to achieve RDU multi- disciplinary approach involved other stakeholders like health professions, academia, patient, pharmaceutical industry, and non-governmental health organizations are required. Policies' impact on RDU needs to be studied and monitored so their effectiveness can be proven and they can be improved.

4.7.2 Clinical guidelines

Evidence-based clinical guideline (i.e. treatment guideline and prescribing policy) is a tool that promotes RDU. It guides the prescriber to make decision decide disease diagnosis and appropriate management and thus reduces IRP. Clinical guideline needs to be accessible and available to health practitioner at all time, easy to read, regularly updated and supported with training. Moreover, clinical guideline needs to target not only physicians, but it is important that it targets other health practitioner specifically pharmacist so adherence to it is enforced more. Also, to avoid implementation failure, clinical guideline needs to be credible and acceptable through the involvement of a variety of experts and at the national level vast number of institutions has to be involved.

4.7.3 Essential medicines lists based on treatments of choice

Essential medicine list (EML) is a list of medicines that 'satisfy the priority health care needs of the population'. EML makes medicine management and handling much easier as fewer numbers of medicines will be available for procurement, storage, and distribution. Also, both physicians and pharmacists will have to handle and know a few numbers of medicines which makes prescribing and dispensing easier. Clinical guidelines and drug formulary need to be developed based on national or institutional EML.

4.7.4 Drugs and therapeutics committees in districts and hospitals

Drug and therapeutic committee (DTC) is a committee responsible for the use of safe and cost-effective drugs in the facility or area. It is recommended that it takes responsibility for clinical guideline development, accreditation, and updating. Also, to approve EML and drug formulary, prescribing restriction policy, and to monitoring drug use and plan for actions. Moreover, it is suggested that DTC controls pharmaceutical activities within the health facility.

Lastly, some recommend to making DTC a stander for institutional accreditation.

4.7.5 Problem-based training in pharmacotherapy in undergraduate curricula

As knowledge gab is a reason for IRP, so building prescriber, as well as pharmacist pharmacotherapy knowledge during undergraduate school, is crucial. Problem-based learning is a more successful mode of learning for knowledge building and supporting.

4.7.6 Continuing in-service medical education as a licensure requirement

Continuing in-service medical education (CME) is a licensure requirement in many countries but in some, it is not. Also, no incentives may be offered for CME and it may be supported by pharmaceutical companies and so bias risk increases and causes IRP. Thus, it is advisable that governments involve university and national professional associations in CME process and reduce dependency on pharmaceutical companies. Also, the recommendation is in favor of a problem-based learning mode for a more effective CME program.

4.7.7 Supervision, audit and feedback

Supportive educational face-to-face supervision is largely accepted and proven to be effective. This may include auditing prescriptions and discussing feedback or peer review. Also, it is important to frequently monitor prescribing and dispensing patterns consistent with the institution's clinical guideline. Monitoring of RDU can be by using WHO indicators that are as listed on the table.

4.7.8 Independent information on medicines

This is through drug information centers, drug formulary, and drug bulletins. For example, previously all physicians in the United Kingdom use to receive free 'Drug and Therapeutic Bulletin' copy but this was cancelled because of financial constraints. Other sources like textbooks, national formularies, therapeutic guidelines, leaflets, and posters all can be a tool of streamline information.

4.7.9 Public education about medicines

It is very important to build up public knowledge and skills to be able to use their prescribed or non-prescribed medicines and be aware of the risks of IRDU. Also, to control and monitor media advertising that may adversely influence public use of the drug. Besides, it is recommended to use the media to educate communities about the advantages of RDU and highlight the consequences of IRDU.

Prescribing indicators	Patient care indicators	Health facility indicators
▪ Mean number of drugs prescription ▪ Percentage of drugs prescribed by generic name ▪ Percentage of antibiotics prescribed prescription ▪ Percentage of antibiotics prescribed from all prescribed drugs ▪ Percentage of injectable drugs prescribed prescription ▪ Percentage of prescriptions containing vitamins/tonic preparations ▪ Percentage of drugs prescribed from EML of the hospital/institution	▪ Average consultation time ▪ Average dispensingtime ▪ Percentage of drugs actually dispensed ▪ Percentageof drugs adequatelylabeled ▪ Patient's knowledge of correct dosage	▪ Availability of copy of essentialdrug list or formulary ▪ Availability of key drugs for thetreatment of common health problems

4.7.10 Avoidance of perverse financial incentives

An example of this is a fee-for-service payment which increases IRP. Some suggest the use of charge per medicine not per prescription as the patient often prefers more than one medicines. Also, to provide reimbursement only for essential medicines as a strategy. However, this can be an obstacle for low-income patients to get good quality of care or a full course of a treatment regimen. Nevertheless, the existence of health system policy and regulation may control IRDU due to this phenomenon.

4.7.11 Appropriate and enforced regulation and monitoring pharmaceutical policy

Regulations are more effective if they are enforced by qualified personnel and securely funded. An uncompromising regulatory system is crucial to implement policies that promote RDU. These policies should not only deal with healthcare institutions, however, it is important that policies care to tackle IRDU due to un- prescribed medicines like OTC. It should also control pharmaceutical promotional activities in communities. The health system regulations and policies need to ensure the availability of only registered medicines of good quality in the market. Also, it is important to require licensing of drug retails shops and wholesalers to enforce maintaining necessary supply and dispensing standards. Moreover, there should be regulations for health professionals' certification and licensing to ensure proficiency that enforces RDU. At the same time, an effective health system requires strong efficacious infrastructure supported with efficient drug procurement and distribution system and qualified staff including experts and talent. Lastly, health policies and regulations require frequent monitoring and assessment to improve quality. This is more beneficial if studied through research and then recommendations translated into practice (Kshirsagar et al., 2016; Chauhan et al., 2018; Rabbie, et al., 2020).

4.8 Impact of COVID-19 pandemic on IRDU

With the spread of COVID-19 globally it is expected that IRDU has been practiced by communities as well as the prescriber. Off-label use of medicines to treat COVID-19 has been widely practiced by prescribers since the virus has first emerged. This was because no evidence- based clinical practice guidelines or protocols or approved antiviral were available. Although off-label cannot be considered as absolute IRP, both prescriber and patient have to take the risk of the ineffectiveness of the tried drug and possible adverse effects. For example, WHO pharmacovigilance report showed fatal cardiovascular effects leading to ventricular arrhythmias due to azithromycin use which can also be precipitated by combination with chloroquine or hydroxychloroquine.

Moreover, the use of antibiotics in COVID-19 patients requires critical clinical judgment and evidence of the need to treat bacterial infection. Thus, overuse of antibiotics without evidence for COVID-19 management is irrational and may lead to harmful consequences like increase rate of multidrug resistance organism and adverse effect of antibiotics such as kidney injury. Another practice during COVID-19 is self-medication to prevent or treat the virus. For instance, a cross-sectional online survey in Daka showed that only 28% of 626 respondents took medication after physician consultation and 71.40% practiced self-medication with a high percentage of 50% use azithromycin and had not been diagnosed with COVID-19. Self- medication is a dangerous practice as it may cause serious adverse drug reactions and may increase the mortality rate. Also, during this pandemic self-medication can exaggerate health crises especially in low-income countries. For this reason, health authorities need to enforce regulations that alleviate self-medication such as banning access to medicines without prescription, and focus on media advertising and make it a tool for positive public education. Also, to educate community pharmacists to participate in reducing self-medication via following the regulations and participating in public education (Paumgartten et al., 2020; Nasir et al., 2021).

4.9 Controlling self-medication in the era of COVID-19

According to World health organization guidelines on self-medication, people should know how to use the drug, its effectiveness, and its side effects, and its management. The practice of self-medication should be viewed appropriately, especially in countries with low- and middle-income, who face economic hardship and often have low educational standards and inadequate health care facilities, particularly during the COVID-19. Self-medication, during the COVID-19 epidemic, could exacerbate the current state of the health crisis that no country has fully prepared for. A comprehensive approach should be taken to improve the use of self- medication through good training of health professionals including pharmacists of the community, education of the public and strict drug laws on public advertising and drug use. Good support from national health authorities will decrease the potential risk of self-medication and reduce the stockpiling of medicines during the epidemic. Authorities should provide appropriate drug use strategies. Easy access, low cost, and appropriate consultation with health care providers should be encouraged to reduce self-medication practices and to promote the rational drug usage by the people. The social and media platforms should be used to address public awareness programs and educational programs on the proper use of drugs and the potential risks associated with their misuse; all campaigns should be evaluated whether they are useful for the public or not (Alhomoud, et al., 2017; Hussain and Dawoud, 2021)

5. Conclusion

RDU is an essential key for safe, effective, and quality health care. Health professionals, patients, and communities are important stakeholders and need to be aware of the RDU and IRDU concept and factors of IRDU. Thus, they can participate in combating IRDU through different strategies. Countries need to build strong qualified health systems and authority bodies to establish and support regulations and policies that support RDU.

To improve the RDU, physicians and drug therapists need to be trained across the board so they can accurately inform the public, given that several unsustainable drug problems can be addressed through instruction. It is necessary to emphasize the need of society as a whole for meaningful learning. Drug practitioners are most open to patient care and play an important role in enhancing RDU addiction and resistance. RDU's efforts to improve will also reduce drug abuse and help save the climate.

We need to change our mindset and start the process of testing prescription drugs in the government and the private sector. Moreover, the importance of the EML and RUM should be emphasized in all possible forums. The concept of essential medicine is also intertwined with other health systems programs and results not only in better utilization of resources but also in better consumption of medicine. It also addresses many other issues such as good treatment and reduced side effects of medications and saves money for people, health care providers, hospitals, and the country.

Similarly, self-medication has become an important area in health care, but the provision of self-medication has become a major concern all around the world, especially during the COVID- 19 epidemic. Self-medication may promote better health care by reducing the cost of medication. But, improper self-medication can lead to misdiagnosis, serious side effects, drug dependence, drug interactions, and resistance to microbes. Therefore, there is a great need to regulate and manage the self-medication practices through strict legislation and by involving policymakers and health care professionals.

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