International Journal of Clinical Pharmacy (2019) 41:1074–1084
https://doi.org/10.1007/s11096-019-00862-y

RESEARCH ARTICLE

Attitudes, knowledge and views on off-label prescribing in children among healthcare professionals in Malaysia

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Received: 8 May 2018 / Accepted: 7 June 2019 / Published online: 13 June 2019

Abstract

Background Off-label prescribing in children is associated with several prerequisites such as ensuring sound and scientific evidence and obtaining written consent prior to use of off-label drugs to ensure that protection is provided to patients and healthcare professionals. Adherence to the pre-requisites depends on the attitude, views and knowledge of the pharmacists and doctors involved in this practice. *Objective* To explore the attitudes, knowledge and views on off-label prescribing in children among hospital—based pharmacists and paediatric doctors. *Setting* The study was conducted in a 620-bedded general hospital located in the urban area of central Peninsular Malaysia. *Method* Face to face, semi-structured interviews with 12 pharmacists and 12 paediatric doctors. Interviews were audio-recorded, transcribed and analysed using constant comparison method. *Main outcome measure* Themes surrounding hospital—based pharmacists' and paediatric doctors' attitude, knowledge and views on off-label prescribing in children. *Results* Four themes were derived: knowledge on off-label prescribing in children, views on off-label prescribing in children, attitude towards off-label prescribing in children and guidance on off-label prescribing in children. *Conclusion* There is a need to increase the knowledge of hospital—based pharmacists and paediatric doctors and address several concerns on off-label prescribing in children. The decision to prescribe or dispense off-label drugs involved collective decision-making mechanisms and guidance is required with regards to offlabel prescribing in children.

Keywords Attitude · Children · Knowledge · Malaysia · Off-label prescribing · Paediatricians · Pharmacists

Impacts on practice

- The communication with parents or guardian regarding treatment with off-label drugs for children need to be enhanced.
- There is a need to provide guidance to hospital-based pharmacists and paediatric doctors on off-label prescribing in children in order to optimise drug therapy in children.

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Introduction

Off-label prescribing is defined as 'drugs prescribed and used outside their licensed indications with respect to dosage, age, indication or route of administration' [1]. Off-label prescribing is common in various fields of medicine, namely oncology and psychiatry as well as in different patient groups, notably in children. Studies [2] conducted in various parts of the world highlighted that drugs prescribed in 14–63% of neonatal intensive care units, 18–60% in paediatric wards and up to 20% in the community setting were off-label. Studies conducted in Malaysia [3–5] reported that 34–61% of prescriptions for children were off-label.

Several pre-requisites and recommendations associated with off-label prescribing are in place in order to ensure that patients are provided with safe and efficacious drugs and healthcare professionals are provided with protection from lawsuits that may arise from such practice. For example, in the United States of America (US) and United Kingdom (UK), a prescribing decision on off-label drugs

is recommended to be based on sound and scientific evidence [6, 7]. In Malaysia, doctors are urged to obtain written consent from patients or parents (for patients below the age of 18 years old) whenever a drug is prescribed in an off-label manner [8]. Off-label prescribing in children is no exception from these pre-requisites. Since pharmacists and doctors are the key stakeholders in the provision of drugs to children, adherence to the pre-requisites associated with off-label prescribing as well as usage of off-label drugs depends on the attitude, views and knowledge of the pharmacists and doctors.

Past studies [9–13] highlighted that there was a mismatch between the views of pharmacists and doctors on off-label prescribing in children, compared to the findings of previous studies on the nature of off-label prescribing in children. The mismatch was mainly observed in the responses of the study participants regarding categories of off-label prescribing, common age group involved and disease state where medicine was commonly prescribed off-label [14]. For example, using a drug outside the licensed age recommendations was highlighted by the study participants, as the most common category of off-label prescribing. Findings from the literature review have concluded that using a drug outside licensed dose recommendations was the most common category of off-label prescribing in children. Additionally, several studies [9–13, 15, 16] also highlighted the lack of awareness on off-label prescribing in children among pharmacists and doctors.

Several methodological-related limitations were highlighted in previous quantitative studies [9–13, 15–19] on awareness, attitude, knowledge and views of off-label prescribing in children, which includes, inaccuracy in assessing behavioural attributes [11, 15, 16], biased results due to low response rates [11, 16], selection bias [11, 16] and recall bias [11, 15, 18]. Two studies [17, 19] highlighted that the quantitative methodology did not allow assessment of reasons behind the responses obtained and suggested that it could have been explored in more depth using qualitative work. In view of the limitations and gaps identified from previous studies, this study utilised qualitative methodology as it was more suitable to explore in-depth information on attitudes, knowledge and views of hospital-based pharmacists and paediatric doctors on off-label prescribing in children.

Aim of the study

This study aimed to explore the attitudes, knowledge and views on off-label prescribing in children among pharmacists and paediatric doctors in a hospital in Malaysia.

Ethics approval

Ethical approval was obtained for this study from the Medical Research and Ethics Committee (MREC) (NMRR-14-1637-23321). The Medical Research and Ethics Committee (MREC) is the ethics committee for Ministry of Health facilities in Malaysia. It is based in the central region of Peninsular Malaysia.

Methods

The study was conducted in a 620-bedded general hospital located in the urban area of central Peninsular Malaysia. Data was collected using qualitative, face-to-face, semi-structured interviews with pharmacists and paediatric doctors in this hospital from May to October 2015. A total of 78 pharmacists and 36 paediatric doctors were approached in person and invited to participate in the study. The pharmacists and paediatric doctors who agreed to participate were then contacted and a convenient location and time was arranged for the interview. The interview sessions lasted between 30 min to an hour. No incentives were offered to the participants.

Separate sets of semi-structured interview guide were developed for the pharmacists and the paediatric doctors after reviewing the literature. While creating the questions, the focus was kept at maintaining the questions as open ended as possible to give participants maximum opportunity to express their views and share their concerns and experiences. The first draft of the semi-structured interview guides were discussed among the researchers and a group of experts who have a wide range of expertise in the research topic. The group of experts consisted of a senior hospital pharmacist, a paediatric specialist and two other pharmacy researchers. A pilot study was conducted using the first draft of the semi-structured interview guides. The semi-structured interview guides were revised after the pilot study. Data obtained from the pilot study was not included in the final analysis.

The participants signed a consent form prior to participation in the interview. The following topics were covered during the interview: demographic and background information of the participants, the participants' perceived knowledge and view on matters related to off-label prescribing in children, the participants' experience of prescribing or dispensing off-label drugs and suggestions to guide the participants to prescribe or dispense off-label drugs. Non-directive style of interviewing encompassing open-ended questions was used to allow the participants the freedom to control pacing and subject matter of the interview. Additionally, a more directive style of

questioning was used as needed when more clarification of information was required. Additional sub-questions were used as needed. The interviews were audio-recorded and transcribed verbatim. Transcription validity was checked by an independent third party. Coding and thematic analysis was undertaken by the primary researcher using constant comparison method [20]. The achievement of data saturation was used as the criteria to determine recruitment of additional study participants. Data saturation is the point at which data replicates and no new information emerges from the interviews [21]. For this study, it was estimated that data saturation could be achieved after 10 interviews in each group. The coding was analysed and the emerging themes were determined by the researchers. The differences in opinion regarding the interpretation of data among researchers were resolved through discussion.

Results

Twelve pharmacists and 14 paediatric doctors agreed to participate in the study. However, two paediatric doctors opted out before commencement of the data collection process (Table 1). Through the data analysis process, four main themes emerged (Table 2). The results of the thematic analysis of this study are presented separately for pharmacists and paediatric doctors as the exposure, experience and nature of job differs between the two professions. Quotations from the interviews were used to support the themes that emerged from the interview data (Tables 3, 4).

Table 1 Demographics of the participants

Characteristics	Pharmacists [n (%)]	Paediatric doctors [n (%)]
Total	12	12
Gender		
Male	1 (8.3%)	2 (16.7%)
Female	11 (91.7%)	10 (83.3%)
Race		
Malay	3 (25.0%)	5 (41.7%)
Chinese	6 (50.0%)	4 (33.3%)
Indian	3 (25.0%)	2 (16.7%)
Others	0 (0%)	1 (8.3%)
Working experience (years)		
≤ 5	1 (8.3%)	6 (50.0%)
6–9	9 (75.0%)	1 (8.3%)
≥ 10	2 (16.7%)	5 (41.7%)
Nature of work		
Paediatric related	3 (25.0%)	12 (100.0%)
Non-paediatric related	9 (75.0%)	0 (0%)
Undergraduate training		
Local	7 (58.3%)	9 (75.0%)
Abroad	5 (41.7%)	3 (25.0%)
Postgraduate training		
Yes	5 (41.7%)	5 (41.7%)
No	7 (58.3%)	7 (58.3%)

Theme 1: Knowledge on off-label prescribing in children

(a) Pharmacists

The pharmacists' knowledge on off-label prescribing in children was expressed mainly through the description of the definition of off-label prescribing. Pharmacists' own definitions for off-label prescribing were explored prior to giving a face value definition. Overall, all pharmacists have experienced off-label prescribing in children, either while processing the drug orders or dispensing drugs for paediatric patients as well as personal experiences while using drugs for their own children. The pharmacists defined off-label prescribing as drugs used for unapproved indication (QP 1, Table 3) as well as a practice of using drugs based on the doctors' experience and discretion (QP2, Table 3).

(b) Paediatric doctors

The paediatric doctors' knowledge on off-label prescribing in children were expressed mainly through at least one of the three subthemes: Paediatric doctors' own definition for off-label prescribing, description about the prevalence of off-label prescribing in children and the perceived reasons for off-label prescribing in children. Paediatric doctors' own definitions for off-label prescribing were explored prior to giving a face value definition. The doctors' definitions of off-label prescribing were: (1) using a drug for unapproved age (QD1, Table 4), (2) unapproved for use in children (QD2, Table 4) (3) use of drugs based on experience (QD3, Table 4). Most of the paediatric doctors pointed out that off-label prescribing is more common among children admitted in the NICU (QD4, Table 4) as compared to those in other settings. The paediatric doctors prescribed off-label drugs due to the perceived benefits of off-label drugs (QD5, Table 4) and because there is a need for them to treat their patients (QD6, Table 4).

Theme 2: Views on off-label prescribing in children

(a) Pharmacists

The pharmacist's view on off-label prescribing in children were expressed in three main sub-themes: (1) acceptance

Table 2 Researchers' description of themes and subthemes and frequency of response to categories that emerged from the thematic analysis of interview transcripts

Theme, *subtheme*	Description	Categories (frequency of response)	
		Pharmacists	Paediatric doctors
Theme 1: knowledge	Understanding or familiarity of the participants about a fact or situation that was gained by experience or education		
Definition	The meaning or description about off-label prescribing that was mentioned by the study participants before the face value definition was explained by the researcher Can be in the form of a direct statement/sentence or derived from the examples given by the study participants	Unapproved indication (8P, 8R) Use based on experience and discretion (7P, 9R) Lack of clinical trials done in children (3P, 3R) Unsuitable age group (3P, 3R) Unregistered use (3P, 3R) Lack of evidence (2P, 2R) Test, trial or theoretical dose of drugs (1P, 1R) Extemporaneous product (1P, 1R)	Unapproved age (5D, 5R) Unapproved for use in children (4D, 5R) Use based on experience (4D,5R) Use based on evidence from literature (3D,3R) Use without clinical trial data (2D,3R) Asking patients to buy their drugs (2D,2R) Unapproved indication (2D, 2R) Unrestricted use (1D, 1R) Unlicensed use (1D, 1R) Use outside PIL recommendations (1D, 1R) Not heard of the term (1D, 1R) Unsure of the definition (1D, 1R)
Prevalence	Statement describing commonness of off-label prescribing in children	–	More prevalent in NICU settings (5D, 9R) More prevalent in community settings (3D, 3R) Not common in paediatric patients (2D, 3R)
Reasons	The perceived reason(s) for off-label prescribing as mentioned by the paediatric doctors	–	Perceived benefits (8D, 9R) Need to treat (5D,5R) No alternative (4D, 4R) Not responding to conventional treatment (4D, 4R) Achieving treatment goal (2D, 2R) Meet patients' expectations (1D,1R)
Theme 2: view	Opinion of the participants about a fact or situation		
Acceptance	Opinion of participants if they are acceptive or not acceptive of the practice of off-label prescribing	Acceptive (11P, 17R) Not acceptive (1P, 3R)	Acceptive (11D, 20R) Not acceptive (1D, 5R)
Concerns	Opinion on the matter related to off-label prescribing that is of interest or importance to pharmacists	Doctor's prescribing out of habit (11P, 13R) Lack of experience among doctors (5P, 6R) Safety of off-label drugs (5P, 10R) Taking ownership (3P, 4R) Efficacy of off-label drugs (3P, 3R)	–
Gate-keeping	Suggestions on the steps to be taken to control the use of off-label drugs	Evidence based (7P, 10R) Dose appropriateness (5P, 5R) Limiting duration of treatment (3P, 3R) Documentation (3P, 5R)	–
Litigation	Paediatric doctors' opinion about the litigation aspects related to off-label prescribing in children	–	Advocating unapproved use of drugs (8D, 11R) Illegal testing of drugs in children (5D, 5R) Unjustified by clinical trial data (3D, 5R) Denotes incompetence (2D, 2R)

Table 2 (continued)

Theme, *subtheme*	Description	Categories (frequency of response)	
		Pharmacists	Paediatric doctors
Pre-requisites	Paediatric doctors' perceived actions or steps to be taken if a drug was to be used in an off-label manner to avoid lawsuits; does not imply that the mentioned action or step was performed by the paediatric doctor	–	Informing parents and obtaining consent (8D, 15R) Follow-up monitoring (4D, 8R) Evidence from literature (2D, 7R) Experience with using the drugs (2D, 2R)
Theme 3: attitude	A way of thinking or feeling that is reflected in the pharmacists' and paediatric doctors' behaviour		
Processing	The act of processing off-label drug prescriptions; whether it was processed just like other prescriptions or processed in a different way	The same as other prescriptions (11P, 13R) Handle differently from other prescriptions (1P, 3R)	–
Awareness	Prescribing off-label drugs knowingly or unknowingly	–	Knowingly prescribe off-label drugs (1D, 1R) Unknowingly prescribe off-label drugs (11D, 13R)
Decision-making	The influences on pharmacists' decision to dispense off-label drugs and the paediatric doctors' decision to prescribe off-label drugs	Opinion of clinical pharmacists (5P, 9R) Opinion of doctors (5P, 5R) Evidence from literature (3P, 4R) Obtained DG approval (2P, 2R) Severity of the disease (1P, 1R)	Specialist/consultant's decision (8D, 13R) Discussion and consensus among peer (5D, 8R) Clinical judgement (4D, 4R) Evidence (2D, 7R) Experience (2D, 2R) Guideline (1D, 1R) Drug company influence (1D, 1R)
Theme 4: guidance	Suggestions given or information needed in order to guide the participants to handle/manage off-label drugs		
Preferred features of guidance	What the participants would like to know more in order to guide them when prescribing/dispensing off-label drugs	Who to refer (10P, 12R) Dosing guide (6P, 7R) What to do (5P, 5R) Evidence (2P, 3R) When to refer (2P, 2R)	What to do (7D, 8R) Dosing guide (4D, 6R) Consent taking (2D, 3R) Who to refer (2D, 2D)
Type of guidance	The preferred form or method of presentation of the guidance	Workflow/guideline (9P, 12R) CME (9P, 10R) Evidence from literature (4P, 4R) List of off-label drugs (2P, 12R) Campaign (2P, 3R) Exam/quiz (2P, 2R) Experience sharing (1P, 2R) Consent form (1P, 1R)	List of off-label drugs (6D, 6R) CME (5D, 8R) Workflow/guideline (5D, 5R) Case discussion (4D, 4R) Journal presentation (2D, 2R)

CME continuous medical education, *D* number of paediatric doctors responded, *DG* director-general of health, *NICU* neonatal intensive care unit, *P* number of pharmacists responded, *PIL* product information leaflet, *R* number of responses obtained for each category

Table 3 Examples of pharmacists' quotations

Themes	Quotation references	Quotations
Knowledge on off-label prescribing in children	QP1	"It means prescribing a drug for indications that is not approved by our formulary or that's not commonly practiced"
	QP2	"It means it's at the discretion of the clinician whether it should be used in that child or not because a lot of times it's based on their experience"
Views on off-label prescribing in children	QP3	"I think it will be a shock to the doctors (and nurses) when they hear that many of the medicine that we use are off-label because what happens is that when they are so used to using certain medicine they tend to forget that it's actually not…. It's actually off-label but because they use it so much that they…. In their mind it's like… it's ok… it's safe"
	QP4	"For off-label prescribing, you know you are afraid that this medication might somewhat, you know, whether it is safe in their developmental… in their growth and stuff like that"
	QP5	"If there are studies which shows that, that medication can be used for the indication which the specialist wants it to be used for then I think can be given to the patient but everything based on evidence…. there's no right or wrong"
	QP6	"I think you can give, just make sure, like I said, make sure they are not given over… they are not… as long as given within the accepted dose I think it's ok"
	QP7	"we can limit it to maybe 2 weeks, so we can try 2 weeks first to see whether efficacious or not, instead of allowing the doctor to order as long as they like"
	QP8	"I think the treatment that have been newly adopted, maybe we need to have it more proper documentation because the previous practice that we already know that there are a good benefit towards giving… already proved by the practice…. For the new drugs I think we need to have a proper documentation to monitor the use"
Attitude towards off-label prescribing in children	QP9	"First I will discuss with my colleagues… I will get their opinions… I will ask the clinical pharmacists first… yeah… I'll get their opinion. Then if it can be continued then I will give… provided I will have some notes… some remarks… I'll make sure there are some remarks and all that… discussed with so and so…"
	QP10	"I'll contact the prescriber and ask why they start this medication for that patient and the indication, whether they have spoken to their specialist and they are aware of it and if they are aware then I will continue to supply the medication"
Guidance on off-label prescribing in children	QP11	"maybe we can do a proper dosing guide or whatever it is…. The proper indications for that off-label treatment… for the use of the drugs and then we can use it widely"
	QP12	"we don't have like a standard procedure like how do we handle off-label… like do we call the doctor, or do we like discuss or we discontinue the medication, I mean recommend…. so a detailed, step-by-step flowchart of what to do would be good because right now we don't have all that"
	QP13	"I think if the pharmacists that come across with such thing (off-label prescribing), if they can gather the evidence in one place, it will be easier for others to look back… yeah… and get some ideas or get some references from that… so that it will be easier for us"
	QP14	"Perhaps something they can work out a guideline or workflow then in the end the ultimate goal will be the guideline that will be able to guide any future off-label prescription…."

CME continous medical education

towards the practice, (2) concerns regarding off-label prescribing in children and (3) possible gate-keeping steps needed to control off-label drug use in children. Overall, the pharmacists appeared to be acceptive of off-label prescribing. There were two main concerns raised by the pharmacists regarding off-label prescribing in children. The first was the concern that doctors might not be aware of off-label prescribing, leading to such practice being done as a routine (QP3, Table 3). Secondly, the pharmacists also raised concerns on the safety of the off-label drugs (QP4, Table 3). The pharmacists stated the importance in gate-keeping of off-label drugs to control the

Table 4 Examples of paediatric doctors' quotations

Themes	Quotation references	Quotations
Knowledge on off-label prescribing in children	QD1	"I know there are certain off-label medications are…. Montelukast for example… not suitable and not approved for less than two and we use that a lot in infant still…"
	QD2	"It's the drug that has been used in children by the paediatrician or those who work with children but not approved by the FDA"
	QD3	"There are certain medication that I think we've been using but is not in the intended use but we use based on our experience…"
	QD4	"So sometimes, in NICU setting, I think we tend to use a lot of off-label drugs sometimes because the patient's outcome is paramount so sometimes we do use a lot of off-label drugs…"
	QD5	"we do practice things where we administer certain off-label drugs which we think might be beneficial for our patients"
	QD6	"we use off-label drugs sometimes because there's a pressure on you to achieve the desired result for which the patient came to you"
Views on off-label prescribing in children	QD7	"It's a huge deal…. One day we might get sued for doing this illegal practice… we don't have much to substantiate us."
	QD8	"If it comes to medico-legal and all that I don't suppose it will stand because you are not supposed to use it. Because that particular medication is only approved for that particular indication so you might not stand your chance if it goes to medico-legal… it's like you are promoting unapproved use…in that case I would say it's illegal…"
	QD9	"So I think we need to explain to parents that something that could be beneficial but…. How do you say…. Could be beneficial but might not work and it's off-label and it's an option for them… then we get consent from them… then we are protected legally"
Attitude towards off-label prescribing in children	QD10	"Some of the medication we don't know that it's off-label medication because we have been using it like for so long"
	QD11	"the use of drugs in that manner (off-label) is based on…. approval and instructions by higher officer"
	QD12	"I suppose it is off-label… by right it shouldn't be prescribed or something like that… and then usually we discuss and then when it comes to the consensus to say that ok… even though it's not labelled in this patient use or something like that but consensus say that maybe we should try and see and then only usually most of us will come and say let's try… at least for me I will use it"
Guidance on off-label prescribing in children	QD13	"so what I mean is that… let's say a patient gets admitted for recurrent bronchiolitis and he's like 1 year old… do you start the montelukast right away or how long does it going to work for this…I need to know what to do… it's not clear in that sense…"
	QD14	"One thing is I should know what to do first… whether it is to consult to somebody, who is in-charge of that or not…. When I can start the drug… I will find out that first… if ok, and then I will follow…."
	QD15	"as a start…. like maybe like common off-label use… I would like to know what are the common drugs that I'm prescribing which are off-label… that would be helpful"
	QD16	"Once we are familiar with the off-label drugs…. We need to know what are off-label drugs that we use first…. then definitely… there is a role for continuous education in this topic… definitely…."

use of off-label drugs in children. Some of the methods of gate-keeping suggested by the pharmacists were evidence—based practice (QP5, Table 3), dose appropriateness (QP6, Table 3), limiting the duration of treatment with off-label drugs (QP7, Table 3) and proper documentation for new off-label drugs (QP8, Table 3).

(b) Paediatric doctors

The paediatric doctors' view on off-label prescribing in children were expressed in three main sub-themes: (1) acceptance towards the practice, (2) concerns regarding litigation aspects related off-label prescribing in children and

(3) pre-requisites for off-label prescribing in children. The majority of the paediatric doctors were acceptive towards off-label prescribing in children. However, most of the paediatric doctors raised concerns regarding litigation aspects related to off-label prescribing in children. Off-label prescribing was viewed as an illegal practice (QD7 and QD8, Table 4). The paediatric doctors viewed prescribing drugs in an off-label manner as advocating unapproved use of drugs which could subject them to lawsuits (QD8, Table 4). In view of litigation fear, some paediatric doctors said that certain actions or steps (pre-requisites) need to be taken if a drug was to be used in an off-label manner. The paediatric doctors expressed that disclosure to parents and obtaining consent should be done before prescribing off-label drugs (QD9, Table 4).

Theme 3: attitude towards off-label prescribing in children

(a) Pharmacists

The pharmacists' attitude towards off-label prescribing were portrayed in the way they processed the off-label prescriptions and the factors influencing their decision to dispense off-label drugs. Eleven out of the twelve pharmacists stated that they will process a prescription for off-label drugs the same way as they would process any other drug prescriptions. However, most of the pharmacists referred to the clinical or ward pharmacists in order to guide them to make decisions whether to dispense an off-label drug to the patients (QP9, Table 3). This was also confirmed by the ward pharmacist, who had encountered questions from colleagues asking for guidance before dispensing a drug. The pharmacists expressed that they will also refer to the doctor's opinion before releasing off-label prescriptions (QP10, Table 3).

(b) Paediatric doctors

The paediatric doctors' attitude towards off-label prescribing in children were expressed in terms of their awareness towards prescribing off-label drugs as well as the factors influencing paediatric doctors' decision to prescribe off-label drugs. Most of the paediatric doctors acknowledged that they were prescribing off-label drugs unknowingly mainly due to the prescribing culture at their workplace (QD10, Table 4). When asked about the influences on their decision to prescribe off-label drugs, many paediatric doctors mentioned that they follow the specialist's or consultant's decision (QD11, Table 4). This was not only observed among junior paediatric doctors, but also among the specialists whereby they decide to prescribe off-label drugs after discussion and consensus among peers (QD12, Table 4).

Theme 4: guidance on off-label prescribing in children

(a) Pharmacists

Guidance on off-label prescribing were explicitly expressed in relation to the preferred features of guidance needed when processing and dispensing off-label drugs as well as the method or form of presentation of the guidance. The act of referring was an overarching subtheme that was mentioned by pharmacists when explaining the decision-making process to dispense off-label drugs and the preferred features of a guidance options. The pharmacists mentioned a few preferred features of guidance when processing and dispensing off-label drugs which includes who to refer, dosing guide (QP11, Table 3), what to do (QP12, Table 3), evidence of use (QP13, Table 3) and when to refer. Additionally, most of the pharmacists quoted that having a guideline or workflow on off-label prescribing would be a valuable reference to guide them in processing off-label prescriptions (QP14, Table 3). Pharmacists also said that guidance information can be shared through continuous medical education (CME) sessions, particularly to initiate and create awareness among junior pharmacists.

(b) Paediatric doctors

Guidance on off-label prescribing were featured throughout the interviews with paediatric doctors, in relation to the preferred features of guidance needed when prescribing off-label drugs as well as the method or form of presentation of the guidance. A common problem with many paediatric doctors was the inability to know what they are supposed to do when prescribing off-label drugs (QD13, Table 4). In view of that, most of the paediatric doctors cited that they need guidance on what they need to do, preferably in a step-by-step manner in order to guide them in prescribing off-label drugs (QD14, Table 4). As described previously, most of the paediatric doctors admitted that they were prescribing off-label drugs unknowingly. In view of that, most of the paediatric doctors expressed preference for a list of common off-label drugs to be available as an initial step of guidance on off-label prescribing in children (QD15, Table 4). The paediatric doctors stated that CMEs on topics related to off-label prescribing in children can be conducted once the doctors are familiar with the common off-label drugs used in their settings (QD16, Table 4).

Discussion

The study participants quoted several different definitions for off-label prescribing. The pharmacists expressed off-label prescribing as using drugs for unapproved indication and

the paediatric doctors stated as using drugs for unapproved age groups. The definition for off-label prescribing that was derived from previously published studies [22–25] included other characteristics such as dose, route of administration, absence of efficacy and safety data in children, absence of dosing information in reference sources as well as contraindication of drug use in children. The findings of this study confirmed the need for the derivation and dissemination of a common definition for off-label prescribing in children to promote better understanding of this practice.

As demonstrated in previous studies [26, 27], the doctors tend to use off-label drugs due to the perceived benefits of off-label drugs. In the past, doctors were responsible for field discovery of off-label uses based on their beliefs and experiences [28]. The doctors were found to try new uses of off-label drugs due to several reasons [29]. The low level of satisfaction with available drug therapy for off-label indications had built a demand for new discoveries resulting in the rapid introduction of such discoveries into the medical profession [30].

In this study, several concerns were raised on off-label prescribing. Among the pharmacists, the main concern was that the doctors might be prescribing off-label drugs out of habit. This concern was reiterated when the paediatric doctors admitted that they prescribed off-label drugs unknowingly. Paediatricians do not regard some of the drugs they most commonly prescribe in their everyday practice as being off-label [31]. Similar to findings from previous studies [11, 12], the pharmacists in this study also expressed their concern on the safety of off-label drugs. This might be explained by the limited availability of paediatric safety data in drug reference sources as well as the well-known fact that adverse effects are more frequent, serious and underreported when drugs are used off-label [32, 33].

Among the paediatric doctors, litigation issues related to off-label prescribing in children was the principal concern, similar to findings reported in previous studies [34, 35]. The paediatric doctors expressed that disclosure to parents and obtaining consent should be done before prescribing off-label drugs in order to protect themselves from medico-legal issues. In Malaysia, obtaining consent prior to commencement of off-label drug treatment is a pre-requisite that was implemented in the year 2012 by the Ministry of Health [8]. However, adherence to the pre-requisite is questionable and is in dire need of further evaluation. Moreover, the concept of taking consent in children and proxy consent from parents were considerably argued in the past [36, 37]. Contrarily, not all off-label use of drug is subjected to obtaining consent [38]. Future pre-requisites related to off-label prescribing needs to consider the aspects of providing protection for both the patients and the healthcare providers, particularly the doctors; as well as supplementing the routines and problems associated with drug use in children.

The act of 'referring' is an overarching subtheme that appeared when discussing the decision making to prescribe or dispense off-label drugs and features of preferred guidance options among the pharmacists. In general, pharmacists feel the need to obtain reinforcements regarding their decisions or recommendations by referring to someone or something, due to the need of using evidence-based practices to achieve effective pharmaceutical care services and to address the inter-professional barriers that exists between pharmacists and doctors [39, 40]. On the other hand, the prescribing culture i.e. the culture of hierarchy was featured as the main factor influencing the decision making of off-label prescribing among the paediatric doctors. Previously published studies [41, 42] have shown that prescribing decisions by doctors (especially junior doctors) were influenced by the instructions and behaviour of clinical leaders or seniors. The lack of engagement with clinical leaders or seniors may fail to account for what truly influences prescribing off-label drugs in children. Efforts need to be concentrated in creating and increasing awareness in junior as well as senior paediatricians.

The pharmacists emphasized the need to identify 'who to refer' to receive guidance when dispensing off-label drugs. The paediatric doctors would like to know 'what to do' to guide them when prescribing off-label drugs. Additionally, the participants also pointed out the need to have a proper dosing guide for off-label drugs. Deriving optimal dosing guide for children continues to be a concern for paediatric caregivers [43]. Since off-label drugs lack dosing guide derived from legitimate clinical trials, many different ranges of dose for off-label drugs have been used [26, 44, 45]. Hence selecting the evidence to determine the dose for off-label use of a drug is of paramount importance.

The pharmacists stated that the preferred features of the guidance for dispensing off-label drugs would be best presented in the form of a workflow while the paediatric doctors preferred a simple and straight-forward list of off-label drugs. Generally, CME was also featured throughout the interview as a method of providing guidance to pharmacists and paediatric doctors. While the benefits of CME in guiding drug use is controversial [46, 47], the real outcome of a CME depends on multiple factors [48]. A well-structured and purposeful form of guidance may be derived by performing a learning needs assessment among targeted participants [49].

The strength of the study lies in the methodology employed. Globally, more than 100 study articles [50] reported quantitative data on off-label prescribing in children. To the best of our knowledge, this was the first qualitative study that was conducted in Malaysia to explore reasons behind the vast quantitative findings. The limitation of this study is the fact that the study was conducted with pharmacists and paediatric doctors in one of the public hospital in

the central region of Malaysia hence the findings are not generalisable to all pharmacists and paediatric doctors in all states of Malaysia and other countries.

Conclusion

The pharmacists and paediatric doctors in this study appeared to be acceptive towards off-label prescribing in children. However, knowledge of the study participants on the extent and nature of off-label prescribing in children was found to be limited. Several concerns with regards to prescribing habits, safety of off-label drugs and litigation aspects related to off-label prescribing were expressed. The study participants indicated that the decision to prescribe or dispense off-label drugs involved collective decision-making mechanisms. The study participants also highlighted the need for prescribing and dispensing guidance with regards to the use of off-label drugs in children.

Acknowledgements The authors would like to thank the Director-General of Health Malaysia for permission to publish this paper. The authors would also like to thank the pharmacists and paediatric doctors who took part in this study.

Funding There is no funding received from any bodies for the conduct of the research.

Conflicts of interest All authors declare that they have no conflict of interest.

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