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Predicting pediatric off-label drug use in Chinese Hospitals: An application of the Theory of Planned Behavior

Zhang Yueqin

Doctor of Management

Supervisor:
PhD Nelson Ramalho, Associate Professor,
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I declare that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university and that to the best of my knowledge it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed:  Date: 10th.Jun. 2020

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作者申明

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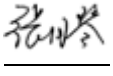
作者签名：  日期：10th.Jun. 2020

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Abstract

The use of drugs is authorized according to guarantees given by drug makers concerning the clinical effectiveness of the drug under the condition that the drug administration follows specific guidelines. These guidelines are indicated in the drug package inserts reflecting knowledge from clinical trials. However, pediatric drugs are rarely included in the study of clinical trials as a result of special physiological and psychological characteristics of users. This leads to a lack of data relating to safety and effectiveness of pediatric marketed drug user groups. Thus, doctors often opt for off-label use of drugs, meaning, they prescribe, use administration route or dose beyond package insert issued by authority. Such off-label use is considered inevitable due to treatment of children diseases. Many countries have made explicit laws, regulations or rules on off-label drug use. In China, off-label drug use has become more common, but not conforming to regulations. In addition, there was no clear stipulation on off-label drug use, especially pediatric off-label drug use. As a result, doctors' medical orders, drug dispensing and distribution of pharmacists, and drug user groups were at greatest risks, laying hidden dangers for doctor-patient disputes. This implies, it is important to generate a behavioral model that allows for the prediction of off-label drug use in pediatrics.

Objective: From the perspective of the Theory of Planned Behavior, this research aims to generate a predictive model of off-label drug use in Chinese hospitals. This model adds to extant state-of-art on behavioral models in off-label pediatric use, and it also intends to help normalize doctors' off-label drug use, prevent and treat drug abuse, and ensure the interests of patients and treatment demands.

Methods: The present research included objective analysis on pediatric drug information of commonly used pediatric drugs package inserts and subjective analysis on behavior and cognition of pediatricians to model effects on off-label prescription.

Results: Findings show pediatricians use of information concerning children's commonly-used drugs in China varied with different subpopulations and drugs. Doctors with different titles have issued off-label prescription in different frequencies. The explanatory model has predictive power on behavioral intention and off-label behavior. It was recommended that permission on issuance of off-label prescription should be limited.

As for treatment of common diseases and rare, refractory diseases, different levels of off-label drug uses should be formulated for generic drugs and high-risk drugs.

Conclusion: There were subjective and objective reasons of pediatric off-label drug use in China, relating to lack of drug information and prescription behavior of doctors. The theory of planned behavior can be used to predict the behavior of pediatricians in off-label drug use. Countermeasure and suggestion for normalization of off-label drug use was proposed to provide reference and basis for normalizing clinical pediatric off-label drug use. China's pediatric off-label drug use can and should be implemented in terms of academics, management, operation, and technology.

Keywords: Pediatrics; Off-Label Drug Use; Theory of Planned behavior; Behavioral model

JEL: H51; I12; I18; M14

Resumo

A utilização de fármacos é autorizada mediante garantias dadas pelas farmacêuticas no que respeita à eficácia clínica sob a condição de que os fármacos sejam administrados de acordo com orientações específicas. Estas orientações estão indicadas nos folhetos informativos refletindo o conhecimento dos ensaios clínicos. Contudo, os fármacos pediátricos são raramente incluídos nos ensaios clínicos devido às características fisiológicas e psicológicas especiais dos utilizadores. Isto leva a uma falta de informação relativa à segurança e eficácia de fármacos comercializados para este grupo de utilizadores. Assim, os médicos frequentemente optam por uma utilização off-label, o que significa que prescrevem, administram ou doseiam para além do indicado nos folhetos informativos aprovados pelas autoridades. Tal uso off-label é considerado inevitável devido ao tratamento de doenças pediátricas. Na China, a utilização off-label de medicamentos tornou-se comum, mas não em conformidade com o regulamentado. Como resultado, as prescrições médicas, distribuição e dispensa pelos farmacêuticos face a grupos de utilizadores podem criar riscos traduzindo-se em disputas médico-paciente. Tal implica que é importante gerar um modelo comportamental que permita prever o uso off-label de medicamentos no contexto pediátrico.

Objectivo: Utilizando a teoria do comportamento planeado, pretende a presente investigação gerar um modelo preditivo da utilização off-label de medicamentos em contexto hospitalar na China. Este modelo acresce ao estado da arte dos modelos comportamentais na utilização off-label pediátrica e também procura ajudar a normalizar o uso off-label de medicamentos por parte dos médicos, a prevenir e tratar o abuso medicamentoso, e a garantir o interesse dos pacientes e as exigências terapêuticas.

Método: O estudo presente compreende a investigação objetiva de folhetos informativos de fármacos comummente usados em pediatria bem como investigação subjetiva sobre o comportamento e cognições dos pediatras relativos à prescrição off-label.

Resultados: A utilização de informação relativa à administração pediátrica de fármacos comuns na China varia de acordo com as diferentes subpopulações pediátricas e o tipo de fármaco. Os médicos com variadas categorias profissionais têm prescrito off-label com frequência diversa. Foi recomendado que a permissão para prescrever off-label seja

limitada. Para o tratamento de doenças comuns e raras, devem ser formulados diferentes níveis de prescrição off-label diferenciando os fármacos de baixo e alto risco.

Conclusão: Há motivos subjetivos e objetivos para que ocorra uso off-label de medicamentos na China, que se relacionam com a falta de informação farmacológica e o comportamento de prescrição dos médicos. A teoria do comportamento planeado pode ser mobilizada para prever o comportamento dos pediatras relativo aos usos off-label. São propostas medidas corretivas e sugestões para a normalização do uso off-label para facultar uma referência e a base para normalizar o uso clínico pediátrico off-label de fármacos. A utilização off-label de fármacos na China pode e deve ser implementada com base no conhecimento científico, gestão, operação e tecnologia.

Palavras-chave: Pediatria; Uso off-label; Teoria do comportamento planeado; Modelo comportamental

JEL: H51; I12; I18; M14

摘 要

在药品监督管理有明确规定的情况下，药品生产企业对药品的临床有效性作出保证，方可批准使用。这些指南显示在反映临床试验知识的药品包装说明书中。然而，儿科药物由于使用者特殊的生理和心理特点，很少被纳入临床试验研究。这导致缺乏关于儿科药物使用者群体的安全性和有效性的数据。因此，医生经常选择药物的说明书外使用，也就是说，他们开的药，使用的给药途径或剂量超出了规定的包装。由于儿童疾病的治疗，这种超说明书外使用被认为是不可避免的。许多国家对标示外药物的使用都制定了明确的法律、法规或规章。在中国，超说明书用药越来越普遍，但不符合规定。此外，对于超说明书用药，特别是小儿超说明书用药没有明确规定。因此，医嘱、药师配药、吸毒者群体风险最大，为医患纠纷埋下隐患。这意味着，建立一个行为模型来预测儿科超说明书用药是很重要的。

目的运用计划行为理论出发，构建中国医院超说明书用药预测模型。该模式是对现有超说明书儿科用药行为模式的补充，有助于规范医生超说明书用药，预防药物滥用，保障患者利益和治疗需求。**方法：**本研究包括对常用儿科药品包装说明书的儿科用药信息进行客观分析，以及对儿科医生对超说明书处方模型效应的行为认知进行主观分析。**结果：**调查结果显示，在中国，儿科医生对儿童常用药物信息的使用因不同亚群和不同药品品规而有所不同。不同职称的医生开具超说明书处方的频率也不同。解释模型对行为意向和标示外行为具有预测能力。建议限制超说明书用药的处方权限。对于常见病、罕见病、难治性疾病的治疗，普通药和高危药应制定不同级别的超说明书用药。**结论：**中国儿童超说明书用药存在主观和客观原因，与药品信息缺乏和医生处方行为有关。计划行为理论可用于预测儿科医生在超说明书用药时的行为。提出规范超说明书用药的对策和建议，为规范临床儿科超说明书用药提供参考和依据。中国儿科超说明书用药可以也应该从学术、管理、操作和技术等维度加以规范。

关键词：儿科；超说明书用药；计划行为理论；行为模型

JEL: H51; I12; I18; M14

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Chapter 1: Introduction

1.1 Research background

Unlabeled uses, off-label uses, out-of-label usage or outside of labeling, refers to the use of pharmaceutical drugs for an indication or in a dosage or route of administration unapproved in the instructions by the drug regulatory agency (American Society of Hospital Pharmacists, 1992).

Children are classified into different age groups in China. Newborn baby: zero to 28 days old, infant: 28 days to one year old, toddler: one to three years old, preschooler: three to six or seven years old, grade schooler: six or seven to 12 or 13 years old, teenager: 12 or 13 to 17 or 18 years old (Chinese National Formulary, 2013).

According to the Notice of the National Health and Family Planning Commission on the Reinforcement of Control over Clinical Drug Use by Pregnant and Lying-in Women and Children (2011), it is necessary to strictly control the selection, route of administration, dosage, the adverse effects and contraindications of drugs used by children, so as to avoid or reduce adverse drug reaction and drug-induced damages (General Office of the National Health and Family Planning Commission of the People's Republic of China, 2011).

It is shown that outside China, unlabeled use by adults account for 7.5% - 40%, but among hospitalized children, it is as high as 50% ~ 90% (McIntyre, 2000; Huang et al. 2009). China has implemented at least seven provisions of law regarding the scope of drug application and usage. The violation of any one of them is regarded as “unlabeled use” (Song, 2010).

There are differences between children and adults in absorption, distribution, metabolism and excretion of drugs, and children’s sensitivity and tolerance of drugs are much lower than adults (Wang, 2009; Lu, 2011). In addition, changes continuously take place along with children’s growth. Studies indicate that unlabeled uses account for 70% in pediatric ICU (Turner, 1998) and 90% in newborn baby wards (Gazarian, 2006).

Among the respondents, 47.39% turns to unlabeled use because of “the limitation of drug preparations”, the result of which is similar to other research findings (Napoleone,

2010). Due to a lack of suitable standards and dosage of drug use by children (Zhang, Li & Liang, 2012), reducing the dosage, pulverizing the drug or dissolving part of the capsule in water are often taken as preparation alternatives, which is highly unsafe (Zeng, 2011). 53.83% of the respondents prescribe unlabeled drugs because “the instruction has not been revised or updated”.

The investigation on drug registration information in China by 31 July, 2010, carried out by Zhang and Wei (2011), shows that only 2.27% of the registered information has labeled “for children”; only 6% of the authorized registration information publicized on the official website of China Food and Drug Administration (CFDA) has labeled “for children”. It is suggested that drug use information for children be set as a compulsory standard on the instruction (Zhang & Wei, 2011).

In China, unlabeled uses have not been verified via clinical trials. When patients use drugs off-label, patients themselves, medical staff and institutions all take risks under standard treatment (Laforgia, 2014). Through investigation, it is found that unlabeled uses are most common among children under two years old and teenagers (11 to 17 years old) (Conroy, Choonara, & Impicciatore, 2000; Sonntag, 2013). Prescription for over half of the children, more than 80% of children with cancer, and approximately 90% of newborn babies are unlabeled (unregistered) uses (Zhang, Li, & Huang, 2011).

The rate of adverse drug reaction caused by unlabeled uses is higher than by labeled uses in hospitals (Bellis, 2013), and the occurrence rate and severity of drug misuse caused by unlabeled uses is much higher. According to the analysis of drug misuse in children’s hospitals in Britain from 2004 to 2006, among the 158 cases, 12 of the 20 moderate damages are induced due to unapproved/unlabeled uses (Bronskill et al, 2004).

According to the study on unlabeled uses for Chinese children by the Chinese scholars Zhang, Li, and Huang (2011), 41% happens in outpatient departments and 78% in inpatient departments.

Although the existence of off-label drug use has its rationality, it may cause several problems.

First, off-label prescribing can jeopardize patient safety in certain clinical scenarios where a positive benefit-risk ratio is not fully established. This is mainly due to the fact that off-label drug use is not systematically appraised by regulators, guideline formulators or even healthcare policymakers.

Second, off-label use raises issues of liability in the case of adverse events which makes physicians vulnerable to potential legal sanctions. Moreover, drugs used in an off-label manner are usually not reimbursed and would ultimately increase costs to patients and society (Zanon, 2014; Dooms, 2017; Saiyed, 2017).

Due to its high prevalence and regulatory challenge in pediatric medical practice, off-label drug use has become a worldwide problem (Dooms, 2017; Aamir, 2018; Balan, 2018; Yackey, 2019).

In order to understand the instruction of common drugs for children in China, this research adopts drug use data of 20 hospitals in Chinese large and medium-sized cities provided by a Beijing prescription analysis research group. The drug use information for children in the instructions of the most frequently used 300 drugs will be analyzed and summarized. This study uses the framework of planned behavior theory to analyze off-label drug use reasons, which can be used to predict and explain the theory of doctor's actual behavior. Theory of planned behavior is an expansion of rational behavior theory (Fishbein & Ajzen, 1975; Ajzen & Fishbein, 1980). TPB root in the limitations of the primary model in dealing with people's fragmentary will control behaviors, see Figure1-1.

Because of the limitations of the original model in dealing with people's incomplete control behavior, Figure 1-1 depicts the theory in the form of a structure diagram. For the convenience of expression, the possible feedback effect of behavior on antecedent variables is not displayed.

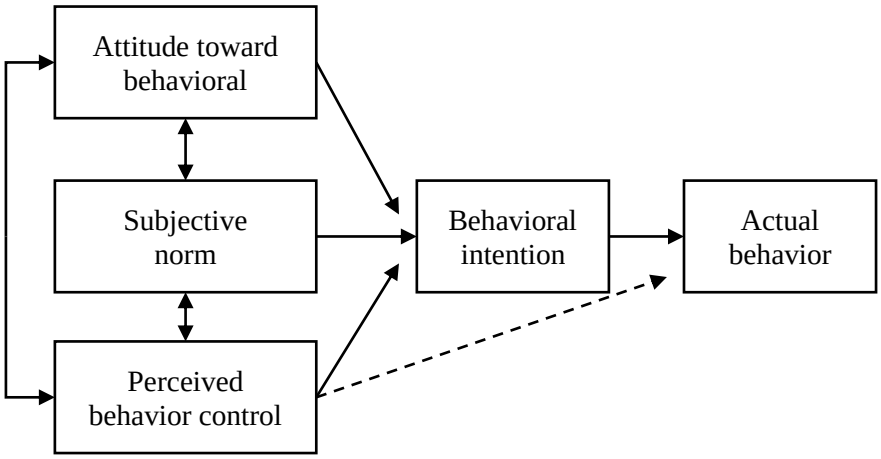

Figure 1-1 Theoretical structure chart

One of the core factors in the theory of planned behavior is the intention of an individual to perform a given behavior. Intentions are presumed to catch the motivational elements that influence behavior; they are the extent to which people are willing to try, an indication of the degree of effort planned to implement an action. Generally speaking, the stronger the intention to engage in an act, the more likely it is to perform. However, it should be clear that only when the behavior is controlled by the will, the intention of the behavior can be expressed in the behavior

The questions raised in this study issue are representative of some of the questions that pediatric off-label drug use in china

1.2 Research significance

Off-label drug use, also known as unlabeled uses, means indication, administration route and dose beyond package insert approved by the drug supervision and administration departments, in particular to dose, applicable user groups, indication or administration route different from package insert.

The regulations pertaining to the practice of off-label drug use have not been harmonized across the world. In some developed countries, such as United States, France and Britain, national legislations, regulations or guidelines concerning off-label drug use have been established, and rational off-label drug use is allowed in these countries (Emmerich, 2012; Frattarelli, 2014; Aronson, 2017). In India, off-label prescribing is illegal according to the Amendments to the Indian Medical Council Act 2 (Mudur, 2004). However, there is no clear description of off-label prescribing according to Chinese laws (Zhang, 2012) In the past few years, great efforts have been made to improve this situation.

Across the world, there were different degrees of off-label drug use problems in all countries. Off-label prescriptions accounted for 25-60% (Conroy, Choonara, & Impicciatore, 2000). Pediatric drugs were rarely included in the study of clinical trials as a result of special physiological and psychological characteristics of users, so, there was lack of data relating to safety and effectiveness of pediatric marketed drug user groups. However, pediatric off-label drug use was inevitable due to treatment of children diseases. According to statistics, rate of off-label drug use in hospitalized children was up to 50%-90% (Conroy, Choonara, & Impicciatore, 2000). Many countries have made explicit laws, regulations or rules on off-label drug use.

In China, off-label drug use was becoming more common, but not conforming to regulations. Moreover, there was no clear stipulation on off-label drug use, especially pediatric off-label drug use; and there was lack of effective implementation and supervision on off-label drug use. As a result, doctors' medical orders, drug dispensing and distribution of pharmacists, and drug user groups were at greatest risks, laying hidden dangers for doctor-patient disputes. Therefore, it was necessary to carry out the study on standardizing pediatric off-label drug use, providing reference and basis for clinical drug use.

This thesis reviews the researches on the theory of planned behavior in various aspects, and discusses some unsolved problems (Ajzen, 1985, 1987). Theoretically, this theory has been strongly supported by empirical evidence. We can predict different types of behavior from three aspects: attitude to behavior, subjective norms and perceived behavior control. These intentions and the perception of behavior control together make up the difference of actual behavior.

Attitude, subjective norm, and perceived behavior control have been proved to be related to behavior, norm and control belief. Expectation and value measurement are a way to deal with measurement limitation, but the exact nature of these relationships remains uncertain. Any value of the expectation formula can only be partially found to be successful in dealing with these relationships. The optimal remeasurement of expectation value and value measurement is a method to deal with measurement limitation. Finally, the inclusion of past behavior in the prediction equation is proved to be a method to test the theoretical sufficiency, which is another unsolved problem. The theory is predicting behavior quite well concerning off-label drug use by behavioral reliability.

1.3 Research problem

Difference in management level with foreign hospitals. This research is intended to know about advanced management experience of hospitals in different countries and regions to improve standardized management of healthcare industry in China.

Many countries in the world have definite laws, regulations or rules on off-label drug use. Off-label prescribing is legal in the United States and European Union countries (Saiyed, 2017). In India, amendments to the Indian Medical Council Act made off-label prescribing illegal because of the ignorance of patients and the domination of

pharmaceutical companies in the prescribing patterns in India (Oberoi, 2015). However, no legal regulations in regard to off-label prescribing in China have been identified; thus, a complex ethical and legal situation might develop, particularly regarding the question of medical liability. Off-label drug use has been increasingly common in pediatric department of China with the practical condition of nonstandard off-label drug use.

In addition, there is no definite regulation on off-label drug use, especially in pediatric department now. Without effective execution and supervision of off-label drug use, there is enormous risk in medical advice issued by doctors, drug deployment of pharmacists and drug use of patients, which brings hidden problems of medical dispute.

Every student of psychology understands that explaining the complexity of human behavior is a difficult task. From an individual process to a focus on other social institutions, it can be explored at many levels. Social and psychologists prefer to focus on an intermediate level that is to give full play to the role of individuals. Its processing of available information regulates the effects of environmental and biological agents on behavior. Concepts related to behavioral tendencies, such as personality characteristics and social attitudes play an important role in explaining and predicting human behavior (Campbell, 1963; Sherman & Fazio, 1983; Ajzen, 1988). At present, there are various theoretical frameworks for dealing with the psychological processes involved.

In the study, I'm going to talk about doctors' cognition of off-label drug use behavior from the perspective of propensity method of behavior prediction. A brief review of past efforts to use propensity measures to predict behaviors, and then use the theoretical model, the theory of planned behavior in which cognitive self-regulation plays an important role. The research result of this theory in various fields are discussed, especially the problems to be solved in this study.

Therefore, researches about off-label drug use in pediatric department shall be taken to provide reference and basis for clinical medication.

1.4 Research purpose

Unlabeled uses are unavoidable in clinical practice. Given children’s specific physical and mental features, unlabeled uses have been the focus all the time.

Problems of different severity concerning unlabeled uses exist in different parts of the world, with unlabeled prescription accounting for 25% - 60% (Conroy, Choonara, &

Impicciatore, 2000). This includes drug dosage, intended age group, indications or route of administration different from those on the instruction.

Instruction refers to the written information concerning the technological information of drugs printed and offered by pharmaceutical companies and approved by CFDA. Instruction is the basis for physicians to prescribe and pharmacists to verify the prescription. Clinical prescription that does not follow the instruction belongs to unlabeled uses (Turner, 1998).

To date, several studies have been carried out to assess the awareness and experiences of different healthcare professionals towards pediatric off-label drug use in Western countries (Balan, 2005; Ekins, 2005; Stewart, 2007; Mukattash, 2011; Saullo, 2013). In 2016, the Chinese Expert Consensus of Pediatric Off-Label Drug Use was published in the Chinese Journal of Pediatrics, which was written by the Chinese Pediatric Society (2016). Given children's specific physical and mental features, clinical drug experiment is seldom carried out, which leads to insufficient data concerning the safety and effectiveness of drugs for children on the market. But due to the necessity of children disease treatment, unlabeled uses in pediatrics are inescapable. Many countries have clear laws and regulations on unlabeled uses. In China, unlabeled uses are increasingly common, along with non-standard unlabeled drug use.

At present, China has no specific regulations regarding unlabeled uses, especially in pediatrics. There is not enough effective implementation and regulation in this field, as a consequence, doctors, pharmacists and patients take great risks when they give advice, prepare and take the drug, which may cause future medical disputes. Therefore, it is essential to carry out a research on the standardization of pediatric unlabeled uses to offer reference to clinical drug use.

It may be argued that the influence of a wide range of attitudes and individual traits on a particular behavior is only indirectly produced by influencing reason that are more closely related to the behavior in question (Ajzen & Fishbein, 1980).

In the theory of planned behavior (TPB), the most detailed information of behavior determinants is contained in a person's control beliefs, norms and behaviors. This theory does not specify the origin of these beliefs but it points out many background elements that may affect people's beliefs - factors of personal, such as individuality and life values; demographic variable characteristics such as age, gender, work and educational background as well as living environment and other information sources. Such factors

indirectly influence intention and behavior by influencing closer determinants in theory.

If only considered as a control variable, many empirical studies assess some demographic characteristics. However, a part of research particular emphasis on one or more background reasons, because of intuitive or theoretical factors. These factors are considered to be related to the behavior under investigation. The theory of planned behavior is an explanation of behavior under specific circumstances, so using the theory of planned behavior (TPB) to investigate on pediatric off-label drug use status of Chinese hospitals. According to the TPB model, this study will focus on behavioral attitudes, subjective norms, perceived behavioral control, and behavioral intentions of pediatricians. These are four aspects of Chinese pediatricians' behavior Off-label drug use.

1.5 Research contents and framework

The objective of this study is to evaluate current practice and awareness of pediatrician towards pediatric off-label drug use, as well as the confusion faced among pediatrician in China. Fur such purpose the study adopts the method of status survey and questionnaire survey. According to the TPB model, this study focuses on behavioral attitudes, subjective norms, perceived behavioral control, and behavioral intentions of pediatricians as well as four aspects of Chinese pediatricians' behavior off-label drug use.

The research would be carried out by following two parts: 1) present situation research, including objective research on pediatric drug information of package insert of commonly used pediatric drugs and subjective research on behavior and cognition of pediatricians' off-label prescription; and 2) countermeasures and recommendations on pediatric off-label drug use based on aforesaid results. China's pediatric off-label drug use should be formally managed in terms of academics, management, operation, and technology to provide a basis for doctors' off-label drug use and perform standardized management on drug abuse, further to ensure interests of patients and treatment demands. Please see research framework see Figure 1-2.

Chapter 1, firstly demonstrates the current situation of off-label drug use by pediatricians in Chinese hospitals, analyzes the practical problems that Chinese pediatricians have to face, introduces the research background, research significance, and research purpose. Lastly, it shows the research contents and framework.

Chapter 2 mainly organizes the literature review related to the topic. First of all, the

related concepts of off-label drug use are reviewed, including the definition, classification, characteristics, and related concepts. Off-label drug use includes the use of a drug product in (1) doses, (2) patient populations, (3) indications, or (4) routes of administration that are not reflected in FDA-approved product labeling. This research will systematically review the situation of off-label drug use around the world, combined with the TPB.

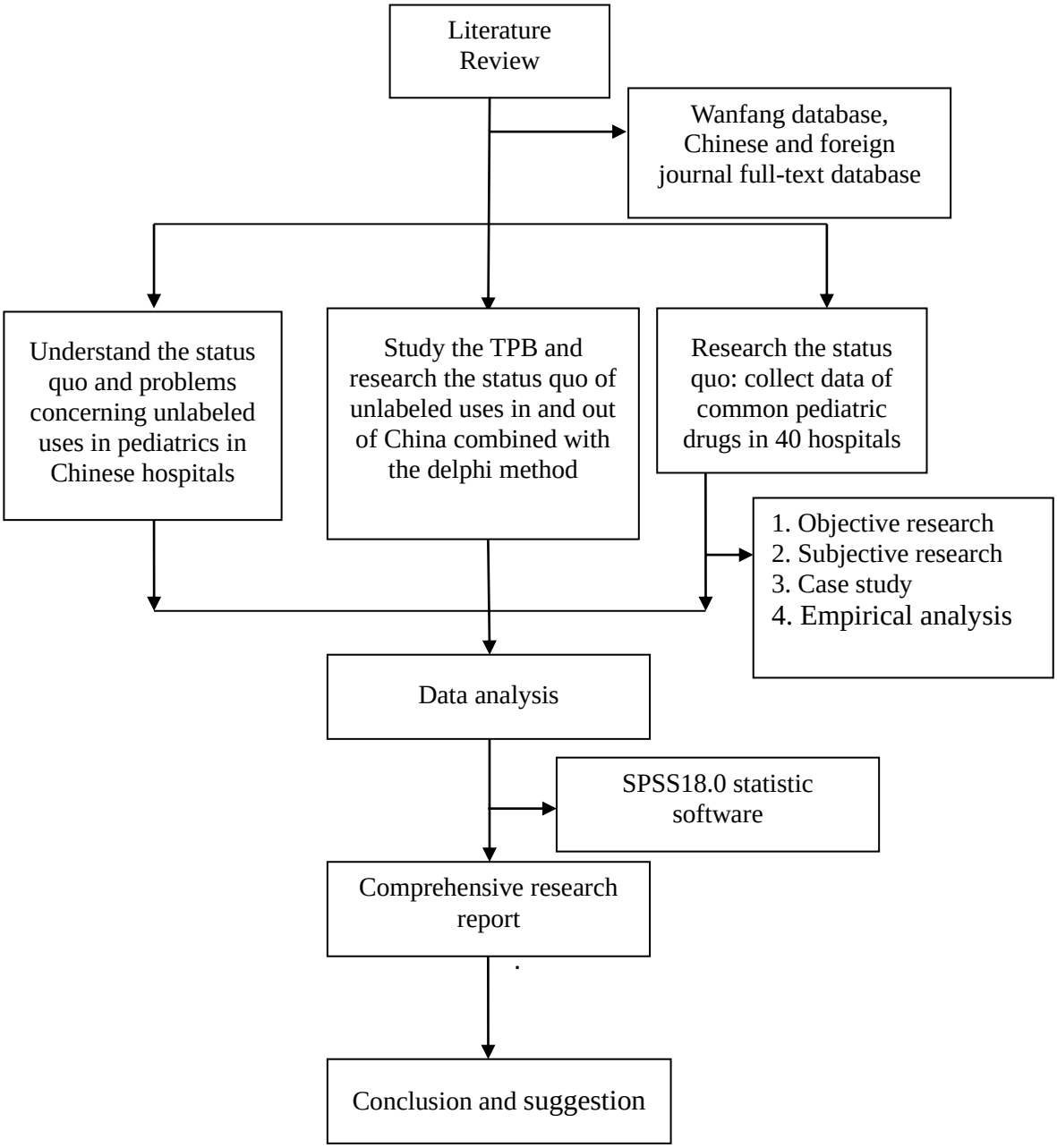

Figure 1-2 Research design

Secondly, we will retrospectively discuss the relevant theoretic framework in management, including the theoretical and conceptual model, as we decided to use the

theory of planned behavior as the theoretical basis of this study. In this chapter, we review the proposal of TPB, the meaning of TPB and its application in health behavior, in clinical treatment as well as in areas concerning health.

At the same time, we reviewed off-label drug use among pediatrics, including the general situation of off-label drug in other countries, some research on pediatric off-label drug use, the general situation of off-label drug use among pediatrics in China. We discuss the reasons for using drugs off-label in pediatrics in China, the differences of off-label use among pediatrics between China and other countries, some measures necessary considering the harms caused by off-label drug use, predisposing factors of adverse drug reactions among children, legal responsibility concerning off-label drug use and the legal validity of package insert.

Both the United States and Europe have regulations, namely the Best Pharmaceuticals for Children Act in the United States, and the European pediatric regulations. However, the conflicts between laws and off-label drug use are still severe in China. There subsists some misunderstanding about solving off-label drug use, necessary legal impediment of off-label drug use, consideration of off-label drug use among pediatric patients, the necessity of off-label drug use, the analysis of the development of off-label drug use among pediatrics, and scientific and efficacy of off-label drug use.

It is extremely urgent to normalize off-label drug use. It is the responsibility of doctors, pharmacists, food and drug administration, and drug manufacturers. In the end, we show and compare the status of off-label drug uses and the theory of planned behavior based on different perspectives and proposes some suggestions.

Chapter 3 concerns the methods.

Firstly, the research methods of this study are introduced, including the status quo and questionnaires. Off-label drug use is widespread among pediatric patients, and the implementation of guidelines concerning this topic remains challenging. With this methodological approach we intent to evaluate current practice and awareness of pediatricians towards off-label drug use in children, as well as the confusion they are facing. The overall research design is depicted in graph 1.1.

Secondly, within the methods chapter, the specific implementation of the questionnaire is described. The clinical pediatrics research group under the Chinese Pediatric Society, Chinese Medical Association carried out a questionnaire survey

concerning “unlabeled uses” among pediatrician in 40 hospitals located in Beijing, Shanghai, Hunan Province, Heilongjiang Province, Yunnan Province, Shanxi Province, and Zhejiang Province.

We design the questionnaire based on the structure of TPB. This study will analyze the behavior of off-label drug use of Chinese pediatricians based on four aspects: attitudes, subjective norms, perceived behavior control, and behavioral intention.

Research on the status quo was conducted based on Beijing prescription analysis research group information. It has provided more than 1.4 million pediatric prescriptions from different departments (such as the department of pediatrics, department of pediatric oncology, pediatric emergency department, NICU, and PICU) of more than 40 hospitals in Beijing, Tianjin, Shanghai, Guangzhou, Hangzhou and Chengdu in 2016 and 2017. The top 300 drugs are chosen to be our investigated subjects. An analysis based on pediatric information in the package insert is conducted to offer insights and make a conclusion.

Investigation methods: On the basis of generic names provided by the analysis research group, drugs were sorted by frequencies. Top 300 drugs with frequencies over 0.1% are selected as investigated objects. By using prescription automatic screening system of Medicom Software Co., Ltd, package inserts of generic names were queried, drug names, doses, and pediatric drug use information in the package insert were recorded by using EXCEL, and medications are classified by using Clinical Drug Use Instruction (2010 edition). Drug statistical classification, as well as descriptive statistics based on pediatric drug information, has been completed.

Medications involved in this study include anti-infective agents, respiratory medication, gastrointestinal medications, and NSAIDs.

As regards the questionnaire, study design, setting, and participants, the content validity of the questionnaire was evaluated by a multidisciplinary group discussion of experts in the Pediatric clinical pharmacology group, Pediatric Society of Pediatrics, Chinese Medical Association, pediatrics, pharmacology, and epidemiology. The rating scale is designed according to the four dimensions of attitudes, subjective norms, perceived behavior control, and behavioral intention. Scoring is based on the benefit of distinguishing off-label drug use. The rating scale is determined by the supervisor, the lowest score is 1, and the highest is 5. The study was aimed at pediatricians, 350 questionnaires were distributed to 40 hospitals in 7 provinces and cities of China, 320 questionnaires were returned, the response rate was 92% (320/350).

Finally, we analyze the attitude of pediatricians, their behavioral intention, the perceived behavior control of the off-label drug use of pediatrician, and the behavior off-label drug use of pediatricians based on data.

Chapter 4 concerns results.

From a professional perspective, it details the frequency of off-label drug prescriptions, the reasons for such prescriptions, factors, and basis concerning off-label prescriptions, applications of off-label drug use, and types of medication. In this questionnaire, we also asked about the types of diseases and contraindications. This chapter mainly analyses the rationality and difference of the calculation results.

According to the TPB model, this study will focus on behavioral attitudes, subjective norms, perceived behavioral control, and behavioral intentions of pediatricians. In this chapter, a physician prescription behavior model based on the TPB was constructed. The model can more clearly explain the effects of behavior attitude, subjective norms, and control beliefs on Chinese pediatricians' off labeled use of drug of instruction.

Chapter 5: Discussion of Results and Conclusion

We discuss findings and summarize the research of this study and propose some suggestions concerning off-label drug use in pediatrics. The status of off-label drug use among children, the reasons why doctors prescribe off-label drug use in pediatrics care: lack of information in a package insert concerning children, lack of dosage forms for children administration, incompleteness of clinical records, differences between packages inserts.

We analyzed the problems and contradictions of off-label drug use among children, the risk of using particular medication and patient situation, relevant law and regulations, the risk of doctors and requirements management of hospitals, problems facing when they practice, suggestions for off-label drug use among children in China, and some analysis of academic level, management level, and technical level. Besides, we also point out the shortcomings and limitations of this research and the next research direction.

1.6 Brief summary

Since no measure has been put forward to comprehensively work out the issue of unlabeled uses and it is held in the medical circle that unlabeled uses are reasonable to some extent, explorations are sure to be made concerning this issue.

This research will analyze the cause of pediatric unlabeled uses in China and aspects from which standards should be implemented. Is this related to insufficient drug information and physicians' prescription behaviors? The research will analyze and summarize the drug information concerning common drugs for children in China and explore if the information differs among different children sub-groups and drug varieties? Whether physicians with different professional titles prescribe drugs off-label at different frequencies? Is it necessary to set permission concerning off-label prescription? Is it necessary to stipulate different levels of unlabeled uses towards common diseases and rare and difficult diseases, as well as for common drugs and highly dangerous drugs?

This research will put forward countermeasures and suggestions regarding unlabeled uses as reference and basis to standardize clinical pediatric unlabeled uses. It aims to set norm for unlabeled uses, prevent drug abuse and guarantee patients' interests and needs.

Since it has put forward 26 years ago, the theory of planned behavior has become one of the most commonly used and influential models for predicting human behavior in any objective way (Ajzen, 1985, 1991).

Actually, this theory depicts a more complex and subtle picture. It is important that, in the theory of planned behavior, there is no assumption, normative or control belief, which is formed in a rational and just way, and there's no assumption that they represent reality.

Faiths reflect the information the public has about the performance of a particular behavior, but this information is usually incomplete and inaccurate; it may rest on irrational or faulty prerequisites, be biased by self-centered motives, by cowardice, indignation as well as other sentiments, in other ways fail to reflect the actual situation.

Obviously, there are calls from some rational behavior. Nevertheless, no matter how people complete at their plan behavior, control beliefs and normative, their attitudes toward themselves, towards behavior, their subjective norms and their views on behavior control will all come out of their beliefs automatically and consistently. Only in this sense actions are said to be planned or reasoned. Even though it is not accurate, and has irrational aspects, our faiths also produce intentions, attitudes and behaviors consistent with those faiths (Geraerts et al., 2008).

Nosek et al. (2010) found that his research project scored the highest in terms of scientific impact among social psychologists in the United States and Canada (Nosek et al., 2010). However, although the theory of planned behavior is very popular, it has many

controversies. Some researchers reject it as a behavioral theory of human social behavior. Many researchers prefer repudiate the importance of consciousness as a causal factor (Wegner & Wheatley, 1999; Wegner, 2002), many human social behaviors are driven by behavioral attitudes (Greenwald & Banaji, 1995) and other unconscious psychological processes (Bargh, 1989; Bargh & Chartrand, 1999; Aarts & Dijksterhuis, 2000; Brandstatter, Lengfelder, & Gollwitzer, 2001; Uhlmann & Swanson, 2004). However, most researchers accept the theory's rational behavior hypothesis, but question its adequacy or explore its restrictive condition, (Fishbein & Ajzen, 2010)

Based on these considerations, in this study, the theory of planned behavior was applied to the behavior of off-label drug use of pediatricians.

Chapter 2: Literature Review

Off-label drug use, also known as unlabeled uses, means indication, administration route and dose beyond package insert approved by the drug supervision and administration departments (Pharmacists, 1992), in particular to dose, applicable user groups, indication or administration route different from package insert.

Since the Theory of Planned Behavior was put forward more than 20 years ago, the research of planning behavior theory has made remarkable progress. Most of the initial studies tested the predictive validity of the theory in different behavioral fields. Comprehensive weight of many empirical proofs, it is also obtained from the analysis included in the current series of articles, it provides a clear support for this theory. Pleased that the theory of planned behavior can predict intentions and behavior very well, so investigator turn their attention to more complex problems Although the behavior directly applied to the new behavior or behaviors in new environment still appear in the print. In this paper, domestic and foreign off-label drug uses were reviewed.

2.1 Theoretical framework and conceptual model

2.1.1 The source of theory of planned behavior

The Theory of Reasoned Action (TRA) is the predecessor of the Theory of Planned Behavior (TPB) (Fishbein, 1963; Conner, 1996; Montano, 2008). The Theory of Reasoned Action dates back to the Theory of Multi-attribute Attitude (Fishbein, 1975). According to this theory, the behavioral attitude determines behavioral intentions while the expected behavioral outcome and outcome evaluation determine behavioral attitude. Then Fishbein and Ajzen developed the Theory of Multi-attribute Attitude and proposed the TRA (Fishbein, 1963; Ajzen, 1991; Beck, 1991).

According to TRA, behavioral intention is the direct factor determining behavior and is affected by behavioral attitude and subjective norms. Because it is presumed in the TRA that individual behavior is controlled by intention, which seriously restricts its wide application, Ajzen added the perceived behavior control variable on the basis of the TRA in

1985 to expand the application scope of the theory. The preliminary Theory of Planned Behavior was proposed. In 1991, Ajzen published the *Theory of Planned Behavior*, marking the maturity of this theory. After the TRA was proposed, the Theory of Planned Behavior developed for nearly 30 years to now. During this period, after continuous revision, enrichment, questioning and perfection, the Theory of Planned Behavior has grown steadily. It has been verified and accepted not only by international psychology circles, but also by many researchers in the whole psychology areas.

As a theoretical model of social psychology which successfully predicts and explains the relationship between attitude and behavior, the Theory of Planned Behavior has been widely used in many fields of human life today. Most studies have proved that the theory can better understand and predict individual behavior intention, self-efficacy and control sense and significantly improve the explanatory power of people's specific attitude to behavior (Zhang & Zheng, 2012).

For this model, the behavioral control is very important. The resources and chances available to a person must to some extent decide the possibility of behavioral success. More psychological interest than behavior control, nevertheless, is the aesthesia of behavioral control as well as its effect on behaviors and intentions. Perceived behavioral control has a major position in the theory of planned behavior. Actually, the theory of planned behavior differs from the TRA in its increase of consciousness behavioral control.

On the basis of the theory of planned behavior, easily acquired behavior, normative beliefs and control perceptions supply the perceived base for attitudes, cognitive control and, subjective norms. We saw it before that emotional condition can affection the behavior, canonical and control faiths that are easy access. When various beliefs are aroused in the survey backgrounds and in the behavior backgrounds, they will lead to various perceptions of control, subjective standards as well as manners, leading to various intentions. For a various purpose is positive in the behavioral environment purpose of assessment at the investigation phase will then be a correspondingly bad forecast of realistic behavior (Ajzen & Sexton, 1999).

2.1.2 Proposal of theory of planned behavior

The Theory of Planned Behavior (TPB) was proposed by Icek Ajzen (1988, 1991) being also the successor of the TRA proposed jointly by Ajzen and Fishbein (1975, 1980). Ajzen found that the human behavior was not of free will one hundred percent but was

under control, so, as stated, he expanded TRA by adding a new concept of Perceived Behavior Control. Thus, it developed into a new study mode of behavior theory - TPB.

TPB has been widely applied in western countries, especially in America. There are only few researches in China and these researches have a common point, which is comparing the predictive power of job attitude and subjective norm to behavioral intention. Hofstede classifies China as a collectivistic country. Chinese under this culture are prone to follow social norms and responsibility and put personal interest, attitude or personal need in a secondary place (Chan & Lau, 2001).

As stated, the TPB is an expansion of TRA, which contends that behavior is controlled by attitudes, social norms and individuals' perception of themselves. People consider all kinds of behaviors and weigh the outcome caused by every choice and then determine how to do take action (Baron & Byrne, 2004).

The TPB can help us understand how people change their behavior model. According to TPB, people's behavior is the outcome of deliberate plan.

According to the theory, behavior comes from rational thinking and relates to consideration of three aspects: individual's attitude to behavior, others' attitude to behavior and individual's perception of behavior feasibility.

On the basis of the archetype or wish model (Gibbons et al., 1998), the reasoned deed procedures represented in the theory of planned behavior are merely a possible way to reach at an actual behavior.

The second way, behavior is even more casual, response in the current circumstances as well as seriously affected by perceived similitude to one behavioural archetype.

When person find themselves in circumstances that hearten some actions, particularly adventuring actions for example smoking and excessive drinking, it is not their envisaged intentions that resolve their behaviors but rather their agreement to partake in these actions, this is people's openness to chance.

People's willingness, conversely, is depended by the degree to which people see themselves as resemble to the typical person who acting the actions, in problem the view that a comparative voluntarily mode of operation pattern in comparison to the TPB on a misconstruing of rational behavior. There is no hypothesis in the TPB that person attentive and organized retrospect all usable messages before they have an intention to participate in an action. On the opposite, the TPB admits that majority actions in daily life are carried out

without much understand attempt. Accord the theory of present social psychology (Petty & Cacioppo, 1986; Carver & Scheier, 1998; Chaiken & Trope, 1999).

Maybe the most often referred to reasons ostensibly ignored in the TPB are influence and moods (Conner & Armitage, 1998; Vries, & Pligt, 1998; Rapaport & Orbell, 2000; Richard, Vries, & Van, 1998). This concern is based on the wrong understanding that the theory hypothesizes a rational person who is unaffected by moods as well as due to the methodology that is usually used to manipulate the theory's variables.

In the TPB, affect and moods go in two modes. They can serve as backdrop ingredients that effect behavior, normative as well as control beliefs. Therefore, as everyone knows the universal moods can have logic effects on belief intensity and assessments. Compared to person in a pessimism mood status, person in an optimistic mood tend to assess events (for example the results of an action) better and to estimate better events as more likely to appear (Johnson & Tversky, 1983; Forgas, Bower, & Krantz, 1984; Schaller & Cialdini, 1990). Besides, emotion conditions can help chosen the action, normative as well as control beliefs that are easily realized in recall (Clark & Waddell, 1983; McKee et al., 2003).

As a key point, the theory of planned behavior (TPB) is interested in the forecast of purposes. Action, normative, control faiths and manners, subjective norms and views of behavior control are sources and explication behavior manners. Whether purposes forecast of action depends in partly on reasons exceed the person's control, i.e. the intensity of the intention and action relevancy is adjusted by practical control over the action. Except method insufficient, a low purpose and behaviour relevancy is a prompting sign showing that we may be achieving the maximum of reasoned action.

2.1.3 Connotation of theory of planned behavior

The TPB holds the following main views (Ajzen, 1985, 2011; Beck, 1991; Conner, 1996):

(1) Behavior is not fully controlled by the individual and it will be affected not only by the behavioral intention but also by the actual control conditions such as the capability of the behavior performer, the chance and resources. With sufficient actual control conditions, behavioral intention determines behavior directly.

(2) Correct perceived behavior control reflects the state of actual control conditions.

Therefore, it can serve as substitutive measurement index of actual control condition to directly predict the possibility of behavior. The accuracy of prediction depends on the true extent of the perceived behavior control.

(3) Behavioral attitude, subjective norm, and perceived behavior control are three major variables determining the behavioral intention. With more positive attitudes, larger support from other important persons and stronger perceived behavior control, behavioral intention is greater. Otherwise, it will be smaller (Conner, 1996).

(4) Individuals hold many beliefs about behavior but only few behavioral beliefs can be acquired in a given time and environment. These beliefs are also called salient beliefs, which are the bases of cognition and emotion of the behavioral attitude, subjective norm, and perceived behavior control.

(5) Individual and social factors (e.g. personality, intelligence, experience, age, gender, cultural background, etc) affect behavioral attitudes, subjective norms, and perceived behavior control indirectly by effects on behavioral beliefs, which affect behavioral intention and, consequently, behavior.

(6) Behavioral attitude, subjective norm, and perceived behavior control are conceptually distinct. However, sometimes they may have the same belief basis. So they are independent from each other but also related to each other (Duan & Jiang, 2008).

The TPB is expressed by a structure model depicted in Figure 2-1 (only major part of the chart is showed for convenience).

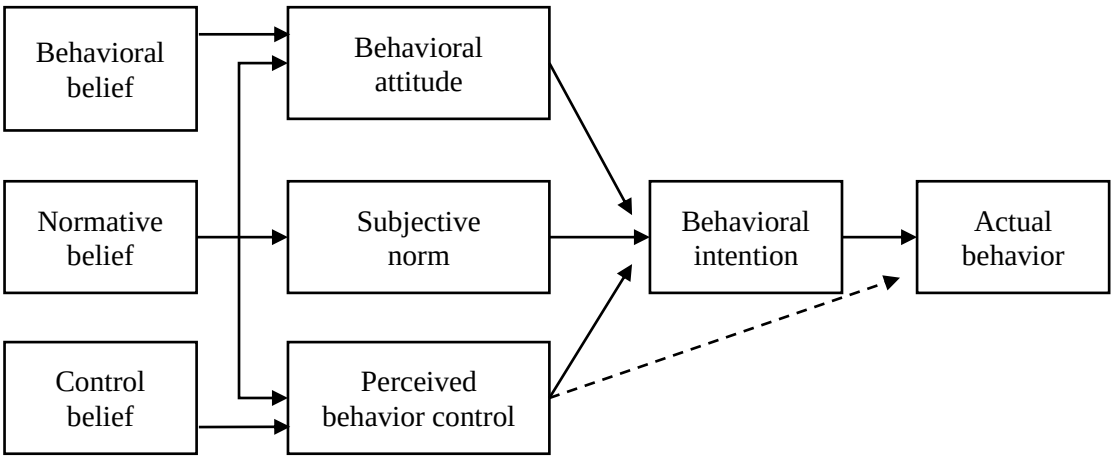

Figure 2-1 Structure model chart of theory of planned behavior

The TPB differentiates between three forms of beliefs, norms, and control as well as between the related structures of attitude, perceived behavior control, and subjective norms. The need for these differences, particularly between behavioral beliefs, canonical beliefs, attitudes as well as subjective norms has been queried (Miniard & Cohen, 1981).

It can clear be seen that all beliefs affect the action of interest with some attribute, whether it is the result or the normative expectation. Research failed to reproduce the outcomes of Budd (1987) test in which randomness of projects significantly decreased the relevance between the structures in the TPB.

A later research (Van & Hoogstraten, 1990) was also unsuccessful in corroborating Budd (1987) findings, or indeed there is a condition needed to implement the action. Therefore, it should be probably to recombine all beliefs relevant to a given action under a single composite to acquire a method of the overall action propensity.

2.1.4 Application of theory of planned behavior

2.1.4.1 Application of theory of planned behavior in health behavior

Han et al. (2015) consider that TPB has great explanatory power for behaviors, so it can serve as a good theoretical basis of study about many health behaviors. Common behavior fields include dietary behavior (Jing et al., 2010; Zhu et al., 2015), motor behavior (Li, 1999; Shan, 2012; Li, 2014), drug addiction behavior (Zhou & Su, 2014), clinical treatment and screening behavior (Cheng, 2009; Sun, 2012; Wan et al., 2012; Kang, 2013), social and learning behavior (Zhang, 2008; Mao & Luo, 2013; Lin & Bai, 2014) among others.

Beliefs and attitudes towards actions are approached by social psychologists via cognitive and information-processing models. The attitude expected value model of Fishbein was an example of this approach (Fishbein & Ajzen, 1975). Based on this model, attitudes expand rational from the belief an individual has about the target of the attitude. By and large, we form beliefs about an object by contacting with some situations, with other targets, features, or incidents. In this situation of attitudes toward an action, each belief associates the action with a result or some other attitude, for instance the cost of execution a given behavior.

2.1.4.2 Application of TPB in motor behavior

Most methods and models that take TPB as a theoretical basis are used in studying

physical human activities. With a good understanding of intention and behavior in physical activities, measures may be taken to facilitate physical human activities, which is advantageous in health domain. Boudreau (2009) studied factors determining intention and behavior in physical activities of type 2 diabetic patients. The results showed that properly designed counseling messages could facilitate physical activities in this type of patients. In a study about supervised physical activities of kidney cancer survivals.

Trinh (2016) found behavioral counseling based on TPB had obvious effects on promoting short-term physical activities. Besides, models based on TPB played an important role in studying about physical activities of pregnant women, children and MS patients.

Under certain situations, the commonly featured variables in the model may face difficulties in forecasting behavior. The common attitudes of teams and companies, minority groups, and particular, individuals with whom they may cooperate were estimated (Ajzen & Fishbein, 1977). This general attitude could not forecast the particular behavior purpose at the attitude target, so there was a call to abandon the idea of general attitude (Wicker, 1969).

Consistent with the goal of expounding human behavior rather than only forecasting it, the TPB involves the antecedents of attitude, subjective norms and perceived behavior control, which ultimately determine intentions and behaviors. At the highest level of interpretation, the theory assumes that action is a function of significant information, or beliefs, relative to the action. People can hold many beliefs concerning any presented action, but at any given time, they can only focus on a relatively small part (Miller, 1956). It is these remarkable beliefs that are thought to be the central determinants of one's purposes and behaviors.

2.1.4.3 Application of TPB in clinical treatment

TPB is an effective theoretical framework to predict intention of pharmacists in using prescription drug monitoring programs. According to researches of Fleming and colleagues (2010, 2014, 2015), attitudes, subjective norms, perceived behavior control and the perceived moral duty of pharmacists are all important factors affecting the intention. Understanding these factors can facilitate the application of Prescription Drug Monitoring Programs so as to reduce morbidity and mortality. Community pharmacists are key intervention points to prevent and reduce prescription drug abuse and misuse.

With TPB as a theoretical framework, Hagemeier (2014) found that effective roles of pharmacists were hindered by lack of self-confidence, training, and time. In addition, TPB was used to study the effects of factors related to self-treatment with medical belief and personal pain experience. The study showed that people were more likely to take OTC (over-the-counter) painkillers when the value of pain relief exceeded the concern about its harm.

Therefore, there is a good application prospect for TPB in monitoring drug use and facilitating rational drug use.

A fine example in viewpoint is reported by the research of Manning and Bettencourt (2011). The researchers used TPB as their framework to check compliance with medical protocols. Different from studies who deal with the behavioral categories of sleep-related activities by evaluating the TPB structure related to each behavior, other scholars have summarized several program compliance behaviors (Kor & Mullan, 2011).

They have summarized several compliance behaviors and evaluated the TPB structure with reference to the whole category. Intentions to insist were well predicted but this theory only account for a small part of the behavioral difference, maybe, due to the long-term hysteresis between the TPB investigation and the behavior. Except to surveying the TPB constructs, the researcher also evaluated depression as a possible background element.

The degree of depression was negatively correlated with intention and reported compliance to the medical plan. Nevertheless, according with the TPB, these influences of depressive symptoms were discovered to be mediated by theoretical predictors.

2.1.4.4 Application of TPB in fields other than health behavior

In Chinese research, application of TPB in fields other than health behavior includes consuming behavior (Zhu, 2010; Lao & Zhu, 2013), recreation behavior (Jin, 2015), online behavior (Cheng, 2009), students' cheat and traffic violation behavior (Zhang & Jiang, 2010) among others.

According to researches, TPB can better explain and predict individual behavior intention, self-efficacy and perceived control and significantly improve the explanatory power of people's specific attitude to behavior. But there are also limitations in TPB and the facilitation of behavioral counseling still needs expanded and long-term experiments.

Further researches of scholars are needed to explore application of TPB in off-label drug use so as to normalize drug use of doctors.

If, as suggested by the TPB, the measurement of the expected impact is the measurement of attitude, then it can be said that research on expected impact actually evaluates two kinds of attitude: a general attitude towards the implementation of a given behavior and an emotional attitude towards not implementing the behavior. Due to the intrinsic uncertainty of not doing something, the attention given to action and inaction may be sufficient to explain the residual prediction of expected emotions, regardless of whether the alternative attitude is emotional in nature or not (Richetin, Conner, & Perugini, 2011).

A review of the literature showed a unique characteristic of most researches involving the role of expected effect. Although the basic variables in the TPB are evaluated according to a behavior of interest, expected emotional responses are usually measured about not fulfilling the behavior (Fishbein & Ajzen, 2010).

In daily life activities like lunching, drinking water, taking a walk, watching a movie and so on, no careful consideration is demanded or assumed. Manners, subjective norms as well as behaviours of control in relation to these actions are presumed to guide conduct implicitly without perceptive effort and frequently lower than subjective consciousness (Ajzen & Fishbein, 2000).

Furthermore, the low empirical relationships between common personality characteristics as well as behavior in particular environments has long ago led theoreticians to assertion that the feature idea, defined as an extensive behavior inclination, is untenable (Mischel, 1968). Now, of special interest to study intentions are the tries to contact universal tendency of control to behaviors in particular situations (Rotter, 1966).

A remedy for the low forecast effectiveness of manners as well as peculiarities is the modulation of particular behaviors across environments, circumstances as well as behaviors (Fishbein & Ajzen, 1974; Epstein, 1983).

The viewpoint that behavioral accomplishment commonly depends on purpose as well as capability is by no methods new. It composes the foundation for theorizing, more than 70 years ago, on such different questions such as learning ability (Hull, 1943), or the level of expectation (Lewin, Dembo, & Festinger, 1944).

Before reflecting on the status of behavioral control in the forecast of purposes as well as behaviors, it is helpful to contrast this structure to other ideas of control. Especially,

perceived behavioral control differences materially from Rotter's idea of perceived source of control (Rotter, 1966). Perceived behavioral control may not be especially informative when people have comparatively less information about the action, when demands or procurable resources have changed, or when previously unknown factors have entered the equation. Under these circumstances, a survey of perceived behavioral control may reduce to correctness of behavioral forecast. Nevertheless, in the situations where perceived control is practical, it may be used to forecast the possibility of a fruitful action intention (Ajzen, 1985). On the whole, the TPB allows very exact forecasting of purposes as well as behaviour, usually coming close to the theoretical restriction (Conner & Armitage, 1998).

2.2 Pediatric off-label overviews

2.2.1 General situation of foreign pediatric off-label

Drugs have characteristics previewed in permissions such as indications, dosage, and adverse reactions. To exceed these characteristics (that is, change administration or dosages, or different age groups) might not be permitted and be deemed as off-label drug use (Jung, 2013). It was thought that off-label drugs were mainly used for life-threatening diseases, severe refractory diseases, or treatment unable to be withstood by standard treatment (Breitkreutz, 2008). There were unlabeled drug uses in some international and regional guidelines, for example, intrathecal injection of prednisolone and low dose heparin use were off-label drug uses.

Children has been divided into four different groups by the European Medicines Agency (EMA): newborns (0-28 days), babies (from 28 days to 24 months), children (under 12 years old), and adolescents (from 12 to 18 years old) (Luo & Li, 2009). Children off-label drug use has further divided into seven classes (I-VII) by Kimland (2012) and Kesselheim, Mello, and Avorn (2013):

If package inserts were not specifically recommended for a certain age group or for children under a certain weight, it belonged to Class I and Class II respectively;

Class III concern the absent children drug use information;

Class IV concerns lack of clinical data of children under 16 years old;

Class V concerns the existence of drug characteristic profile (SmPC) but prohibition to use in children;

Class VI concerns the existence of drug characteristic profile of SmPC, but not listed in the indications of package inserts;

Class VII concerns the use of prescriptions unconfirmed by SmPC.

If package inserts showed that it could be applicable to all children under normal circumstances, without age, specifications, and dosage limits, it belonged to Class I off-label drug use for children under 1 year old. Thus, a prescription could be classified into a variety of off-label categories.

Research showed that for more than half of children prescriptions, over 80% of which was issued to children with cancer and about 90% of newborn prescriptions, were issued off-label (FDA, 2008). In the whole group, the incidence of off-label prescriptions was 25%-60% and the highest incidence occurred in children under 2 years old and adolescents (11 to 17 years old) (Rocchi et al., 2010; Zhang, 2010).

11-37% of children among outpatients have received off-label descriptions. In the wards of general departments of pediatric internal medicine and departments of pediatric surgery, 36% of children have received at least one off-label prescription while in hospital. The ratio in pediatric ICU as rise to 70% (Stafford, 2008; Fairman, 2010) and neonatal wards were up to 90% (Xue & Wang, 2008).

Off-label prescriptions mainly included beyond-recommended dose, super indications, beyond administration route, and over applicable ages (Huang, Shen, & Chen, 2009; Zhang & Zheng, 2013). The incidence and severity of off-label drug use errors were increased significantly. According to findings on drug use errors occurrences in British children's hospitals between 2004 and 2006, 20 of 158 drug use errors were moderately harmful, of which 12 (60%) was caused by unauthorized / off-label drug uses (He, 2005).

2.2.2 Research on pediatric off-label drug use

McIntyre (2000) carried out retrospective investigation on prescriptions of 160 types of drugs. 10 of the most common off-label drugs were: acetaminophen, amoxicillin, salbutamol, beclomethasone, hydrocortisone, water frost, penicillin, oilatum, chloramphenicol, and malathion. Prescriptions of antibacterial drugs took the largest share, followed by anti-asthmatics and emollients or protective agents.

Aforesaid three types accounted for nearly half of the total prescriptions and half of the total off-label prescriptions. As for 667 prescriptions of antibacterial drugs, there were

101 prescriptions for overdose, 88 prescriptions below recommended dose, and 10 prescriptions higher than recommended dose; and the remaining 3 prescriptions adopted dosing intervals which were not recommended. Inhaled steroid anti-asthmatics were often higher than approved dose and inhaled anti-asthmatics were usually lower than approved dose.

Prospective study of Conroy, Choonara, and Impicciatore (2000) found that almost half (46%) of prescriptions (n=1,036) belonged to off-label or unlabeled drug use. Among them, 872 prescriptions were off-label and 164 prescriptions belonged to unlabeled drug use. More than half (67%) of the patients (n=421) have received off-label drug uses. For example, diazepam rectal administration of children under one year old (over age use).

Research results of Kimland (2012) showed that the most commonly used drugs were associated with pain, infection, premature birth, nutrition and operation with anesthesia. Acetaminophen was the most commonly used prescription and off-label drug used. Nearly half of prescriptions (49%) were off-label drugs or freshly prepared drugs and accounted for 69% or higher in the newborns (Salpeter, 2004; Sekhsaria, 2004).

In the hospital, at least 60% of children were administered with off-label drugs once (Conroy, Choonara, & Impicciatore, 2000; Gazarian, 2006). The most common prescriptions were acetaminophen, carbohydrate, electrolyte, and morphine. 41% of authorized drugs were used off-label. The highest incidence of off-label drug uses occurred in infants and newborns. In the study sample, 60% of people used one type of off-label drugs; 17% used three types, and 6% used at least five types. Results of several studies have reached similar conclusions (Bajcetic, 2005; SFDA Statute file, 2009).

Sen, Verhamme, and Neubert (2011) retrospectively analyzed outpatient medical records of three countries in Europe. Results showed that for children with asthma, the most common off-label drug use in Italy was to use beta two receptor analogues in children under 18 months. However, there was no such combined application in another two countries.

For off-label descriptions, Italy had the highest rate of budesonide; Netherlands had salbutamon; and the UK beclomethasone. But, long-term use of beta 2 receptor agonists rather than inhaled corticosteroids (ICS) might cause the increase of asthmatic children's airway inflammation and the deterioration of asthma control, even death (Cuzzolin, Atzei, & Fanos, 2006; Henk van & Nanda, 2011).

Combination of ICS and long-acting beta 2 receptor agonists (LABS) was only applicable to children over 4 years old, but, was able to be used for children under 2 years old in Netherlands. So far, there was just one small retrospective investigation on combined application of ICS and LABS for children under 4 years old; and it showed combined application was able to reduce incidence rate and the safety was acceptable (Di Paolo et al., 2006). Other studies have had similar results (Pandolfini & Bonati, 2005).

2.2.3 General situation of pediatric off-label drug use in China

Zhang, Li, and Liang (2012) have researched pediatric off-label drug uses in China and found that off-label drugs accounted for 41% in outpatient pediatrics and 78% in inpatient pediatrics.

They have investigated pediatric off-label drug uses in West China Second University Hospital: 749 hospitalized children and 14,374 pieces of doctors' advices were chosen, involving 385 types of drugs.

By calculation based on children patients, doctors' advices and drugs categories, the incidence rates of off-label drug uses were 98.00%, 78.96%, and 88.05%, respectively.

Types of off-label drugs mainly included: without children drug use information (29.41%, indications (18.35%), doses (17.61%) and dose ranges (±20%), (13.52%).

Ages groups with top 2 incidence rates in off-label drug uses were adolescents (83.56%) and children (80.58%).

Off-label drugs with top four doctors' advices were drugs for digestive and metabolic systems (82.28%), anti-infection drugs for system (75.06%), drugs for blood and hematopoietic system (79.27%) and respiratory drugs (58.27%).

Departments with top 2 incidence rates of off-label drug uses were department of pediatric hematology (88.27%) and departments of neonatology (79.12%).

Zeng and Zhou (2011) have selectively examined doctors' advices of 1,112 cases and found that 507 copies of doctors' advices belonged to off-label drug uses, with incidence rate of 45.59%.

Xue and Wang (2008) have investigated 3,142 copies of outpatient pediatric prescriptions and found that off-label drug uses accounted for 11.0% (345 copies), of which respiratory drugs and antibiotics accounted for 48.4% and 40.6% respectively. Drug categories were dominated by expectorant and antibacterial drugs.

2.3 Reasons of pediatric off-label drug uses

2.3.1 Shortage of children drug use information

There was lack of reliable children data for safety and effectiveness study before drugs were on the market (Pandolfini & Bonati, 2005). Pediatric drugs not conducting adequate research accounted for 50-75% (Cuzzolin, Atzei, & Fanos, 2006; Lindell-Osuagwu, Korhonen, & Saano, 2009). Specific problems included: limited availability of safety data due to lack of clinical trials in children (Dell et al., 2007), and inadequate or excessive dose of some age groups due to lack of pharmacokinetic data or dose finding study. Lanes, Garcia, and Huerta (2002) showed that pediatric off-label drug uses were mainly caused by no children information in SmPC, in contrast, super indications were usually in adult off-label drug uses.

There was evidence that the incidence rate of adverse reactions caused by pediatric unauthorized drug uses or off-label drug uses was higher than that authorized (Salpeter, 2004) as "children drugs were not used in accordance with adult dose reduction".

Adults and children differ in the absorption, distribution, metabolism and excretion. Meanwhile, children change with ageing. At present, only 15% of listed drugs were dedicated to children and considered to be less than half. There was children risks in basic clinical research - income evidence (Sekhsaria, 2004).

For drugs used to treat diseases in children (Conroy, Choonara, & Impicciatore, 2000), information was insufficient due to lack of research data, resulting in adverse reactions like the increases of mortality. Low drug doses would lead to ineffective treatment. For example, carbohydrate and electrolyte for liquid treatment took up a large part of off-label drug uses (Gazarian et al., 2006).

2.3.2 Shortage of formulation for children drug use

One of the reasons why children off-label drug had high usage rate was insufficient drug formulation applicable to children's ages and body weights (SFDA Statute file, 2009), in other words, lack of oral solution or tablets with small enough doses. Children dose was usually calculated in proportion to adult doses, although there is lack of sufficient evidence to evaluate (Bajcetic, Jelisavcic, & Mitrovic, 2005). The further results in drug overdose

(increases of adverse drug reactions) and drug ineffectiveness (due to dose) (Zhao & Luo, 2002).

Therefore, it was necessary to develop accurate drug doses for different ages of children such as newborns, babies and children, so as to ensure the safety of drugs. Zhang and Wei (2011) investigated Chinese drug registration information as of July 31, 2010 and found that drug registration information clearly marked with babies or children only accounted for 2.27%; and drug registration information clearly marked for babies or children on the official website of the State Food and Drug Administration (SFDA) only accounted for 6%, mainly drugs for digestive system, respiratory system, and antipyretic and analgesic.

Owing to the lack of applicable children specifications and formulations (Zhang, 2012), drugs were usually prepared by medical personnel and children guardians through alternatives such as adult drugs reduction, crushing tablets, and dissolving part of capsules in the water (Zeng & Zhou, 2011). Under these circumstances, pharmacokinetics was unknown, and it was more likely to cause high drug expenses of patients' family and health resources waste (Zhang & Wu, 2001).

2.3.3 One of the important reasons of pediatric off-label drug uses was lack of clinical records.

Research results of Kimland (2012) showed there was almost half of prescriptions without children drug use records such as oral administration of intravenous drugs (glucose injection) for pain relief, and suspension made by tablets from pharmacy. Confused administration routes would lead to security risks. Especially freshly prepared drugs would cause tremendous risks for children and lay hidden dangers for medical disputes owing to following characteristics: made through corresponding dilution of adult dose or adult drugs reduction, without clear dose dilution or reduction, and lack of effective check.

2.3.4 Differences of children package inserts in China and abroad

In addition, for some drugs, certain differences also existed in Chinese and foreign package inserts. So, it was likely for clinical doctors to use off-label drugs. For example, for the five proton pump inhibitors used in Chinese clinical application, infants were prohibited for omeprazole; there was no evidence showing children have used pantoprazole; rabeprazole was not recommended for children; and children were not

mentioned in the information of clinical application of lansoprazole and esomeprazole. However, in Europe, it was clearly stipulated that omeprazole was adapted to pediatric patients.

But evidence-based medicine analysis has proved that at least omeprazole, esomeprazole and lansoprazole were suitable for treatment of gastroesophageal reflux diseases and there was no need for repeated clinical trials in children (Wang & Zhang, 1992).

For example, fluoroquinolone antibacterial drugs should be used with extreme caution due to joint damage or was not recommended to children under 18 years old. However, in foreign countries, such drugs could still be used for some special cases (Huang, 2007).

2.4 Drug use above indications of package inserts

Drug use above the scope of package insert refers to behaviors taking drugs for clinic use without conformance to package insert. Package insert is the basis for doctors to issue prescription. It generally consists of several aspects of indication, usage, dosage and contraindication and is an explanation about drug composition and side effects.

Drug use above indication of package insert in prescription refers to the unconformity between prescription issued by doctors and indication in package insert. In general, the indication in package insert is extended arbitrarily. This phenomenon is relatively common in China, which have hidden dangers.

2.4.1 Current situation of drug use above indication of package insert in prescription

In March 2010, Eyedrop Gate of Avastin made drug use above indication known to the public. In fact, drug use above indication is very common not only in China but also in the world.

According to foreign data, off-label drug use takes up 7.5%-40.0% in general drug use of adults. According to statistics, off-label drug use takes up 50%-90% inpatients of the pediatric department. In a survey about the pediatric wards in 5 countries of the Europe, off-label drug use exists in more than 46% prescriptions (Bianehard, Clark, & Winikoff, 2002; Dell et al., 2007; Shao, 2007; Liu, Chen, & Xie, 2008; Huang, Shen, & Chen, 2009; Zhu et al., 2010). Off-label drug use in the special groups is the severest. It causes untoward effect of drugs on patients, which severely impairs their health.

2.4.2 Reasons for drug use above indication of package insert in prescription

(1) The development of clinical medicine: With the development of science and technology, medical science also develops in continuous exploration. Doctors have accumulated rich experience in clinical medication and there will also be new discovery for the drug use, which leads to drug use above indication of package insert.

(2) The package insert itself: There are defects in package inserts as sometimes, package inserts of the same drug made by different manufacturers are different. Thus, doctors may not know which one to follow. When original package insert needs to be amended because of new clinical findings, manufacturers always give up amendment because of large input of human power, finance and material, which causes lagging of package inserts (Zhang & Li, 2004).

(3) Special groups: Because of restrictions on the participation of special groups such as children and pregnant women in clinical trials, there are very few clinical data and the package inserts are in general academic state. In addition, the drugs used by special groups are scarce. The dosage forms of children are few and drugs for adults are often used by children. The drug use of pregnant women mainly depends on the clinical experience of doctors. These also lead to drug use above indication of package insert in prescription.

(4) Profit-driven doctors and effects of drug advertisement on patients: Drug use above indication of package insert in prescription may be caused because doctors lack professional ethics or are tempted by financial benefits. Patients may be affected by commercial advertisement on media such as TV, which sometimes also affects the judgment of doctors.

2.4.3 Harm of drug use above indication of package insert in prescription and measures to be taken

(1) Harm of drug use above indication of package insert in prescription:

a) Patients: The probability of drug use above indication of package insert in prescription increases for patients, because the untoward effects of drugs may not be found yet and there is no guarantee for safe drug use. Once this is found, patients shall stop taking drugs immediately and safeguard legal rights actively.

b) Hospitals and doctors: Hospitals and doctors will break the law and shall bear corresponding legal responsibility if they provide drug use above indication of package

insert in prescription for patients that do not meet the necessary conditions for application and use of off-label drug use, irrespectively if they take the interests of the patients into consideration or not (Zeng & Zhou, 2011).

At present, doctors shall obtain approval of hospitals and administrative license for off-label drug use. Now there are at least two methods to realize off-label drug use. One is Experimental Clinical Treatment specified in Clause 2, Article 26 of the *Law of the People's Republic of China on Medical Practitioners* and the other is Clinical Trial of Drugs in *Good Clinical Practice*. Patients shall be informed of treatment steps, prognosis and possible risks and patients shall sign an informed consent to the drug use as appropriate.

According to Article 59 of *Tort Law of the People's Republic of China*, where any harm to a patient is caused by the defect of any drug, medical disinfectant or medical instrument or by the transfusion of substandard blood, the patient may require compensation from the manufacturer or institution providing blood, or require compensation from the medical institution. If the patients require compensation from the medical institution, the medical institution that has paid the compensation shall be entitled to be reimbursed by the liable manufacturer or institution providing blood. Thus, patients may ask for legal responsibility of hospitals after they are harmed according to the provisions, which bring harm to hospitals (Zhang, Li, & Hu, 2012).

c) Public medical safety: If drug use above indication of package insert is not restrained and widely used by doctors in clinical treatment, public medical safety will be harmed, and our normal life will be affected.

(2) Measures to be taken:

a) Government supervision departments shall actively fulfill supervision function. On the basis of learning from advanced management concepts and experiences of foreign countries, feasible laws and regulations shall be formulated in combination with basic conditions of our country to regulate clinical drug use by legislation. False advertisements or advertisements expanding efficacy arbitrarily shall be managed in combination with other government departments to avoid drug use above indication of package insert caused by advertisement.

b) Medical associations shall actively cooperate with government departments in supervision management. Standard management shall be exercised in medical institutions

with pharmacy management and supervision systems prepared to normalize doctors.

c) Clinicians shall enhance professional ethics and resist temptation of economic interest consciously. Drugs shall be provided carefully with patient interests as the core to guarantee medication safety.

d) The awareness about significance of western medicine prescription shall be enhanced. In the whole process from the issuance of western medicine prescription to drug use, efficacy will be affected no matter problems emerge in which link. Once an adverse event happens, medical dispute is unavoidable. In addition, society, patients and hospitals and other aspects will be affected to some extent.

e) Thus, the significance of western medicine prescription is reflected. Apart from necessary professional knowledge, doctors shall also be of high sense of responsibility and keep positive attitude to work. They shall monitor and warn themselves to decrease careless mistakes in western medicine prescription.

In clinical treatment, doctors shall develop the habit of reading package insert carefully. It shall be guaranteed that patients needing drug use above indication of package insert are informed of treatment steps, prognosis and possible risks. The informed consent shall be signed, and the drug may be used after consultation with superior clinicians.

If drug use above indication of package insert is found in providing drugs, pharmacists shall ask doctors to note reasons and sign the prescription. In a word, drug use shall be normalized in all aspects to avoid drug use above indication of package insert and guarantee life health of patients.

2.5 Off-label drug uses and adverse drug reactions

Countries of the world had respective regulations and reporting system for adverse drug reactions (Zhang & Li, 2012). Children's growth was easily affected by drugs such as: growth and developmental disorders and delayed adverse drug reactions not easily found in adults**.**

2.5.1 Reasons for children' adverse drug reactions

Adverse drug reactions of children were mainly caused by off-label drug uses or unauthorized drug uses (Zhang & Li, 2004). More concern should be given to freshly prepared drugs. The usage rate of freshly prepared drugs (EPDs) on babies, especially

newborns, was very high, because there was no clear scheme for drug dispensing, such as the lack of safety lock system, dilution errors of concentrated solution, and unconscious intake of drugs with different names and different indications, but with the same active ingredients. Newborns and infants were very fragile and sensitive. Body weights were low. Kidney and liver functions were immature. So, evidence to further research drug safety and efficacy of this age group was urgently required.

2.5.2 Research on adverse reactions of children off-label drugs

During 1998 to 2007, Aagaard and Hansen (2011) have collected 4,388 copies of spontaneously reported adverse reactions data of groups from 0 to 17 years old in Denmark. The result showed that the lack of related knowledge of adverse drug reactions (Cui, 2015; Zhang, Wang, & Zhang, 2016) was the most noteworthy problem in children off-label drug uses. In the study of Li, Hang, and Yu (2014) and Tang, Fan, and Zhao (2015) treatment groups of anticonvulsive drugs, radiotherapy drugs, antitussives, and gastrointestinal tract drugs had higher incidence rate of off-label adverse reactions; and ADRs accounted for 50% in the treatment group was serious.

2.6 Legal responsibility of off-label drug use

Package inserts are legally valid documents issued by drug manufacturers that contain detailed information of drugs and can guide medical personnel and patients to use drugs. The standardization degree of package inserts is closely related to healthcare quality. However, the discrepancy between clinical medication and package insert is very common and doctors often provide drugs above the package insert according to their clinical experience. Whether hospitals shall bear full responsibility for consequent medial disputes? There is no final conclusion at present

2.6.1 Legal nature of package insert

According to Article 54 of *Law of the People's Republic of China on the Administration of Drugs*, packages of pharmaceuticals must be labeled and include directions for use in accordance with the regulations. The label or directions must indicate the generic name of the medicine, components, specifications, the producer, registration the number, batch the number of the product, production date, expiry date, indications or

major functions, directions for use, dosage, restrictions, adverse reactions and precautions.

This Article is compulsory. Drug manufacturers must prepare package inserts according to this Article strictly and doctors must exercise strict control on drug use according to package inserts. Apart from basic information of drugs, “Please follow doctors’ advice” or “Please take drugs under guidance of doctors” are labeled. Discretion about drug use is given to doctors to some extent. But the right shall be fulfilled within package inserts (Zhang, Li, & Liang, 2012).

Therefore, package inserts are absolute legal force in clinical medication and major legal documents for medical disputes.

2.6.2 Inevitability of off-label drug use

Sine package inserts are specified by law, why is off-label drug use very common in clinical medication? There is certain realistic inevitability behind it.

2.6.2.1 Lagging of package inserts

With limited number of cases, time and objects studied and single purpose of the trial before marketing of drugs, the safety information and indications of drugs obtained during the trial may not be complete. After drugs are marketed, with the increase of clinical experience, the indication or the main treatment function of drugs may change, which requires package inserts to be updated in time. But it needs a lot of human power and materials to update package inserts. Because of economic interest, drug companies usually do not change package inserts actively. Thus, package inserts may be different from actual medication (Wu, 2010).

2.6.2.2 Limitation of objects studied for drug tests

In the research and development stage of drugs, because of protection of special groups such as children, pregnant women and the old, they are strictly restrained in participating in clinical trials. So, reaction of them after drug use cannot be obtained. But the object of off-label drug use is mainly special groups. So, hidden dangers are brought in drug safeties (Yan, 2006).

In consideration of the above objective factors, according to the humanitarianism principle of healing the wounded and rescuing the dying, medical personnel have the obligation to make decisions about drug use to remedy these defects on the basis of actual clinical condition. So off-label drug use is inevitable.

2.6.2.3 Legal responsibility of doctors for off-label drug use

As previously mentioned, on the one hand, package inserts are of legal effect and doctors shall provide drugs according to them. On the other hand, package inserts may be lagging and incomplete and doctors are required to provide drugs above package inserts. Therefore, in case of medical dispute caused by off-label drug use, it becomes very complicated to investigate the legal responsibility of doctors.

2.6.2.4 Doctors shall bear legal responsibility

Medical service is also a special commodity, which is of greatly specialized. Serious information asymmetry is caused between patients and patients. Specifically speaking, in the process of medical service, patients do not have the knowledge and ability to judge medical service quality in advance.

Thus, doctors may take advantage of their superiority to issue larger prescription and ask unnecessary examinations, which impairs patient interests for their own interests. Besides, the essence of off-label drug use is to add indications of package inserts arbitrarily without approval of legal process. It increases possible risks of patients. From the equity principle advocated in civil law, doctors shall not be fully exempted from responsibility even off-label drug use happens in reasonable situation.

2.6.3 Legal responsibility of doctors shall be diminished in specified conditions

2.6.3.1 Legal responsibility of doctors shall be diminished

Medical science relates to life health. If package inserts are obviously lagging and incomplete, it does not conform to the spirit of scientific development and ignores patients' right of life and health to restrain doctors strictly to package inserts.

According to Article 6 of Tort Law of the People's Republic of China and Article 4 of Several Provisions of the Supreme People's Court on Evidence in Civil Procedures, in an infringement action of damages caused by medical acts, the medical institution shall be responsible for producing evidences to prove that there is no causal relationship between the medical act and the harmful consequences or it is not at fault (Liu, 2005).

It means that legal responsibility of doctors shall be diminished if they can prove there is no fault in their medical acts in medical dispute caused by off-label drug use.

2.6.3.2 Application conditions

As previously mentioned, in case of medical dispute caused by off-label drug use, doctors shall bear responsibility for compensation. But in certain conditions, the responsibility of doctors for compensation shall be diminished. Therefore, it is necessary to discuss the application conditions. At first, doctors shall obtain approval from Committee of Pharmacy Management and Pharmacotherapeutics and Ethics Committee of the hospital before off-label drug use. It is a necessary important document. Committee of Pharmacy Management and Pharmacotherapeutics and Ethics Committee represent interests of the hospital. The approval of drugs for new indications directly relates to medical service quality of the hospital. Improper approval will lead to investigation of legal responsibility (Xu, 2005).

Thus, the committee mentioned above will make a choice carefully according to consultation opinions, clinical practice and related scientific literature and research reports. Subjectively, the decision of off-label drug use is made by doctors when the life quality of patients is affected or the life is in danger and there is no alternative drug.

According to Article 33 of Regulations on Treatment of Medical Accidents, unfavorable consequences resulting from emergent medical measures taken under dangerous circumstances for rescuing the life of the patient shall not be deemed as a medical accident. For example, it is off-label drug use to apply lots of antibiotics to patients infected by SARS. But to save the life of patients, the acts of hospital cannot be deemed as tort.

Finally, doctors must obtain consent of patients. Doctors must conform to basic principles of *Declaration of Helsinki* to make medical decisions for patient interests with protection of patient interest as guideline. Off-label drug use is a treatment activity that is dangerous and may cause adverse outcome. Doctors must inform patients of treatment purpose, expected results and possible risks and patients shall sign informed consent willingly with drug risks fully known. If doctors select off-label drug use when the above application conditions are not met or completely met, they shall bear full legal responsibility for medical dispute.

2.7. Legal issues of children off-label drug uses

Lack of applicable children drugs was a well-known problem. High quality ethical

research should be carried out to treat sick people. Also, clear authorization was required. Many countries in the world had formulated corresponding provisions for off-label drug uses, as shown in appendix 2 Table 1. The United States and Europe have promulgated regulations to standardize and improve the safety of children drug uses.

2.7.1 Best pharmaceuticals for children act in the unites state

The U.S. Food and Drug Administration (FDA) has made it clear that "doctors are not forced to have to fully comply with package inserts for drug uses". In 1992, the FDA required to add pediatric drug information on package inserts of prescription drugs. In 1994, the FDA stipulated that pediatric drug information must be included in the application forms for package inserts of all new drugs. In the same year, the *Pediatric Labeling Rule (Pediatric Labeling Rule)* was approved by the FDA and put pediatric drug use information into drug labels. For the revised 430 labels, 15% of which had label information of all ages and 8% of which had label information of part of age groups (Roberts, Rodriguez, & Murphy, 2003).

After that, the United States has also introduced a number of laws and regulations for pediatric drug research and safe drug uses (Roberts, Rodriguez, & Murphy, 2003). In 2007, the FDS regulated that drug holders must submit pediatric research reports. If the report was completely consistent with written request and written agreement, the FDS should grant the drug 6 months of pediatric exclusivity protective period (Huang & Xiao, 2013). For drugs approved on the market and finished pediatric research as stipulated, even if studies showed that such drugs could not be used in pediatrics, the drugs also could get 6 months of pediatric exclusivity protective period.

If specified pediatric researches are completed for drugs approved for marketing, these drugs may obtain pediatric exclusivity for 6 months even if researches show that they cannot be used in pediatric department. The exclusivity period is adjusted according to drugs and change information of drug labels shall be published in time.

2.7.2 European pediatric regulations

European *Pediatric Regulation* was revised by the European Commission in January, 2007 for the following purposes: to research and develop high quality and high ethical standards of drugs for children from 0 to 7 years old, prevent children from unnecessary tests, or delay information acquisition, and provide convenience for children to use adult

drugs (Jin, 2007). Pediatric Regulation has, for the first time, provided legal basis for clinical trials of European children and changed the way of drug development. Therefore, high quality drug research was more conducive to the development of pediatric drugs.

At the same time, unnecessary clinical trials for children were avoided and authorization of adults' drugs on children information was not delayed. Children subpopulation such as newborns and children with cancer were received special attention. Ethical issues of children's psychological sensibility and vulnerability were considered.

Clinical trials in children were exempted when the following conditions appeared: drugs might be potentially harmful or ineffective; drugs couldn't give children important benefits; or drugs had obvious treatment effects, but could not cure.

At the same time, direct economic support shall be provided for clinical trials of children and indirect support shall be provided for drug companies. The purpose of this provision is to minimize treatment with low efficacy, incorrect treatment and adverse drug reaction, decrease hospitalization rate and mortality, improve life quality and obtain economic interests (Zheng, 2011).

At the beginning of research and development of drugs, drug companies shall accept PIP and patent protection duration of 6 months will be increased for drug companies agreeing with clinical trials of children. The exclusive patent expansion period for orphan drugs is 2 years. PUMA is established in the provision to increase financial support for drugs out of the term of protection. With effective cooperation, EMA improves safety and efficacy of drugs for children and enhance public health. In addition, information availability can prevent unnecessary repeated trials of children.

2.7.3 Situations in China

China had at least 7 legal boundaries for applicable range and use of drugs. China has successively promulgated laws and regulations such as *the Specification Rules of Package Insert, the Notice on Further Standardizing Punishment Behavior of Package Inserts, the Regulations for the Management of Package Inserts and Labels, and the Prescription Management Methods.* So, package inserts were technologically strict and legally serious (Song, 2010). At present, there were no laws and regulations for clinical trials of children drugs in China. Children drug uses were lack of scientific basis because clinical trials specifically for children were not conducted on more than 60% of listed drugs.

Expert Consensus on Unregistered Drug Use was issued by Guangdong Pharmaceutical Association in 2010. It is the 1st standard about off-label drug use issued by professional association in China. But because of regional limit, its application range and legal effect need to be further defined.

2.7.3.1 Conflicts of laws about off-label drug use are still severe.

a) Feasible ideas and methods (including suggestions such as clarifying the legal status of package insert, encouraging authoritative guidance for package inserts and determining subject of evaluation in rationality of off-label drug use) are expected to further promote off-label drug use out of current legal dilemma in China.

There are some misunderstandings (wishing drug manufacturers to apply for change of package insert, asking medical institutions to reinforce approval management of off-label drug use and evading legal risks by informed consent) about existing measures solving present off-label drug use in China. Defects in these measures are pointed out. On this basis, some feasible ideas and methods (including suggestions such as clarifying the legal status of package insert, encouraging authoritative guidance for package inserts and determining subject of evaluation in rationality of off-label drug use) are proposed to solve rationality and legality problems of off-label drug use to promote off-label drug use out of current legal dilemma in China (Lu, 2013).

In current clinical diagnosis and treatment in China, off-label drug use aiming at curing diseases is no longer a new thing. With many off-label drug uses verified effective, the medical field recognizes that off-label drug use is very common. Off-label drug use is very common in clinical treatment no matter in China or other countries. According to foreign survey data about 160 common clinical drugs, 89 million (21%) prescriptions belong to off-label drug use in 423 million prescriptions and there is not or few scientific bases for most of them (73%). In case of special drug users such as pregnant women and children, off-label drug use becomes more common because of limitation of clinical trial data in drug registration. Its rate in hospitalized pediatric patients even reaches 50%~90% (Guo, Tian, & Shen, 2012; Liu, 2012; Guo, Ouyang, & Wang, 2013). According the survey of Xue Liping and others about 3,142 pediatric outpatient prescriptions in China, prescriptions with off-label drug use takes up 11.0% (345) (Xue & Wang, 2008).

At present, apart from the above common problems, the problems of previous drugs for new indications and drug use above dosage in package insert are all examples of

off-label drug use (China National prescription set, 2013).

b) Legal disputes caused by off-label drug use take place frequently. Medical dispute and even judicial action caused by off-label drug use are not scarce. For example, in a medical tort action tried by a court in Henan province about a fever and pain reliever called Puwei, the hospital provided half tablet for the patient and the patient died by serious protopathy more than half a month later. A lawsuit was exercised between the patient and the hospital for change of package insert from "Used with caution" to "Forbidden".

In another case of clinical medication, the manufacturer of Methotrexate cancelled the administration route of "intrathecal injection" in the package insert to avoid trouble of itself. But intrathecal injection of Methotrexate for treatment of blood diseases was used for decades. Facing patients with clinical demands and changed package insert, doctors did not know how to do it. The above cases are just an epitome, but they reflect serious problem. Some reasonable off-label drug use may be doubted for legality just because of off-label drug use itself. And the doctors may undertake presumption of fault and bear responsibility for compensation according to Article 58 of *Tort Law of the People's Republic of China*. (Wang & Shu, 2012)

2.7.3.2 Some misunderstandings about measures solving present off-label drug use

The above-mentioned conflict of laws for off-label drug use has raised attention of the industry and many views to solve the problem have been proposed. But the operability and legality of some views shall be discussed.

a) It is unrealistic to wish drug manufacturers to apply for change of package insert. According to some views, a proper solution to off-label drug use, especially previous drug for new indications is as follows. Drug manufacturers apply for approval of indication expansion after obtaining data from clinical drug trials according to laws and then obtain approval to add them in package insert. Obviously, this is the most basic and thorough method to solve off-label drug use and also unrealistic. One reason is the cost of time. It will be a long process from trial initiation to approval, so it cannot solve this urgent problem.

Another reason is economic cost. The economic cost to implement clinical trials for multiple phases is very high, but drug manufacturers may not obtain obvious interests. So, there is no impetus for revision of package inserts. Obviously, drug demands of patients are not always the determining factor for relevant departments to revise package inserts in

economic society. It means off-label drug use will exist for a long time and it is unrealistic to solve the problem by change of package inserts (Shao & Lu, 2010).

b) Medical institutions are required to reinforce approval management of off-label drug use.

Illegal: Another idea to solve off-label drug use is to ask medical institutions to normalize off-label drug use by preparation of internal management standard, management process and approval mechanism. Thus off-label drug use may obtain a reasonable and legal status. Some scholars point out that there is no prohibitive provision in national laws, regulations and rules for off-label drug use. And it is clearly specified in *Graded Hospital Evaluation Standard* that regulations on management of off-label drug use must be established in tertiary hospitals.

It means that it is known that some off-label drug use is reasonable and inevitable. But package inserts are documents with legal effects approved or ratified by drug administration department. Doctors cannot provide drugs above package inserts arbitrarily and approval must be obtained. Thus, whether off-label drug use is feasible shall not be discussed now. The concrete issue of how medical institutions implement inspection shall be discussed seriously.

The above views are quite reasonable, but an important fact that consensus on rationality of off-label drug use may be concluded in medical field but whether it is admitted by law is another matter is neglected. According to Article 14 of *Prescription Management Regulations* issued by Ministry of Health in 2006, doctors shall prescribe according to rules of diagnosis and treatment and indications, usage, dosage, contraindication, untoward effect and cautions in package inserts as required by medical treatment, prevention and healthcare.

According to Article 46 and Article 57, if serious consequences are caused because doctors do not prescribe as required, the right of prescription shall be cancelled by their medical institutions or they may be warned by health administrative department above county level or stop medical practice for 6 months to 1 year. The practicing certificate may be revoked in case of serious condition (China Legal Publishing House, 2007).

The word “shall” used in above provisions refers to obligations that must be undertaken in law. And it is banned by law to violate the obligation. Therefore, judges hold the opinion in many cases that prohibitive provisions are specified in law for off-label drug

use.

The consensus of medical field is not certainly that of legal field. As for *Graded Hospital Evaluation Standard*, although it caused high attention in medical field, it is no more than a management guideline in legal effect and there is no possibility for it against laws and regulations (Lu, Yao, & Liu, 2015).

Therefore, if management system is prepared for off-label drug use with illegal risks by medical institutions and off-label drug use is implemented under management of hospitals, it just transfers the illegal responsibility that may be undertaken by doctors to legal person responsibility of hospitals and the dispute about off-label drug use for legality is not changed. This is why many managers of medical institutions are opposed or reluctant to manage off-label drug use.

c) It is infeasible to evade legal risks by informed consent. There is also a common view that the completion of informed consent is a feasible to evade legal risks of off-label drug use. According to this view, if clinicians think some off-label drug use is reasonable, they can provide clear introduction and full explanation. Then patients are required to sign the informed consent to show that they accept off-label drug use. Once patients sign the informed consent, hospitals may claim responsibility exemption on the basis of the informed consent. This view comes from misunderstanding about the system of informed consent. Statutory obligations cannot be exempted by agreement, so legal obligations caused by illegal practice cannot be exempted or diminished by the informed consent (Gao & Zheng, 2011).

The essence of the system of informed consent means medical institutions and medical personnel make a piece of legal advice on diagnosis and treatment conforming to the medical level at that time for patients according to related laws, administrative regulations, departmental rules and standards on diagnosis, treatment and nursing.

But if the advice contains unavoidable risks of damage, it shall be informed to patients and the right of patients for choice shall be respected. The premise of informed consent is that there is no defect in the advice of doctors on diagnosis and treatment. If there are defects in the advice of doctors, such as operation without indications and drug use against contraindication, doctors must bear responsibility for their fault. And signature of patients on the informed consent makes no contribution to judging the fault of doctors.

This is the situation against standards on diagnosis and treatment, let alone violation

of law. If doctors prescribe patients drugs above package inserts, their practice may be judged illegal and they may be required to bear related legal responsibility. Because of the identity of laypeople and status in diagnosis and treatment, patients do not need to bear responsibility for illegal act of doctors. Even if they are informed of off-label drug use and agree with the practice in signing the informed consent, the affirmation of legality and responsibility of such practice will not be hindered.

2.7.3.3 Necessary measures to solve legal impediment of off-label drug use

Since there are no measures solving off-label drug use fundamentally and off-label drug use is considered reasonable to some extent by medial field, we need obviously to continue to seek measures solving the problem.

a) The legal status of package inserts shall be clarified. It is always a basic point in solving conflict of laws caused by off-label drug use to determine the legal status of package inserts and clarify their connotation and denotation. It is infeasible to take any circuitous solution with this contradiction neglected. Of course, foreign existing regulations are good examples in this aspect (Xie, 2012).

For example, Food and Drug Administration (FDA) of America notices that there is no limit in *Federal Food, Drug, and Cosmetic Act* for how doctors use drugs. For post-marketing drugs, the intended population of doctor's treatment may not be included in package inserts. In some situations, off-label drug use reported in medical literature is reasonable. American laws certainly do not apply to China, so definite laws and regulations are needed in China.

For this purpose, it may be propelled in the following three steps:

First, the medical field concludes in guidelines for medical associations the consensus that package inserts are important guidelines for drug use but there are not standards on diagnosis and treatment and do not serve as absolute limitations to prescription right of doctors.

Second, health administration departments revise *Prescription Management Regulations* or make new laws higher than legal hierarchy of it with definite provisions similar to that of Food and Drug Administration (FDA) of America.

Third, the judicial system issues judicial interpretation or at least embodies in typical precedents that off-label drug use is not equal to violation of standards on diagnosis and treatment. Whether it is illegal shall be subject to professional evaluation and illegal

responsibility does not emerge deservedly.

Expert Consensus on Unregistered Drug Use issued by Guangdong Pharmaceutical Association in March 2010 is the 1st consensus of medical field about off-label drug use and is concrete practice of the 1st step among the three steps. It is of great significance and influence. On this basis, national level consensus shall be impelled as soon as possible. And it is expected to be issued by associations such as Chinese Medical Association, Chinese Pharmaceutical Association, Chinese Hospital Association, Chinese Medical Doctor Association and China Health Law Society to establish its authority.

b) Authoritative guidance for off-label drug use is encouraged. With efforts made into principle consensus, the medical filed shall also realize that an importance reason causing worry of the society and hindering management of off-label drug use is the fact that there are some improper practices of drug use. It is unreasonable off-label drug use and may cause harm to patients. This is why related departments do not dare to issue provisions similar to that of Food and Drug Administration (FDA) of America. To avoid malicious use of off-label drug use after it is approved, with efforts made into principle consensus, more efforts shall be made by the medical field to provide concrete authoritative guidance for off-label drug use (Hu, Xu, & Zhao, 2012). *Guidance for Off-label Drug Use* published by relevant experts of Peking Union Medical College Hospital and pharmacists nationwide jointly is one of the attempts.

Some domestic pharmacists are developing a scoring system to endow different scores for different situations such as whether specific off-label drug use is included in domestic or foreign package inserts, whether basis for evidence-based medicine exists or whether evidences of study on large samples exist. The strength of probative value is determined on the basis to provide concrete guidance for drug use of clinicians.

c) Reasonable subject of evaluation for off-label drug use shall be determined. Civil tort action caused by off-label drug use is unavoidable in the future. The problem to evaluate whether the off-label drug use is legal and reasonable is involved in the case. The subject of evaluation for the problem is judges certainly. But laws and regulations involved in off-label drug use are concrete provisions of medical administrations, certain medical knowledge and hospital management knowledge are generally needed to understand them, let alone completely professional medical and pharmaceutical problems of involved medical technologies.

Therefore, judges may not necessarily make correct judgment on the basis of their

common knowledge. So, judges are expected to seek help from professional fields in fulfilling their responsibility as subject of evaluation. In short, judges trying cases of off-label drug use shall entrust a medical damage appraisal with participation of medical and pharmaceutical experts first. Then they may judge the rationality of off-label drug use according to the expert conclusion. They shall not simply make the literal meaning of package inserts basis of illegal off-label drug use without reference to professional opinions.

To achieve the above goals, the health law field shall fully communicate with the judicial circle and strive to embody this concept in related judicial interpretation. With unsound laws and regulations, the professional association/society also plays an irreplaceable role in guiding and normalizing off-label drug use. Take American Society of Health-System Pharmacists as an example, *American Hospital Formulary Service: Drug Information* is published and updated annually in the legal framework of Food and Drug Administration (FDA) of America to provide direct guidance for off-label drug use of doctors. In addition, the Society actively cooperates with other professional associations, such as American Cancer Society, to issue guidance information for off-label drug use jointly (WHO, 2004).

Expert Consensus on Unregistered Drug Use was organized and issued by Guangdong Pharmaceutical Association in 2010. It is the 1st standard about off-label drug use issued by professional association/society in China and provides legal and practical operation methods for clinical treatment.

Several high-quality domestic and foreign evidence-based medicine researches about off-label drug use are completed by Chinese Cochrane Center and the research results provide a scientific basis for decision makers to make policies and guide reasonable off-label drug use of doctors and patients.

A series of activities about management of off-label drug sue are exercised by Chinese Society of Clinical Pharmacy, Chinese Medical Association successively.

Off-label drug use is a right of doctors and is not always wrong and not allowed. But the advantages and disadvantages must be weighted with interests of clinical treatment and patients maximized. If patients can obtain better treatment, doctors shall be encouraged. Off-label drug use must be based on scientific and reasonable explanation. It shall also be supported by evidences of evidence-based medicine to guarantee efficacy and safety.

2.8. Thinking of off-label drug use in pediatric department

Package inserts are written materials with related technical information of drugs that are printed and provided by drug manufacturers and approved by national drug supervision and administration department. Package inserts are the basis for prescription of doctors and check of pharmacists. Clinical medication not conforming to package inserts all belongs to off-label drug use (Yao, 2015).

2.8.1 Necessity of off-label drug use

2.8.1.1 Development trend of off-label drug use in pediatric department:

For off-label drug use, American Society of Health-System Pharmacists makes the following definition: Off-label use is the use of drugs in an indication, dosage or route of administration unapproved by Food and Drug Administration (FDA) of America (Li & Yang, 2010). The meaning includes intended population, dosage, indication or route of administration different from that of the package insert. Off-label drug use differs from drug abuse. There is no definite legislation for off-label drug use in China at present, (Zhang, Wang, & Zhang, 2016) but it is common in clinical treatment. In America, drug manufacturers are required in *Federal Food, Drug, and Cosmetic Act* (FDCA) and related laws and regulations of Food and Drug Administration (FDA) of America to provide data of efficacy and safety about the indication, which takes about 10 years (Zhang & Li, 2004).

If package inserts must be changed after marketing of drugs, drug manufacturers shall provide lots of data of efficacy and safety about new usages of drugs with review of Food and Drug Administration (FDA) of America. With lots of time and costs needed, most drug manufacturers are reluctant to change package inserts initiatively, so package inserts may not necessarily represent current information of the drug. On the other side, off-label drug use is obtained by doctors from clinical practice, professional discussion or literature report. Thus off-label drug use is widely used in clinical treatment before approval of Food and Drug Administration (FDA) of America (Hu, 2013; Frattarelli, Galinkin, & Green, 2014). In April, FDA expressed its standpoint about off-label drug use and FDCA did not limit doctors in how to use drugs. In some situations, off-label drug use reported in literature reports is reasonable (Zhang & Zheng, 2013).

FDA clearly expresses that doctors are not forced to fully follow the package inserts approved officially. If off-label drug use is obtained by reasonable scientific theory, expert

opinion controlled clinical trial and is used for patient interests without deceit, it is reasonable (Stafford, 2008).

American Society of Hospital Pharmacists published in 1992 the statement that off-label drug use represented the treatment mostly needed by patients. If off-label drug use was regarded as experimental use, the right of patients to obtain treatment would be restrained (Gazarian et al., 2006). One of the principles of American Society of Hospital Pharmacists is that the treatment adopted by doctors shall conform to patient demands (Zhang & Wei, 2011).

The statement published by other organization such as Health Care Financing Administration, BlueCross Blue Shield (Li, Yang, & Wang, 2012), Health Insurance Association of America (Li, Cai, & Zheng, 2015) is basically the same. In March 2017, FDA issued *Drug Safety Information-FDA's Communication to the Public* (Xu, Sun, & Shao, 2015) to explain how drug safety information was delivered to the public, facilitate medical institutions and the public to obtain the newest information about potential risks of post-marketing drugs and promote reasonable drug use of medical personnel and patients.

The use of drug safety information is still in the primary stage. Researches about finding, assessment and mechanism of post-marketing adverse drug reaction and data collection need to be further strengthened. And drug manufacturers do not fully fulfill the responsibility to track adverse reaction (Lu, Yao, & Liu, 2015).

2.8.1.2 Off-label drug use is of scientificity and efficacy.

During long-term practice of clinical medication, many off-label drug uses are based on scientific theories and concluded through controlled clinical trial with reference to some domestic and foreign medical literatures. With the development of medical science and emergence of lots of evidences in evidence-based medicine, the clinical application of many post-marketing drugs is not limited to the package inserts. Thus, the application scope of drugs is expanded (Li, Zhao, & Zhang, 2015).

2.8.2 It is extremely urgent to normalize off-label drug use

The occurrence rate of off-label drug use is 7.5%~40% for adults but reaches up to 80% in pediatric department (Li, Guo, & Zhang, 2016). Although the use is supported by many evidences, indication expansion without any evidence is not excluded because drug manufacturers lack enough capital or market incentives to add new indications (Cui, Shi, & Shi, 2016).

In some situations, off-label drug use is the only choice for further treatment. In recent years, drug safety monitoring system has been established in China gradually. State Food and Drug Administration (SFDA) collected, analyzed and evaluated adverse drug reaction or other potential risks related to drugs by methods such as pharmacovigilance and ordered change of package inserts for 33 drugs (including category) from 2003~2009 (Tan, Chen, & Liu, 2016). According to a European pediatric cardiology research, 76% hospitalized children from 2~11 once obtained off-label drug use (Chen, Gu, & Zhu, 2014).

Children are special group and they grow fast. Therefore, attention shall be paid to effects of drugs by different mechanisms on growth and development of children. Apart from the efficacy of drug use, the potential adverse drug reaction shall also be closely noticed (Li, Song, & Liu, 2009).

2.8.2.1 Responsibility of doctors

Off-label drug use may be the only effective method for special groups such as children and pregnant women with some diseases and must be based on strict evidence-based medicine (Liang, Tang, & Zhang, 2012). It is a code of conduct in medical practice that doctors shall be responsible for patients. It has two meanings:

The first is the right of doctors to use new therapies.

The second is the right of patients to be informed. The rights of them can be unified in the informed consent. In case of off-label drug use, doctors must guarantee that the interests of patients are larger than potential risks. If doctors choose drug used only for the sake of patients instead of experimental study, it belongs to innovative therapy. Corresponding with the right ethically and legally given to doctors by related FDA laws and regulations, doctors shall inform patients of treatment steps, prognosis and potential risks for off-label drug use.

If off-label drug use is not accepted widely, doctors shall inform patients of unpredictable potential risks. And it is better to ask patients to sign the informed consent.

2.8.2.2 Responsibility of pharmacists

The review of pharmacists for prescriptions shall be based on package inserts. Pharmacists shall be careful about off-label drug use. They shall analyze and judge whether the drug use is reasonable and safeguard reasonable drug use.

In addition, pharmacists shall go deep into clinical treatment. They shall reinforce

learning to know about the development trend of medical science and pharmacy and communicate with doctors about clinical treatment. The shall also study literatures and study structural property, pharmacokinetics, pharmacodynamics, drug interactions, adverse reaction and contraindication of drugs to improve their ability to judge rationality and scientificity of off-label drug use continuously.

To make off-label drug use safer, more reasonable and normative, it needs reliable scientific theory, authority, academic materials and clinical evidences provided by using departments. With discussion, research, approval and registration of pharmaceutical affairs council of hospitals, it shall be included in the dispensatory and serve as basis for prescription review and deployment of pharmacists (Wang & Liu, 2011).

2.8.2.3 Responsibility of drug administration departments and drug manufacturers

At present, researches about off-label drug use are mainly executed by developed countries such as Europe and America and domestic researches are very few. State Food and Drug Administration shall reinforce management with strict review and check for package inserts. Package inserts of the same drug shall be unified nationally to adapt to the development need of clinical medicine. For indications of off-label drugs use proved effective by evidence-based medicine, drug manufacturers shall be urged to revise and perfect package inserts (Liang, Wang, & Xue, 2009; Zhang & Jiang, 2010; Zeng & Zhou, 2011; Chen & Tong, 2012; Yang, Jin, & Hou, 2013).

Drug manufacturers shall reinforce leaning of drug knowledge. They shall be responsible for the public and guarantee integrity and scientificity of package inserts. Safe, effective and reasonable drug use is not only embodied in drug quality. The preparation of package inserts is also important (Yang, Tang, & Yang, 2014).

Package inserts are the basis for clinicians and pharmacists to guide reasonable drug use of patients and shall be normative, detailed and correct. In addition, they shall conform to *Pharmacopoeia of the People's Republic of China: Notice on Clinical Medication*. Thus, the safety and efficacy of clinical medication can be guaranteed (Zeng, Jin, & Lu, 2014).

2.8.2.4 Suggestions

Pediatric drug use was a hot topic discussed by many representatives in the Two Sessions. There are about 400 million children in China and the number of children patients is very large. But the children special drugs and drug use information are extremely scarce.

According to statistic data of All-China Federation of Industry and Commerce Medical Pharmaceutical Chamber, there are only 60 exclusives to children among more than 3,500 preparations in pharmaceutical market of China with the ratio of only 1.52%. There are no preparations applicable to children for more than 90% drugs in the Chinese market. Even in America where the levels of drug research, development, production and supervision are high, more than 75% drugs lack information for children use (Cai, Lu, & Wu, 2012).

It directly leads to frequent drug use in clinical practice above the indication, usage, dosage and even contraindication of package inserts, i.e. off-label drug use. From the perspective of monitoring of adverse drug reaction, adverse reaction of children less than 14 years old takes up more than 10% of all cases (Liu et al., 2014).

Off-label drug use is not strictly verified. It may have significant efficacy, but the side effect is not clear for the moment. Off-label drug use is expected to draw on advantages and avoid disadvantages with expected effect. However, in case of discrepancy with expected effect and medical dispute, who shall bear the responsibility? There is no clear definition and permission for off-label drug use in above mentioned laws such as Law of the People's Republic of China on the Administration of Drugs, Administrative Regulation on Package Inserts of Drugs and Prescription Management Regulations

As for laws and regulations such as Tort Law of the People's Republic of China and Regulations on Treatment of Medical Accidents for disposal of medical accidents, the disposal of medical accidents caused by off-label drug use is not clearly mentioned and it just generally states that medical personnel shall abide by laws and regulations of medical field and standards on diagnosis and treatment. It shows that the legal basis considered in cases of medical disputes caused by off-label drug use is mainly Pharmacopoeia of the People's Republic of China, package inserts and Guideline for Clinical Diagnosis and Treatment.

The consensus or guideline of the medical field not approved by health administrative departments is not included. Therefore, medical institutions and medical personnel are always vulnerable in such dispute, which greatly increases the risks of medical practice. It may avoid unreasonable off-label drug use and reduce medical risks to takes measures such as flow of off-label drug use, informed consent, determination of prescriptions right and responsibility. Medical personnel and patients are those guiding drug use and using drugs directly. Scientific and normalized package inserts will affect proper drug use of

patients directly (Lao et al., 2014).

Therefore, communication between medical personnel, patients and drug administration departments and drug manufacturers shall be reinforced to report problems in drug use in time and propose reasonable improvement suggestions for package inserts.

Thus, package inserts can be perfected, normalized, scientific and reasonable continuously. With the development of medical science and pharmacy, off-label drug use will be more frequent. On the one hand, relevant laws and regulations shall be made to ask drug manufacturers to be adapted to demands of clinical medicine development according to literature reports in recent years.

For indications with off-label drug use proved effective by evidence-based medicine, package inserts must be revised with update within 3~5 years to provide basis for safe clinical medication and make legalization of off-label drug use as soon as possible. At the same time, off-label drug use plays an important role in present drug therapy. Doctors must master reasonable scientific theoretical basis for off-label drug use. They shall exercise flexible drug use via their medical and pharmaceutical knowledge in combination with specific conditions of patients. They shall provide better medical service for patients for the sake of patients.

Clinical medicine develops in exploration, which necessarily leads to continuous new findings and experience in drug use. Because present package inserts are updated slowly and represents only general academic status, they cannot reach leading academic level. Thus off-label drug use is inevitable, which facilitates the development of clinical pharmacotherapeutics to some extent. Off-label drug use is a double-edged sword. It can bring benefits for patients when used properly and cause a loss to patients and medical personnel when used improperly. For better off-label drug use, the government shall be open. Medical personnel shall be strict and patients shall be tolerant.

2.9 Conclusion and conceptual model

In 2010, the World Health Organization firstly released the WHO Model Formulary for Children for all countries. The model formulary has provided information on how to use more than 240 kinds of essential drugs to treat diseases of children aged 0 to 12. This meant that the practitioners all over the world were able to get standard information about recommended usages, doses, side effects and contraindications of children drugs.

However, based on the present situation of China, it is urgent to solve pediatric drug research and development problems, providing pediatricians with drugs to use. It is required to clarify the problems on legal status of “pediatric off-label drug uses”, providing medical personnel with legal basis. Standard procedures of off-label drug uses are called for to guarantee common interests of patients and medical personnel. Guidelines of off-label drug use are made by industry association, providing academic support for doctors' decisions on drug uses.

This study is intended to integrate, to provide a comprehensive view of off-label drug use in China, and to explore an explanatory model that allows for the prediction of off-label use behavior by doctors. The tacit conceptual model is the one previewed by TPB and the hypotheses are those established by literature where all predictors are expected to positively associate to behavioral intention, which is expected to lead to behavior. For parsimony sake these hypotheses are depicted in the following conceptual model (see Figure 2-2).

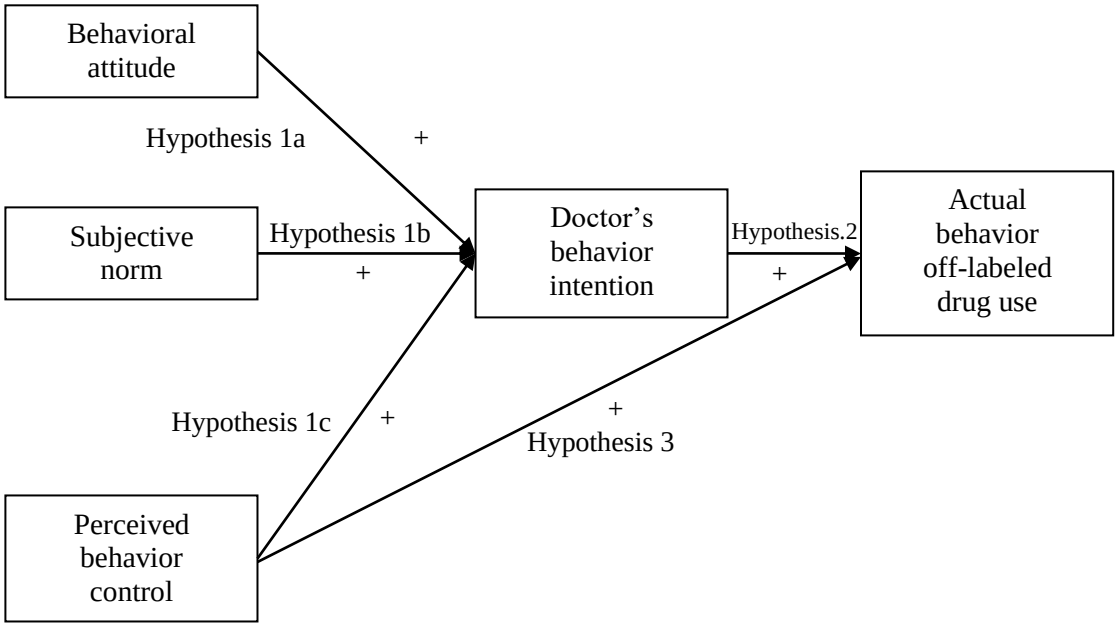

Figure 2-2 Conceptual model and hypotheses

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Chapter 3: Methods

Off-label drug use is widespread in pediatric drug treatment, and the implementation of guidelines on this topic remains challenging. For the overall research design, see Figure 1-2.

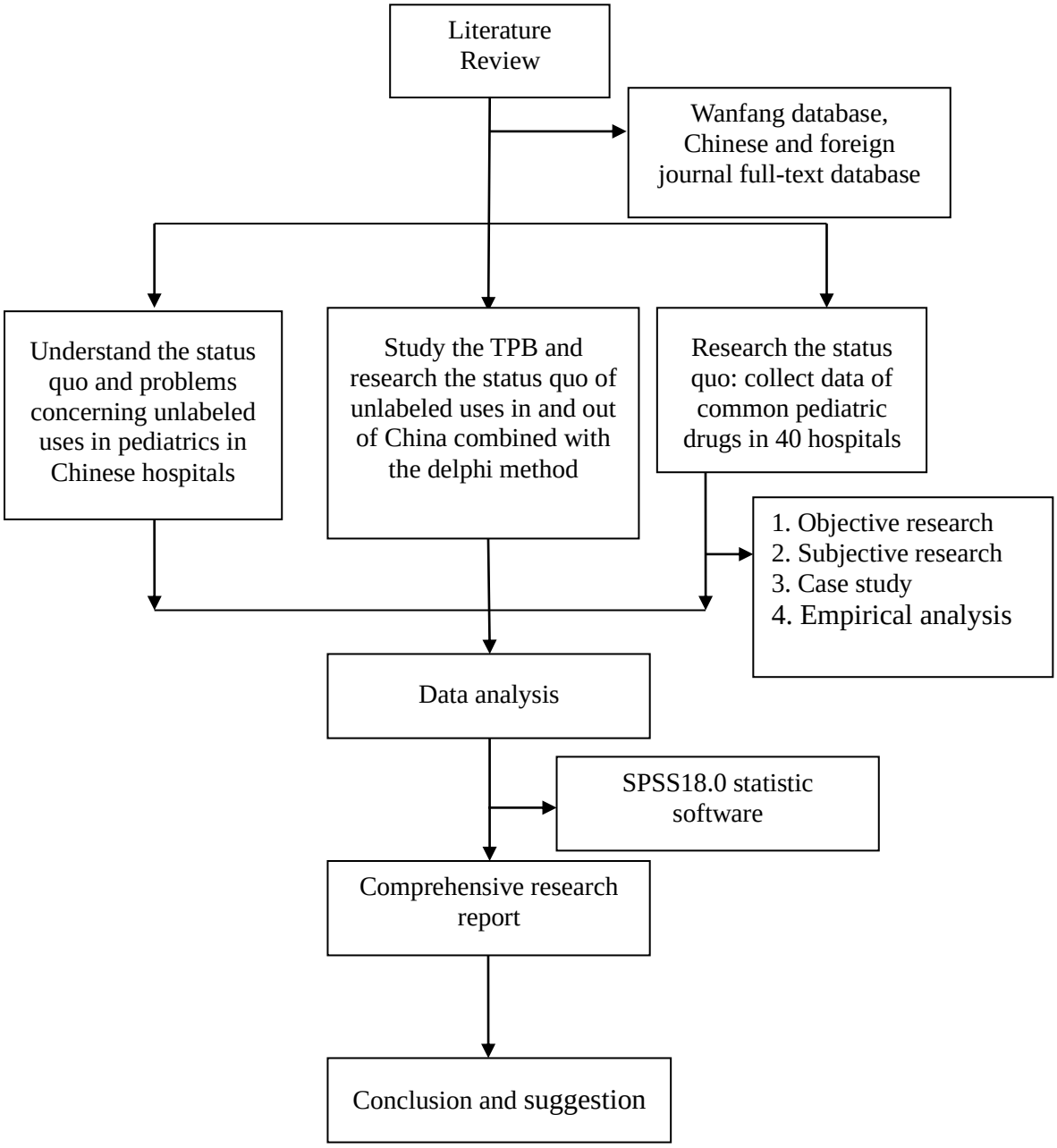

Figure 1-2 Research design

The objective of this study is to evaluate current practice and awareness of pediatrician towards pediatric off-label drug use, as well as the confusion faced among pediatrician in China. Adopt the method of survey and questionnaire.

If, as suggested by the TPB, the measurement of the expected impact is the measurement of attitude, then it can be said that research on expected impact actually evaluates two kinds of attitude: a general attitude towards the implementation of a given behavior and an emotional attitude towards not implementing the behavior. Due to the intrinsic uncertainty of not doing something, the attention given to action and inaction may be sufficient to explain the residual prediction of expected emotions, regardless of whether the alternative attitude is emotional in nature or not (Richetin, Conner, & Perugini, 2011).

A review of the literature showed a unique characteristic of most researches involving the role of expected effect. Although the basic variables in the TPB are evaluated according to a behavior of interest, expected emotional responses are usually measured about not fulfilling the behavior (Fishbein & Ajzen, 2010).

3.1 Research design

According to the TPB model, this study will focus on behavioral attitudes, subjective norms, perceived behavioral control, and behavioral intentions of pediatricians. According to this model there are four aspects of Chinese pediatricians' behavior off-label drug use.

The behavior and attitude of pediatricians is theoretically mainly influenced by two factors: consciousness of drug dependence and expectation of therapeutic effect.

The subjective norms of pediatricians are mainly influenced by three aspects: the influence of doctors, medical patients, and the influence of doctors' compliance motivation consciousness.

The control of perception and behavior of pediatricians is mainly affected by three aspects: national policies, hospital management standards, and doctors' awareness of the rational use of drugs. These factors are expected to affect the behavioral intention of pediatricians, so as to affect the behavior of pediatricians in the use of drugs beyond the instructions

Based on the above factors, in this study, a physician prescription behavior model based on the Theory of Planned Behavior was constructed. The model can more clearly

explain the five effects of behavior attitude, subjective norms and control beliefs on Chinese pediatricians' off labeled use of drug of instruction.

These four factors are theoretically independent concepts, so we do not discuss the relationship between concepts. The relationship between them can finally be reflected through the comprehensive action on behavioral intention. Therefore, it is not elaborated in the model (see Figure 3-1).

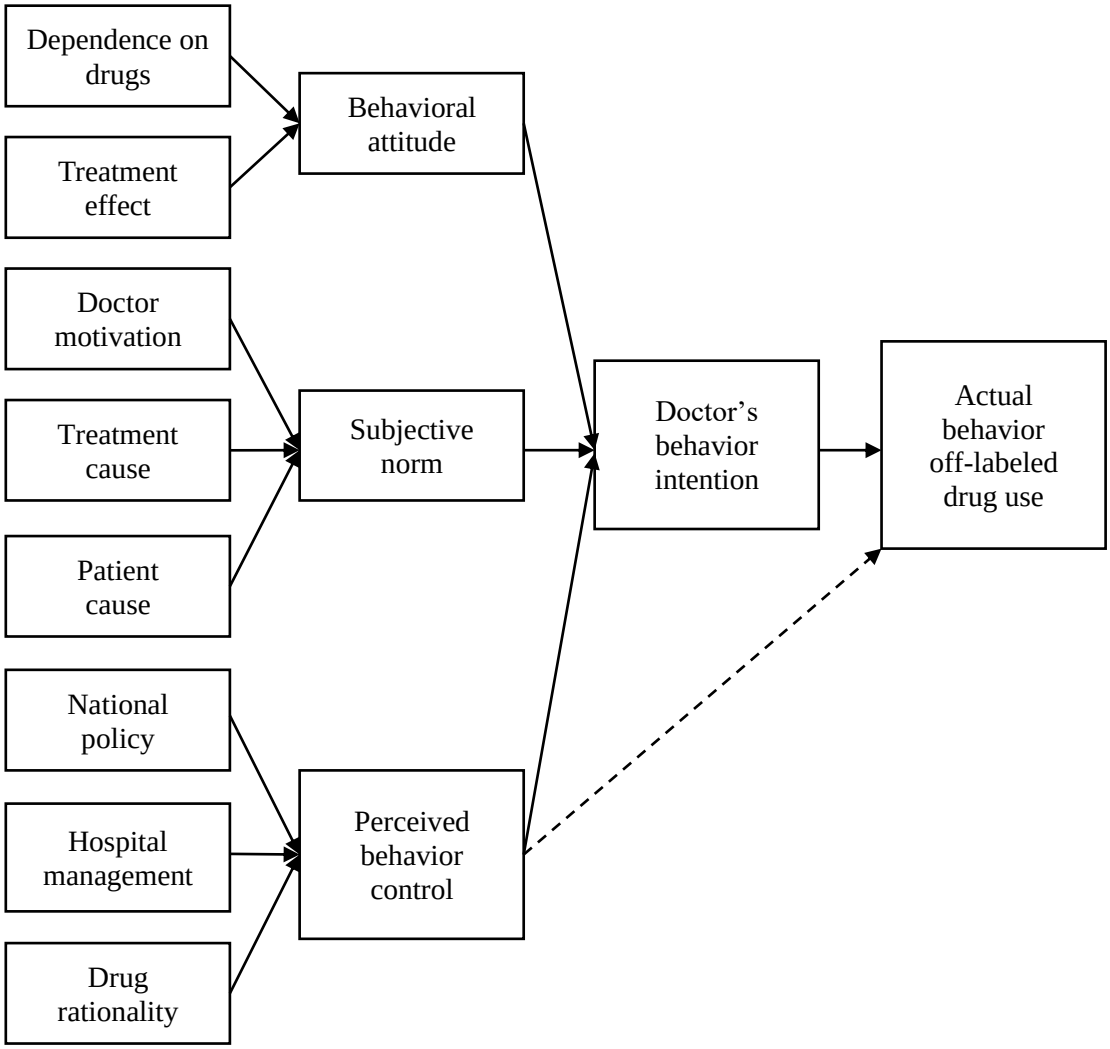

Figure 3-1 The model of TPB in behavior off labeled use of drug of doctors

3.1.1 Research on the status quo

Based on the data provided by the Beijing prescription research group, the most frequently used 300 drugs were selected as the research objects and the drug use information for children in the insert package instructions was analyzed and summarized.

3.1.2 Questionnaire

The clinical pediatrics research group under the Chinese Pediatric Society, Chinese Medical Association, carried out a questionnaire survey concerning “unlabeled uses” among pediatricians in 40 hospitals located in Beijing City, Shanghai City, Hunan Province, Heilongjiang Province, Yunnan Province, Shanxi Province, and Zhejiang Province.

The questionnaire was designed according to the structure of the theoretical model of TPB. The survey focused on four aspects, namely, basic information, professional knowledge, legal consciousness and management rules of the pediatricians.

3.2 Research on the status quo: pediatric drug information of package inserts commonly used in pediatrics

Off-label drug use was inevitable in the process of clinical practice and has been the focus of attention as a result of special physiological and psychological characteristics of children. In order to understand pediatric drug information of package insert commonly used in pediatrics, the research has adopted pediatric drug data of more than 40 hospitals of Chinese large-sized and medium-sized cities provided by the Beijing prescription analysis research group and has chosen the most frequently used top 300 drugs as investigated objects to analyze and summarize pediatric drug information of package insert.

3.2.1 Data and methods

3.2.1.1 Data sources

Beijing prescription analysis research group has provided more than 1.4 million pediatric prescriptions from different pediatrics units (such as department of pediatrics, department of pediatric oncology, pediatric emergency department, NICU, and PICU) of more than 40 hospitals in Beijing, Tianjin, Shanghai, Guangzhou, Hangzhou and Chengdu in 2016 and 2017.

3.2.1.2 Investigation methods

Based on generic names provided by the analysis research group, drugs were sorted by frequencies. The top 300 drugs with frequencies over 0.1% were selected to analyze the package insert commonly used in pediatrics. By using prescription automatic screening system of Medicom Software Co., Ltd, package inserts of generic names were queried; by

EXCEL software, drug names, doses, and pediatric drug use information in the package insert were recorded; and by drug classification of the Clinical Drug Use Instruction (2010 edition**)**, drug classification statistics as well as descriptive statistics based on pediatric drug information has been completed.

3.2.2 Results

3.2.2.1 Basic information of commonly used pediatric drugs

There were 300 types of commonly-used pediatric drugs involved in 18 classifications, including anti-infection drugs, respiratory drugs, and drugs for enteral and parenteral nutrition, water regulation, electrolyte and acid-base balance. Respiratory drugs were 86, 37, 37, and 36 and were in top three. See Table 3-1.

Table 3-1 Classification of 300 types of commonly-used pediatric drugs

S/N	Drugs classification	No. of categories
1	Drugs for infectious diseases	86
2	Drugs for respiratory diseases	37
3	Drugs for parenteral and enteral nutrition, water regulation, electrolyte and acid-base balance	37
4	Drugs for digestive system	36
5	Drugs for nervous system	16
6	Drugs for immune system	14
7	Antipyretic and analgesic drugs	14
8	Drugs for blood system	13
9	Drugs for cardiovascular system	11
10	Anesthesia drugs and anesthesia adjuvant drugs	7
11	Tumor drugs	6
12	Chinese patent drug	5
13	Drugs for endocrine and hereditary metabolic diseases	5
14	Drugs for urinary system	4
15	Drugs for skin diseases	3
16	Immune preparation and vaccines	3
17	Ophthalmic drugs	2
18	Stomatological drugs	1
	Total	300

3.2.2.2 Abbreviation

NICU	Neonatal intensive care unit
PICU	Pediatric intensive care unit
SFDA	State Food and Drug Administration
FDA	Food and Drug Administration
RCT	Randomized Controlled Trial
Im	Intramuscular
Ivgtt	Intravenous glucose tolerance test
SmPC	Summary product characteristics
EPDs	Extemporaneously prepared drugs
ADRs	Adverse drug reactions
PIP	Pediatric Investigational Plan
PUMA	Pediatric use marketing authorization
EMA	European Medicines Agency
BA	Behavior Attitude
SN	Subjective Norms
PBC	Perceptual behavior control
BI	Behavioral intention
DBI	Doctor's Behavioral intention
TBODU	The behavior off-label drug use

3.2.2.3 Description of pediatric information of commonly-used pediatric drugs

Pediatric drugs information of package inserts was roughly divided into three classes: without pediatric drug information, incomplete pediatric drug information, and with pediatric drug information. Without pediatric drug information mainly described as: drug use safety of children was unclear and never tested before; and there was no reference and children drug use information project. Incomplete pediatric drug information described as: it was forbidden in children and there were precautions or warnings for children drug use. With pediatric drug information described as: children drug use, dose and administration route were fully or partially applicable to different ages of children. See appendix 2 Table 2, Table 3, Table 4 and Table 5.

3.2.2.4 Description on applicable ages of pediatric drugs

Text description of applicable people in the package insert showed lack of uniform

standards. They were named as "children", "infant", "baby" and “young children". The children age groups in the package insert were more complicated and confused, specifically described as "under 3 months", "15-30 days", "9-30 months", "3-5 years old", "3-8 years old", "5-10 years old", and "adult dose applicable to children over 7 years".

3.2.2.5 Description on drug use information of different ages of children in commonly-used pediatric drugs

In this research, the top 3 commonly used pediatric drugs were anti-infection drugs, respiratory drugs, and drugs for digestive system (drugs for parenteral and enteral nutrition, electrolyte and acid-base balance were mostly vitamins and nutritional medicines and excluded from this research). According to the research results, children drug use information at different ages was different and categories of drugs were gradually increased with increasing of age. There was less drug use information about newborn babies. See Table 3-2.

Table 3-2 Drug use information of different ages of children in package insert commonly used in pediatrics

Drug use information of package insert	Anti-infection drug	Categories of drugs respiratory drugs	Drugs for digestive system
Newborn	10	4	4
Baby within 2 months	18	5	6
Baby within 6 months	23	6	6
Baby within 1year	27	9	6
Children within 3 years old	28	16	10
Children from 3 to 6 years old	30	16	10
Children from 6 to 12 years old	31	16	11
Children older than 12	67	20	13
Dose conversion of children’s body weight	67	4	2
Calculation by children’s ages	2	16	9
Dose conversion of body surface area	1	1	0
No age division	1	2	7
Calculation by ages + calculation by babies’ body weight	2	3	5

3.2.3 Discussion

3.2.3.1 Selected samples

Drugs from more than 700 prescriptions and with use frequency above 0.1% were selected for this research. For commonly used 300 types of pediatric drugs, 194 (64.67%) had pediatric drug information. There was no clear pediatric drug use information of 63 (21.00%) package inserts. Commonly used pediatric drugs included pediatric forbidden drugs, such as ofloxacin.

3.2.3.2 Drugs involved

For drugs involved in this research, anti-infection drugs came in first and had 86 categories. Respiratory drugs tied with drugs for enteral and parenteral nutrition, water, electrolyte and acid-base balance for the second place. Drugs for digestive system ranked fourth. Drugs for nervous system as well as drugs for immune system and antipyretic and analgesic drugs ranked fifth and sixth, respectively.

Thus, distribution of commonly used pediatric drugs was similar to, but different, from research of other scholars. Zhang, Li, and Huang (2011) conducted a statistical analysis of medical orders involving pediatric drug use and found that the top 4 off-label drug uses were drugs for digestive and metabolic system (82.28%), anti-infection drugs for system (75.06%), drugs for blood and hematopoietic system (79.27%), and drugs for respiratory system (58.27%).

3.2.3.3 Sample information

Fourteen types of antipyretic and analgesic drugs had pediatric drug use information and have covered different ages of children in whole or in part. This showed that pediatric drug use information of antipyretic and analgesic drugs in this research, comparatively speaking, was the most comprehensive one.

For commonly used pediatric drug use information, anti-infection drugs, drugs for enteral and parenteral nutrition, respiratory drugs, and drugs for digestive system were top-ranked and had pediatric drug use information with numbers of categories and proportions as follows: 69 (80.23%), 26 (70.27%), 23 (63.89%), and 21 (56.76%), respectively. Therefore, anti-infection drugs had the largest number of drugs with pediatric drug use information. It was different from analysis investigation result of off-label prescription by some scholars (Xue, 2008; Zhang, 2011).

In my review, this investigation belonged to objective investigation of package inserts of commonly used pediatric drugs, but investigation of off-label prescription had much to do with doctors' subjective behaviors. Package inserts has given pediatric drug use, dose, and administration route. If drugs were not used by pediatricians as required, the fact of off-label drug use appeared.

3.3 Questionnaire

The research settled the degree to which interviewees fare on intentions, subjective norms, and attitudes in respect of off-label use behaviors. This was accomplished by building a questionnaire that contained contents reflecting the main constructs and shown in a random sequence, applying paper and computer-administered methods. A cautious stance in approaching this issue is needed when predicting the intention on the basis of attitudes and subjective norms, because the measure emphasizes and overall attitude and beliefs. This view is widely supported, especially by testing study in the field of persuasive communication (McGuire, 1985; Petty & Cacioppo, 1986).

3.3.1 Study design, setting and participants

The content validity of the questionnaire was evaluated by a multidisciplinary group discussion of experts in Pediatric clinical pharmacology group from the Pediatric Society of Pediatrics, part of the Chinese Medical Association, pediatrics, pharmacology and epidemiology. The scales were designed according to the four dimensions of behavior attitude, subjective norm, perceived behavior control and behavior intention in the TPB. Scores were done according to the benefit of distinguishing of off-label drug use. The rating scale ranged from 1 (lowest score) to 5 (highest).

The questionnaire focused primarily on the off-label drug use in children and consisted of four sections. Rating scale to be finalized by supervisor:

The first section focused on participants’ general information (5 items).

The second section focused on the off-label prescribing, Cause, basis and hazard of off-label drug use in the participants’ units (9 items).

The third section focused on the legal awareness of pediatrician regarding off-label drug use (5 items).

The fourth section focused on the awareness of pediatrician regarding off-label drug use and the management of off-label drug use in the participants' units (13 items). The definition of off-label drug use was provided as an integral part of the questionnaire to guide respondents who were not familiar with the terminology (Appendix 3).

3.3.2 Questionnaire sample

The study was aimed at pediatricians, where 350 questionnaires were distributed to 40 hospitals in seven provinces and cities of China. 320 questionnaires were returned total:

a) 80 questionnaires were returned from Beijing city,

b) 40 questionnaires from Shanghai city,

c) 70 questionnaires from Hunan Province,

d) 60 questionnaires from Zhejiang Province,

e) 40 questionnaires from Heilongjiang Province,

f) 10 questionnaires from Shanxi Province,

g) 20 questionnaires from Yunnan Province

(See Figure 3-2 and Figure 3-3).

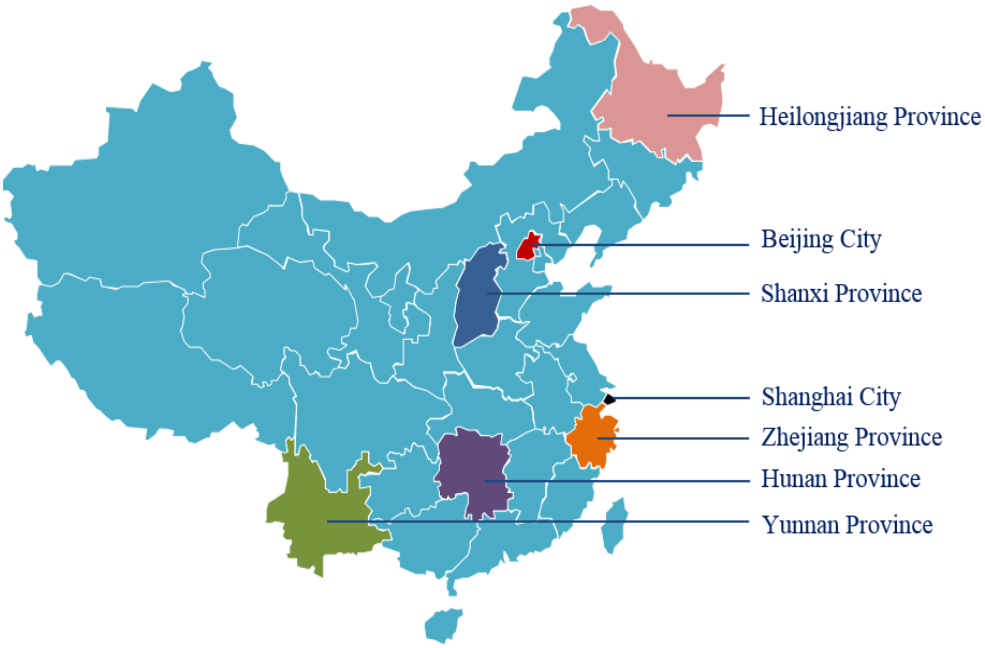

Figure 3-2 Questionnaire subdivision

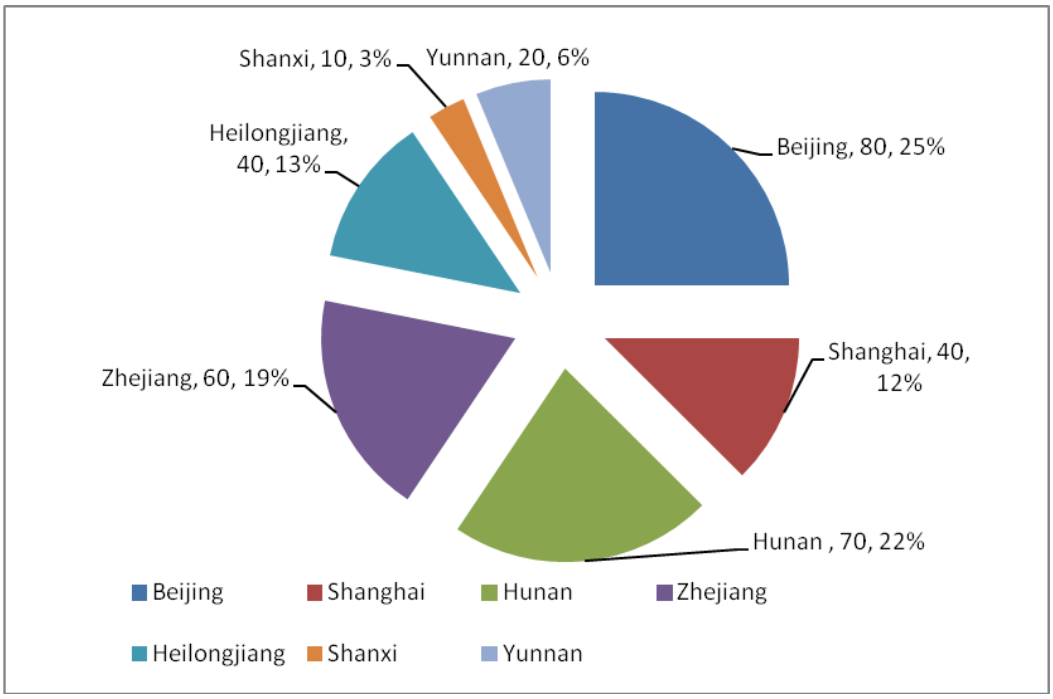

Figure 3-3 Distribution proportion of Chinese pediatric on off-label drug use questionnaire

3.3.3 Results

3.3.3.1 Demographics

By the end of December 2019, 320 questionnaires were returned from the 40 hospitals in China. The response rate was 92% (320/350). Two questionnaires were excluded because of poor quality (with missing data or contradictory answers); thus, 318 questionnaires were included in the final analysis. A total of 320 pediatricians, replied. Among these, 127 (39.93%) had junior titles, 93 (29.25%) had intermediate titles and 98 (30.82%) had senior titles.

Demographics of the study participants

(1) Childrens' hospital, Junior title,52; Intermediate title, 33; Senior title 44

(2) Pediatrics in the general hospital: hospital, Junior title,60; Intermediate title, 55; Senior title 47;

(3) Other hospital: hospital, Junior title,15; Intermediate title, 5; Senior title 7;

A fine example in viewpoint is reported by the research of Manning and Bettencourt (2011). The researchers used TPB as their framework to check compliance with medical protocols. Different from studies who deal with the behavioral categories of sleep-related activities by evaluating the TPB structure related to each behavior, other scholars have

summarized several program compliance behaviors (Kor & Mullan, 2011).

Including 129 specialized children's hospitals, 162 general hospitals (100 tertiary hospitals ang 62 secondary hospitals), and 27 other hospitals, participated in the questionnaire (see Figure 3-3). The doctors who took part in the questionnaire were from departments of pediatrics, departments of pediatric internal medicine, departments of neonatology, departments of pediatric respiration, departments of pediatric neurology, departments of pediatric digestion, departments of pediatric surgery, departments of pediatric nephrology and rheumatism, department of pediatric cardiology, other. It can represent the conscious behavior of the team of doctors (see Figure 3-4).

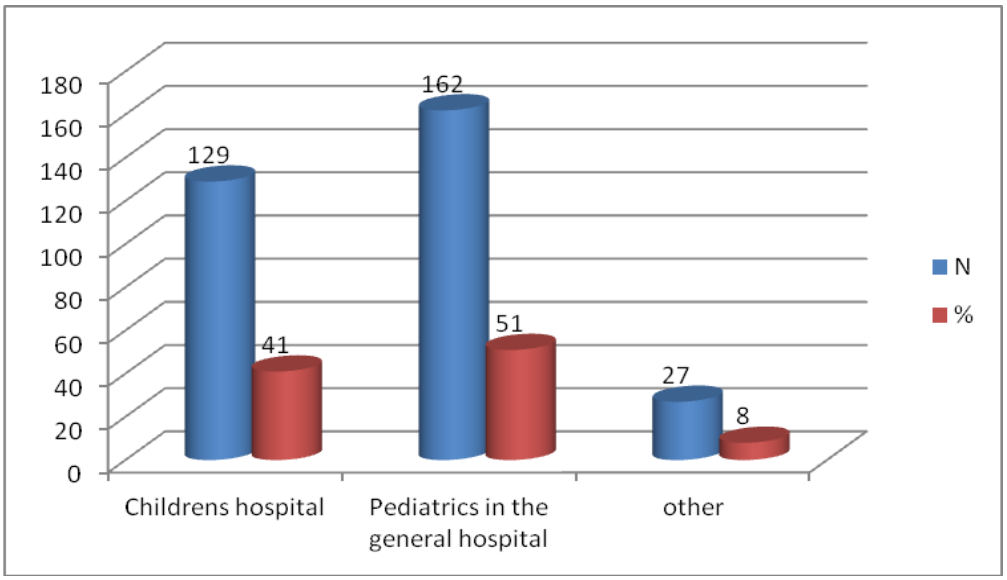

Figure 3-4 Hospital level

Specialty and department of pediatrics: The top three are departments of pediatrics (87.27%), departments of pediatric internal medicine (66.21%) and departments of pediatric respiration (39.12%). The fourth to the tenth are departments of pediatric digestion (35.11%), departments of pediatric neurology (19.6%), departments of neonatology (18.6%), other (17.5%), departments of pediatric nephrology and rheumatism (13.4%), departments of pediatric surgery (12.4%), departments of pediatric cardiology (12.4%), see Figure 3-5.

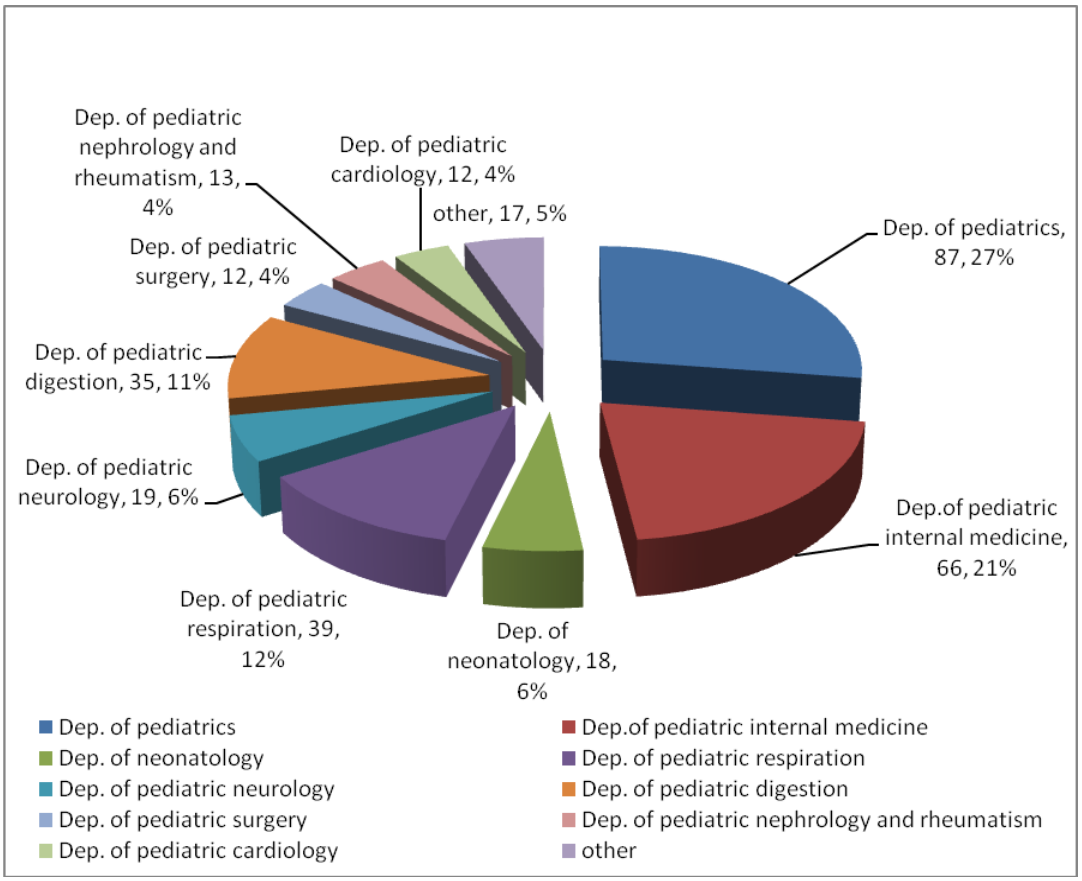

Figure 3-5 Proportion of departments of pediatricians

3.3.3.2 Current practice and management of pediatric off-label drug use in China

Professional dimension survey: Reasons for off-label drug use. Perceived behavioral dominate may not be special actual when people have comparatively less news about the action, when demands or procurable resources have altered, or when unacquainted factors have entered into the condition. Under these circumstances, a survey of perceived behavioral control may reduce to correctness of behavioral forecast. Nevertheless, to the situation that perceived control is practical, it may be used to forecast the possibility of a fruitful action try (Ajzen, 1985).

According to the questionnaire, doctors think that the reason for the disease types of patients of off-label drug use is, very rare diseases 117 questionnaires (37%), uncommon diseases 88 questionnaires (28%), common diseases but posing life in danger 69 questionnaires (22%), very uncommon diseases 37 questionnaires (11%), common diseases, and non-life-threatening seven questionnaires (2%). See Figure 3-6.

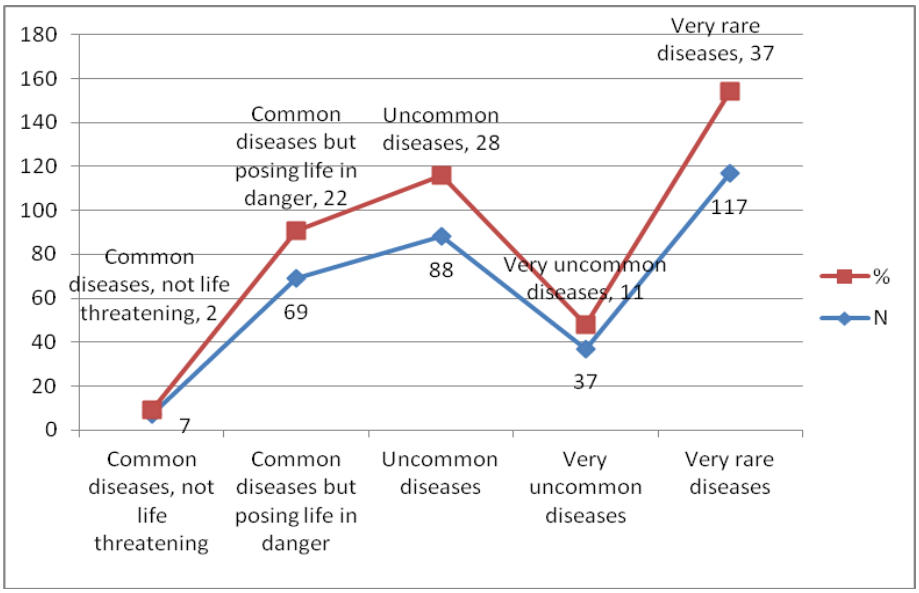

Figure 3-6 Disease types of patients of off-label drug use

As regards management dimension analysis, adverse drug reactions due to the off-label drug use, over-indications population is the highest 43%, over-medication 40%, over-drug delivery pathway 35%, overdose administration 14%, over contraindications 1%, (see appendix 2 Table 6).

As regards informed consent by the guardian, 32% of investigated objects have obtained informed consent of guardian while issuing off-label prescriptions while 21% of respondents did not inform patients, 30% of respondents sometimes inform patients, 13% of the respondents did asked for informed consent in most cases, and 4% of the respondents gave neutral inform to the patients (see Figure 3-7).

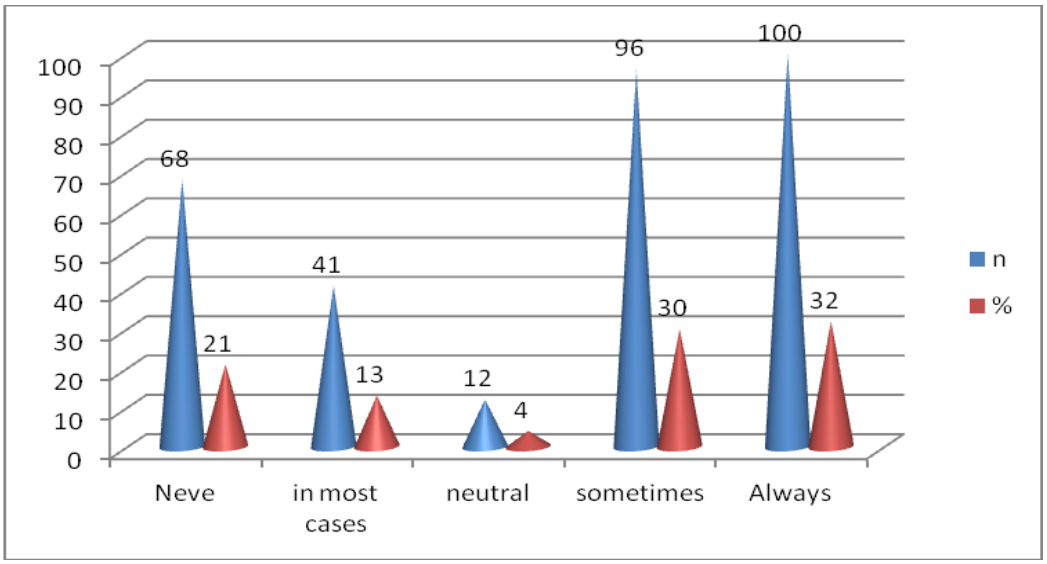

Figure 3-7 The off-label drug use be subjected to informed consent by the guardian

As regards the legal dimension investigation, the off-label drug use is legal or illegal, for 318 questionnaires, 89% of physicians believed that issuance of off-label prescription was illegal, while 28% of physicians believed that off-label drug use is legal (see appendix 1 Figure 1).

3.4 Data analysis strategy

3.4.1 Statistical analysis

Epidata 3.1 is employed for data entry. A database was established, containing drug names, dosage form, and pediatric drug use information in the package inserts, organized according to the drug classification in Drug Clinical Application Guidelines (version 2010). SPSS18.0 statistical software package was used to analyze the data. The drugs are categorized and the pediatric drug use information is statistically analyzed in a descriptive way. χ^2 is adopted, where the test standard is $\alpha = 0.05$, $p < 0.05$, to determine statistical significance.

Likewise, exploratory and confirmatory factor analyses are used as well as structural equations modelling with AMOS software to test the measurement quality of the constructs and model as well as hypotheses.

3.4.2 Age division of children

Description of children age groups in the package inserts were very confused and lack of unified division. In China, children ages were divided correspondingly: neonatal period, 0 to 28 days; babyhood, 28 days to 1 year old; infant period, 1 to 3 years old; preschool age, 3 to 6, 7 years old; school age, 6, 7 to 12, 13 years old; and adolescence, from 12, 13 to 17, 18 years old (Chinese National Formulary, 2013).

3.4.3 Dose conversion for children

With regard to conversion problems of children drug doses, children doses of anti-infection drugs were calculated mainly on weights; children doses of respiratory drugs were converted mainly by ages; and children doses of drugs for digestive system were calculated mainly by ages or without age division.

According to the Notice on Strengthening Management of Maternal and Children

Clinical Drug Use from Ministry of Health (China Ministry of Health General Office, 2011), the following must be tightly controlled to avoid or reduce adverse reactions and drug-induced damages: children drug selection, administration route, dose calculation, adverse drug reactions, and contraindication.

3.4.4 Standardize management and control

5 types of drugs for endocrine system only had children warning information. For 5 types of Chinese patent drugs, 1 type had children drug use and dose; 1 type was required for dosage reduction or as professionally prescribed; and the remaining 3 types had no children drug use information. Pediatric information in package insert of tumor drugs was incomplete. The author believed that these drugs would lead to serious pediatric off-label drug use problems. Hence, each relevant department should standardize off-label drug use aiming to subpopulation required for pediatric drugs and different pediatric diseases.

3.5 Measures

3.5.1 The variable assignment

According to the theory of planned behavior, gain access to actions, standards and control beliefs can provide understand basis for manner, subjective norms as well as perceived control. We discovered earlier that Emotional conditions can affect behaviors, norms, as well as control beliefs. If different beliefs are activated in the investigation and behavior situations, they appear different attitudes, subjective standards or a sense of control, different intentions eventually come into being. For different intentions are active in the behavioral environment, therefore, the intention of evaluation in the investigation stage is relatively poor in predicting the actual behavior (Ajzen & Sexton, 1999).

According to theory of planned behavior, there are four dimensions, i.e. behavioral attitude, subjective norm, behavioral intention and perceived behavioral control. Off-labeled use of drug behavior is measured by Likert scale. The lowest score is 1, and the highest score is 5.

Participants' emotional state can be considered as part of the measurement situation. If participant experience an emotional state when assessing their intentions, and it goes through another emotional state when it's executing. Finally, the intention behavior

relationship may be destroyed.

Perceived behavioral dominate may not be special actual when people have comparatively less news about the action, when demands or procurable resources have altered, or when unacquainted factors have entered into the condition. Under these circumstances, a survey of perceived behavioral control may reduce to correctness of behavioral forecast. Nevertheless, to the situation that perceived control is practical, it may be used to forecast the possibility of a fruitful action try (Ajzen, 1985).

3.5.2 Each dimensions of theory of planned behavior

3.5.2.1 Behavior attitude of pediatricians

Behavior attitude of pediatricians depends on the awareness of drug dependence and the expectation of treatment results. For example, which factors a doctor needs to consider when prescribing off-label drug use, and how to determine such responsibility, even when the patient gave the informed consent, we should see the off-label drug use from special perspective: three questions to reflect, see Table 3-3.

Table 3-3 Measurement of behavior and attitude of pediatricians

Item	Score	Num.	%
a doctor needs to consider when prescribing off-label drug use: Cost of drugs for patients (blank :1) 9c			
not important at all	1	0	0
somewhat unimportant	2	1	0.31
neither important nor unimportant	3	38	11.99
somewhat important	4	211	66.56
very important	5	67	21.14
a doctor needs to consider when prescribing off-label drug use: Cost of drugs for the health system（blank :4）9d			
not important at all	1	0	0
somewhat unimportant	2	0	0
neither important nor unimportant	3	14	4.46
somewhat	4	260	82.8

important			
very important	5	40	12.74
When the patient gave the informed consent, if the patient himself has a taboo on drug use, the drug should not be used. If there is a problem, the doctor must be held responsible (blank :3) 17c			
strongly disagree	1	18	5.71
moderately disagree	2	25	7.93
neither agree not disagree/neutral	3	1	0.32
moderately agree	4	146	46.35
strongly agree	5	125	39.69
We should see the off-label drug use from special perspective: General and high-risk drugs (blank :4) 29a			
strongly disagree	1	29	9.24
moderately disagree	2	0	0
neither agree not disagree/neutral	3	0	0
moderately agree	4	65	20.7
strongly agree	5	220	70.06
We should see the off-label drug use from special perspective: Foreign pharmacopoeia, clearly documented in the treatment guidelines, and our country did not make any changes or updates. 29b			
strongly disagree	1	21	6.61
moderately disagree	2	1	0.31
neither agree not disagree/neutral	3	0	0
moderately agree	4	108	33.96
strongly agree	5	188	59.12
We should see the off-label drug use from special perspective: Treatment of common diseases with rare, refractory diseases (blank :3) 29c			
strongly disagree	1	24	7.62
moderately disagree	2	5	1.59
neither agree not disagree/neutral	3	12	3.81
moderately agree	4	101	32.06
strongly agree	5	173	54.92

3.5.2.2 Subjective norms of pediatricians

Subjective norms of pediatricians are influenced by the doctors' subjective

consciousness and the patients' influence and depends on the doctors' cognition about management dimension. Reflecting in the increasingly serious situation of the off-label drug use, as a doctor, one is asked to express his / her agreement with sentences such as: We should increase our own self-discipline, avoidance of drug abuse; Must have sufficient clinical experience in the use of the off-label drug use, avoid the randomness of medication; The use of high-risk drugs should be reported to the superior and put on record; Raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug. See Table 3-4.

Raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug, ① 275 questionnaires strongly agree ,

②39 questionnaires moderately agree,

③0 questionnaires neither agree not disagree/neutral.

④ 4 Moderately disagree

We should increase our own self-discipline, avoidance of drug abuse,

① 263 questionnaires strongly agree,

② 51 questionnaires moderately agree,

③ 0 questionnaires neither agree not disagree/neutral.

④ 4 Moderately disagree

The use of high-risk drugs should be reported to the superior and put on record,

① 259 questionnaires strongly agree,

② 55 questionnaires moderately agree,

③ 0 questionnaires neither agree not disagree/neutral.

④ 4 Moderately disagree

Must have sufficient clinical experience in the use of the off-label drug use, avoid the randomness of medication,

① 251 questionnaires strongly agree,

② 63 questionnaires moderately agree,

③ 0 questionnaires neither agree not disagree/neutral.

④ 4 Moderately disagree

Table 3-4 Measurement of subjective standard of pediatricians

Item	Score	Num.	%
Raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug 34b			
Strongly disagree	1	0	0
moderately disagree	2	4	1.26
neither agree not disagree/neutral	3	0	0
moderately agree	4	39	12.26
Strongly agree	5	275	86.48
We should increase our own self-discipline, avoidance of drug abuse 34a			
Strongly disagree	1	0	0
moderately disagree	2	4	1.26
neither agree not disagree/neutral	3	0	0
moderately agree	4	51	16.04
Strongly agree	5	263	82.7
The use of high-risk drugs should be reported to the superior and put on record34f			
Strongly disagree	1	0	0
moderately disagree	2	4	1.26
neither agree not disagree/neutral	3	0	0
moderately agree	4	55	17.29
Strongly agree	5	259	81.45
Must have sufficient clinical experience in the use of the off-label drug use, avoid the randomness of medication34c			
Strongly disagree	1	0	0
moderately disagree	2	4	1.26
neither agree not disagree/neutral	3	0	0
moderately agree	4	63	19.81
Strongly agree	5	251	78.93

3.5.2.3 Behavior intention of pediatricians

It depends on pediatrician's cognition of professional dimension and legal dimension. The cognition of professional dimension is embodied in which basis do you think lead to prescribing off-label drug use, such as: has been incorporated into the standard of diagnosis and treatment in China, has been incorporated into foreign diagnostic and treatment norms, although not regulated, it is supported by expert advice or evidence from clinical trials. The cognition of legal dimension is embodied in which of the following reasons do you think justify prescribing without asking for informed consen, because nobody is concerned with it at the organizational level, and so on these reasons to reflect. See Table 3-5.

Table 3-5 Measurement of behavioral intention of pediatricians

Item	Score	Num.	%
Which basis do you think lead to prescribing off-label drug use: Has been incorporated into the standard of diagnosis and treatment in China (blank :2) 8b			
Strongly disagree	1	52	16.46
moderately disagree	2	26	8.23
neither agree not disagree/neutral	3	0	0
moderately agree	4	84	26.58
Strongly agree	5	154	48.73
Which basis do you think lead to prescribing off-label drug use: Has been incorporated into foreign diagnostic and treatment norms (blank :1) 8c			
Strongly disagree	1	50	15.77
moderately disagree	2	70	22.08
neither agree not disagree/neutral	3	31	9.78
moderately agree	4	122	38.49
Strongly agree	5	44	13.88
Which basis do you think lead to prescribing off-label drug use: Although not regulated, it is supported by expert advice or evidence from clinical trials (blank :2) 8d			
Strongly disagree	1	52	16.45
moderately disagree	2	35	11.08

neither agree not disagree/neutral	3	0	0
moderately agree	4	175	55.38
Strongly agree	5	54	17.09
Which of the following reasons do you think justify prescribing without asking for for informed consent: Because nobody is concerned with it at the organizational level (blank :7) 19c			
Strongly disagree	1	178	57.24
moderately disagree	2	60	19.29
neither agree not disagree/neutral	3	11	3.54
moderately agree	4	61	19.61
Strongly agree	5	1	0.32

3.5.2.4 Perceived behavior control off-label drug use

The cognitive level reflected in the professional dimension of doctors. Through doctors what motives do you think make doctors prescribe off-label drug use for patient, such as: the limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children; Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time, and so on these factors to reflect, see Table 3-6.

Off-label - Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time, blank 1, 153 questionnaires moderately agree.

Motive Off-label - The limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children, blank 6, 142 questionnaires moderately agree.

Motive Off-label - Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time, blank 5, 141 questionnaires moderately agree.

Table 3-6 Measurement of perceived behavior control of pediatricians

Item	Score	Num.	%
Motive Off-label - Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time. (blank :1) 6f			
Strongly disagree,	1	40	12.62
moderately disagree	2	13	4.1
neither agree not disagree/neutral	3	10	3.15
moderately agree	4	153	48.27
Strongly agree	5	101	31.86
Motive Off-label - The limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children (blank :6) 6g			
Strongly disagree,	1	33	10.58
moderately disagree	2	39	12.5
neither agree not disagree/neutral	3	17	5.45
moderately agree	4	142	45.51
Strongly agree	5	81	25.96
Motive Off-label - Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time (blank :5) 6h			
Strongly disagree,	1	38	12.14
moderately disagree	2	11	3.51
neither agree not disagree/neutral	3	10	3.2
moderately agree	4	141	45.05
Strongly agree	5	113	36.1

3.5.2.5 The behavior off-label drug use of pediatricians

The above factors result in the behavior off-label drug use of Chinese pediatricians and the frequency of over prescribing. It can be measured by risk of adverse drug reactions, increase in medical disputes, disputes over increasing drug cost. See Table 3-7.

Table 3-7 Measurement of the behavior of off-label drug use of pediatricians

Item	Score	Num.	%
What hazards to happen in off-label drug use prescribing - Risk of adverse drug reactions (blank 3) 14a			
very improbable	1	8	2.54
moderately improbable	2	1	0.32
50/50 probability	3	14	4.44
moderately probable	4	72	22.86
very probable	5	220	69.84
What hazards to happen in off-label drug use prescribing - Increase in medical disputes (blank 2) 14b			
very improbable	1	8	2.53
moderately improbable	2	0	0
50/50 probability	3	30	9.49
moderately probable	4	64	20.26
very probable	5	214	67.72
What hazards to happen in off-label drug use prescribing - Disputes over increasing the cost of drugs (blank 2) 14c			
very improbable	1	8	2.53
moderately improbable	2	2	0.63
50/50 probability	3	56	17.73
moderately probable	4	90	28.48
very probable	5	160	50.63

In case of adverse events and medical disputes, whether or not need hospital and professional society to provide management and technical assistance, Whether pharmacists are needed to play a role in promoting rational use of drugs, whether or not need industry organization support analysis, whether it is necessary for the hospital and the competent department of health to issue the corresponding regulations for the use of drugs beyond the instructions.

Off-label drug use is not strictly verified. It may have significant efficacy, but the side effect is not clear for the moment. Off-label drug use is expected to draw on advantages and avoid disadvantages with expected effect.

Off-label drug use is a double-edged sword. It can bring benefits for patients when used properly and cause a loss to patients and medical personnel when used improperly. For better off-label drug use, the government shall be open. Medical personnel shall be strict and patients shall be tolerant.

Clinical medicine develops in exploration, which necessarily leads to continuous new findings and experience in drug use. Because present package inserts are updated slowly and represents only general academic status, they cannot reach leading academic level. Thus off-label drug use is inevitable, which facilitates the development of clinical pharmacotherapeutics to some extent.

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Chapter 4: Results

Since no measure has been put forward to comprehensively work out the issue of unlabeled uses and it is held in the medical circle that unlabeled uses are reasonable to some extent, explorations are sure to be made concerning this issue.

According to the TPB model, this study focused on behavioral attitudes, subjective norms, perceived behavioral control, and behavioral intentions of pediatricians. Four aspects of Chinese pediatricians' Off-label drug use behavior: The behavior and attitude of pediatricians are mainly influenced by two factors: Consciousness intensity of drug dependence and expectation of therapeutic effect. The subjective norms of pediatricians are mainly influenced by three aspects: the influence of doctors, medical patients and the influence of doctors' compliance motivation consciousness.

The perceived behavioral control of pediatricians is mainly affected by three aspects: National policies, hospital management standards, and doctors' awareness of the rational use of drugs. These factors as expected to affect the behavioral intention of pediatricians, so as to lead to actual off-label behavior of pediatricians. Based on the above factors, in this study, a physician prescription behavior model based on the TPB was constructed.

The model can more clearly explain five effects of behavioral attitude, subjective norms, and control beliefs on Chinese pediatricians' about off-labeled use of drug. These four factors are conceptually distinct constructs, so we do not discuss the relationship between concepts. The relationship between them can finally be reflected through the comprehensive action upon behavioral intention.

4.1 Professional dimension

4.1.1 Frequency to issue off-label prescription

Of which, frequency of 164 doctors (318, 51.57%) to issue off-label prescription is less than one time every month; and only 20 doctors (318, 6.29%) often issued prescriptions, almost every day. Frequencies of doctors from different hospitals to issue off-label prescriptions were statistically different (χ^2=6.358, p=0.042). The junior the

technical titles, the greater the chance to issue off-label prescriptions, the higher the frequency (χ^2=143.157, p=0.000). See Table 4-1 the question about frequencies was unfilled in for 2 questionnaires of physicians with primary titles, so it was not included in the statistics.

Table 4-1 Comparisons on frequencies of doctors with different titles to issue off-label prescriptions [cases (%)]

Titles	N.	Issue off-label prescriptions or not		N	Frequencies to issue off-label prescriptions			
		Yes	No		Daily	Weekly	Monthly	Barely
Junior	127	58(45.67)	69(54.33)	58	8(13.79)	13(22.41)	35(60.34)	2(3.45)
Intermediate	93	55(59.14)	38(40.86)	55	6(10.91)	14(25.45)	35(63.64)	0(0.0)
Senior	98	51(52.04)	47(47.96)	51	8(15.69)	14(27.45)	26(50.98)	3(5.88)
χ^2	6.358	0.314			143.157			
df	2	1			3			
p	0.042	0.575			0			

Table 4-1 shows the chi square test statistics, which is to test whether the number of observations of each option is a random distribution of 1:1:1. As for the variable of "professional title", it means that X^2 is equal to 6.358, and the p value of asymptotic significance is equal to 0.042 and less than 0.05, reaching the significant level, rejecting the null hypothesis, indicating that there are significant differences in the number of times that three levels (junior, intermediate and senior titles) are selected by samples.

In terms of the variable "whether to prescribe the over instruction", X^2 is equal to 0.314, p value of asymptotically significant is equal to 0.575 and greater than 0.05, fail to attain the significant level of 0.05, accept the null hypothesis and reject the opposite hypothesis rejects the opposite hypothesis, which means that the two levels (yes, no) are not significantly different in the number of times selected by the sample. In terms of "frequency of prescribing over instructions", it means that it is equal to 143.157, and the p value of asymptotically significant is equal to 0.000 and less than 0.001, reaching the significant level, rejecting the null hypothesis, indicating that the four levels (daily, weekly,

monthly, almost none) are significantly different in the number of times selected by samples.

4.1.2 Reason to issue off-label prescriptions

180 (318, 56.60%) for "disease needs", 254 (318, 79.87%) for "package inserts not revised and updated in time", 226 (318, 71.69%) for "limitations of pharmaceutical preparations", 172 (318, 54.01%) for "defects and deficiencies of package inserts", 121 (318, 38.01%) for "insufficient self-knowledge of doctors", and 7(318, 2.20%) for "promotional materials of drug companies".

The reasons of doctors with different titles to issue off-label drugs were statistically different in terms of "insufficient self-knowledge of doctors", "limitations of pharmaceutical preparations" and "package insert not updated in time". See Table 7. The question about reasons was unfilled in for 6 of 318 questionnaires, so it was not included in the statistics.

4.1.3 Factors and basis considered to issue off-label prescriptions

Factors considered by physician to issue prescriptions: 286 (318, 89.94%) for "drug efficacy", 258 (318, 81.13%) for "adverse drug reactions", and 278 (318, 87.42%) for " Cost of drugs for patients ". 300 (318, 94.332%) for Cost of drugs for the health system. Basis to issue prescriptions: 238 (318, 74.84%) for "excluded from specification, but supported by expert opinions or clinical trial ", 229 (318, 72.01%) for "included in domestic clinical rules of diagnosis and treatment", and only 40 (318, 12.57%) for "treatment based on personal experiences". The question about basis was unfilled in 2 of 318 questionnaires, so it was not included in the statistics.

4.1.4 Applicable conditions to issue off-label prescriptions and types of drugs

There were statistically significant differences for doctors with different titles as regards issuing off-label prescriptions in terms of "overdose", "super counter-indications", "beyond drug user groups", and "new uses for old drugs". The aforesaid question was unfilled in for 6 of 318 questionnaires, so it was not included in the statistics. See Table 4-2. Also, there were statistically significant differences for doctors from different hospitals in issuing off-label prescriptions in terms of "super contraindications", "beyond administration route", and "new uses for old drugs". The question was also unfilled in for 6

of 318 questionnaires, so it was not included in the statistics (see appendix 2 Table 8). The top 3 drugs in the off-label prescriptions were antimicrobial drugs, respiratory drugs, and antipyretic and analgesic drugs.

Table 4-2 Applicable conditions of drugs in off-label prescription issued by doctors with different titles [cases (%)]

Titles	N.	Over dose		Beyond drug user groups		Over indications		New uses for old drugs	
		Yes	No	Yes	No	Yes	No	Yes	No
Junior	117	35(29.91)	82(70.09)	80(68.38)	37(31.62)	79(67.52)	38(32.48)	43(36.75)	74(63.25)
Interm-ediate	86	40(46.51)	46(53.49)	45(52.32)	41(47.68)	45(52.33)	41(47.67)	40(46.51)	43.496(5)
Senior	85	35(41.18)	50(58.82)	56(65.89)	41(34.11)	57(67.01)	28(32.89)	40(47.01)	45(52.89)
χ^2	6.358	194.728		67.418		48.321		17.937	
df	2	4		4		4		4	
p	0.042	0.000		0.000		0.000		0.000	

4.1.5 Types of patients' diseases and groups prohibited for off-label drug use

For questionnaires with types of patients' diseases for pediatric off-label drug uses, "common diseases" were predominant in general hospitals while in children's hospitals "refractory diseases" were predominant (see appendix 2: Table 9). For questionnaires with prohibited pediatric off-label drug user groups, newborns were predominant in general hospitals while adolescent predominate in children's hospitals (see appendix 2: Table 10).

4.1.6 Adverse reactions and harm caused by off-label prescription

For 318 valid questionnaires, general hospitals paid more attention to adverse drug reactions, compared to children's hospitals. Adverse drug reactions caused by off-label drug use of physicians accounted for 13.21%. The majority of physicians (60.16%) considered the adverse drug reactions belonged to adverse drug events. Specifically: "beyond drug user groups" accounted for 48.17%; "super indications" for 39.75%; "overdose" for 41.74%; "beyond administration route" for 25.39%; and "super contraindications" for 20.05%. With respect to the harm of off-label drug use in 318 valid questionnaires, "increase medical disputes" accounted for 91.13%; "raise risk of adverse drug reactions" for 88.94%; and "increase disputes of drug expenses" for 45.75%. However, doctors with elementary titles paid the most attention to payment disputes.

4.2 Legal dimension

4.2.1 Informed consent

318 of investigated objects have obtained informed consent from the guardian while issuing off-label prescriptions. For questionnaires of “why was off-label drug use occurred without informed consent of guardian”, "fear of parents' misunderstanding" accounted for 42%; "everybody was doing it" for 23%; and "afraid of trouble" for 29%.

Doctors with elementary titles had the highest ratio due to "fear of parents' misunderstanding" 44% of physicians supported that adverse events occurred should be adverse reactions marked on the drugs and doctors shall not bear the responsibilities. For the questionnaire, 40% of physicians supported that if patients had contraindication of such drugs and shouldn't use the drugs, doctors must take responsibilities in case of any problems. Of which, doctors from general hospitals had a relatively high ratio. To which extent should the off-label drug use be subjected to informed consent by the guardian? 32% of guardians must consent always,21% of guardian should not condition this decision(never), 13% of in most cases (guardian should not condition this decision), sometimes they tell the guardian is 30%, neutral (50/50) is 4%.

4.2.2 Legality

For 318 questionnaires, 27.98% of physicians believed that issuance of off-label

prescription was illegal (see appendix 1 Figure 1) while 76.73% of physicians believed that off-label drug use was inevitable to some extent. 36.48% of physicians believed that off-label drug use was beneficial to the development and improvement of medicine.

4.3 Management dimension

4.3.1 Off-label drug use related systems

Hospitals with 23.58% of investigated physicians had unified regulation. 65.09% of physicians expressed that it was necessary for hospitals and health departments to issue corresponding provisions. 64.47% of physicians reflected that their hospitals had no corresponding files, records and summaries. In view of off-label drug use, 77.35% of hospitals had issued relevant guidelines, 22.64% of hospitals had enacted the ban; and 0 of hospitals has tacitly consented.

4.3.2 Role of pharmacists

85.22% of pharmacists expressed that it was badly in need of prescription intervention of pharmacists in the view of off-label drug use. As for responsibilities of pharmacists, " pharmacists should file, record, and summarize off-label drug use on a regular basis and gave feedback to clinical doctors" accounted for 74.20% "pharmacists should collect and sort domestic and foreign off-label drug uses and summarize appropriately" for 71.97% "pharmacists should review descriptions and carry out appropriate intervention" for 57.64%; and "prescriptions should be signed by doctors and patients and be issued by pharmacists" for 55.97%.

4.3.3 Doctors' responsibilities

79.24% of doctors said it should be forbidden to issue off-label prescription in violation of guidelines and clinical application guidelines.

As for off-label description of "Which drugs should be treated differently?", "clearly recorded in the foreign pharmacopoeia and treatment guidelines, but not revised or updated in China" accounted for 59.12%; "for the treatment of common diseases and rare and refractory diseases" for 54.92%; and "generic drugs and high-risk drugs" for 70.06%.

Doctors considering " avoid off-label drug use as much as possible for the disease

situation of children" accounted for 65.41%; doctors considering "correspondingly file, record, and summarize medical history on a regular basis" for 77.36%; and doctors considering "with informed consent of patients guardian" for 70.66%.

4.3.4 Support of industry organizations

"Hope to receive technical support from associations" accounted for 78.93%; "hope to receive policy support from associations" for 81.13%; and "hope to receive legal and compensation support from associations in case of disputes" for 58.49%. As for a great deal of off-label drug use problems, doctors considering the competent administrative department should establish off-label drug use guidelines as soon as possible accounted for 94.33%; doctors considering the competent administrative department should formulate management regulations for off-label drug use accounted for 94.03%; and doctors considering the medical insurance department should give full play to its supervisory functions accounted for 81.44%.

In the face of increasingly serious situation of off-label drug use, as a doctor, 86.48% of them expressed "raise the level of professional knowledge and understand pharmacology, drug efficacy and side effects"; 78.93% of them considered "had to have enough off-label clinical experiences to avoid drug arbitrariness"; 82.70% of them said "avoided drug abuse through strengthening their self-disciplines"; 78.30% of them expressed "doctors should self-protection awareness and signed informed consent form for off-label drug use"; 86.16% of them considered "had responsibility to assess the benefit risk ratio to ensure drug safety"; and 81.45% of them considered" high risk drugs should be reported to the superiors and filed"

4.4 Empirical analysis

In this section, both exploratory and confirmatory factor analyses are shown followed by measurement and structural model testing with structural equations modelling (SEM). Findings will be reported to test the conceptual model.

According to the TPB, there are four predictive dimensions, i.e. behavioral attitude, subjective norm, behavioral intention and perceived behavioral control. Off-labeled use of drug behavior is measured by a 5-point Likert scale. The lowest score is 1, and the highest score is 5.

The behavioral attitude of pediatricians depends on the awareness of drug dependence and the expectation of treatment results. Namely, a doctor needs to consider if he or she should prescribe off-label, how to determine such responsibility, even when the patient gave the informed consent.

Another dimension, as stated, is the subjective norms of pediatricians. Subjective norms of pediatricians are a product of doctors' subjective consciousness and patients' influence. It depends on the doctors' social cognition reflected when facing an increasingly serious situation due to the off-label drug use, as a doctor, how much one agrees with some assertions concerning normative beliefs.

Assertions can be represented with some examples such as: “we should increase our own self-discipline, avoidance of drug abuse”; “we must have sufficient clinical experience in the use of the off-label drug use, to avoid the randomness of medication”; “the use of high-risk drugs should be reported to the superior and put on record”; “raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug”, among others.

Another dimension pertains to the behavioral intention of pediatricians and depends on pediatrician's cognition about the professional and legal dimensions. The cognitions about the professional dimension are embodied in the basis one thinks that lead to prescribing off-label drug, such as: “has been incorporated into the standard of diagnosis and treatment in China”, “has been incorporated into foreign diagnostic and treatment norms”, “although not regulated, it is supported by expert advice or evidence from clinical trials”.

The cognitions about the legal dimension are embodied in the basis one thinks the following reasons justify prescribing without asking for informed consent, e.g. “because nobody is concerned with it at the organizational level”.

Lastly, the perceived behavior control about off-label drug use depends on the cognitive level reflected in the professional dimension of doctors. It concerns one’s own belief about motives that make one assume control due to many reasons such as: “the limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children”; “some old drugs have new indications”, “indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time”.

The ultimate dependent variable in the model, “actual behavior about off-label drug use by pediatricians”, translates their frequency of off-label prescribing. It can be measured by the risk of adverse drug reactions, the increase of medical disputes, the disputes over increasing drug costs.

A remedy for the low forecast effectiveness of manners as well as peculiarities is the modulation of particular behaviors across environments, circumstances as well as behaviors (Fishbein & Ajzen, 1974; Epstein, 1983).

On the whole, the TPB allows very exact forecasting of purposes as well as behaviour, usually coming close to the theoretical restriction (Conner & Armitage, 1998).

4.4.1 Exploratory factor analysis

In order to test the validity of the scale, factor analysis is needed for the whole scale. The purpose of factor analysis is to find out the potential structure of the scale. Table 12 in Appendix 2 reports the result of KMO test of the scale. When KMO is closer to 1, it means that the more common factors among variables, the lower the net correlation among variables, and the more suitable for factor analysis. Here KMO in this case is 0.768, greater than 0.7, indicating that it is middling. In addition, Bartlett's sphere test = 5971.134, df = 190 ($p < 0.05$) reached a significant level of 0.05, suggesting correlation matrix is an identity matrix.

KMO and Bartlett's test of the scale

The upper half of Table 4-3 and Table 4-4 shows anti-image covariance matrix and the second half is anti-image correlation matrix. The diagonal value of the anti-image correlation matrix represents the measure of sampling adequacy (MSA) of each variable. The right side of MSA will be marked with "a". Similar to the KMO value, the closer MSA is to 1, the more the item is suitable for factor analysis. As shown in Table 4-3 and Table 4-4, common factors existed and needed further to extracting.

Table 4-3 analyze by the following questions:

1) 6f: Motive Off-label - Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time.

2) 6g: The limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children

3).6h, some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time

4) 8b, has been incorporated into the standard of diagnosis and treatment in China.

5) 8c, has been incorporated into foreign diagnostic and treatment norms.

6) 8d, although not regulated, it is supported by expert advice or evidence from clinical trials.

7) 9c, Factors to prescribe - Cost of drugs for patients.

8) 9d, Factors to prescribe –Cost of drugs for the health system.

9) 14a, risk of adverse drug reactions.

10) 14b, increase in medical disputes.

11) 14c, Disputes over increasing the cost of drugs.

12) 17c: If the patient himself has a taboo on drug use, the drug should not be used. If there is a problem, the doctor must be held responsible.

13) 19c, because nobody is concerned with it at the organizational level

14) 29a: General and high-risk drugs

15) 29b, foreign pharmacopoeia, clearly documented in the treatment guidelines, and our country did not make any changes or updates.

16) 29c: Treatment of common diseases with rare, refractory diseases.

17) 34a, we should increase our own self-discipline, avoidance of drug abuse.

18) 34b: Raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug.

19) 34c: Must have sufficient clinical experience in the use of the off-label drug use, avoid the randomness of medication.

20) 34f, the use of high-risk drugs should be reported to the superior and put on record.

Table 4-3 Reflection image matrix 1

		6f	6g	6h	8b	8c	8d	9c	9d	14a	14b
Reflection image covariate	6f	.114	-.005	-.084	-.003	.010	.004	.031	-.016	.022	-.008
	6g	-.005	.333	-.042	.072	-.032	-.081	-.013	-.032	-.002	.002
	6h	-.084	-.042	.090	-.021	.018	-.006	-.028	.052	-.023	.000
	8b	-.003	.072	-.021	.164	-.080	-.062	.064	-.029	-.024	.022
	8c	.010	-.032	.018	-.080	.170	-.067	.021	-.014	-.053	.001
	8d	.004	-.081	-.006	-.062	-.067	.191	-.081	.061	.058	-.027
	9c	.031	-.013	-.028	.064	.021	-.081	.288	-.183	-.034	.018
	9d	-.016	-.032	.052	-.029	-.014	.061	-.183	.396	-.010	.007
	14a	.022	-.002	-.023	-.024	-.053	.058	-.034	-.010	.188	-.111
	14b	-.008	.002	.000	.022	.001	-.027	.018	.007	-.111	.197
	14c	-.018	.046	.025	.007	.027	-.007	.009	-.020	-.045	-.098
	17c	.006	.033	-.004	-.049	-.029	.027	-.070	-.003	.059	-.072
	19c	-.015	-.108	.028	-.094	-.033	.033	.001	.055	.036	.010
	29a	.005	-.056	-.005	-.004	.033	-.013	.013	.003	-.017	.001
	29b	-.006	.029	-.001	.057	-.043	.002	.032	-.033	.015	.050
	29c	-.017	.020	.004	-.023	-.026	.013	-.069	.013	.002	-.001
	34a	-.006	-.002	.014	-.005	.002	-.008	-.015	.032	-.044	.019
	34b	-.004	.022	.004	.010	.011	-.018	.025	.001	.011	-.035
	34c	-.015	-.027	-.003	-.006	-.012	.007	.025	-.089	.026	.034
	34f	.023	-.012	-.004	-.015	.028	.005	-.048	.060	-.002	.010
Reflection correlation	6f	.767[a]	-.026	-.825	-.024	.068	.028	.170	-.076	.148	-.051
	6g	-.026	.838[a]	-.239	.306	-.133	-.322	-.043	-.089	-.007	.007

6h	-.825	-.239	.754[a]	-.173	.141	-.044	-.173	.276	-.176	.001
8b	-.024	.306	-.173	.774[a]	-.479	-.353	.296	-.115	-.136	.120
8c	.068	-.133	.141	-.479	.800[a]	-.370	.094	-.054	-.298	.007
8d	.028	-.322	-.044	-.353	-.370	.832[a]	-.344	.222	.307	-.137
9c	.170	-.043	-.173	.296	.094	-.344	.686[a]	-.541	-.145	.076
9d	-.076	-.089	.276	-.115	-.054	.222	-.541	.539[a]	-.036	.026
14a	.148	-.007	-.176	-.136	-.298	.307	-.145	-.036	.650[a]	-.577
14b	-.051	.007	.001	.120	.007	-.137	.076	.026	-.577	.640[a]
14c	-.108	.165	.169	.035	.135	-.035	.035	-.066	-.214	-.455
17c	.031	.107	-.024	-.222	-.132	.116	-.243	-.009	.253	-.300
19c	-.059	-.246	.124	-.305	-.104	.100	.002	.115	.108	.029
29a	.041	-.270	-.047	-.031	.227	-.080	.067	.012	-.112	.004
29b	-.036	.103	-.008	.290	-.216	.012	.125	-.109	.073	.234
29c	-.145	.102	.036	-.165	-.181	.084	-.378	.062	.016	-.005
34a	-.042	-.009	.105	-.029	.010	-.041	-.065	.118	-.239	.101
34b	-.034	.097	.037	.065	.067	-.108	.123	.004	.065	-.205
34c	-.092	-.100	-.022	-.030	-.060	.035	.101	-.301	.129	.165
34f	.127	-.039	-.022	-.066	.124	.021	-.166	.175	-.007	.043

Table 4-4 analyze by the following questions:

1) 6f: Motive Off-label - Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time.

2) 6g: The limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children

3) 6h, some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time

4) 8b, has been incorporated into the standard of diagnosis and treatment in China.

5) 8c, has been incorporated into foreign diagnostic and treatment norms.

6) 8d, although not regulated, it is supported by expert advice or evidence from clinical trials.

7) 9c, Factors to prescribe - Cost of drugs for patients.

8) 9d, Factors to prescribe –Cost of drugs for the health system.

9) 14a, Risk of adverse drug reactions.

10) 14b, Increase in medical disputes.

11) 14c, Disputes over increasing the cost of drugs.

12) 17c: If the patient himself has a taboo on drug use, the drug should not be used. If there is a problem, the doctor must be held responsible.

13) 19c, because nobody is concerned with it at the organizational level

14) 29a: General and high-risk drugs

15) 29b, foreign pharmacopoeia, clearly documented in the treatment guidelines, and our country did not make any changes or updates.

16) 29c: Treatment of common diseases with rare, refractory diseases.

17) 34a, we should increase our own self-discipline, avoidance of drug abuse.

18) 34b: Raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug.

19) 34c: Must have sufficient clinical experience in the use of the off-label drug use, avoid the randomness of medication.

20) 34f, the use of high-risk drugs should be reported to the superior and put on record.

Table 4-4 Reflection image matrices 2

		14c	17c	19c	29a	29b	29c	34a	34b	34c	34f
Reflection image covariate	6f	-0.018	0.006	-0.015	0.005	-0.006	-0.017	-0.006	-0.004	-0.015	0.023
	6g	0.046	0.033	-0.108	-0.056	0.029	0.02	-0.002	0.022	-0.027	-0.012
	6h	0.025	-0.004	0.028	-0.005	-0.001	0.004	0.014	0.004	-0.003	-0.004
	8b	0.007	-0.049	-0.094	-0.004	0.057	-0.023	-0.005	0.01	-0.006	-0.015
	8c	0.027	-0.029	-0.033	0.033	-0.043	-0.026	0.002	0.011	-0.012	0.028
	8d	-0.007	0.027	0.033	-0.013	0.002	0.013	-0.008	-0.018	0.007	0.005
	9c	0.009	-0.07	0.001	0.013	0.032	-0.069	-0.015	0.025	0.025	-0.048
	9d	-0.02	-0.003	0.055	0.003	-0.033	0.013	0.032	0.001	-0.089	0.06
	14a	-0.045	0.059	0.036	-0.017	0.015	0.002	-0.044	0.011	0.026	-0.002
	14b	-0.098	-0.072	0.01	0.001	0.05	-0.001	0.019	-0.035	0.034	0.01
	14c	0.234	0.066	-0.087	-0.034	-0.015	-0.005	0.017	0.05	-0.088	-0.017
	17c	0.066	0.292	0.083	-0.055	-0.112	0.044	0.004	-0.019	0.003	-0.005
	19c	-0.087	0.083	0.579	0.016	-0.073	0.011	0.02	-0.02	0.047	-0.049
	29a	-0.034	-0.055	0.016	0.127	-0.037	-0.075	-0.005	-0.01	0.038	-0.003
	29b	-0.015	-0.112	-0.073	-0.037	0.234	-0.047	-0.009	0.023	-0.008	-0.003
	29c	-0.005	0.044	0.011	-0.075	-0.047	0.117	0.012	-0.013	-0.018	0.005
	34a	0.017	0.004	0.02	-0.005	-0.009	0.012	0.183	-0.087	-0.043	-0.048
	34b	0.05	-0.019	-0.02	-0.01	0.023	-0.013	-0.087	0.148	-0.068	-0.053
	34c	-0.088	0.003	0.047	0.038	-0.008	-0.018	-0.043	-0.068	0.219	-0.057
	34f	-0.017	-0.005	-0.049	-0.003	-0.003	0.005	-0.048	-0.053	-0.057	0.294
Reflection correlation	6f	-0.108	0.031	-0.059	0.041	-0.036	-0.145	-0.042	-0.034	-0.092	0.127
	6g	0.165	0.107	-0.246	-0.27	0.103	0.102	-0.009	0.097	-0.1	-0.039
	6h	0.169	-0.024	0.124	-0.047	-0.008	0.036	0.105	0.037	-0.022	-0.022
	8b	0.035	-0.222	-0.305	-0.031	0.29	-0.165	-0.029	0.065	-0.03	-0.066
	8c	0.135	-0.132	-0.104	0.227	-0.216	-0.181	0.01	0.067	-0.06	0.124
	8d	-0.035	0.116	0.1	-0.08	0.012	0.084	-0.041	-0.108	0.035	0.021
	9c	0.035	-0.243	0.002	0.067	0.125	-0.378	-0.065	0.123	0.101	-0.166
	9d	-0.066	-0.009	0.115	0.012	-0.109	0.062	0.118	0.004	-0.301	0.175

14a	-0.214	0.253	0.108	-0.112	0.073	0.016	-0.239	0.065	0.129	-0.007
14b	-0.455	-0.3	0.029	0.004	0.234	-0.005	0.101	-0.205	0.165	0.043
14c	.632[a]	0.254	-0.236	-0.195	-0.063	-0.027	0.084	0.269	-0.387	-0.065
17c	0.254	.761[a]	0.201	-0.286	-0.429	0.24	0.017	-0.094	0.013	-0.016
19c	-0.236	0.201	.668[a]	0.059	-0.199	0.041	0.06	-0.07	0.132	-0.118
29a	-0.195	-0.286	0.059	.834[a]	-0.214	-0.614	-0.035	-0.075	0.225	-0.013
29b	-0.063	-0.429	-0.199	-0.214	.814[a]	-0.283	-0.042	0.122	-0.036	-0.012
29c	-0.027	0.24	0.041	-0.614	-0.283	.835[a]	0.085	-0.097	-0.111	0.03
34a	0.084	0.017	0.06	-0.035	-0.042	0.085	.803[a]	-0.53	-0.213	-0.206
34b	0.269	-0.094	-0.07	-0.075	0.122	-0.097	-0.53	.751[a]	-0.376	-0.252
34c	-0.387	0.013	0.132	0.225	-0.036	-0.111	-0.213	-0.376	.738[a]	-0.226
34f	-0.065	-0.016	-0.118	-0.013	-0.012	0.03	-0.206	-0.252	-0.226	.867[a]

Commonality analysis: Extraction: principal component analysis

Table 4-5 shows the initial commonality of each variable and the commonality after the principal components are extracted by principal component analysis. The estimated value of commonality of all items in the table is higher than 0.20, that is to say, there is commonality between variables.

Table 4-5 Commonality

Item	Initial	extraction	Item	Initial	Item
6f	1	0.866	14c	1	0.807
6g	1	0.638	17c	1	0.671
6h	1	0.92	19c	1	0.54
8b	1	0.849	29a	1	0.842
8c	1	0.865	29b	1	0.732
8d	1	0.782	29c	1	0.856
9c	1	0.725	34a	1	0.874
9d	1	0.711	34b	1	0.898
14a	1	0.859	34c	1	0.796
14b	1	0.847	34f	1	0.801

Extraction: principal component analysis

Table 4-6 analyze by the following questions:

1) 6f: Motive Off-label - Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time.

2) 6g: The limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children.

3) 6h: Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time.

Table 4-6 Total variance explained

Component	Initial eigenvalue			Extraction sums of squared loadings			Rotation sums of squared loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	6.179	30.894	30.894	6.179	30.894	30.894	3.676	18.38	18.38
2	3.439	17.196	48.091	3.439	17.196	48.091	3.391	16.954	35.335
3	2.699	13.496	61.587	2.699	13.496	61.587	3.296	16.481	51.816
4	2.135	10.674	72.26	2.135	10.674	72.26	2.795	13.973	65.788
5	1.427	7.136	79.396	1.427	7.136	79.396	2.722	13.608	79.396
6	0.821	4.106	83.503						
7	0.734	3.668	87.171						
8	0.512	2.561	89.732						
9	0.346	1.729	91.461						
10	0.324	1.621	93.082						
11	0.271	1.357	94.438						
12	0.222	1.111	95.549						
13	0.198	0.989	96.538						
14	0.157	0.785	97.323						
15	0.143	0.713	98.036						
16	0.102	0.512	98.548						
17	0.089	0.447	98.995						
18	0.085	0.423	99.418						
19	0.065	0.324	99.742						
20	0.052	0.258	100						

Extraction: principal component analysis

4) 8b: Has been incorporated into the standard of diagnosis and treatment in China. 8c-Has been incorporated into foreign diagnostic and treatment norms.

5) 8d: Although not regulated, it is supported by expert advice or evidence from clinical trials.

6) 9c: Factors to prescribe - Cost of drugs for patients. 7) 9d-Factors to prescribe - Cost of drugs for the health system.

8) 14a: Risk of adverse drug reactions.

9) 14b- Increase in medical disputes

Table 4-6 shows the results of principal components extracted by principal component analysis, and the method of rotation is varimax with orthogonal rotations. In the table, there are 5 factors whose eigenvalue is greater than 1, suggesting that there are 5 common factors extracted from factor analysis. Together, 5 common factors accounted for 79.369% of the variation.

Table 4-7 represents rotated component matrix by varimax with Kaiser Normalization. Rotation converged in 7 iterations. The cut-off value for factor loading is 0.45. if it is better than 0.45, the factor could explain 20% variance. Factor one is named "behavior attitude", factor two is named "subjective norm", factor three is named "perceived behavior control", factor four is named "doctor's behavior control", factor five is named "doctor's medication behavior beyond instruction".

Axis converges to 5 iterations.

Analyze by the following questions:

(1) 9c, Factors to prescribe - Cost of drugs for patients.

29b, foreign pharmacopoeia, clearly documented in the treatment guidelines, and our country did not make any changes or updates;

29c, Treatment of common diseases with rare, refractory diseases.

17c, if the patient himself has a taboo on drug use, the drug should not be used. If there is a problem, the doctor must be held responsible.

29a, General and high-risk drugs. 9d, Factors to prescribe –Cost of drugs for the health system

(2) 34b, Raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug.

34a, we should increase our own self-discipline, avoidance of drug abuse. 34f, the use of high-risk drugs should be reported to the superior and put on record.

34c, Must have sufficient clinical experience in the use of the off-label drug use, avoid the randomness of medication.

Table 4-7 Composition matrices after rotating shaft

Item	element				
	Behavior attitude	Subjective norms	Perceived behavior control	Behavioral intention	The behavior off-label drug use of pediatricians
9c	0.837	0.046	0.079	-0.043	0.121
29b	0.774	-0.044	0.19	0.225	-0.21
29c	0.733	0.062	0.427	0.308	0.194
17c	0.716	0.074	0.161	0.247	-0.258
29a	0.713	-0.001	0.49	0.216	0.217
9d	0.61	0.033	-0.528	-0.189	0.154
34b	0.024	0.943	0.048	0.037	-0.063
34a	0.005	0.934	-0.014	0.048	-0.005
34f	0.004	0.894	-0.046	-0.005	-0.014
34c	0.07	0.887	-0.054	-0.037	0.006
6h	0.167	-0.073	0.928	0.157	0.024
6f	0.145	-0.018	0.91	0.123	0.034
6g	0.298	-0.006	0.7	0.237	-0.059
8c	0.362	-0.023	0.11	0.846	0.076
8b	0.201	0.065	0.31	0.838	0.076
19c	-0.106	-0.041	0.061	0.718	0.091
8d	0.345	0.124	0.454	0.661	-0.072
14b	-0.012	-0.031	0.086	0.075	0.912
14a	0.042	-0.02	0.038	0.162	0.911
14c	0	-0.019	-0.114	-0.038	0.89

Extraction: principal component analysis.

Rotation axis method: varimax method with Kaiser normalization

(3) 6h, some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time.

6f: Motive Off-label - Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time.

6g: The limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children.

(4) 8c: has been incorporated into foreign diagnostic and treatment norms.

8b: has been incorporated into the standard of diagnosis and treatment in China.

19c: because nobody is concerned with it at the organizational level.

8d: although not regulated, it is supported by expert advice or evidence from clinical trials

(5) 14b: Increase in medical disputes; 14a, Risk of adverse drug reactions; 14c, Disputes over increasing the cost of drugs

Figure 4-1 shows scree test result. It can be seen from the figure that after the sixth factor, the slope line is relatively flat, indicating that there is no special factor worth extracting, so it is more appropriate to retain the first five factors.

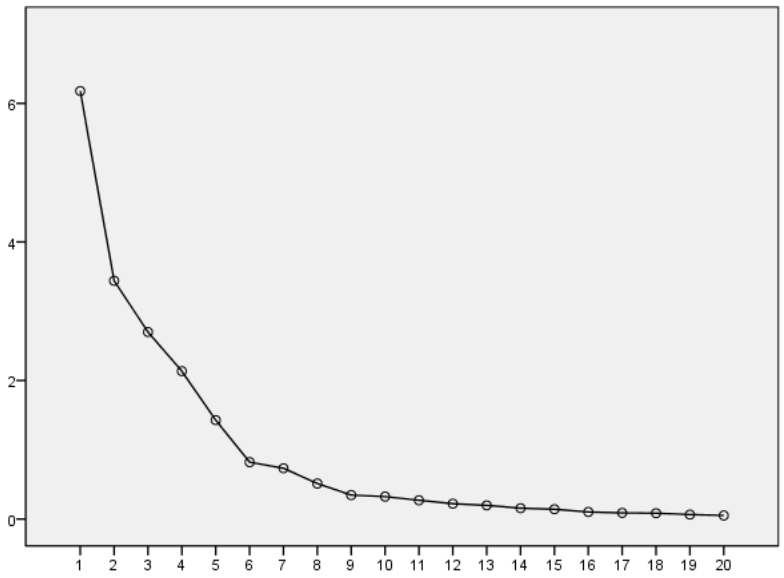

Figure 4-1 Factor gradient

4.4.2 Reliability analysis

Reliability refers to the consistency of scale. The greater the reliability of a scale, the smaller the error of its measurement. SPSS was used to analyze the reliability of "behavior attitude", "subjective norm", "perceived behavior control", "doctor behavior control" and "doctor's medication behavior beyond instructions". The analysis results are shown in Table 4-8. According to behavior and social sciences, the reliability of variable should be at least above 0.6. If it is lower than 0.5, it means that the reliability of variable is not good. From Table 4-8, it is found that the Cronbach's alpha values of each variable are all above 0.8, indicating that the internal consistency of the variables is very good.

Table 4-8 Reliability

Variable	Cronbach's alpha	Cronbach's alpha based on standardization items	Number of items
Behavior attitude	0.889	0.894	5
Subjective norm	0.935	0.936	4
Perceived behavior control	0.897	0.897	3
Doctor behavior control	0.858	0.852	4
Doctor's behavior off-label drug use	0.897	0.900	3

4.4.3 Confirmatory factor analysis

Confirmatory factor analysis is mainly used to explain and observe the correlation or covariance between variables, in order to test the construct validity of the scale. Amos 22 was used for confirmatory factor analysis, and the output is shown in Figure 4-2.

The model includes 20 estimated parameters (see Table 4-9). Except for five fixed indicators, the other estimated parameters are significant at the level of 0.001. Moreover, there is no negative variance in the load estimation of the nonstandard factor, and the standard error of each estimation parameter is small, so the model is acceptable.

Analyze by the following questions:

(1) Behavior attitude:

29c, Treatment of common diseases with rare, refractory diseases

29b, foreign pharmacopoeia, clearly documented in the treatment guidelines, and our country did not make any changes or updates

29a, General and high-risk drugs

17c, If the patient himself has a taboo on drug use, the drug should not be used. If there is a problem, the doctor must be held responsible

9c, Factors to prescribe - Cost of drugs for patients

(2) Subjective norm:

34f: The use of high-risk drugs should be reported to the superior and put on record

34c: Must have sufficient clinical experience in the use of the off-label drug use, avoid the randomness of medication

34b: Raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug

34a: We should increase our own self-discipline, avoidance of drug abuse

(3) Perceived behavior:

6h, some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time

6g: The limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children

6f: Motive Off-label - Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time.

(4) Behavior of off-label drug use

14a: Risk of adverse drug reactions. 14b, Increase in medical disputes. 14c, Disputes over increasing the cost of drugs

(5) Behavioral intention:

19c, because nobody is concerned with it at the organizational level

8d, although not regulated, it is supported by expert advice or evidence from clinical trials

8c, has been incorporated into foreign diagnostic and treatment norms

8b, has been incorporated into the standard of diagnosis and treatment in China

9d: Factors to prescribe –Cost of drugs for the health system

Figure 4-2 abbreviation:

BA: Behavior Attitude;

SN: Subjective Norms;

PBC**:** Perceived behavior control;

DBI**:** Doctor's Behavioral intention;

TBODU: The behavior off-label drug use

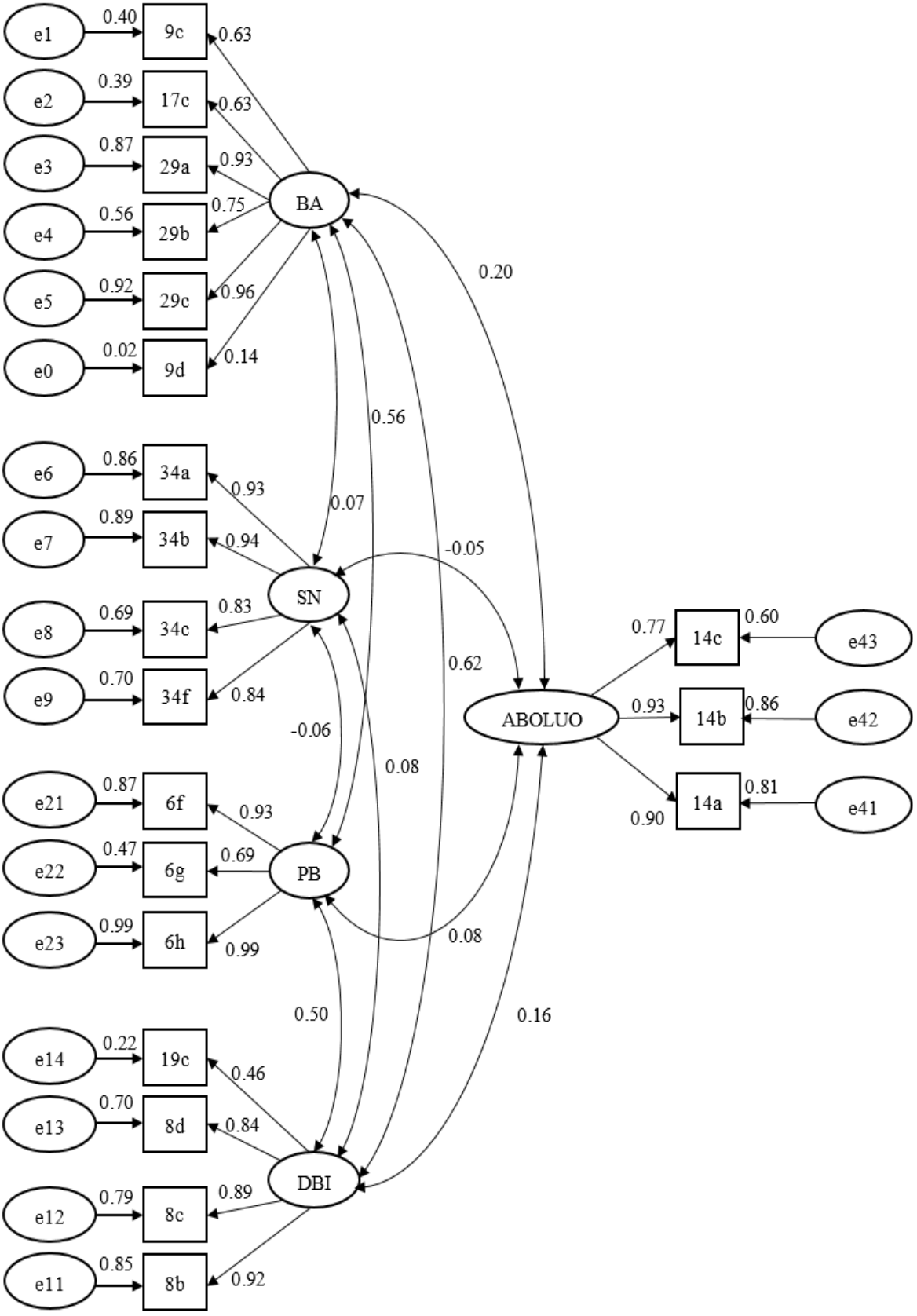

Figure 4-2 Variable confirmatory factor analysis

Table 4-9 Confirmatory factor analysis

		Path	Non-standard estimates	S. E.	t	P	Standardized estimates
29c	<---	Behavior attitude	2.94	0.215	13.65	***	0.958
29b	<---	Behavior attitude	2.091	0.182	11.464	***	0.748
29a	<---	Behavior attitude	2.94	0.219	13.448	***	0.931
17c	<---	Behavior attitude	1.885	0.19	9.934	***	0.626
9c	<---	Behavior attitude	1				0.632
34f	<---	Subjective norm	0.921	0.041	22.224	***	0.839
34c	<---	Subjective norm	0.94	0.043	21.855	***	0.833
34b	<---	Subjective norm	0.966	0.032	30.047	***	0.944
34a	<---	Subjective norm	1				0.925
6h	<---	Perceived behavior	1.056	0.031	34.186	***	0.993
6g	<---	Perceived behavior	0.734	0.047	15.706	***	0.687
6f	<---	Perceived behavior	1				0.933
14a	<---	behavior of off-label drug use	1				0.9
14b	<---	behavior of off-label drug use	1.1	0.05	22.18	***	0.93
14c	<---	behavior of off-label drug use	0.994	0.057	17.383	***	0.773
19c	<---	Behavioral intention	1				0.464
8d	<---	Behavioral intention	2.056	0.243	8.474	***	0.836
8c	<---	Behavioral intention	2.173	0.252	8.637	***	0.888
8b	<---	Behavioral intention	2.552	0.292	8.724	***	0.924
9d	<---	Behavioral intention	0.156	0.064	2.453	*	0.142

4.4.4 Structural equation model analysis of TPB model

Figure 4-3 shows the results of standardized estimate of SEM analysis of pediatrician's medication behavior beyond the instruction. Table 13 is the summary of model fit, indicating that the overall model is acceptable. Table 14 shows the path analysis results. Empirical study found that the path of "behavioral attitude > behavioral intention" is significant, the path of "perceived behavior > behavioral intention" is significant, and the path of "behavioral intention > drug use beyond instruction" is significant. However, the paths of "subjective norm > behavioral intention" and "perceived behavior > drug use beyond instruction" have not been verified.

Fiest : Model Fit Summary: Index

1) NFI 0.is 942, >0.9

2)RFI is 0.903, >0.9

3) IFI is 0.962, >0.9

4) TLI is 0.925, >0.9

5) CFI is 0.961, >0.9

Second: Structural equation path analysis results:

(1) Estimate:

1) Behavior attitude --> Behavioral intention is 0.707

2) Subjective norm --> Behavioral intention is 0.081

3) Perceived behavior control --> Behavioral intention is 0.113

4) Behavioral intention --> behavior off-label drug use is 0.226

5) Perc. behavior control --> behavior off-label drug use is 0

(2) S.E.

1) Behavior attitude --> Behavioral intention is 0.119

2) Subjective norm --> Behavioral intention is 0.058

3) Perceived behavior control --> Behavioral intention is 0.025

4) Behavioral intention --> behavior off-label drug use is 0.093

5) Perc. behavior control --> behavior off-label drug use is 0.037

(3) t

1) Behavior attitude --> Behavioral intention is 5.938

2) Subjective norm --> Behavioral intention is 1.395

3) Perceived behavior control --> Behavioral intention is 4.469

4) Behavioral intention --> behavior off-label drug use is 2.421

5) Perc. behavior control --> behavior off-label drug use is -0.001

(4) *P*

1) Behavior attitude --> Behavioral intention is ***

2) Subjective norm --> Behavioral intention is 0.163

3) Perceived behavior control --> Behavioral intention is ***

4) Behavioral intention --> behavior off-label drug use is *

5) Perc. behavior control --> behavior off-label drug use is 0.999

The TPB has been strongly supported by empirical evidence. We can predict different types of behavior from three aspects: attitude to behavior, subjective norms and perceived behavior control. These intentions and the perception of behavior control together make up the difference of actual behavior.

Attitude, subjective norm, and perceived behavior control have been proved to be related to behavior, norm and control belief. Expectation and value measurement are a way to deal with measurement limitation, but the exact nature of these relationships remains uncertain. Any value of the expectation formula can only be partially found to be successful in dealing with these relationships. The optimal remeasurement of expectation value and value measurement is a method to deal with measurement limitation. Finally, the inclusion of past behavior in the prediction equation is proved to be a method to test the theoretical sufficiency, which is another unsolved problem. The theory is predicting behavior quite well concerning off-label drug use by behavioral reliability.

There are differences between children and adults in absorption, distribution, metabolism and excretion of drugs, and children’s sensitivity and tolerance of drugs are much lower than adults.

Across the world, there were different degrees of off-label drug use problems in all countries

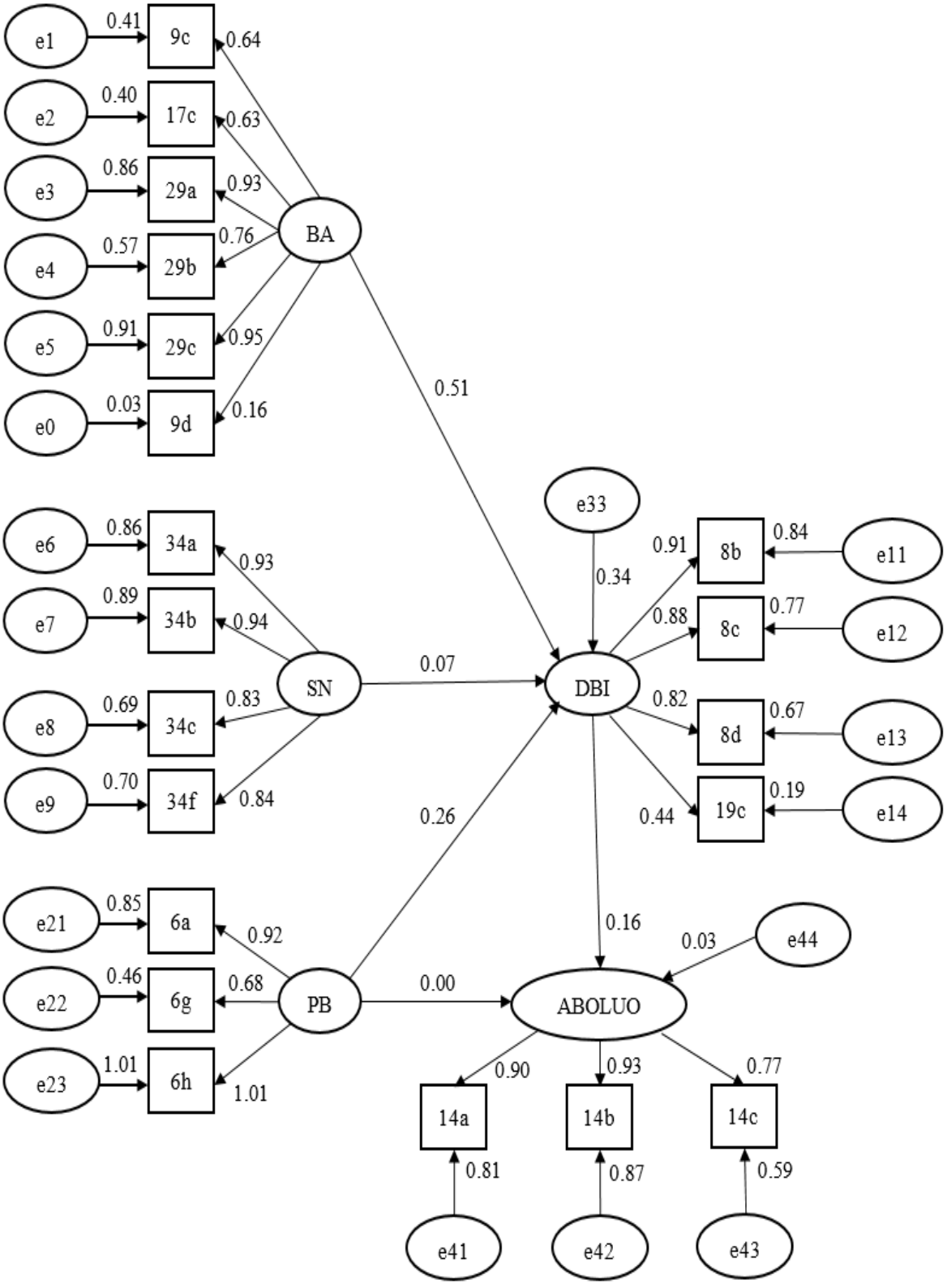

Figure 4-3 Standardized analysis results of TPB structural equation mode

Figure 4-3 abbreviation:

BA**:** Behavior Attitude,

SN: Subjective Norms,

PBC: Perceived behavior control,

DBI: Doctor's Behavioral intention,

TBODU: The behavior off-label drug use

Since no measure has been put forward to comprehensively work out the issue of unlabeled uses and it is held in the medical circle that unlabeled uses are reasonable to some extent, explorations are sure to be made concerning this issue.

In addition, there is no definite regulation on off-label drug use, especially in pediatric department now. Without effective execution and supervision of off-label drug use, there is enormous risk in medical advice issued by doctors, drug deployment of pharmacists and drug use of patients, which brings hidden problems of medical dispute.

The above factors result in the off-label drug use behavior by Chinese pediatricians and the frequency of over prescribing. The questions raised in this study issue are representative of some of the questions that pediatric off-label drug use in china.

One of the core factors in the theory of planned behavior is the intention of an individual to perform a given behavior. Intentions are presumed to catch the motivational elements that influence behavior; they are the extent to which people are willing to try, an indication of the degree of effort planned to implement an action.

Generally speaking, the stronger the intention to engage in an act, the more likely it is to perform. However, it should be clear that only when the behavior is controlled by the will, the intention of the behavior can be expressed in the behavior

This thesis reviews the researches on the theory of planned behavior in various aspects, and discusses some unsolved problems (Ajzen, 1985, 1987). Theoretically, this theory has been strongly supported by empirical evidence. We can predict different types of behavior from three aspects: attitude to behavior, subjective norms and perceived behavior control. These intentions and the perception of behavior control together make up the difference of actual behavior.

The overall model has good fit indices, thus being validly interpreted. The larger functioning of the variables follows the expected hypothesized relationship where the behavioral intention is positively explained by both behavioral attitude and perceived behavioral control, thus supporting Hypothesis 1a and Hypothesis 1c.

However, the subjective norm is not significantly associated to the behavioral intention and thus Hypothesis 1b was not supported by our findings. As expected, actual off-label behavior was positively predicted by behavioral intention, thus supporting Hypothesis 2.

Lastly, perceived behavioral control is not predicting actual off-label behavior, therefore not supporting hypothesis 3. Finding show that the model is able to at least partially account for behavioral intention and actual behavior. This is important because based on the present situation in China, it is an urgent-to-solve pediatric issue, providing pediatricians with drugs to use safely.

It was required to clarify the problems on legal status of "pediatric off-label drug uses", providing medical personnel with legal basis. Standard procedures of off-label drug uses were formulated to guarantee common interests of patients and medical personnel. Guidelines of off-label drug uses were made by industry association, providing academic support for doctors' decisions on drug uses

Chapter 5: Discussion of Results and Conclusion

Pediatric off-label drug use was becoming more common in China. Currently, off-label drug use, especially pediatric off-label drug use was not clearly stipulated. Thus, doctors' advice and drug users were at greater risk and a series of problems occurred with respect to laws, children's ethics, medical management and adverse drug reactions. It was required to carry out research related to pediatric off-label countermeasures and recommendations. This study intends to offer an answer to that call.

5.1 Present situation of pediatric off-label drug use

According to the investigation, the highest incidence of pediatric off-label drug use was due to children under 2 years old and adolescent (11 to 17 years old) (Conroy, Choonara, & Impicciatore, 2000; Lindell-Osuagwu, 2009). For more than half of children prescriptions, over 80% of which was issued to children with cancer and about 90% of newborn prescriptions were off-label (unlabeled) use (McIntyre, 2000) the incidence of adverse reactions of pediatric off-label drug use in hospitals was higher than that of drugs within package inserts (Turner, 1999); and the incidence of drug use errors and severity increased significantly. According to the analysis of drug use errors occurred in British children's hospitals from 2004 to 2006, 20 out of 158 drug use errors were of moderate injure magnitude, of which 12 (60%) was caused by unlabeled / off-label drug uses (Conroy, 2011).

Chinese scholar Zhang, Li, and Huang (2011) carried out research on Chinese pediatric off-label drugs, showing that off-label drug uses in outpatient pediatrics accounted for 41% and the ratio of hospitalized children with off-label drug uses up to 78%. Zeng and Zhou (2011) has selectively examined doctors' drug use advices of 1,112 cases and found that there were 507 copies of doctors' advice for off-label drug uses, with incidence of 45.59%. Xue and Wang (2008) has investigated 3,412 copies of pediatric outpatient prescriptions and found that off-label drug use accounted for 11.0% (345 copies), of which respiratory drugs and antibiotics accounted for 48.4% and 40.6% respectively and it was occurred most frequently in young children. Types of drugs focused on expectorant

and antibiotics.

5.2 Reasons for pediatric off-label drug use

5.2.1 Defects of package inserts – lack of children drug use information

Zhang and Wei (2011) had carried out research on drug registration information as of July 31, 2010 and found that drug registration information clearly marked with infants or children only accounted for 2.27%; and drug registration information clearly marked with infants or children on the official website of SFDA only accounted for 6%, mainly drugs for digestive system, respiratory system and antipyretic and analgesic. The lack of children drug use information was due to limited availability of safety data caused by few or no children clinical trials (Roberts, 2003; Hoppu, 2008; Aagaard, 2010). Lack of pharmacokinetic data or dose-finding study led to inadequate or excessive doses of drugs in some age groups, resulting in serious consequences such as increases of mortality or ineffective treatment.

5.2.2 Lack of children drug formulations–leading to inaccurate children drug dose

Pediatric drug use was often lack of drug formulation applicable to ages and body weights (Turner, 1998) while alternatives were used to prepare children drugs as follows: adult drugs reduction, crushing tablets, and dissolution of part of capsules in the water. These methods were not evaluated due to shortage of sufficient evidence and easily resulted in pharmacokinetic changes, even increasing drug costs and wasting health resources. Children dose was usually calculated as a proportion of adult doses, which could lead to drug overdose (increases of adverse drug reactions) and ineffective drugs (because of dose) (Ettore, 2010).

5.2.3 Lack of clinical records

Olsson (2012) showed that there were nearly half of prescriptions without children drug use records. For example, freshly prepared suspension was made of tablets from pharmacy before use, usually by means of dilution or reduction of adult dose. So, it was not reviewed and would cause great risk to children drug uses, laying troubles for drug errors.

5.2.4 Difference of package inserts

It was likely for clinical doctors to use off-label drugs due to difference between domestic and foreign package inserts. For example, for the five proton pump inhibitors used in domestic clinical application, infants were prohibited for omeprazole; there was no evidence showing children have used pantoprazole; rabeprazole was not recommended for children; and children were not mentioned in the information of clinical application of lansoprazole and esomeprazole. However, in Europe, it was clearly stipulated that omeprazole was adapted to pediatric patients (Tafuri, 2009).

5.3 Problems and contradictions of pediatric off-label drug use

5.3.1 Patients demands and drug use risks

50%-75% of children drugs were not fully studied in children (Roberts, 2003; Hoppu, 2008), namely, was not verified through strict phase I-IV clinical tests. The safety and effectiveness were lack of reliable children data. Contradiction between supply and demand of children patients resulted in not only forced pediatric off-label drug use, but also risks of drug insufficiencies or overdose in some age groups.

5.3.2 Legal issues

The U.S. Food and Drug Administration (FDA) has made it clear that "doctors are not forced to have to fully comply with package inserts for drug uses". Pediatric use information was included into drug labels in accordance with Pediatric Labeling Rule approved by FDA in 1994. It prescribed that drug holders had to submit pediatric research report to FDA and obtain 6 months of pediatric exclusivity protective period of such drugs according to the contents (FDA, 2008). Pediatric Regulation was also issued in Europe (Rocchi et al., 2010). Legal basis of children clinical trials provided by Europe and the United States has brought high-quality children drug research. Inefficient treatment, incorrect treatment and adverse drug reactions were minimized. Unnecessary clinical trials were avoided.

Children subpopulation such as newborns and children with cancer were received special attention. Ethical issues of children's psychological sensibility and vulnerability were considered. Finally, children would be the important beneficiaries.

In China, there were at least seven legal boundaries for applicable scope of drugs, so, the package inserts were technologically strict and legally serious (Zhang, 2010). At present, there were no laws and regulations on drug clinical trials for children in China, so, children drug use was lack of scientific basis.

5.3.3 Responsibilities and risks of medical personnel

Although off-label drug use was reasonable in most cases, who would bear the corresponding liabilities needed to be clarified in case of adverse drug events. As for clinical practice of off-label drug use, Guangdong pharmaceutical society has issued the *Expert Consensus on Off-Label Drug Use* in 2010 (China Medical Journal, 2010). This was the first time for professional societies/association to issue regulations involved in "off-label drug use". The purpose was to provide guidance for clinical doctors and physicians to carry out "off-label drug use".

5.3.4 Requirements of hospital management

Currently, many medical institutions are lack of files to normalize off-label drug use. Therefore, doctors' off-label drug use became an individual behavior. At the same time, there was no management support from hospital level. The risks of doctors' practices were increased. As a special group, children needed more detailed and clear regulations on off-label drug uses.

5.3.5 Problems in practical operations

Patients' Informed Consent Form in off-label drug use was implemented with different standards in real life. Some doctors just spoke to patients based on their own understanding of diseases and drugs; and some doctors did not take informed consent for fear of misunderstanding of patients. At the same time, pharmacists were at risks of drug dispensing and distribution during off-label prescriptions review.

5.4 Strategies and recommendations for pediatric off-label drug use

5.4.1 Academic level

Each professional society, especially pediatric professional society, was on the one hand to urge relevant authorities to establish laws and regulations related to pediatric drug

clinical trials, on the other hand, to organize personnel to investigate and issue expert opinions (consensus) on pediatric off-label drug use applied to the country as soon as possible, and to provide professional guidance for management and operational process of pediatric off-label drug uses. Society could give technical support in case of disputes of off-label drug uses.

5.4.2 Management level

Pediatric off-label drug should be used in accordance with the following six principles: no alternatives, with evidence, non-test, approval, with informed consent, and monitoring. Classification management of pediatric off-label drug use was implemented at five aspects, including:

(1) Classification management on sources of evidence; there were four different levels of evidences of off-label drug uses mainly from: included in foreign diagnosis standard, included in domestic diagnosis standard, not included in norms, but with expert consensus, and based on personal experiences. Accordingly, classification management should be formulated in line with reliability of levels of evidence;

(2) Classification management of drugs; classification management was performed on drug categories in accordance with characteristics of generic drugs and special drugs (high-risk drugs), as well as the adverse consequences of off-label drug use. However, off-label drug use norms of special drugs such as traditional Chinese medicine injection and antitumor drugs should be stricter and clearer;

(3) Classification management on doctors' prescription rights; China has issued three levels of antibiotic drugs prescription rights management methods for antibiotic drugs: non-restricted, restricted, and special level. With reference of such prescription right management methods, different doctors could have different rights to write out off-label prescriptions;

(4) Classification management of drug user groups; based on ages of pediatric patients, classification management of off-label drug uses should be performed for different subpopulations such as newborns, infant, children, and adolescent;

(5) Classification management on types of diseases; classification management on off-label drug use for different types of diseases should be formulated, such as common diseases, rare diseases, and refractory diseases.

5.4.3 Operational level

Hospitals should form expert groups to evaluate off-label drug uses, establish perfect operational processes for off-label drug uses, and provide professional technical guidance. Clinical doctors should apply for off-label drug uses with approval of the Ethics Committee and/or the pharmaceutical management committee and permission of off-label drug uses. The application form should include off-label drug use information and evidence, patients' informed consent, and reasons and effects of off-label drug uses. In addition, off-label drug use should be a shared responsibility of doctors and pharmacists. As a main body of off-label drug uses, doctor should strictly abide by relevant provisions of hospital and strengthen self-discipline to avoid drug abuses. As an examiner of off-label prescription, pharmacists should strictly review prescriptions and drug dispensing and refuse to dispense drugs in case of violation (Ge, 2013).

5.4.4 Technical level

Off-label drug use database should be established (Ge, 2013) to offer convenience for clinical doctors and pharmacists. Experts were organized to assess and update the database regularly. Off-label drug use management was included in the operating system and drug management system of doctors. Therefore, there were prompt, records and warnings for issuance of off-label drug uses and there were intervention evidences, results, and information feedbacks on the review of off-label drug uses. Off-label drug uses in the system were able to be statistically summarized and analyzed by pharmacists on a regular basis.

5.4.5 Empirical analysis

5.4.5.1 Exploratory factor analysis

In order to test the validity of the scale, factor analysis is needed for the whole scale. The purpose of factor analysis is to find out the potential structure of the scale, suggesting correlation matrix is an identity matrix. The diagonal value of the anti-image correlation matrix represents the measure of sampling adequacy (MSA) of each variable. The right side of MSA will be marked with "a". Similar to the KMO value, the closer MSA is to 1, the more the item is suitable for factor analysis. As shown in common factors existed and needed further to extracting.

Commonality analysis: Extraction was used principal component analysis. Shows the initial commonality of each variable and the commonality after the principal component are extracted by principal component analysis. that is to say, there is commonality between variables.

The results of principal components extracted by principal component analysis, and the method of rotation is varimax with orthogonal rotations. In the table, there are 5 factors whose eigenvalue is greater than 1, suggesting that there are 5 common factors extracted from factor analysis. Together, 5 common factors accounted for 79.369% of the variation.

5.4.5.2 Reliability analysis

Reliability refers to the consistency of scale. The greater the reliability of a scale, the smaller the error of its measurement. SPSS was used to analyze the reliability of "behavior attitude", "subjective norm", "perceived behavior control", "doctor behavior control" and "doctor's medication behavior beyond instructions". The analysis results are shown in Table 4-8. According to behavior and social sciences, the reliability of variable should be at least above 0.6. If it is lower than 0.5, it means that the reliability of variable is not good. From Table 4-8, it is found that the Cronbach's alpha values of each variable are all above 0.8, indicating that the internal consistency of the variables is very good.

5.4.5.3 Confirmatory factor analysis

Confirmatory factor analysis is mainly used to explain and observe the correlation or covariance between variables, in order to test the construct validity of the scale.

The model includes 20 estimated parameters. Except for five fixed indicators, the other estimated parameters are significant at the level of 0.001. Moreover, there is no negative variance in the load estimation of the nonstandard factor, and the standard error of each estimation parameter is small, so the model is acceptable.

5.4.5.4 Structural equation model analysis of TPB model

The results of standardized estimate of SEM analysis of pediatrician's medication behavior beyond the instruction. The summary of model fit, indicating that the overall model is acceptable. The path analysis results. Empirical study found that the path of "behavioral attitude > behavioral intention" is significant, the path of "perceived behavior > behavioral intention" is significant, and the path of "behavioral intention > drug use beyond instruction" is significant. However, the paths of "subjective norm > behavioral

intention" and "perceived behavior > drug use beyond instruction" have not been verified.

5.5 Summary

a) For top 300 commonly used pediatric drugs, 194 (64.67%) had pediatric drug use information and 63 (21.00%) had no clear pediatric drug use information in its package inserts. This pertained to both commonly-used pediatric drugs and prohibited pediatric drugs.

b) Package inserts with pediatric drug use information were mainly suitable for part ages of children and rarely applied to all ages. There was lack of neonatal medicine information.

c) The theory of planned behavior comprehends four dimensions, i.e. behavioral attitude, subjective norm, behavioral intention and perceived behavioral control.

(1) The behavior attitude of pediatricians: Behavior attitude of pediatricians depends on the awareness of drug dependence and the expectation of treatment results. For example, which factors a doctor needs to consider when prescribing off-label drug use, and how to determine such responsibility, even when the patient gave the informed consent, we should see the off-label drug use from special perspective. It is suggested to standardize doctors' medication, treating drugs in off-label drug use differently, define the scope of responsibility

(2) The subjective norms of pediatricians: Subjective norms of pediatricians influenced by doctors' subjective consciousness and patients' influence, it depends on doctors' cognition of management dimension, in the face of the increasingly serious situation of the off-label drug use, suggest doctor:

1) We should increase our own self-discipline, avoidance of drug abuse.

2) Must have sufficient clinical experience in the use of the off-label drug use, avoid the randomness of medication.

3) The use of high-risk drugs should be reported to the superior and put on record; Raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug.

(3) The behavior intention of pediatricians: It depends on pediatrician's cognition of professional dimension and legal dimension:

The cognition of professional dimension is embodied in which basis do you think lead to prescribing off-label drug use, such as: has been incorporated into the standard of diagnosis and treatment in China, has been incorporated into foreign diagnostic and treatment norms, although not regulated, it is supported by expert advice or evidence from clinical trials.

The cognition of legal dimension is embodied in which of the following reasons do you think justify prescribing without asking for informed consent, because nobody is concerned with it at the organizational level, and so on these reasons. Suggest doctor: There are sufficient grounds and reasons for the prescription of off-label drug use, with the informed consent of the guardian.

(4) The perceived behavior control off-label drug use: The cognitive level reflected in the professional dimension of doctors, Through doctors what motives do you think make doctors prescribe off-label drug use for patient, such as: the limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children; Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time, and so on these factors to reflect. It is suggested to increase dosage forms for children. Timely revision of drug instructions

(5) The behavior off-label drug use of pediatricians: The above factors result in the behavior off-label drug use of Chinese pediatricians and the frequency of over prescribing. It can be measured by risk of adverse drug reactions, increase in medical disputes, disputes over increasing drug cost. It is suggested that doctors should strengthen the monitoring of adverse drug reactions, reduce medical disputes caused by off-label drug use, reduced disputes over increased drug payments

d) Findings showed the text description of applicable user groups in package insert were not unified. Children's age groups in package inserts were more complicated and confused and lack of unified standards and norms.

e) Findings showed off-label prescriptions issued by doctors were not only related to insufficient pediatric drug use information of package inserts, but also subjective behavior of doctors.

f) Findings showed management of off-label drug use should be standardized with respect of subpopulation of pediatric drug use and different children diseases.

g) Findings showed cognition of doctors with different titles to off-label drug use were different. It was recommended to set permissions for different off-label drug use.

h) Findings showed off-label drug use of doctors should lead to different results due to different sources of evidence, so it was necessary to carry out classification management on evidences of off-label drug use.

i) Findings showed according to different sources, the behavior off-label drug use is different, which leads to different results. We should carry out the hierarchical management of the basis of drug use beyond the instructions and standardize the drug use behavior of doctors.

j) Findings showed TPB can reasonably explain off-label drug use in the sample, but some relations were not observed which can be attributed to the specific context regarding subjective norm as well as the centrality of behavioral intention about this topic.

5.6 Innovation and limitations

5.6.1 Innovation

In this study, TPB was applied to Chinese off-label drug use of pediatrician for the first time, the influencing factors of Chinese pediatricians' off-label drug use behavior were discussed, this paper explores and analyzes the off-label drug use of pediatrician and the relationship between each part of the theory of planned behavior.

5.6.2 The limitations

Due to the limited variety of drug specification data in this study, and the questionnaire survey of pediatricians involves and covers a limited scope, the outcomes may be inevitably influenced by individual subjective factors. The nature of this survey meant that we were only able to superficially explore this area. The results are not comprehensive. Therefore, more detailed work would be of value in the future, including exploring off-label drug use with a China's larger scope and strategies to standardize its usage.

5.7 Future prospects

In addition, there are several influencing factors of the behavior. To fully grasp the formation mechanism of behavior, based on the TPB, it is suggested that some variables such as the behavioral suggestion, behavioral habit, and expected regret be added to the model. Likewise, it is possible to combine multiple theoretical models to explore and analyze the influencing factors of the behavior from all aspects, comprehensively. This should be considered in future research.

5.8 Conclusions

Pediatric off-label drug use is a common practice in China. Chinese pediatricians have some recognition of the concept but a low awareness rate of the Chinese Expert Consensus of Pediatric Off-Label Drug Use. Based on the present situation of China, this is an important and urgent issue especially in pediatrics. The legal status of pediatric off-label use is very much needed.

Standard procedures of off-label drug uses were formulated to guarantee common interests of patients and medical personnel. Guidelines of off-label drug uses were made by industry association, providing academic support for doctors' decisions on drug uses. However, a comprehensive understanding of the current situation is required, especially from a scholar approach.

Based on the results, we suggest the following:

(1) Off-label drug use has its rationality and necessity, while the potential risks cannot be ignore, a legally recognized national guideline with a broad scope of application is urgently needed in China.

(2) Targeted pediatric healthcare professionals’ education and training on off-label drug use should be taken into consideration to guide clinical practice and improve guideline adherence.

(3) As a pilot study in China, our results should be of interest to off-label stakeholders in other cities and a subsequent nationwide survey may be conducted in the future.

(4) Pediatric off-label drug use in China should be implemented from academics, management, operation, and technology level. Classification and standardized management

of off-label drug use should be carried out according to pediatric drug use subpopulation, different pediatric diseases, evidences of off-label drug use, and permission of off-label drug use. Management standards and implementation processes of pediatric off-label drug uses should be promoted in various aspects.

The results of this investigation and study show that TPB has a strong ability to explain and predict the drug use behavior of pediatric hyperinstruction. Perceived behavior control and behavior attitude are the most important influencing factors of off-label drug us of pediatrician and behavior intention, respectively.

In line with hypothesized relations, this empirical study found that the path of "behavioral attitude > behavioral intention" is significant, the path of "perceived behavior > behavioral intention" is significant, and the path of "behavioral intention > drug use beyond instruction" is significant.

On the whole, this study further validates the feasibility of the application of the TPB in the use of pediatric hyperinstruction and provides a theoretical basis for Chinese pediatricians' use of hyperinstruction, which has a certain reference value.

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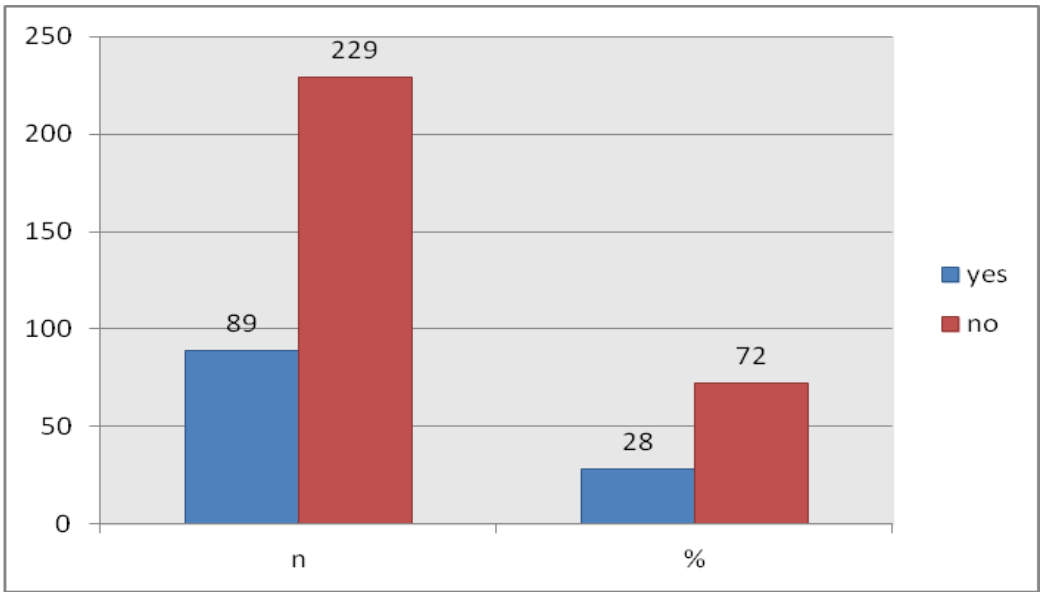
Appendix 1: Related Figures



Figur.1 It is legal or illegal to prescribe off-label drug use

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Appendix 2: Related Tables

Table 1 Relevant regulations of off-Label drug uses in 10 countries

S/N	Countries	Off-Label drug uses allowed or not	Relevant information and evidence	Patients informed consent	Approved by ethics committee and pharmacy administration committee	Prescription rights	Records on reasons and efficacy of off-label drug uses	Monitor adverse reactions of off-label drug uses
1	U.S.A	Yes*	√	√	√#		√	
2	UK		√		√	√△	√	√
3	Germany	Yes	√				√	
4	Netherlands	Yes	√	√				√
5	Italy	Yes	√	√				√
6	Australia		√	√				√
7	New Zealand	Yes*		√				
8	Japan	Yes	√	√				
9	South Africa		√	√				
10	India	No*						

***** In China, whether off-label drug use is allowed or not was explicitly stipulated at the legal level. However, for other countries, if off-label drug uses were not explicitly prohibited and were stipulated in related specifications, off-label drug uses were allowable.

Regulations of U.S FDS was only applied to research drug uses. Off-label drug was able to be used for treatment without application of the ethics committee.

△ Ireland included.

Table 2 Description of pediatric drug information of commonly-used pediatric drugs

Description of package insert	Number of categories	Total number of categories	Percentage	Total percentage
Children prohibited	2	63	0.67%	21%
Dosage reduction or as professionally prescribed	3		1.00%	
No such as test and reliable reference	16		5.33%	
Unclear to safety of children drug use	21		7.00%	
No children drug use information	21		7.00%	
With precautions or warnings of children drug use	43		14.33%	
With children drug use, dose and applicable ages	194		64.67%	
Total	300		100.00%	

Table 3 Details on pediatric information of different types of package inserts 1

Drug use information	Anti-infection drugs	Drugs for respiratory diseases	Drugs for parenteral and enteral nutrition, water regulation, electrolyte and acid-base balance	Drugs for digestive system	Drugs for nervous system	Antipyretic and analgesic drugs	Drugs for immune system	Drugs for blood system	Drugs for cardiovascular system
Unclear to safety of children drug use	3	2	5	2	3		3	0	2
No such a test and no reliable reference	3	1	5	1				3	2
Without children drug use information	5	3		6					
Dosage reduction or as professionally prescribed		1						1	
Children prohibited	1			1					
With precautions or warnings of children drug use	5	4	6	3	4		3	3	3
With children drug use information	69	26	21	23	9	14	8	6	4
Total	86	37	37	36	16	14	14	13	11

Table 4 Details on pediatric information of different types of package inserts 2

Drug use information	Anesthesia drugs and anesthesia adjuvant drug	Tumor drugs	Chinese patent drug	Drugs for endocrine system	Drugs for urinary system	Immune preparation and vaccines	Drugs for skin diseases	Ophthalmic drugs	Stomatological drugs
Unclear to safety of children drug use	1								
No such a test and no reliable reference		1							
Without children drug use information			3			1	2	1	
Dosage reduction or as professionally prescribed			1						
Children prohibited									
With precautions or warnings of children drug use	1	3		5			1	1	1
With children drug use information	5	2	1		4	2			
Total	7	6	5	5	4	3	3	2	1

Table 5 Details on pediatric information of different types of package inserts 3

Drug use information	Stomatological drugs	Total	Percentage
Unclear to safety of children drug use		21	7.00%
No such a test and no reliable reference		16	5.33%
Without children drug use information		17	5.67%
Dosage reduction or as professionally prescribed		3	1.00%
Children prohibited		2	0.67%
With precautions or warnings of children drug use	1	43	14.33%
With children drug use information		194	64.67%
Total	1	300	98.67%

Table 6 Adverse drug reaction factors of the off-label drug use

Ccategory	Yes		No	
	Num.	%	Num.	%
Overdose administration	44	14	274	86
Over-indications	136	43	182	57
Over-medication population	128	40	190	60
Over-drug delivery pathway	112	35	206	65
Over counter-indications	3	1	315	99

Table 7 Comparison on reasons of doctors with different titles to issue off-Label prescriptions [cases (%)]

Titles	N.	Insufficient self-knowledge of doctors		Limitations of pharmaceutical preparation		Package inserts not updated in time	
		yes	no	yes	no	yes	no
Junior	127	55(43.31)	72(56.69)	94(74.02)	33(25.98)	96(75.59)	31(24.41)
Intermediate	92	29(31.52)	63(68.48)	73(79.35)	19(20.65)	78(84.78)	14(15.22)
Senior	94	37(39.36)	57(60.64)	59(62.76)	37(39.36)	80(85.11)	14(14.89)
χ^2	6.358	205.770		154.759		250.873	
df	2	4		4		4	
P	0.042	0.000		0.000		0.000	

Table 8 Comparison on applicable conditions of drugs in off-label prescriptions issued by doctors from different hospitals [cases (%)]

Hospitals	N.	Over indications		Beyond drug delivery route		New uses for old drugs	
		Yes	No	Yes	No	Yes	No
Children's hospitals	129	81(62.79)	48(37.21)	86(66.67)	43(33.33)	68(52.71)	61(47.29)
General hospitals	162	92(56.79)	70(43.21)	46(28.40)	116(71.60)	42(25.93)	120(74.07)
Others	27	8(29.63)	19(70.37)	8(29.63)	19(70.37)	13(48.15)	14(51.85)
χ^2	93.453	11.253		7.532		4.212	
df	2	4		4		4	
p	0.000	0.000		0.000		0.001	

Table 9 Comparison on diseases in off-Label prescriptions issued by doctors from different hospitals [cases (%)]

Hospitals	N.	Emergency disease		Refractory diseases	
		No	Yes	No	Yes
Children's hospitals	129	26(32.68)	103(67.32)	42(64.59)	87(35.41)
General hospitals	162	35(50.00)	127(50.00)	66(53.69)	96(46.31)
Others	27	8(44.44)	19(55.56)	9(72.22)	18(27.78)
χ^2	93.453	17.021		8.098	
df	2	4		3	
p	0.000	0.000		0.000	

Table 10 Comparison on prohibited off-label prescription user groups of different hospitals [cases (%)]

Hospitals	N.	The newborn prohibited		The adolescent prohibited	
		Yes	No	Yes	No
Children's hospitals	129	105(81.40)	24(18.60)	20(15.50)	109(84.50)
General hospitals	162	132(81.48)	30(18.52)	11(6.79)	151(93.21)
Others	27	18(66.67)	9(33.33)	1(3.70)	17(96.30)
χ^2	93.453	332		127.079	
df	2	4		4	
p	0.000	0.000		0.000	

Table 11 Demographics of the study participants

Professional title[a] N (%)	Childrens' hospital (n =129)	Pediatrics in the general hospital (n = 162)	other (n = 27)
Junior title	52 (40.31)	60 (37.04)	15 (55.55)
Intermediate title	33 (25.58)	55 (33.95)	5 (18.52)
Senior title	44 (34.11)	47 (29.01)	7 (25.93)

Note: [a] Health worker in China are often classified as "senior", "intermediate" or "junior" title according to their skill levels and specialization. For example, doctors with junior title refer to residents, intermediate title refer to attending physicians, and senior title refer to director physicians or assistant director physicians

Table 12 KMO and bartlett's test of the scale

Kaiser-meyer-olkin mMeasure of sampling adequacy		0.768
Bartlett's test of sphericity	Approx. Chi-square	5971.134
	df	190
	Sig.	0.000

Table 13 Model fit summary

	NFI	RFI	IFI	TLI	CFI
Index	0.942	0.903	0.962	0.925	0.961
	>0.9	>0.9	>0.9	>0.9	>0.9

Table 14 Structural equation path analysis results

Path	Estimate	S.E.	t	*p*
Behavior attitude --> behavioral intention	0.707	0.119	5.938	***
Subjective norm --> behavioral intention	0.081	0.058	1.395	0.163
Perceived behavior control --> behavioral intention	0.113	0.025	4.469	***
Behavioral intention --> behavior off-label drug use	0.226	0.093	2.421	*
Perc. behavior control --> behavior off-label drug use	0	0.037	-0.001	0.999

Appendix 3: "Off labeled use of drug" questionnaire

The so-called "off labeled use of drug" refers to the use of drugs for people not mentioned in the instructions. The clinical diagnosis is not consistent with the provisions of the instructions for drug use, and the route, dose, frequency, compatibility taboos, precautions, etc. are not consistent with the provisions of the instructions for drug use. In foreign countries, it is a common practice to use drugs beyond the drug specification in clinical practice, which accounts for 7.5% - 40% in general adult drugs and 50% - 90% in hospitalized pediatric children.

This questionnaire is designed to collect data destined to identify a behavioral model of off-label drug use prescription decision and help in managing it. The previous message is repeated here.

(1). Essential information

1. Which hospital

1. Childrens' hospital
2. Pediatrics in the general hospital
3. Other

2. Your specialty and department:

1. departments of pediatrics
2. departments of pediatric internal medicine
3. departments of neonatology
4. departments of pediatric respiration
5. departments of pediatric neurology
6. departments of pediatric digestion
7. departments of pediatric surgery
8. departments of pediatric nephrology and rheumatism
9. department of pediatric cardiology
10. other

3. Your professional title

1. junior titles
2. intermediate titles
3. senior titles

4.Have you ever prescribed off-label drug use prescription in the last year?

1.yes
2.no

5.How often do you write prescriptions in off-label drug use

1. It is very common, almost every day
2. Once a week
3. Once every month
4. Hardly ever

(2). Professional dimension

6) What motives do you think make doctors prescribe off-label drug use? (use scale 1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree).
   a) Motive Off-label - 1. The childrens' condition needs, and the drugs lack the necessary data of childrens' medication, and there are no corresponding guidelines for childrens' drug use.
   b) Motive Off-label - 2. The defects and deficiencies of the drug instruction itself make the contents of the same drug instruction different.
   c) Motive Off-label - 3. Doctor insufficient knowledge about the drug
   d) Motive Off-label - 4. Promotional materials for pharmaceutical enterprises
   e) Motive Off-label - 5. The limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children
   f) Motive Off-label - 6. Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time.

g) The limitations of pharmaceutical preparations lead to fewer dosage forms suitable for children
h) Some old drugs have new indications. Indications and usage have been included in the guidelines for the use of pharmacopoeia and various diseases, but the instructions have not been revised and updated in time

7) Which situations are most frequent in prescribing off-label drug use? (1-very rare, 2-somewhat rare, 3-occasional, 4-common, 5-very common)
   a) Overdosage
   b) overindications
   c) over medication population
   d) overr drug delivery pathway
   e) over contraindications
   f) Medicines added new indication

8) Which basis do you think lead to prescribing off-label drug use? (use scale 1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree).
   a) Basis1 - Empirical own experience with the drug
   b) Basis2 - Has been incorporated into the standard of diagnosis and treatment in China
   c) Basis3 - Has been incorporated into foreign diagnostic and treatment norms
   d) Basis4 - Although not regulated, it is supported by expert advice or evidence from clinical trials

9) Which factors a doctor needs to consider when prescribing off-label drug use? (1-not important at all, 2-somewhat unimportant, 3-neither important nor unimportant, 4-somewhat important, 5-very important)
   a) Factors to prescribe - 1. Efficacy of drugs
   b) Factors to prescribe - 2. Adverse drug reactions

c) Factors to prescribe - 3. Cost of drugs for patients
d) Factors to prescribe – 4. Cost of drugs for the health system

11) Do you think that the disease situation of the patients with prescribing off-label drug use is classified as... (single choice)

1-Common diseases, not life threatening, 2-Common diseases but posing life in danger, 3-Uncommon diseases, 4-Very uncommon diseases, 5-Very rare diseases

12) In your opinion, off-label drug use must not be used in (1-strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree,5-strongly agree)

a) Neonatus (0-28 days old)
b) Infants (up to 6 years old)
c) Children (7 to 12 years old)

14) What probability have the following hazards to happen in off-label drug use prescribing? (1-very improbable, 2-moderately improbable 3-50/50 probability 4-moderately probable 5-very probable)

a) Risk of adverse drug reactions
b) Increase in medical disputes
c) Disputes over increasing the cost of drugs

15) In the course of your practice, did you ever experience any serious adverse drug reactions due to the off-label drug use?

1. Yes, it is very frequent
2. Yes, several times
3. Yes, rarely
4. Yes, only once
5. No, never

16) Please indicate how much you agree or disagree with the following sentence: "I think adverse reactions to off-label drug use prescribed should be classified as adverse drug reactions".

1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree

(3). Legal dimension:

17) And how to determine such responsibility, even when the patient gave the informed consent? (1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree)
   a) Hope for technical and administrative support from hospitals and associations
   b) If the adverse event is a related adverse reaction that has been identified by the drug itself, it should not be held responsible
   c) If the patient himself has a taboo on drug use, the drug should not be used. If there is a problem, the doctor must be held responsible.

18) To which extent should the off-label drug use be subjected to informed consent by the guardian?

   1- Never (guardian should not condition this decision)
   2- In most cases (guardian should not condition this decision)
   3- Neutral (50/50)
   4- Sometimes (guardians must consent always)
   5- Always (guardians must consent always)

19) Which of the following reasons do you think justify prescribing without asking for informed consent?

(1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree)

   a) To avoid trouble. Informed consent will only make trouble
   b) To avoid misunderstanding among parents of patients
   c) Because nobody is concerned with it at the organizational level
   d) Because doctors do not ask for informed consent in these cases (it is usual).

20) How much you think it is legal or illegal to prescribe

off-label drug use?

1-It is illegal and an offense, … 5-it is not illegal at all.

21) Do you think a doctors' behavior of prescribing off-label drug use for a patient… (use scale 1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree).
   a) Exceeds the specification is an act of helplessness
   b) Super-instruction medication is beneficial to the development and improvement of medicine
   c) Super instruction medication is inevitable to some extent

(4). Management dimension

22) To which extent off-label drug use prescription is uniformly regulated in your organization?

1-No regulation at all, 2-Some regulation but incomplete, 3-Contradictory regulations, 4-one regulation not totally clear, 5-A single uniform and clear regulation

23) To which extent hospitals and health authorities should carry out guidelines for off-label drug use prescription?

1- There is really no need for that,
2- May of not be needed
3- May or may not be
4- Need
5- -It is an urgent matter that must be addressed

24) Please indicate how much the following describes your situation: Your hospital carries out corresponding record and record off-label drug use, and summarize regularly. (1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree)

25) To which extent is it necessary that pharmacists review prescription and find out prescription intervention after discovery off-label drug use?

1-Badly needed, 2-May of not be needed, 3-No, its hindering normal treatment

26) It should be forbidden to prescribe off-label drug use, when contrary to the guidelines and clinical medication instructions.

1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree

27) Considering the general forms that off-label drug use prescription can take, how should the hospital deal with it as regards its policy?

1-Strictly prohibiting off-label issuing, 2-Tacitly consent, 3-There are relevant guidelines, can write the prescription

28) To which extent the following kind of support provided by the Association could be helpful? (1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree)
   a) Give technical support
   b) Give policy support
   c) Give legal and compensation support in case of dispute

29) We should see the off-label drug use from special perspective: (1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree).
   a) General and high-risk drugs
   b) Foreign pharmacopoeia, clearly documented in the treatment guidelines, and our country did not make any changes or updates.
   c) Treatment of common diseases with rare, refractory diseases

30) To which extent do you believe the pharmacist should do the following when facing an off-label drug use prescription? (1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree).

a) Prescription audit, and rational intervention.
b) The prescription needs two doctors signature. Then pharmacists can issue drugs.
c) Pharmacists regularly record and record the drugs used in the off-label drug use, and summarized periodically, and feedback to clinicians.
d) Pharmacists collect information about the off-label drug use at home and abroad, organize and draw up the corresponding summary

31) There is a large number of problems in off-label drug use. What to do as a doctor? (1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree).
a) The informed consent of the patients' guardian is required when prescribing a off-label drug use.
b) Make a good record on the medical record, and summarize it regularly
c) According to the disease situation of children, try not to prescribe off-label drug use

32) In view of the existence of a large number of the off-label drug use, how should the administrative departments do? (1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree).
a) Guidelines for the off-label drug use should be established as soon as possible
b) Formulation of management off-label drug use
c) Supervision function of medical insurance department

33) In the course of your practice, the adverse drug reactions that occurred as a result of the off-label drug use include which of the following? (1-Never, 5-Several times)
a) Overdose administration
b) overindications
c) over medication population
d) over drug delivery pathway
e) over contraindications

34) In the face of the increasingly serious situation of the off-label drug use, as a doctor, how much you agree with the following sentences? (1-Strongly disagree, 2-moderately disagree, 3-neither agree not disagree/neutral, 4-moderately agree, 5-Strongly agree).

a) We should increase our own self-discipline, avoidance of drug abuse
b) Raise the level of professional knowledge, understand the pharmacology, efficacy toxic and side effects of the drug.
c) Must have sufficient clinical experience in the use of the off-label drug use, avoid the randomness of medication
d) Duty to assess the ratio of benefits to risks, to ensure the safety of drug use
e) Doctors should have a sense of self-protection and should sign an informed consent to the situation of the off-label drug use.
f) The use of high-risk drugs should be reported to the superior and put on record

Thank you for your cooperation and support.