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Chinese physicians' attitudes toward eco-directed sustainable prescribing from the perspective of ecopharmacovigilance

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ABSTRACT

Objective Eco-directed sustainable prescribing (EDSP) is an effective upstream way to reduce the environmental footprints of active pharmaceutical ingredients (APIs), a kind of emerging contaminants, from the patients' excretion. EDSP is one of key steps in the program of ecopharmacovigilance (EPV), a drug administration route on API pollution. The study aimed to assess the attitudes of physicians prescribing medicines regarding EDSP from the perspective of EPV.

Design and setting This cross-sectional study was conducted using a self-administered questionnaire instruction delivered to 400 physicians in Hubei Province, China from March to June, 2019. And 262 valid questionnaires were obtained.

Results Most physicians agreed the existence of APIs in environment, worried about the potential environmental and ecological risks of API residues, supported the effectiveness

and necessity of EDSP under an EPV perspective in decreasing environmental exposure of excreted APIs, and showed their willingness to participate in the EDSP practices. Nevertheless, no respondent identified the environmental impacts as the aspects regarding medicines affecting his(her) prescription decision, showed their self-satisfaction with knowledge on EDSP and confidence toward EDSP. The most important barrier to the effective implementation of EDSP was identified as "*poor awareness of EDSP and EPV*". And 97% responding physicians reported that they held the wait-and-see or conservative attitudes towards EDSP practice. The biggest concerns in low-dose prescribing and prescribing of drugs possessing environment-friendly excretion profiles, two EDSP approaches, were "*It can not achieve ideal therapeutic efficacy, and might delay treatment*" and "*Drug evaluation based on the excretion profile and pharmacokinetics is too complicated and professional*", respectively.

Conclusions Chinese physicians had positive attitudes towards EDSP from the perspective of EPV. However, their environmental consciousness during prescribing and the related education were insufficient. Some recommendations for implementing EDSP from the perspective of EPV were proposed.

Strengths and limitations of this study

- To the best of our knowledge, this is the first study that explored the physicians' perceptions and attitudes toward eco-directed sustainable prescribing (EDSP) from the perspective of ecopharmacovigilance (EPV), a sustainable prescription approach to minimize the environmental loads and risks of excreted active pharmaceutical ingredient (API) residues from the source.
- Based on the survey results, we proposed some recommendations for further implementing EDSP from the perspective of EPV in practice.

- This study only enrolled physicians from one province in China, which might weaken the generalizability of results.

INTRODUCTION

The occurrence of active pharmaceutical ingredients (APIs), a kind of emerging contaminants (ECs) without standard regulations, in the environment worldwide has become an issue of special importance.[1-5] As a critical part of modern life, pharmaceutical drugs are abundantly used in health-care practices around the world.[5] The environmental discharge of APIs in a continuous and unsupervised way as well as their inadequate removal during wastewater treatment processes have led to their detection in the various environmental matrices at levels of concern.[2-5] Considering their potent biological activities even at very low concentrations, API residues have been recognized to pose potential risks and hazards to the natural environment, ecology and human health due to long-term exposures.[6-9] Therefore, it is urgent to address this issue, aiming to minimize the environmental loads and risks of API residues.

Despite the fact that conventional and advanced end-of-pipe wastewater treatment optimizations have been proposed, studied and conducted from the perspective of environmental science, more effective, economic and better control activities for API pollutants emphasizing on input prevention are currently needed to eliminate pollution at the root source.[6,10,11] As a drug administration route on environment pollution caused by APIs, ecopharmacovigilance (EPV) is an emerging science of detection, evaluation, understanding and prevention the adverse effects of APIs in the environment.[6, 11-18] Based the fact that API pollution could be ultimately traced back to the use of medications in health-care practices, EPV focuses on the clinical application of active pharmaceutical management strategies to decrease the API emission from the sources and minimize the environmental footprint of the health-care industry.[13,17] The sources of APIs in environment include excretion from drug-consuming patients and animals, inappropriate deposition of expired or unwanted pharmaceutical products, manufacturing plant wastes, hospital wastes, *etc*.[19-23] Thereinto, patients' excretion in forms of parent APIs or active metabolites has been well-accepted to constitute the major contribution to most API pollutants in the environment, and the disposal of leftovers has been judged as the

secondary source.[10,24-26] Therefore, the implementation of EPV should encourage the effective control of these two routes of API entry to the environment. EPV-directed pharmaceutical disposal management has been proposed and many guidelines for discouraging inappropriate disposal of leftover and unwanted medicines have been implemented in some areas around the world.[13,24,25] However, effective upstream ways to reduce API releases to environment from the primary route (excretion) are still needed under the principle of EPV.

Since normal physiological excretion of APIs in drug-consuming patients cannot be prevented, the optimized administration of pharmaceuticals ensuring satisfactory but not too high pharmacologically active concentrations in patients might be a key protective measure against excessive API entry to the environment from excretion.[24,27-29] Driven by this idea, an approach termed eco-directed sustainable prescribing (EDSP) has been recommended by Daughton [24] to reduce the environmental load of excreted APIs. As prescribers are commonly confronted with more than one choice of drug treatment,[30] EDSP provides a new and more established decision support system to include environmental considerations in drug prescription. The term of EDSP is used to describe the combination of two prescription optimization methods – reducing the usage or doses of medications, and prescribing decisions basing on the excretion profiles of APIs. The dose of drugs prescribed plays a paramount role on the quantities of APIs entering into the environment.[31] Certainly, any reduction in API prescribing would lead to a proportional reduction in excreted APIs released into wastewater.[24,27,32] Moreover, lower doses also hold the potential to eliminate the subsequent need for disposal of leftovers, relieve adverse events associated with drug overdose, improved patient/ physician communication, avoid the accidental exposures as well as reduce health-care costs.[24,27] On the other hand, EDSP places an additional emphasis on the metabolism and excretion profiles of drugs rather than only the dose initially used by the patient. Within a same therapeutic class, and with similar therapeutic efficacies, more extensively metabolizable medicines which have more environment-friendly excretion profiles resulting in less

excretion of bioactive API residues would produce more negligible environmental footprints, thus could be favored for EDSP.[24,25] EDSP has been endorsed by International Pharmaceutical Federation [33] as a means to promoting the sustainable application of drugs. More importantly, as a drug administration route to prevent the adverse effects of APIs in the environment resulting from medical prescriptions, encouraging EDSP *i.e.* improved and rational prescribing practices has been well-accepted as an indispensable part during EPV implementation.[12,16,17]

Theoretically, optimistic efficiencies of EDSP should and can minimize the entry of APIs into the environment through excretion via urine and fecal material. However, EDSP might conflict with long-accepted clinical prescribing guidelines and tenet, so the translation of EDSP concept into clinical practice will mean to change the conventional prescribing behavior of physicians, which would certainly be a major challenge.[24,25,34] It is necessary to explore the attitudes of physicians as prescribers toward EDSP and the willingness of physician participation.[24] The opinions toward EDSP held by physicians play a pivotal role in determining its acceptability and future application. China is a populous country where prescribing practices of physicians may have a significant impact on the global environment. Therefore, the present study was carried out among Chinese physicians prescribing medications in Hubei, a province locating in Central China, to assess their perceptions about API pollution in environment and EPV, and most importantly, their attitudes regarding EDSP from the perspective of EPV. The findings can provide an insight into the potential opportunities and challenges for EDSP and EPV implementation.

METHODS

A descriptive, cross-sectional survey involving authorized physicians presently working at government general hospitals in Hubei province, China, who were willing to participate in the study, was undertaken to assess their perceptions about API pollution in environment and EPV, in particular, their attitudes toward EDSP using a self-developed questionnaire. The study was granted approval from the Ethics Committee of Wuhan University of

Science and Technology, and was conducted for over a period of 4 months from March to June, 2019.

The initial draft of survey questionnaire was developed using information from the relevant published studies about API pollution in environment , EPV and EDSP. The respondents were informed about the basic concepts of EPV and EDSP on the first page of the questionnaire. And a total of 25 structured questions divided into three sections were included in the survey questionnaire, which required about 10-15 minutes to complete. The first section consisted of 5 questions about respondent physicians' socio-demographic characteristics, including gender, age, education background, specialty, and years of experience. The second section included 7 question items designed to capture the perceptions toward API pollution in environment and EPV. A 5-point Likert-scale format was used in the data collection in this section (1: strongly disagree, 2: disagree, 3: neutral, 4: agree, and 5: strongly agree). The third section of the survey questionnaire included 13 items designed to assess the physicians' perceptions and attitudes toward EDSP from the perspective of EPV.

Two specialists in the investigated field were asked to evaluate the clarity, content validity, relevance, and conciseness of the items in the questionnaire. Then pretesting of the questionnaire was done on a convenient sample of 20 physicians, who were not included in the final survey, to examine the validity and acceptability of the questionnaire. The overall Cronbach's alpha value was obtained as 0.788. Based on the comments and suggestions on the content, quantity of questions and the questionnaire structure provided by 2 specialists and 20 physicians from the pre-test stage, the final survey questionnaire was prepared. The final questionnaire was developed in English as the original language, then translated into Chinese and back into English.

The initial list of about 809 physicians distributed among 5 hospitals was used as the target sampling frame. The sampling of the hospitals was a convenient one, determined by the proximity of the hospital administrators to the authors. From this list, 400 physicians were randomly selected for inclusion in this survey. The developed questionnaire was

mailed to collect data from physicians *via* email addresses provided by the hospital administrators. A confirmation email together with an explanatory letter about the survey's purpose and objectives were firstly sent to the respondents. After returning their confirmation letters, the responding physicians received copies of the electronic questionnaire *via* email, and were requested to complete the questionnaire then return it within next 3 days to the researchers. Two weeks after sending the questionnaire, a follow-up reminder postcard was sent to the non-responder to increase the response rate. Each respondent participated in the survey voluntarily. Those who were not willing to participate in or did not return completed questionnaires within the stipulated time period were excluded from this study.

The collected data were entered into SPSS20.0 for analysis. Results were presented as numbers (percentages) for categorical variables, and mean (standard deviation (S.D.)) for quantitative variables. Any relationship between the categorical data was determined using Chi-square test. Independent t test was applied to compare the mean perception scores of the two groups. The differences between pair-wise groups were detected using the one-way ANOVA with post hoc Tukey's HSD analysis for multiple comparisons. Differences were statistically significant when the p value was less than 0.05.

RESULTS

Respondents' Characteristics

By the end of the study period, 284 (71%) of 400 randomly selected Chinese physicians had agreed to participate and responded to the survey, yielding 262 completed questionnaires available for analysis (overall effective response rate: 66%). The respondents' age ranged between 25 and 63 years with a mean of 43.6 (S.D.:12.3) years. Table 1 presented the demographic information of respondents. The gender, age, specialty, or years of experience distribution of physician respondents was approximately equal. Majority of respondents (65%) held postgraduate qualifications, which was in accordance with the popularization and advances of medical postgraduate education in

China.[35]

Perceptions toward API pollution in environment and EPV

EDSP has been well-accepted as an essential element of EPV practice in the control of API pollution in environment.[12,16,17] Therefore, the perceptions toward API pollution and EPV were collected from 262 physicians using 5-point Likert scales. Data shown in Table 2 revealed that the responding physicians' overall perception towards API pollution in environment and EPV was positive. Most respondents (80%, 89%, 88% and 80%, respectively) agreed or strongly agreed the entry of API residues into the environment (Q1), their environmental and ecological adverse effects (Q2), the necessity to minimize the entrance of APIs into the environment (Q3), as well as the importance of the administration of medication use in health-care practices for the API pollution control (Q5). As for the reverse-score item "*The control of API pollution is none of my business, because it should be the responsibility of environmental experts and regulators*."(Q4), only 4% respondents agreed, suggesting most physicians realized their own responsibility in the control of API pollution. Then the physicians were asked about whether they agree with EPV, an intervention emphasizing the control of upstream routes of APIs entry to the environment (Q6-7). It was encouraging to find that 60% believed that "*EPV is an effective tool to control the entrance of APIs into the environment*", and 64% claimed that they would endorse and were very pleased to participate in. However, there were a considerable portion (36-37%) of respondents felt undecided, suggesting their uncertainty regarding EPV. The results of the univariate analysis using independent t or one-way ANOVA test of the above variables in perceptions with regards to the respondents' gender, age, education background, specialty, and years of experience groups were not significant (p>0.05).

Perceptions and attitudes toward EDSP

The emphasis of this survey was to determine the perceptions and attitudes of physicians toward EDSP, an emerging prescribing concept as an environmentally better alternative in

the clinical use of medicines,[24,25] in order to support its usage, participation and feasibility. As shown in Table 3, we firstly detect the possible factors affecting the physicians' decision process for drug prescription (Q1). An overwhelming majority (94-100%) of physicians supported that efficacy, safety or cost of medicines affected their prescription decisions, which was in line with the well-accepted traditional rational prescription principle, that is, that the selection of drugs should be based on efficacy, safety and cost considerations.[30,36] However, none was environmentally conscious in their prescribing. And the evaluation of pharmacokinetic property as the key basis for EDSP [24] was incorporated into the prescribing process only by 22% respondents. Nevertheless, it was encouraging that 65% physicians were aware of their responsibilities for reducing API releases to environment, despite the fact that 31% were undecided (Q2). Almost all the physician respondents had not previous heard of EDSP (Q3), however, the effectiveness of EDSP in the control of the entrance of APIs into the environment was agreed or strongly agreed by about half (53%) respondents (Q4).

In view of two different 'front-of-pipe' approaches under the EDSP design,[24,25,28,29] we explored the physicians' attitudes toward reducing the dosage or usage of medications (low-dose prescribing), and basing prescribing decisions on drugs' excretion profiles (prescribing of drugs possessing environment-friendly excretion profiles), respectively. According to the theoretical analysis on the lower-dose prescribing,[24,25,27] a total of 8 possible benefits of low-dose prescribing had been summarized (Q5). Among them, 3 benefits related to the environmental issues (i.e. *Reducing the environmental loading of API residues from patients' excretions*, *Eliminating the subsequent need and cost for disposal of pharmaceutical leftovers*, and *Improving public trust—by reducing hidden and unwelcomed exposure of humans to trace levels of numerous APIs via potable water and contaminated foods*.) were supported by most physicians (92-98%). However, the item "*Improving therapeutic efficacy via minimizing off-target side-effects related to dosage, and thus enhancing pharmaceutical compliance*." was least recognized as the positive outcome of low-dose prescribing. This finding was in accordance with the result that all

the respondents worried that the low-dose prescribing could not achieve ideal therapeutic efficacy, and might delay treatment (Q6). On the other hand, the importance of prescribing based on drugs' excretion profiles, the other element of EDSP, was agreed or strongly agreed by a solid majority (75%) of respondents (Q7). However, being different from findings from the same question posed for low-dose prescribing (Q6), few (13%) respondents worried about the therapeutic efficacy of prescribing on drugs' excretion profiles (Q8). Most (84%) physicians placed misgivings about the complexity and professionalization of drug evaluation and EDSP design based on the excretion profile and pharmacokinetics (Q8). In addition, the availability of the related data as well as the long time period that will be taken to popularize in clinical practice were considered by most respondents (73-99%) as physicians' concerns regarding these two ways to achieve EDSP (Q6 and Q8).

All the responding physicians were not satisfied with knowledge on EDSP (Q9), as well as did not feel confident toward EDSP (Q10). Accordingly, about half (51%) respondents would adopt a wait-and-see approach for EDSP. And 46% reported that they would follow conservative EDSP strategies, such as promoting rational prescribing at precise doses, avoiding overprescribing and mis-prescribing (Q11). The most important perceived barrier to the effective implementation of EDSP under the perspective of EPV in China was "*poor awareness of EDSP and EPV*", which was supported by 39% respondents. And the item "*lack of available data related to EDSP under the perspective of EPV*" was ranked as the second important barrier, which was supported by 37% respondents (Q12). A majority of (78%) respondents claimed that, if EDSP is successfully translated into clinical treatment, they would be very pleased to participate in the related activities in their future practice(Q13).

When assessing for differences in demographic factors (gender, age, education background, specialty, and years of experience), we only found the responses from two questions (Q1 and Q11) on perceptions and attitudes toward EDSP could be significantly influenced by specialty. Compared to surgeons and physicians in other specialties, the

internal medicine physicians appeared to offer significantly more support that the pharmacokinetics of medicines currently affected their prescription decisions (Q1), and want to firstly choose the EDSP behaviors rather than take a wait-and-see approach (Q11) ($p<0.01$). In particular, all 7 respondents who wanted to *implement the low-dose prescribing* or *prescribe drugs possessing environment-friendly excretion profiles as much as possible* were physicians working in the internal medicine specialties.

DISCUSSION

It has been five years since the concept of EDSP was first proposed.[24] And the indispensable role of EDSP in the practice of EPV, a promising source control strategy for API pollution from the perspective of drug administration, has already been well accepted in theory.[12,16,17] But unfortunately, this theoretically efficacious solution for the environmental issues caused by excreted APIs is so far still on the conceptual level, and its conceptualisation has been rarely applied to real cases, which also restricts the empirical domain of EPV. In order to assure and promote the practical application of EDSP and EPV, it is necessary to firstly explore the acceptance of these new concepts by the involved stakeholders, which is prerequisite to subsequent behavioral change and efficient participation.

In China, the main prescribers were physicians within health-care systems. Of course, physicians should be environmentally conscious in their prescribing, and prescribe those drugs that might have minimal environmental impact.[37] Hubei province is one of the national leaders in health-care industry and pharmaceutical consumption in China.[18] The 2018 China Health Statistical Yearbook reported that, in China, there were 64.4% health workers were working in hospitals in 2017, with 81.0% of them in government general hospitals.[38] Therefore, the physician samples included in this study were randomly selected from 5 government general hospitals in Hubei province. Demographic data based on gender, age, education background, specialty, and years of experience indicated the surveyed physician samples were generally representative of Chinese physicians.

The survey data suggested that the environmental consciousness of Chinese physicians during prescribing was insufficient, which was demonstrated by the finding that no respondent identified the environmental impacts as the aspects regarding medicines affecting his(her) prescription decision. The possible reason might be due to the utter lack of the related education or training, which is in alignment with respondents' self-satisfaction with knowledge on EDSP (100% were not satisfied) and respondents' confidence toward EDSP (100% were not confident), considerable portions of respondents who chose "undecided" option in many Likert-type attitude and perception questions, as well as the conservative wait-and-see attitudes towards EDSP practice held by physicians. And "poor awareness of EDSP and EPV" was conceived as the most important barrier to the effective implementation of EDSP under the perspective of EPV. Therefore, the environmental sustainability considerations should begin to be included in the physicians' choice of prescription in China, and the long-established norms and guidelines in the practice of clinical prescribing should be accordingly modified under the principle of treating the environment and the patient as an interconnected, integral whole.[24] There is a need to optimize the prescribing of drugs with a view to reducing environmental exposure. Hospitals, medical centers and colleges could develop training and educational programs to inform physicians prescribing medications and medical students about APIs in environment, the environmental consciousness during prescribing, the environmental impact of their professions, EPV and EDSP.

However, it is encouraging that the responding physicians' overall attitudes and perception concerning API pollution in environment as well as EDSP under an EPV perspective were positive, which would shape the motivation for the future practice. In recent years, along with the increasingly serious environmental pollution which has attracted the particular attention of Chinese government, the environmental awareness and initiatives of Chinese people have gradually been awakened.[18] Accordingly, most Chinese physician respondents showed their concerns about the environment problems caused by APIs. Using their professional knowledge on APIs, a majority of physicians

agreed the existence, potential risks of APIs in environment, and the effectiveness of EDSP under an EPV perspective in decreasing environmental exposure of excreted APIs based on the description on the basic concepts of EPV and EDSP provided in the questionnaire. Most respondents posed the eco-responsible attitudes and perceived their own responsibility for the control of API pollution linked to medical prescriptions as well as the implementation of EDSP under an EPV perspective, and importantly, expressed their wiliness to participate in EDSP and EPV activities.

In order to explore the possible factors influencing their future EDSP decision making, this survey studied the perceive benefits and concerns of two EDSP approaches, low-dose prescribing and prescribing of drugs possessing environment-friendly excretion profiles, respectively. Despite the fact that the necessity and benefits of these two EDSP approaches in the aspect of environmental protection were accepted by most responding physicians, the biggest concerns in low-dose prescribing and prescribing of drugs possessing environment-friendly excretion profiles were "*It can not achieve ideal therapeutic efficacy, and might delay treatment*" and "*Drug evaluation based on the excretion profile and pharmacokinetics is too complicated and professional*", respectively. Therefore, during the EDSP design from the perspective of EPV, special emphases should be given to how to ensure the therapeutic efficacy of the "environment-friendly" doses, and how to standardize and simplify the process of prescribing based on the drugs' environment-friendly excretion profiles.

Moreover, many physicians voiced their concerns about the availability of the related information required in EDSP design. In China, no data system is currently available to guide medical prescribing decisions in the clinical for selection of drugs having a low probability of environmental risks and hazards. However, there is a Swedish model which could be used as a reference.[26,37] Swedish Environmental Classification of Pharmaceuticals developed by Stockholm County Council is a simple and straightforward classification system for prescribing non environmentally- hazardous drugs, and has been widely used and well accepted among Swedish medical doctors. This easy-to-understand

classification classifies APIs on the Swedish market according to environmental risks and hazards of drugs in view of their persistence, bioaccumulation and toxicity data, and suggests substitution by alternatives with a lower risk or hazard index. We proposed to construct the similar classification system in China, so that physicians who wish to be environmentally conscious in their prescribing could have a reference to allow them to select the API with the lowest possible environmental impact with equivalent therapeutic activity.

Interestingly, as the major challenge for EDSP implementation which was worried about by its advocate Daughton,[24] the issue "*changing the prescribing behavior of physicians*" appeared to be regarded as a small matter by most physicians, because only 21% and 24% respondents chose the item "*It will change my prescribing habits, thus is too troublesome*" as their concern regarding the low-dose prescribing and prescribing of drugs possessing environment-friendly excretion profiles, respectively (Table3, Q6 and 8). And only 6% physician respondents considered the item "*It conflicts with long-accepted prescribing guidelines*" as the most major perceived barrier to the effective implementation of EDSP (Table3, Q12).This results suggested the physicians were willing to change their prescribing habits in order to make their due contributions to control the environmental pollution by APIs.

In addition, we found there was a tendency among the internal medicine physicians to have stronger intentions to attempt EDSP practice than physicians from other specialties, which might be due to their better acquaintance with the pharmacokinetic properties and excretion profile of drugs. There is thus the expectation that it is feasible to first implement EDSP practice from the perspective of EPV in the internal medicine department. Furthermore, nearly half responding physicians were inclined to adopt rational prescribing as the EDSP behavior that they want to firstly choose. Rational prescribing is a classical principle concept of drug selection of in the field of personalized treatment or health-care.[30] Based on its high acceptability, further promoting rational prescribing to control excess medication prescription is a good first approach to

implement EPV in the health-care system to reduce API pollution at the source. In fact, recent emphasis of rational prescribing has been given to Personalized Health-care through selection of optimal APIs and determination of individual dosages.[26] Personalized adjustment of drug administration holds the potential for enhancing therapeutic outcomes, while simultaneously reducing the environmental risks of APIs. Furthermore, considering the faithfulness of physicians prescribing medicines to rational prescribing principles, it is necessary to refine the rational prescribing concept through integrating the environmental constituent into the prescribing decision, under the premise that this integration does not jeopardize the quality of delivered health care. This upgraded rational prescribing principle would guide physicians to include environmental sustainability considerations in their practical choice of prescription.

This study only enrolled physicians from one province in China, which might weaken the generalizability of results. Further studies with larger samples should be conducted to verify our findings.

In conclusion, to the best of our knowledge, this is the first study that explored the physicians' perceptions and attitudes toward EDSP from the perspective of EPV, a sustainable prescription approach to minimize the environmental loads and risks of excreted API residues from the source. The results suggested that the majority of Chinese physicians had positive attitude towards EDSP from the perspective of EPV. Physicians agreed the existence of APIs in environment, worried about the potential environmental and ecological risks of API residues, supported the effectiveness and necessity of EDSP under an EPV perspective in decreasing environmental exposure of excreted APIs, and importantly, showed their willingness to participate in the EDSP practices. Nevertheless, at present, the environmental consciousness of Chinese physicians during prescribing is seriously insufficient, which was demonstrated by the finding that no respondent identified the environmental impacts as the aspects regarding medicines affecting his(her) prescription decision, showed their self-satisfaction with knowledge on EDSP and confidence toward EDSP. The most important barrier to the effective implementation of

EDSP was identified as "*poor awareness of EDSP and EPV*". And most responding physicians reported that they held the wait-and-see or conservative attitudes towards EDSP practice. Furthermore, the biggest concerns in low-dose prescribing and prescribing of drugs possessing environment-friendly excretion profiles, two EDSP approaches, were "*It can not achieve ideal therapeutic efficacy, and might delay treatment*" and "*Drug evaluation based on the excretion profile and pharmacokinetics is too complicated and professional*", respectively. In addition, the availability of the related information required in EDSP design was also taken into consideration. An unexpected finding in this survey was that only few respondents were bothered by the issue that EDSP changed the prescribing behavior of physicians, which was identified as the major challenge for EDSP implementation by its advocate Daughton (2014a). This was in line with the responding physicians' eco-responsible attitudes toward API pollution in environment. Moreover, we found that the internal medicine physicians might be more initiative to engage in EDSP behaviors than physicians from other specialties.

Based on the above findings, we concluded some recommendations for implementing EDSP from the perspective of EPV:

1. Introducing and strengthening the medical training and education about APIs in environment, environmental consciousness during prescribing, the environmental impact of their professions, EPV and EDSP.

2. Further promoting rational prescribing to control excess medication prescription, which is a good first approach to implement EPV in the health-care system.

3. Integrating the environmental constituent into the rational prescribing principles.

4. Building the database to allow for acquiring the related information to prescribe non environmentally-hazardous drugs, select the effective and "environment-friendly" doses, understand the drugs' environment-friendly excretion profiles, *etc*. And the Swedish Environmental Classification of Pharmaceuticals could provide helpful sample materials.

5. Constructing the process model of EDSP from the perspective of EPV, in order to ensure the quality, standardization and convenience of EDSP process.

6. Implementing EDSP practice from the perspective of EPV first in the internal medicine department.

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Contributors JW conceived of the original idea for the study, designed the questionnaire, obtained ethical approval, carried out the statistical analysis, drafted the paper and is overall guarantor. SL contributed to the preparation of the data set and interpreted results . BH contributed to the study design, interpretation of results and commented on drafts of the paper.

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Competing interests None declared.

Patient consent Not required.

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Table 1 Demographic information and knowledge score of Chinese physicians participating in the study. (*n*=262)

Participant attribute	Number	% of respondents
Gender		
Male	124	47
Female	139	53
Age		
20-40 years	125	48
> 40 years	137	52
Postgraduate training		
Yes	170	65
No	92	35
Job category		
Internal medicine	102	39
Surgery	98	37
Others	62	24
Years of experience		
≤10	92	35
11-20	96	37
>20	74	28

Table 2 Chinese physicians' perceptions toward API pollution in environment and EPV. (*n*=262)

Survey Question/Statement	Responses, number (%)				
	Strongly agree	Agree	Undecided	Disagree	Strongly Disagree
Q1: APIs used in health-care practices could finally enter into the environment.	96(37)	113(43)	45(17)	8(3)	0(0)
Q2: API residues in environment could cause adverse effects on ecosystem, wildlife species, even human beings.	126(48)	108(41)	26(10)	2(1)	0(0)
Q3: It is necessary to minimize the entrance of APIs into the environment.	104(40)	125(48)	31(12)	2(1)	0(0)
Q4: The control of API pollution is none of my business, because it should be the responsibility of environmental experts and regulators.	5(2)	6(2)	73(28)	80(31)	98(37)
Q5: API pollution could be ultimately traced back to the use of medications in health-care practices.	113(43)	96(37)	50(19)	3(1)	0(0)
Q6: If there is an intervention emphasizing the control of upstream routes of API entry to the environment, I would endorse it, and be very pleased to cooperate in its implementation, if my participation is needed.	68(26)	99(38)	94(36)	1(0)	0(0)
Q7: According to the description on the basic concept of EPV provided on the first page of this questionnaire, I think EPV is an effective tool to control the entrance of APIs into the environment.	83(32)	74(28)	98(37)	5(2)	2(1)

Table 3 Assessment of Chinese physicians' perceptions and attitudes toward EDSP. (*n*=262)

Survey Question/Statement	Response	Number	% of respondents
Q1: At present, the aspects regarding medicines affecting my prescription decision include: *	● Efficacy	262	100
	● Safety	258	98
	● Cost and economy	246	94
	● Convenience	188	72
	● Pharmacokinetics	57	22
	● Marketing and promoting	139	53
	● Environmental impacts	0	0
Q2: As prescribers, physicians bear a responsibility for reducing API releases to environment.	Strongly agree	86	33
	Agree	83	32
	Undecided	81	31
	Disagree	12	5
	Strongly disagree	0	0
Q3: Previous to this survey, I have heard of EDSP.	Yes	260	99
	No	2	1
Q4: According to the description on the basic concept of EDSP provided on the first page of this questionnaire, I think EDSP is an effective tool to control the entrance of APIs into	Strongly agree	54	21
	Agree	96	37
	Undecided	101	39
	Disagree	9	3

the environment.	Strongly disagree	2	1
Q5: I think the benefits of low-dose prescribing include:*	• Reducing the environmental loading of API residues from patients' excretions.	257	98
	• Eliminating the subsequent need and cost for disposal of pharmaceutical leftovers	240	92
	• Reducing health-care expenditures for patients.	104	40
	• Improving therapeutic efficacy *via* minimizing off-target side-effects related to dosage, and thus enhancing pharmaceutical compliance.	75	29
	• Protecting public health by unintended poisonings by drugs (especially infants, toddlers, and children) resulted from inappropriate storage or disposal.	238	91
	• Reducing drug diversion and the profound problems with attendant abuse of certain drugs and misuse of others.	215	82
	• Improving public trust—by reducing hidden and unwelcomed exposure of humans to trace levels of numerous APIs via potable water and contaminated foods.	242	92

	● Improving patient/ physician communication.	89	34
Q6: My concerns regarding the low-dose prescribing are:*	● It can not achieve ideal therapeutic efficacy, and might delay treatment.	262	100
	● The lowest effective dose with environmental safety is not certain and available.	259	99
	● It is a new prescribing concept, therefore, a long time will be taken to popularize it in clinical practice.	207	79
	● It will change my prescribing habits, thus is too troublesome.	55	21
Q7: It is necessary to emphasize on the metabolism and excretion of drugs rather than the initially ingested dose by the patient, because the emission of APIs into the environment *via* sewers is dictated by the excretion profile and pharmacokinetics of the different types of pharmaceutical compounds.	Strongly agree	79	30
	Agree	123	45
	Undecided	48	18
	Disagree	11	4
	Strongly disagree	1	0
Q8: My concerns regarding the prescribing of drugs possessing environment-friendly excretion profiles are:*	● It can not achieve ideal therapeutic efficacy, and might delay treatment.	35	13
	● Under the EDSP design, drug evaluation based on the excretion profile and pharmacokinetics is too complicated and	219	84

	professional.		
	● There is no available accurate data on the excretion profile and pharmacokinetics of drugs.	190	73
	● It is a new prescribing concept, therefore, a long time will be taken to popularize it in clinical practice.	211	81
	● It will change my prescribing habits, thus is too troublesome.	62	24
Q9: My self-satisfaction with knowledge on EDSP.	Agree	0	0
	Disagree	262	100
Q10: My confidence toward EDSP.	Agree	0	0
	Disagree	262	100
Q11: For now, the EDSP behavior that I want to firstly choose is:	● None. I will take a wait-and-see approach.	134	51
	● I will promote rational prescribing at precise doses, avoid over-prescribing and mis-prescribing.	121	46
	● I will implement the low-dose prescribing.	3	1
	● I will prescribe drugs possessing environment-friendly excretion profiles as much as possible.	4	2

Q12: I think the most major perceived barrier to the effective implementation of EDSP under the perspective of EPV in China is：	● Poor awareness of EDSP and EPV.	101	39
	● Lack of an administrative framework for EDSP under the perspective of EPV.	50	19
	● Lack of available data related to EDSP under the perspective of EPV.	96	37
	● It conflicts with long-accepted prescribing guidelines.	15	6
Q13: I am very pleased to participate in EDSP activities in my future practice if it is successfully translated into clinical treatment.	Strongly agree	85	32
	Agree	121	46
	Undecided	53	20
	Disagree	3	1
	Strongly disagree	0	0

574 * Multiple responses were permitted, percentages do not add to 100%.

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	Reporting Item	Page Number
Title		
#1	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patientcenteredness, timeliness, cost, efficiency, and equity of healthcare)	Page 1
Abstract		
#02a	Provide adequate information to aid in searching and indexing	Page 1-2
#02b	Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	Page 1-2

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Available knowledge	#4	Summary of what is currently known about the problem, including relevant previous studies	Page 3-5
Rationale	#5	Informal or formal frameworks, models, concepts, and / or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	Page 5
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Chinese physicians' attitudes toward eco-directed sustainable prescribing from the perspective of ecopharmacovigilance: a cross-sectional study

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ABSTRACT

Introduction Eco-directed sustainable prescribing (EDSP) is an effective upstream way to reduce the environmental footprints of active pharmaceutical ingredients (APIs), a kind of emerging contaminants, from the patients' excretion. EDSP is one of key steps in the program of ecopharmacovigilance (EPV), a drug administration route on API pollution.

Objective To assess the attitudes of physicians prescribing medicines regarding EDSP

from the perspective of EPV.

Design A cross-sectional study conducted from March to June, 2019.

Setting 5 government general hospitals in Hubei Province, China.

Participants 405 physicians were randomly selected, and 262 valid questionnaires were obtained.

Outcome measures A self-developed questionnaire, which inquired about participant characteristics, perceptions and attitudes toward API pollution, EPV and EDSP from an EPV perspective, was e-mailed to collect data from physicians.

Results Most physicians agreed the existence of APIs in environment, worried about the potential environmental and ecological risks of API residues, supported the effectiveness and necessity of EDSP under an EPV perspective in decreasing environmental exposure of excreted APIs, and showed their willingness to participate in the EDSP practices. Nevertheless, no respondent identified the environmental impacts as the aspects regarding medicines affecting his(her) prescription decision, none was satisfied with knowledge on EDSP and showed confidence toward EDSP. The most important barrier to the effective implementation of EDSP was identified as "*poor awareness of EDSP and EPV*". Most responding physicians (97%) reported that they held the wait-and-see or conservative attitudes towards EDSP practice. The biggest concerns in *low-dose prescribing* and *prescribing of drugs possessing environment-friendly excretion profiles*, two EDSP approaches, were the possible negative impact on therapeutic outcomes, and too complicated and professional drug evaluation process, respectively.

Conclusions Chinese physicians had positive attitudes towards EDSP from the perspective of EPV. However, their environmental consciousness during prescribing and the related education were insufficient.

Strengths and limitations of this study

- To the best of our knowledge, this is the first study that explored the physicians' perceptions and attitudes toward eco-directed sustainable prescribing (EDSP) from the perspective of ecopharmacovigilance (EPV), a sustainable prescription approach to minimize the environmental loads and risks of excreted active pharmaceutical ingredient (API) residues at their sources.
- Based on the survey results, we proposed some recommendations for further implementing EDSP from the perspective of EPV in practice.
- The main limitation of this study is the sampling bias.

INTRODUCTION

The occurrence of active pharmaceutical ingredients (APIs), a kind of emerging contaminants (ECs) without standard regulations, in the environment worldwide has become an issue of special importance.[1-5] As a drug administration route on environment pollution caused by APIs, ecopharmacovigilance (EPV) is an emerging science of detection, evaluation, understanding and prevention the adverse effects of APIs in the environment.[6-14] In recent years, an approach termed eco-directed sustainable prescribing (EDSP), [15] which was proposed to prevent the adverse effects of APIs in the environment resulting from medical prescriptions, has been well-accepted as an indispensable part during EPV implementation.[8,12,13] However, EDSP might conflict with long-accepted clinical prescribing guidelines and tenet. It is necessary to explore the attitudes of prescribers toward EDSP. [15]

As a critical part of modern life, pharmaceutical drugs are abundantly used in health-care practices around the world.[5] The environmental discharge of APIs in a continuous and unsupervised way as well as their inadequate removal during wastewater treatment processes have led to their detection in the various environmental matrices at levels of concern.[2-5] Considering their potent biological activities even at very low concentrations, API residues have been recognized to pose potential risks and hazards to the natural environment, ecology and human health due to long-term exposures.[6,16-18] Therefore, it is urgent to address this issue, aiming to minimize the environmental loads and risks of API residues. Based the fact that API pollution could be ultimately traced back to the use of medications in health-care practices, EPV focuses on the clinical application of active pharmaceutical management strategies to decrease the API emission at the sources and minimize the environmental footprint of the health-care industry.[9,13] The sources of APIs in environment include excretion from drug-consuming patients and animals, inappropriate deposition of expired or unwanted pharmaceutical products, manufacturing plant wastes, hospital wastes, *etc*.[19-23] Thereinto, patients' excretion in

forms of parent APIs or active metabolites has been well-accepted to constitute the major contribution to most API pollutants in the environment.[15,24-26]

Since normal physiological excretion of APIs in drug-consuming patients cannot be prevented, the optimized administration of pharmaceuticals ensuring satisfactory but not too high pharmacologically active concentrations in patients might be a key protective measure against excessive API entry to the environment from excretion.[15,27-29] Driven by this idea, EDSP was recommended by Daughton [15] to reduce the environmental load of excreted APIs. As prescribers are commonly confronted with more than one choice of drug treatment,[30] EDSP provides a new and more established decision support system to include environmental considerations in drug prescription. The term of EDSP is used to describe the combination of two prescription optimization methods – *low-dose prescribing* and *prescribing of drugs possessing environment-friendly excretion profiles*. The dose of drugs prescribed plays a paramount role on the quantities of APIs entering into the environment.[31] Certainly, any reduction in API prescribing would lead to a proportional reduction in excreted APIs released into wastewater.[15,27,32] Moreover, lower doses also hold the potential to eliminate the subsequent need for disposal of leftovers, relieve adverse events associated with drug overdose, improved patient/ physician communication, avoid the accidental exposures as well as reduce health-care costs.[15,27] On the other hand, EDSP places an additional emphasis on the metabolism and excretion profiles of drugs rather than only the dose initially used by the patient. Within a same therapeutic class, and with similar therapeutic efficacies, more extensively metabolizable medicines which have more environment-friendly excretion profiles resulting in less excretion of bioactive API residues would produce more negligible environmental footprints, thus could be favored for EDSP.[15,25] EDSP has been endorsed by International Pharmaceutical Federation [33] as a means to promoting the sustainable application of drugs.

However, the translation of EDSP concept into clinical practice will mean to change the conventional prescribing behavior of physicians, which would certainly be a major

challenge.[15,25,34] The opinions toward EDSP held by prescribers play a pivotal role in determining its acceptability and future application. China is a populous country where prescribing practices of physicians may have a significant impact on the global environment. In order to explore the attitudes of prescribers toward EDSP and their willingness of participation, the present study was carried out among Chinese physicians prescribing medications in Hubei, a province locating in Central China, to assess the physicians' attitudes toward EDSP from the perspective of EPV and obtained some interesting findings. This is an innovative subject and may contribute to policy development.

METHODS

Study design

A descriptive, cross-sectional survey involving authorized physicians presently working at government general hospitals in Hubei province, China, who were willing to participate in the study, was undertaken to assess their perceptions about API pollution in environment and EPV, in particular, their attitudes toward EDSP using a self-developed questionnaire. The study was granted approval from the Ethics Committee of Wuhan University of Science and Technology, and was conducted for over a period of 4 months from March to June, 2019.

Study population

The initial list of about 809 physicians distributed among 5 hospitals was used as the target sampling frame. The sampling of the hospitals was a convenient one, determined by the proximity of the hospital administrators to the authors. From this list, 405 physicians were randomly selected for inclusion in this survey using an 2:1 proportion.

The sample size was determined by considering the availability of subjects and the feasibility of enrolling physicians. A review of existing literature [35-38] indicated a sample size of 200-400 physicians would be adequate to ensure data analysis and generalisability of responses.

Questionnaire development

A self-developed questionnaire was used in this study, since there is no standardized material for testing attitudes about EDSP. The initial draft of survey questionnaire was developed using information from the relevant published studies regarding to API pollution in environment,[1-5,1,16-26] EPV [6-14] and EDSP [15,25,27-29] after performing a thorough literature review. The initial questions were devised, developed and refined for clarity by all authors during several in-person group discussions.

The respondents were informed about the basic concepts of EPV and EDSP on the first page of the questionnaire. A total of 25 structured questions divided into three sections were included in the survey questionnaire, which required about 10-15 minutes to complete. The first section consisted of 5 questions about respondent physicians' socio-demographic characteristics, including gender, age, education background, specialty, and years of experience. The second section included 7 question items designed to capture the perceptions toward API pollution in environment and EPV. A 5-point Likert-scale format was used in the data collection in this section (1: strongly disagree, 2: disagree, 3: neutral, 4: agree, and 5: strongly agree). The third section of the survey questionnaire included 13 items designed to assess the physicians' perceptions and attitudes toward EDSP from the perspective of EPV.

Two specialists in the investigated field were asked to evaluate the clarity, content validity, relevance, and conciseness of the items in the questionnaire. For validation of the questionnaire, pretesting of the questionnaire was done on a convenient sample of 20 physicians, who were not included in the final survey, to examine the validity and acceptability of the questionnaire. After discussion and minor modification, the final survey questionnaire was approved with overall and separate Cronbach's alpha values, and Kaiser-Meyer-Olkin (KMO) measures >0.700. The final questionnaire was developed in English as the original language, then translated into Chinese and back into English.

Data collection

The developed questionnaire was mailed to collect data from physicians *via* email addresses provided by the hospital administrators. A confirmation email together with an explanatory letter about the survey's purpose and objectives were firstly sent to the respondents. After returning their confirmation letters, the responding physicians received copies of the electronic questionnaire *via* email, and were requested to complete the questionnaire then return it within next 3 days to the researchers. Two weeks after sending the questionnaire, a follow-up reminder postcard was sent to the non-responder to increase the response rate. Each respondent participated in the survey voluntarily. All questionnaires were check by J.W. and S.L to ensure data quality. Those who were not willing to participate in or did not return completed questionnaires within the stipulated time period were excluded from this study.

Statistical analysis

The collected data were entered into SPSS20.0 for analysis. Results were presented as numbers (percentages) for categorical variables, and mean (standard deviation (S.D.)) for quantitative variables. Reliability and validity of the questionnaire were assessed using Cronbach's alpha coefficient and Bartlett's test of sphericity/KMO measures, respectively. Any relationship between the categorical data was determined using Chi-square test or Fisher's exact test. Independent t test was applied to compare the mean perception scores of the two groups. The differences between pair-wise groups were detected using the one-way ANOVA with post hoc Tukey's HSD analysis for multiple comparisons. Differences were statistically significant when the p value was less than 0.05.

Patient and public involvement

Patients and the public were not involved in the design and conception of this study.

RESULTS

Respondents' Characteristics

By the end of the study period, 284 (71%) of 405 randomly selected Chinese physicians

had agreed to participate and responded to the survey, yielding 262 completed questionnaires available for analysis (overall effective response rate: 65%). The respondents' age ranged between 25 and 63 years with a mean of 43.6 (S.D.:12.3) years. Table 1 presented the demographic information of respondents. The gender, age, specialty, or years of experience distribution of physician respondents was approximately equal. Majority of respondents (65%) held postgraduate qualifications, which was in accordance with the popularization and advances of medical postgraduate education in China.[39]

Reliability and validity of the questionnaire

The overall Cronbach's alpha and KMO values were obtained as 0.788 and 0.716, respectively. For the reliability of separate items of *API pollution in environment, EPV* and *EDSP*, the Cronbach's alpha values were 0.801, 0.792 and 0.865. The result for Bartlett's test of sphericity was $\chi_{(190)}$=938.8 and was statistically significant (p <0.001), suggesting a factorable intercorrelation matrix. For the construct validity of separate items of *API pollution in environment, EPV* and *EDSP*, KMO measures were 0.741, 0.789 and 0.712 , respectively.

Perceptions toward API pollution in environment and EPV

The perceptions toward API pollution and EPV were collected from 262 physicians using 5-point Likert scales. Data shown in Table 2 revealed that the responding physicians' overall perceptions towards API pollution in environment and EPV was positive. Most respondents (80%, 89%, 88% and 80%, respectively) agreed or strongly agreed the entry of API residues into the environment (Q1), their environmental and ecological adverse effects (Q2), the necessity to minimize the entrance of APIs into the environment (Q3), as well as the importance of the administration of medication use in health-care practices for the API pollution control (Q5). As for the reverse-score item indicating the control of API pollution is not physicians' responsibility (Q4), only 4% respondents agreed, suggesting most physicians realized their own responsibility in the control of API pollution. Then the

physicians were asked about whether they agree with EPV, an upstream intervention for controlling API entry to the environment (Q6-7). It was encouraging to find that 60% believed that EPV is an effective tool to control API entry to the environment, and 64% claimed that they would endorse and be very pleased to participate in. However, there were a considerable portion (36-37%) of respondents felt undecided, suggesting their uncertainty regarding EPV. The results of the univariate analysis using independent t or one-way ANOVA test of the above variables in perceptions with regards to the respondents' gender, age, education background, specialty, and years of experience groups were not significant (p>0.05).

Perceptions and attitudes toward EDSP from the perspective of EPV

Possible factors affecting the physicians' decision process for drug prescription

As shown in Table 3, an overwhelming majority (94-100%) of physicians supported that efficacy, safety or cost of medicines affected their prescription decisions (Q1), which was in line with the well-accepted traditional rational prescription principle, that is, that the selection of drugs should be based on efficacy, safety and cost considerations.[30,40] However, none was environmentally conscious in their prescribing. As the key basis for EDSP [15], the evaluation of pharmacokinetic property was incorporated into the prescribing process only by 22% respondents. Nevertheless, it was encouraging that 65% physicians were aware of their responsibilities for reducing API releases to environment, despite the fact that 31% were undecided (Q2). Almost all the physician respondents had not previous heard of EDSP (Q3), however, the effectiveness of EDSP in the control of the entrance of APIs into the environment was agreed or strongly agreed by about half (53%) respondents (Q4).

Physicians' attitudes toward *low-dose prescribing and prescribing based on drugs' excretion profiles,* two EDSP approaches

Low-dose prescribing is one of two different 'front-of-pipe' approaches under the EDSP design.[15,25,28,29] According to its theoretical analysis,[24,25,27] a total of 8 possible benefits of *low-dose prescribing* had been summarized (Q5). Among them, 3 benefits related to the environmental issues (i.e. reducing the API environmental loading from patients' excretions, reducing pharmaceutical leftovers, and improving public trust) were supported by most physicians (92-98%). However, the improvement on therapeutic efficacy was least recognized as the positive outcome of *low-dose prescribing*. This finding was in accordance with the result that all the respondents worried that the *low-dose prescribing* could not achieve ideal therapeutic efficacy, and might delay treatment (Q6).

On the other hand, the importance of *prescribing based on drugs' excretion profiles*, the other element of EDSP, was agreed or strongly agreed by a solid majority (75%) of respondents (Q7). However, being different from findings from the same question posed for *low-dose prescribing* (Q6), few (13%) respondents worried about the therapeutic efficacy of *prescribing on drugs' excretion profiles* (Q8). Most (84%) physicians placed misgivings about the complexity and professionalization of drug evaluation and EDSP design based on the excretion profile and pharmacokinetics (Q8).

In addition, the availability of the related data as well as the long time period that will be taken to popularize in clinical practice were considered by most respondents (73-99%) as physicians' concerns regarding these two ways to achieve EDSP (Q6 and Q8).

Physicians' attitudes toward EDSP

All the responding physicians were not satisfied with knowledge on EDSP (Q9), as well as did not feel confident toward EDSP (Q10). Accordingly, about half (51%) respondents would adopt a wait-and-see approach for EDSP. Furthermore, 46% reported that they would follow conservative EDSP strategies, such as promoting rational prescribing at precise doses, avoiding overprescribing and mis-prescribing (Q11). The most important perceived barrier to the effective implementation of EDSP under the perspective of EPV in

China was "*poor awareness of EDSP and EPV*", which was supported by 39% respondents. The lack of available data related to EDSP under the perspective of EPV was ranked as the second important barrier, which was supported by 37% respondents (Q12). A majority of (78%) respondents claimed that, if EDSP is successfully translated into clinical treatment, they would be very pleased to participate in the related activities in their future practice(Q13).

Group comparisons

When assessing for differences in demographic factors (gender, age, education background, specialty, and years of experience), we only found the responses from two questions (Q1 and Q11) on perceptions and attitudes toward EDSP could be significantly influenced by specialty. Compared to surgeons and physicians in other specialties, the internal medicine physicians appeared to offer significantly more support that the pharmacokinetics of medicines currently affected their prescription decisions (Q1), and want to firstly choose the EDSP behaviors rather than take a wait-and-see approach (Q11) (p<0.01). In particular, all 7 respondents who wanted to implement the *low-dose prescribing* or *prescribe drugs possessing environment-friendly excretion profiles* as much as possible were physicians working in the internal medicine specialties.

DISCUSSION

It has been more than five years since the concept of EDSP was first proposed.[15] The indispensable role of EDSP in the practice of EPV, a promising source control strategy for API pollution from the perspective of drug administration, has already been well accepted in theory.[8,12,13] But unfortunately, this theoretically efficacious solution for the environmental issues caused by excreted APIs is so far still on the conceptual level, and its conceptualisation has been rarely applied to real cases, which also restricts the empirical domain of EPV. In order to assure and promote the practical application of EDSP and EPV, it is necessary to firstly explore the acceptance of these new concepts by

the involved stakeholders, which is prerequisite to subsequent behavioral change and efficient participation.

In China, the main prescribers were physicians within health-care systems. Of course, physicians should be environmentally conscious in their prescribing, and prescribe those drugs that might have minimal environmental impact.[41] Hubei province is one of the national leaders in health-care industry and pharmaceutical consumption in China.[14] The 2018 China Health Statistical Yearbook reported that, in China, there were 64.4% health workers were working in hospitals in 2017, with 81.0% of them in government general hospitals.[42] Therefore, the physician samples included in this study were randomly selected from 5 government general hospitals in Hubei province. Demographic data based on gender, age, education background, specialty, and years of experience indicated the surveyed physician samples were generally representative of Chinese physicians.

The emphasis of this survey was to determine the perceptions and attitudes of physicians toward EDSP, an emerging prescribing concept as an environmentally better alternative in the clinical use of medicines.[15,25] But EDSP has been well-accepted as an essential element of EPV practice in the control of API pollution in environment.[8,12,13] Therefore, the perceptions toward API pollution and EPV were first studied. The results from Table 2 showed the positive overall perception of responding physicians towards API pollution in environment and EPV. Accordingly, it is encouraging that the responding physicians' overall attitudes and perceptions concerning API pollution in environment as well as EDSP under an EPV perspective were positive (Table 3), which would shape the motivation for the future practice. In recent years, along with the increasingly serious environmental pollution which has attracted the particular attention of Chinese government, the environmental awareness and initiatives of Chinese people have gradually been awakened.[14] Accordingly, most Chinese physician respondents showed their concerns about the environment problems caused by APIs. A majority of physicians agreed the existence, potential risks of APIs in environment, and the

effectiveness of EDSP under an EPV perspective in decreasing environmental exposure of excreted APIs. Most respondents posed the eco-responsible attitudes and perceived their own responsibility for the control of API pollution linked to medical prescriptions as well as the implementation of EDSP under an EPV perspective, and importantly, expressed their wiliness to participate in EDSP and EPV activities.

Our survey data suggested that the environmental consciousness of Chinese physicians during prescribing was insufficient, which was demonstrated by the finding that no respondent identified the environmental impacts as the aspects regarding medicines affecting his(her) prescription decision. The possible reason might be due to the utter lack of the related education or training, which is in alignment with respondents' self-satisfaction with knowledge on EDSP (100% were not satisfied) and respondents' confidence toward EDSP (100% were not confident), considerable portions of respondents who chose "undecided" option in many Likert-type attitude and perception questions, as well as the conservative wait-and-see attitudes towards EDSP practice held by physicians. "*Poor awareness of EDSP and EPV*" was conceived as the most important barrier to the effective implementation of EDSP under the perspective of EPV. Therefore, the environmental sustainability considerations should begin to be included in the physicians' choice of prescription in China, and the long-established norms and guidelines in the practice of clinical prescribing should be accordingly modified under the principle of treating the environment and the patient as an interconnected, integral whole.[24] There is a need to optimize the prescribing of drugs with a view to reducing environmental exposure.

In order to explore the possible factors influencing their future EDSP decision making, this survey studied the perceive benefits and concerns of two EDSP approaches, *low-dose prescribing* and *prescribing of drugs possessing environment-friendly excretion profiles*, respectively. Despite the fact that the necessity and benefits of these two EDSP approaches in the aspect of environmental protection were accepted by most responding physicians, the biggest concerns in *low-dose prescribing* and *prescribing of drugs possessing environment-friendly excretion profiles* were the possible negative impact on

therapeutic outcomes, and too complicated and professional drug evaluation process, respectively. Therefore, during the EDSP design from the perspective of EPV, special emphases should be given to how to ensure the therapeutic efficacy of the "environment-friendly" doses, and how to standardize and simplify the process of prescribing based on the drugs' environment-friendly excretion profiles.

Moreover, many physicians voiced their concerns about the availability of the related information required in EDSP design. In China, no data system is currently available to guide medical prescribing decisions in the clinical for selection of drugs having a low probability of environmental risks and hazards. However, there is a Swedish model which could be used as a reference.[26,41] Swedish Environmental Classification of Pharmaceuticals developed by Stockholm County Council is a simple and straightforward classification system for prescribing non environmentally- hazardous drugs, and has been widely used and well accepted among Swedish medical doctors. This easy-to-understand classification classifies APIs on the Swedish market according to environmental risks and hazards of drugs in view of their persistence, bioaccumulation and toxicity data, and suggests substitution by alternatives with a lower risk or hazard index. We proposed to construct the similar classification system in China, so that physicians who wish to be environmentally conscious in their prescribing could have a reference to allow them to select the API with the lowest possible environmental impact among the candidates with equivalent therapeutic activities.

Interestingly, as the major challenge for EDSP implementation which was worried about by its advocate Daughton,[15] the issue "changing the prescribing behavior of physicians" appeared to be regarded as a small matter by most physicians, because only 21% and 24% respondents chose this item as their concern regarding the *low-dose prescribing* and *prescribing of drugs possessing environment-friendly excretion profiles*, respectively (Table3, Q6 and 8). Only 6% physician respondents considered the item "*It conflicts with long-accepted prescribing guidelines*" as the most major perceived barrier to the effective implementation of EDSP (Table3, Q12).This results suggested the

physicians were willing to change their prescribing habits in order to make their due contributions to control the environmental pollution by APIs.

In addition, we found there was a tendency among the internal medicine physicians to have stronger intentions to attempt EDSP practice than physicians from other specialties, which might be due to their better acquaintance with the pharmacokinetic properties and excretion profile of drugs. There is thus the expectation that it is feasible to first implement EDSP practice from the perspective of EPV in the internal medicine department. Furthermore, nearly half responding physicians were inclined to adopt rational prescribing as the EDSP behavior that they want to firstly choose. Rational prescribing is a classical principle concept of drug selection of in the field of personalized treatment or health-care.[30] Based on its high acceptability, further promoting rational prescribing to control excess medication prescription is a good first approach to implement EPV in the health-care system to reduce API pollution at the sources. In fact, recent emphasis of rational prescribing has been given to Personalized Health-care through selection of optimal APIs and determination of individual dosages.[26] Personalized adjustment of drug administration holds the potential for enhancing therapeutic outcomes, while simultaneously reducing the environmental risks of APIs.

The main limitation of this study is the sampling bias. This study only enrolled physicians from one province in China, which might weaken the generalizability of results. Moreover, the sample size was not determined by precision analysis technique. Further studies with larger samples should be conducted to verify our findings.

In conclusion, to the best of our knowledge, this is the first study that explored the physicians' perceptions and attitudes toward EDSP, a sustainable prescription approach to minimize the environmental loads and risks of excreted API residues at their sources. The results suggested that the majority of Chinese physicians had positive attitude towards EDSP. Respondents agreed the existence of APIs in environment, worried about the potential environmental and ecological risks of API residues, supported the effectiveness and necessity of EDSP, importantly, showed their willingness to participate

in the EDSP practices. Nevertheless, at present, the environmental consciousness of Chinese physicians during prescribing is seriously insufficient, which is demonstrated by the finding that no respondent identified the environmental impacts as the aspect regarding medicines affecting his(her) prescription decision, none was satisfied with knowledge on EDSP and showed confidence toward EDSP. The most important barrier to the effective implementation of EDSP was identified as "*poor awareness of EDSP and EPV*". Accordingly, most responding physicians reported that they held the wait-and-see or conservative attitudes towards EDSP practice. Furthermore, the biggest concerns in *low-dose prescribing* and *prescribing of drugs possessing environment-friendly excretion profiles*, two EDSP approaches, were the possible negative impact on therapeutic outcomes, and too complicated and professional drug evaluation process, respectively. In addition, the availability of the related information required in EDSP design was also taken into consideration. An unexpected finding in this survey was that only few respondents were bothered by the issue that EDSP changed the prescribing behavior of physicians, which was identified as the major challenge for EDSP implementation by its advocate Daughton [15] This was in line with the responding physicians' eco-responsible attitudes toward API pollution in environment. Moreover, we found that the internal medicine physicians might be more initiative to engage in EDSP behaviors than physicians from other specialties.

Based on the above findings, we concluded some recommendations for implementing EDSP from the perspective of EPV:

1. Introducing and strengthening the related medical training and education. Hospitals, medical centers and colleges could develop training and educational programs to inform physicians prescribing medications and medical students about APIs in environment, the environmental consciousness during prescribing, the environmental impact of their professions, EPV and EDSP.

2. Further promoting rational prescribing to control excess medication prescription, which is a good first approach to implement EPV in the health-care system based on the

survey finding on the respondent physicians' preferred EDSP behaviors.

3. Integrating the environmental constituent into the rational prescribing principles. Considering the faithfulness of physicians prescribing medicines to rational prescribing principles, this upgraded rational prescribing principle would guide physicians to include environmental sustainability considerations in their practical choice of prescription.

4. Building the database to allow for acquiring the related information to prescribe non environmentally-hazardous drugs, select the effective and "environment-friendly" doses, understand the drugs' environment-friendly excretion profiles, *etc*. The Swedish Environmental Classification of Pharmaceuticals could provide helpful sample materials.

5. Constructing the process model of EDSP from the perspective of EPV, in order to ensure the quality, standardization and convenience of EDSP process.

6. Implementing EDSP practice from the perspective of EPV first in the internal medicine department.

Contributors JW conceived of the original idea for the study, designed the questionnaire, obtained ethical approval, carried out the statistical analysis, drafted the paper and is overall guarantor. SL contributed to the preparation of the data set and interpreted results . BH contributed to the study design, interpretation of results and commented on drafts of the paper.

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578 **Table 1** Demographic information and knowledge score of Chinese physicians
579 participating in the study. (*n*=262)

Participant' characteristics	Respondents No. (%)
Gender	
Male	124 (47)
Female	139 (53)
Age	
20-40 years	125 (48)
> 40 years	137 (52)
Postgraduate training	
Yes	170 (65)
No	92 (35)
Job category	
Internal medicine	102 (39)
Surgery	98 (37)
Others	62 (24)
Years of experience	
≤10	92 (35)
11-20	96 (37)
>20	74 (28)

Table 2 Chinese physicians' perceptions toward API pollution in environment and EPV. (*n*=262)

Survey Question/Statement	Respondents No. (%)				
	Strongly agree	Agree	Undecided	Disagree	Strongly Disagree
Q1: APIs used in health-care practices could finally enter into the environment.	96(37)	113(43)	45(17)	8(3)	0(0)
Q2: API residues in environment could cause adverse effects on ecosystem, wildlife species, even human beings.	126(48)	108(41)	26(10)	2(1)	0(0)
Q3: It is necessary to minimize the entrance of APIs into the environment.	104(40)	125(48)	31(12)	2(1)	0(0)
Q4: The control of API pollution is none of my business, because it should be the responsibility of environmental experts and regulators.	5(2)	6(2)	73(28)	80(31)	98(37)
Q5: API pollution could be ultimately traced back to the use of medications in health-care practices.	113(43)	96(37)	50(19)	3(1)	0(0)
Q6: If there is an upstream intervention for controlling API entry to the environment, I would endorse it, and be very pleased to participate in its implementation.	68(26)	99(38)	94(36)	1(0)	0(0)
Q7: Based on the description of EPV given on the first page of this questionnaire, I think EPV is an effective tool to control API entry to the environment.	83(32)	74(28)	98(37)	5(2)	2(1)

584 **Table 3** Assessment of Chinese physicians' perceptions and attitudes toward EDSP.
585 (*n*=262)

Survey Question/Statement	Response	Respondents No.(%)
Q1: At present, the aspects regarding medicines affecting my prescription decision include: *	● Efficacy	262 (100)
	● Safety	258 (98)
	● Cost and economy	246 (94)
	● Convenience	188 (72)
	● Pharmacokinetics	57 (22)
	● Marketing and promoting	139 (53)
	● Environmental impacts	0 (0)
Q2: As prescribers, physicians bear a responsibility for reducing API releases to environment.	Strongly agree	86 (33)
	Agree	83 (32)
	Undecided	81 (31)
	Disagree	12 (5)
	Strongly disagree	0 (0)
Q3: Previous to this survey, I have heard of EDSP.	Yes	260 (99)
	No	2 (1)
Q4: According to the description on the basic concept of EDSP provided on the first page of this questionnaire, I think EDSP is an effective tool to control the entrance of APIs into the environment.	Strongly agree	54 (21)
	Agree	96 (37)
	Undecided	101 (39)
	Disagree	9 (3)
	Strongly disagree	2 (1)
Q5: I think the benefits of *low-dose prescribing* include:*	● Reducing the environmental loading of API residues from patients' excretions.	257 (98)
	● Eliminating the subsequent need and cost for disposal of pharmaceutical leftovers	240 (92)
	● Reducing health-care expenditures for patients.	104 (40)
	● Improving therapeutic efficacy *via* minimizing off-target side-effects related to dosage, and	75 (29)

	thus enhancing pharmaceutical compliance.	
	● Protecting public health by unintended poisonings by drugs (especially infants, toddlers, and children) resulted from inappropriate storage or disposal.	238 (91)
	● Reducing drug diversion and the profound problems with attendant abuse of certain drugs and misuse of others.	215 (82)
	● Improving public trust—by reducing hidden and unwelcomed exposure of humans to trace levels of numerous APIs *via* potable water and contaminated foods.	242 (92)
	● Improving patient/ physician communication.	89 (34)
Q6: My concerns regarding the *low-dose prescribing* are:*	● It can not achieve ideal therapeutic efficacy, and might delay treatment.	262 (100)
	● The lowest effective dose with environmental safety is not certain and available.	259 (99)
	● It is a new prescribing concept, therefore, a long time will be taken to popularize it in clinical practice.	207 (79)
	● It will change my prescribing habits, thus is too troublesome.	55 (21)
Q7: It is necessary to emphasize on the metabolism and excretion of drugs rather than the initially ingested dose by the patient,	Strongly agree	79 (30)
	Agree	123 (45)

because the emission of APIs into the environment *via* sewers is dictated by the excretion profile and pharmacokinetics of the different types of pharmaceutical compounds.	Undecided	48 (18)
	Disagree	11 (4)
	Strongly disagree	1 (0)
Q8: My concerns regarding the *prescribing of drugs possessing environment-friendly excretion profiles* are:*	● It can not achieve ideal therapeutic efficacy, and might delay treatment.	35 (13)
	● Under the EDSP design, drug evaluation based on the excretion profile and pharmacokinetics is too complicated and professional.	219 (84)
	● There is no available accurate data on the excretion profile and pharmacokinetics of drugs.	190 (73)
	● It is a new prescribing concept, therefore, a long time will be taken to popularize it in clinical practice.	211 (81)
	● It will change my prescribing habits, thus is too troublesome.	62 (24)
Q9: My self-satisfaction with knowledge on EDSP.	Agree	0 (0)
	Disagree	262 (100)
Q10: My confidence toward EDSP.	Agree	0 (0)
	Disagree	262 (100)
Q11: For now, the EDSP behavior that I want to firstly choose is:	● None. I will take a wait-and-see approach.	134 (51)
	● I will promote rational prescribing at precise doses, avoid over-prescribing and mis-prescribing.	121 (46)
	● I will implement the low-dose prescribing.	3 (1)
	● I will prescribe drugs	4 (2)

	possessing environment-friendly excretion profiles as much as possible.	
Q12: I think the most major perceived barrier to the effective implementation of EDSP under the perspective of EPV in China is：	● Poor awareness of EDSP and EPV.	101 (39)
	● Lack of an administrative framework for EDSP under the perspective of EPV.	50 (19)
	● Lack of available data related to EDSP under the perspective of EPV.	96 (37)
	● It conflicts with long-accepted prescribing guidelines.	15 (6)
Q13: I am very pleased to participate in EDSP activities in my future practice if it is successfully translated into clinical treatment.	Strongly agree	85 (32)
	Agree	121 (46)
	Undecided	53 (20)
	Disagree	3 (1)
	Strongly disagree	0 (0)

586 * Multiple responses were permitted, percentages do not add to 100%.

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In your methods section, say that you used the SQUIREreporting guidelines, and cite them as:

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	Reporting Item	Page Number
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Abstract		
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#02b	Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	Page 1-2

Introduction			
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Available knowledge	#4	Summary of what is currently known about the problem, including relevant previous studies	Page 3-5
Rationale	#5	Informal or formal frameworks, models, concepts, and / or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	Page 5
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Methods			
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Intervention(s)	#08b	Specifics of the team involved in the work	Page 6-7
Study of the Intervention(s)	#09a	Approach chosen for assessing the impact of the intervention(s)	Page 6
Study of the Intervention(s)	#09b	Approach used to establish whether the observed outcomes were due to the intervention(s)	Page 7
Measures	#10a	Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability	Page 6-7
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Analysis	#11a	Qualitative and quantitative methods used to draw inferences from the data	Page 7
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	#13a	Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project	Page 7
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