PERSPECTIVE

Ethical Off-label Drug use: Need for a Rethink?

ZHIHUA ZHENG, *MIN YANG AND #JUNYAN WU

*From Guangdong Province Pharmaceutical Association; *Department of Pharmacy, Guangdong General Hospital, Guangdong Academy of Medical Science; and #Clinical Pharmacy, Sun Yat-sen Memorial Hospital, Sun Yat-sen University; China. Correspondence to: Zhihua Zheng, Guangdong Province Pharmaceutical Association, 753-2, Dongfengdong Road, Guangzhou 510080, China. snownotrace@126.com*

Off-label drug use is unavoidable, especially in children. Legal justice originates from ethical justice; therefore, ethical off-label drug use can be considered legal. We share our successful experiences with this issue in China, which may provide a reference to Indian healthcare professionals, to develop a common executable standard to be applied to evaluate the off-label drug use in clinical practice.

Keywords: *Ethics, Neonate, Pharmacotherapy*.

In the United States, "unlabeled uses" (namely "off-label drug use") are defined as drug uses that not included in the indications or dosage regimens listed in the US Food and Drug Administration (FDA)-approved labeling. Unlabeled use includes the use of a drug product in doses, patient populations, indications, or routes of administration that are not reflected in FDA-approved product labeling [1]. Off-label drug use is common in many clinical areas such as psychiatry, pediatrics, oncology and intensive care unit [2-5]. Sometimes off-label drug use is the only option for the patient's treatment. For example, methotrexate is the current gold standard for rheumatoid arthritis treatment, which is off-label use in China. However, off-label drug use is not uniformly regulated across the globe. The Indian Medical Association had launched a campaign to permit off-label drug use in India [6], but its legality still remains disputed.

Although off-label drug use is legal in many countries, its safety has attracted much attention. No law prohibits off-label drug use in the United States and Canada [7,8]. Off-label drug promotion is not allowed in many countries, but it is also not absolutely prohibited. In the United States, the legislation governing insurance reimbursement for off-label drug use varies from state to state [9]. The Canadian Agency for Drugs and Technologies in Health (CADTH) conducts cost-benefit assessments of drugs for their approved indications through its Common Drug Review (CDR) process, and then issues a recommendation to provinces and territories as to whether the drug should be reimbursed by public programs. In Germany, the off-label drug use is regulated by either the Medicines Law or the Social Law [10]. Physicians are permitted to prescribe drugs outside the labels within their therapeutic flexibility [11]. However, drugs can only be prescribed at the expense of the statutory health insurance if they are used for the treatment of a disease for which the pharmaceutical company has obtained a marketing authorization from the relevant authority [12]. According to the British General Medical Council (GMC), off-label prescriptions must better serve patient needs than alternatives and must be supported by evidence or experience to demonstrate safety and efficacy [13]. In special circumstances, National Institute for Health and Clinical Excellence (NICE) provides advice on the use of unlicensed and off-label uses of drugs [14]. Pharmaceutical companies operating in the European Union need to collect and report information on the off-label use of their drugs under new obligations making its way from draft to final form at the European Medicines Agency (EMA) in the summer of 2016 [15].

There is no legislation on off-label drug use in China. Some public media in China once raised the issue of off-label drug use being illegal, bringing a big headache to Chinese healthcare professionals. The Guangdong Province Pharmaceutical Association (GDPA) issued the consensuses on off-label drug use in 2010 and 2014, the first set of standards for off-label drug use in China, and has done a lot of work that changed the perspective of off-label drug use in China [16,17]. In both China and India, the demand for healthcare is increasing speedily with the rapid economic development. Therefore, our working idea on off-label drug use may provide a reference to Indian healthcare professionals.

Ethics is the framework of guiding principles that brings order and purpose into what would otherwise be a void between laws, and goes beyond law. India has medical ethical guidelines, but no item refers to off-label drug use [18]. However, we can find the basis of off-label drug use from the principles of medical ethics, which is a system of moral principles that apply values and judgments to the practice of medicine. In our opinion, it is unethical not to treat a patient just because the necessary drug use is not in the label, and a law preventing patients from the suitable treatment is not a good law. Making off-label drug use illegal makes the best available therapy for some patients impossible. For example, special populations, such as children, pregnant women and elderly people, are often excluded from drug trials. Thus many of their medications are off-label, but we must try our best to treat them if they are ill. Off-label drug use is common in children in Indian healthcare system. In neonatal intensive care units of two institutions in Chandigarh, India, half of the prescriptions in neonates were off-label [19]. In the pediatric intensive care unit at a tertiary care hospital in another Indian metropolitan city, 71% of the prescriptions were off-label in nature [20]. Similar experience is available from other parts of the country [21,22].

Human physiological pathways are always interlaced, thus a drug effective for one disease may be effective for another. However, it is impossible to include all the information in the drug label. For example, both bevacizumab and ranibizumab are targeted biological drugs that inhibit vascular endothelial growth factor, an angiogenic cytokine that promotes vascular leakage and growth, thereby preventing pathological angiogenesis. Ranibizumab is indicated for the treatment of patients with neovascular age-related macular degeneration (AMD), but bevacizumab was initially approved for the treatment of colorectal cancer. The off-label use of bevacizumab and the approved use of ranibizumab have equivalent efficacy for neovascular AMD [23]. However, it is much cheaper to use bevacizumab than ranibizumab to treat neovascular AMD. If treating neovascular AMD with bevacizumab is banned, some neovascular AMD patients who cannot afford ranibizumab will therefore not get the treatment. Reducing the price would still not fundamentally solve the affordability problem, the subcommittee of the National List of Essential Medicines of Thailand (NLEM) listed bevacizumab in the NLEM for AMD and diabetic macular edema in 2012 [24], making Thailand the first country to officially endorse bevacizumab for macular treatment.

As clinical situations are constantly changing, we need to establish a strict but flexible management mechanism for off-label drug use. The four principles of medical ethics are: respect for autonomy, beneficence, non-maleficence and justice. In order to meet these principles, we have the following consideration:

(*i*) The off-label use must not be for research purposes.

(*ii*) If there is no reasonably replaceable drug to treat the patient's condition, the benefits of the off-label use outweigh its risks, and the use is the best choice for the patient.

(*iii*) The off-label use must be based on reasonable medical practice evidence. In order to be more objective and avoid medication and medical errors, the pharmacy department of the hospital should verify the evidence of off-label use, and expert advice should be sought. It will be better that the advice comes from the drug control society of a country, but this practice cannot adapt to rapid clinical change. Thus we propose that the hospital's pharmacotherapy and hospital ethics committees are good choices, which is similar to the practice in some countries [25-27]. If the risk is low, the off-label drug use just needs to be approved by the hospital's pharmacotherapy committee. However, the off-label drug use should also be approved by the hospital ethics committee in case the use poses high risk to the patients. Previously, hospital ethics committees in China mainly looked after research ethics by reviewing and approving research projects, but they are now involved in various ethical aspects of clinical practice, as clinical ethical committees do in the US and the United Kingdom [28]. However, the off-label drug use may be exempted from application for approval in an emergency situation.

(*iv*) As the off-label drug use may not have been formally evaluated, the risk should be fully realized and the contingency plan must be ready. The use must be monitored continuously, and then the progress note must be written in detail.

(*v*) As the drug knowledge is developing and the label may change, the off-label drug use should be improved continuously.

The above five items meet the principles of beneficence and non-maleficence. The principle of respect for autonomy means that patients have the right to refuse the treatment [29]. Thus, consent should be obtained from the patient or guardian. Although some items above could be considered as imposed requirements [30], we hold the opinion that these requirements make the off-label use more reasonable, especially against the backdrop of already existing

physician-patient disharmony. The above consideration is also consistent with Article 37 of the Declaration of Helsinki 2013 on Unproven Interventions in Clinical Practice, and can be deemed as the embodiment of duty of care in law.

Legal justice originates from ethical justice; therefore, ethical off-label drug use can be considered legal. In 2012, the China Ministry of Health (MOH) issued the GDPA consensus in its working document. In 2015, the key points of the GDPA consensus have been put into the clinical pharmacy textbook of the China National Health and Family Planning Commission (Formerly MOH) [31]. More and more hospitals in China have established regulations to manage off-label drug use according to the GDPA consensuses. Indian medical professionals should develop a common executable standard on off-label drug use, which can be applied to evaluate such use in clinical practice. It is better that the center for drug control of a country issues a list of off-label drug uses with high-level of evidence.

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