THE USE OF IRRATIONAL DRUG ON ANTIBIOTICS AND OFF-LABEL DRUGS FROM INDUSTRY PERSPECTIVE: ARTICLE REVIEW

Irma Rahayu Latarissa, Norisca Aliza Putriana, Intan Merita, Yuda Hardianto, Hengki Sutrisno, Muhammad Nur Iqbal
Faculty of Pharmacy Universitas Padjadjaran
Jl. Raya Bandung Sumedang km.21 Jatinangor 45363
irmarahayulatarissa@gmail.com

ABSTRACT

Rational use of drugs is when the patient receives treatment as clinical needed, dose as needed, time period was right, and a cost affordable to the patient's condition. The World Health Organization (WHO) estimates that approximately 50% of all drug use is not appropriate in prescribing, preparing and selling. Some cases of irrational use of drugs occur in the use of antibiotics and off-label drugs. One cause of irrational drug use is due to the cooperation between doctors as prescribing and pharmaceutical industry as a producer. In the pharmaceutical industry perspective, this will have an impact on the pharmaceutical profit industry. This review aims to provide an overview about the use of irrational drugs on antibiotics and off-label drugs from industry perspective.

Keywords: *irrational drugs, antibiotics, off-label drugs, pharmaceutical industries*

Diserahkan: 28 Juni 2018, Diterima 2 Agustus 2018

INTRODUCTION

Medication is one of the important factors in health services. However, the World Health Organization (WHO) estimates that approximately 50% of all drug use is inappropriate in prescribing, preparing and selling (WHO, 2002). The inappropriate use of drugs will cause many problems. These issues include aspects of effectiveness, side effects, interactions, economics and drug abuse. Therefore, drug use requires appropriate consideration for effective and efficient use (Pharmaceutical Care Network Europe Foundation, 2003).

Rational use of drugs according to the WHO conference in Nairobi in 1985: when the patient receives treatment as clinical needed, dose as needed, time period was right, and a cost affordable to the patient's condition (WHO, 1985). The use of the drug must be compatible with the disease, therefore the diagnosis that is enforced must be appropriate, the linkage of the pharmacology of the drug with the pathophysiology of the disease and the dose given must be appropriate, the time of administration of the drug must be appropriate, and the costs incurred must be in accordance with the ability of the patient (Hussain, et al., 2012; Sastramihardja, 2005; Holloway, 2004).

Antibiotics are drugs that have saved hundreds of thousands of lives each year. But on the other hand gives us "antibiotic resistance" which is a serious problem and one of the most threatening health problems worldwide. Low-cost

drugs, and excessive use of these drugs contribute significantly to the emergence of bacterial drug resistance. Irrational use causes allergies, toxicities, super infections and more importantly, antimicrobial resistance. Antibiotics are often prescribed irrationally in terms of type, dose, duration and indication (Sutradhar, 2014).

On the other side, in the world of medicine, it is often known with the applicable provision that all drugs in circulation must have a license to be distributed Market License or Marketting Authorization issued by BPOM. Off-label drug term which means drug use outside of its Market License or its actual Marketting Authorization (Yewale and Dhanya, 2012). As is the case in Europe regarding the use of off-label drugs is quite high for certain therapeutic diseases such as medicines oncology field. These drugs in their use reach 50% and even more where patients are mostly pediatric (Casala, 2007) but the European party has issued regulations related to the use of off-label drugs (Corny, et al., 2015).

This article review will discuss some of the irrational drug use cases seen from industry perspective. Some examples of cases of irrational drug use include the use of antibiotics and off-label drugs.

METHOD

The method used is literature study. The literature study was conducted using a browser and search site with the keywords "Irrational Use of Drugs", "Antibiotics", "Off-label Drugs", "pharmaceutical industry". This keyword search is done in English. The findings of the articles and research journals are presented descriptively. The range of journals used in this article review 1985-2017. The number of the journals used in this article review is twenty journals, and eight supporting literature. The total literature used in this review article is twenty-eight.

RESULT

Table 1. A summary of irrational drug use issues on antibiotics and off label drugs.

Problem	
Antibiotic	Off-label drugs
Medication prescribing for ARI (Acute Respiratory Infection) patients tends to be excessive, especially in antibiotic drugs reaches 90.2%, though various studies show that the ARI is caused by a virus and can heal itself so that the use of antibiotics is not needed (Dwiprahasto, 2006).	The use of off-label drugs may lead to an increased risk of medication error (Tefera, et al., 2017).
The irrational use of drugs in antibiotics leads to antibiotic resistance (Sutradhar, 2014).	Other studies have also shown that any off-label drug added to prescriptions will significantly increase the severity of ADR (Adverse Drug Reaction) (Tefera, et al., 2017).

DISCUSSION

Antibiotics

In 1993, prescription in Indonesia was still categorized as irrational. The highest problem presentation was that excessive use of antibiotics reached 43% (Hogerzeil, et al., 1993). The problem of drug administration in patients with ARI (Acute Respiratory Infection) is a common problem in Indonesia. Some research results indicate that the given drug tends to be excessive, especially in antibiotic drugs reaches 90.2%. Though various studies show that the ARI is caused by a virus and can heal itself so that the use of antibiotics is not needed (Dwiprahasto, 2006).

The intensity of the use of antibiotics is relatively high cause various problems and is a global threat to health, especially bacterial resistance to antibiotics. Besides impacting morbidity and mortality, it also has a very negative economic and social impact (The Republic of Indonesia's Health Department, 2011).

The use of irrational antibiotics is one of them caused by the cooperation between the Industry with a Hospital, Clinic, and Doctor. The doctor prescribes antibiotics irrationally, always prescribes antibiotics even though the patient does not need to get the incentive from the prescribing. To avoid this, pharmaceutical companies do not provide incentives to physicians who prescribe antibiotics so irrational use of antibiotics can be avoided (Bergstrom, 2011).

Government and industry are working together for the creation and implementation of industry regulations that produce antibiotics that ensure public health strategy, especially
regarding pricing Strategy antibiotics is

very influential for rational usage (Littmann, 2014).

Another role of the Pharmaceutical Industry in rational antibiotic use is the regulations advertising and promotion by pharmaceutical companies to provide education for the community to use the medicine properly (Hassan and Hagnour, 2012).

Off-label Drugs

In Indonesia, Off-Label drug use can be highly categorized. Mentioned in the results of research conducted on 357 patients and given as many as 984 drugs, class of Off-Label highest drug that is Antibiotics with percentage of 56,1%. This drug is the most commonly prescribed drug in neonates. This occurs because there is no brochure that describes the use in neonates patients and the majority is used to treat infections in patients. In addition, in the absence of suitable dosage forms and doses for pediatrics (Kartinah, et al., 2013).

The use of drugs off-label can be caused by several factors. First the use of drugs for a pathological and physiologically similar or drug in the same group. Second, life-threatening conditions or medical conditions that encourage doctors to provide logical and available treatment regardless of FDA approval. Third, drugs have not been studied and approved for specific populations (pediatric, geriatric, or pregnant women) (Wittich, et al., 2012).

Research conducted by Neubert et al. (2004) and Saiyed et al. (2015) showed that patients receiving off-label drugs experienced more frequent ADRs than patients who received only licensed drugs (Neubert et al. 2004; Saiyed, et al., 2015). Other studies have also shown that any off-label drug added to the prescription will significantly increase the severity of ADR (Saiyed, et al., 2015; Bellis, et al., 2013; Bellis, et al., 2014). The significant relationship between off-label and ADR use is mainly due to the fact that the drug is indicated to be different from the product specification (Horen, et al., 2002).

In terms of industry a variety of reasons why the drug given permission to circulate but not to include for children, among others because the drug does not mention the use of Off-Label drugs, among others, because the drug is not tested in children This is due to limited funds and the difficulty of drug test children (Cousins, et al., 2002). The use of off-label drugs may lead to an increased risk of medication error. Other studies have also shown that any off-label drug added to prescriptions for children will significantly increase the severity of ADR (Adverse Drug Reaction) (Tefera, et al., 2017).

In this case, the pharmaceutical industry as a holder of drug marketing license must monitor every security confrontation and take precautions to avoid any side effects caused by its products. To

overcome the use of irrational drugs in pediatrics that cause many adverse side effects. the industry as the product owner develops in the form of a correct and safe formulation for pediatrics. In addition to doing clinical testing on pediatrics so that it can be the best intervention to offer appropriate medicines to children (Shivhare, et al., 2010).

Solution

Viewed from several cases above, many factors that affect the rationale of drug use. However, the WHO concludes three main factors are prescribing patterns, services provided by patients, and the availability of facilities to rationalize drug use (WHO, 1993).

To overcome the problem of irrational drug use, some improvement and intervention efforts are needed, both at the provider level ie prescriber, dispenser and patient (consumer) to national drug policy system (Indonesian Ministry of Health, 2011). Based on the Indonesian Ministry of Health (2011) pharmaceutical industry can play a role in education efforts and information efforts, namely by rectifying drug information in order not "unclear" to certain types / products. The pharmaceutical industry works closely with physicians and pharmacists as well as governments to provide information related to rational use of drugs (Reppe, et al., 2016).

The pharmaceutical industry should also not intervene to the Doctor as prescribing to continue using the drug from its own industry regardless of the rationale of drug use. The quality of the available information should be maintained by strictly selecting reliable, unbiased / impartial sources of information and free from the promotion of the pharmaceutical industry (Indonesian Ministry of Health, 2011).

In the pharmaceutical industry perspective, this will have an impact on the pharmaceutical profit industry, nowadays in Indonesia pay more attention to rational use of drugs (the right price indicator), supported by the current pharmaceutical era of health care shifted from Money oriented or drug oriented to patient oriented.

CONCLUSION

The use of irrational drugs is caused by many factors, such as cooperation between industry, hospital, clinic, and doctor in the case of drug prescription. In the pharmaceutical industry perspective, this will have an impact on the pharmaceutical profit industry, nowadays in Indonesia pay more attention to rational use of drugs (the right price indicator), supported by the current pharmaceutical era of health care shifted from Money oriented or drug oriented to patient oriented. To solve the problem, it should be reviewed from various viewpoints of consumers,

medical personnel, and producers with the main objective is patient safety. All parties are patient-oriented but keep the producers prosperous with the benefit of rational use of drugs based on existing indicators.

ACKNOWLEDGEMENT

The author would like to thank Mrs. Norisca Aliza Putriana, M. Farm., Apt. as a supervisor who has taken time to guide the author, give criticism, suggestions and improvements in writing this review article.

REFERENCE

1. Bergstrom, R. 2011. "The Role of the Pharmaceutical Industry in Meeting the Public Health Threat of Antibacterial Resistance." Drug Resistance Updates, 14(1), pp.77–78.
2. Casala, P.G. 2007. "The Off-Label Use of Drugs in Oncology: A Position Paper by The European Society for Medical Oncology (ESMO)." Ann Oncol, 18(12), pp.1923-1925.
3. Corny, J., Lebel, D., Balley, B. 2015. "Unlicensed and Off-Label Drug Use in Children Before and After Pediatric Governmental Inutiatives." J Pediatr Pharmacol Ther. 20(4), pp.316-328.
4. Cousins, A., Clarkson, S., Conroy, I., Chonoonara. 2002. "Medication Errors in children – An eight year review using press reports." Paedatric and Perinatal Drug Therapy, 5(2), pp. 52-58.
5. Dwiprahasto, I. 2006. "Peningkatan Mutu Penggunaan Obat di Puskesmas Melalui Pelatihan Berjenjang pada Dokter dan Perawat." Jurnal Manajemen Pelayanan Kesehatan, 9(2), pp.94-101.
6. Hassan , S.A.K. and Hagnour, B.S. 2012. "Rational Use of Medicine." Sudan Journal of Rational Use of Medicine, 1(2), pp.18-24.
7. Hogerzeil, H.V., Ross-Degnan, D., Laing, R.O., Ofori, A.D., Santoso, B., Chowdhury, A.K., Das, A.M., Kafle, K.K., Mabadeje, A.F.B., and Massele, A.Y. 1993. "Field Test for Rational Drug Use in Twelve Developing Countries." The Lancet, pp.1408-1410.
8. Holloway, K. 2004. "Rational use of drugs: an overview. Technical Briefing Seminar: Essential Drug and Medicines Policy." Geneva: World Health Organization.
9. Horen, B., Montastruc, J.L. and Lapeyre-Mestre, M. 2002. "Adverse drug reactions and off-label drug use in paediatric outpatients." British journal of clinical pharmacology, 54(6), p.665.
10. Hussain, A., Ibrahim, M.I., Baber, Z.U. 2012. "Using the potentials of community pharmacies to promote rational drug use in Pakistan: an opportunity exists or lost." J Pak Med Assoc, 62(11), pp.1217–22.

11. Indonesian Ministry of Health. 2011. "Kurikulum Pelatihan Penggunaan Obat Rasional." Jakarta: Kemenkes RI
12. Kartinah, N., Dasupantini, S., Intannia, D. 2013. "Penggunaan Obat Off-Label pada Pasien Neonatus Rawat Inap RSUD ULIN Banjarmasin Periode Januari-Desember 2013." Jurnal Pharmascience, 1 (1), pp. 23-27.
13. Littmann, J. 2014. "The Ethical Significance of Antimicrobial Resistance." Public Health Ethics. 8(3), pp.209–224.
14. Neubert, A., Dormann, H., Weiss, J., Egger, T., Criegee-Rieck, M., Rascher, W., Brune, K. and Hinz, B. 2004. "The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients." Drug safety, 27(13), pp.1059-1067.
15. Pharmaceutical Care Network Europe Foundation. 2003. Classification for Drug Related Problems. The Netherlands: PCNE, 5(1).
16. Reppe ,L.A., Spigset, O., Schjott, J. 2016. "Drug Information Services Today: Current Role and Future Perspectives in Rational Drug Therapy." Clinical Therapeutics, 1(1), pp. 1-8.
17. Saiyed, M.M., Lalwani, T. and Rana, D. 2014. "Off-label medicine use in pediatric inpatients: a prospective observational study at a tertiary care hospital in India." International journal of pediatrics, 2014.
18. Sastramihardja, H.S. 2005. "Farmakologi klinik. Farmakologi III. Edisi ke-2." Bandung: Universitas Padjadjaran.
19. Shivhare, S.C., Kunjwati, H.K., Manikrao, A.M., Bondre, A.V. 2010. "Drugs Hazards and rational use of drugs: a review." Journal of Chemical and Pharmaceurical Research, 2(1), pp. 106-112.
20. Sutradhar, K.B. 2014. "Irrational Use of Antibiotics and Antibiotic Resistance in Southern Rural Bangladesh: Perspectives from Both the Physicians and Patients." Annual Research & Review in Biology, 1(1), pp.1-11.
21. Tefera, Y.G., Gebresillassie, B.M., Mekuria, A.B., Abebe, T.B., Erku, D.A., Seid, N. and Beshir, H.B. 2017. "Off-label drug use in hospitalized children: a prospective observational study at Gondar University Referral Hospital, Northwestern Ethiopia." Pharmacology research & perspectives, 5(2).
22. The Republic of Indonesia's Health Department. 2011. "Pedoman penggunaan antibiotika". Jakarta: Depkes RI
23. Wittich, C.M., Burkle, C.M. and Lanier, W.L. 2012. "Ten common questions (and their answers) about off-

label drug use." In Mayo Clinic Proceedings (Vol. 87, No. 10, pp. 982-990). Elsevier.

24. Woo, Y., Kim, H.E., Chung, S. and Park, B.J. 2015. "Pediatric Medication error Reports in Korea Adverse Event Reporting System Database, 1989-2012: Comparing with Adult Reports." Journal of Korean medical science, 30(4), pp.371-377.
25. World Health Organization. 1985. The Ratonal Use of drugs Mexico : A case Study Conference of Experts On The Rasional Use of Drugs. Naiarobi, Kenya 25-29 November 1985. Geneva: World Health Organization
26. World Health Organization. 1993. "How to Investigate Drug Use in Health Facilities." Geneva: World Health Organization.
27. World Health Organization. 2002. Promotional Rational Use of Medicines: Core Components. Geneva: World Health Organization.
28. Yewale, N.V., and Dhanya, D. 2012. "Review Article Promoting Appropraiate Use of Drugs in Children." Hindawi Publishing Corporation International Journal of Pediatrics.