Perceptions and attitudes towards off-label dispensing for pediatric patients, a study of hospital based pharmacists in Jordan

Tareq L. Mukattasha a,⁎, Karem H. Alzoubia a, Amani M. Abuirjiea, Anan S. Jaraba, Rana K. Abu Farhab b, Mohammad B. Nusairc, James C. McElnayd

a Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box 3030, Irbid 22110, Jordan
b Department of Therapeutics and Clinical Pharmacy, Faculty of Pharmacy, Applied Science Private University, Amman, Jordan
c Department of Pharmacy Practice, Faculty of Pharmacy, Yarmouk University, Irbid, Jordan
d Clinical and Practice Research Group, School of Pharmacy, Medical Biology Centre, Queen’s University Belfast, 97 Lisburn Road, BT9 7BL Belfast, UK

Abstract

Background: With growing responsibility of the pharmacists in ensuring public health and safe medicine use, an understanding of the issues surrounding off-label prescribing is crucial to allow pharmacists to make informed decisions about such practice. The aim of this study is to assess the perceptions and attitudes of hospital based pharmacists toward off-label medicine dispensing to children.

Methods: After obtaining the required approvals, a validated questionnaire about off-label dispensing to pediatric patients was administered to 250 randomly selected hospital pharmacists.

Results: One hundred and fifty (150) completed questionnaires were returned. Less than half of the respondents (44%, n = 66) admitted to being familiar with the concept of off-label dispensing, claiming to have obtained this knowledge basically through their dispensing experience rather than education. A minority of respondents (36%, n = 54) reported dispensing off-label medicines within their practice knowingly. The majority of respondents had concerns regarding the efficacy (82%, n = 123) and safety (98%, n = 147) of off-label medicines. The most common reasons given by respondents for a dispensed prescription being off label were younger age than recommended (88%, n = 132). Most of respondents (94%, n = 141) claimed to double check the calculations of doses of medicines before dispensing off-label medicines and 60% (n = 90) of them felt that parents and guardians should be told when an off-label medicine has been prescribed for their children.

Conclusion: The majority of respondents were not familiar with the concept of off-label medicines. While reporting to have gained their knowledge from their professional experience, only a minority of respondents reported knowingly dispensing off-label medicines for pediatric patients. Respondents indicated that manufacturing more appropriate formulations for pediatric patients would reduce such practices in this population. Having concerns regarding the efficacy and safety of off-label medicines used for pediatric patients, respondents felt that the use of off-label medicines would increase the likelihood of adverse drug reactions (ADRs). Finally, respondents felt that such practice of prescribing and dispensing should receive parental consent.

© 2017 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The off-label prescription of medicine for pediatric patients is a common practice worldwide (Pandolfini and Bonati, 2005). Off-label medicines are medication that have been prescribed outside of their product license in terms of their recommended age, recommended dosage, method of administering or advised use (Pandolfini and Bonati, 2005). A review from 1985 to 2004 by Conroy et al., (2000) revealed that up to 80% of prescriptions to children were prescribed in an off-label manner. Such a finding
raises concerns about the safety and effectiveness of medication when they are prescribed to pediatric patients in this manner (Mukattash et al., 2011a, 2011b). It therefore emphasizes the importance of the role of healthcare providers in making sure that pediatric medicines are employed in the most appropriate manner (Turner et al., 1999).

The prescription of pediatric off-label medication has raised significant concerns with respect to reported increased rates and seriousness of adverse drug reactions (ADRs): There are also issues surrounding the possibility that the prescribed treatments will fail, as well as the problem of ensuring the safety and efficacy of any treatments administered over long term (Turner et al., 1999). Nonetheless, the prescription of off-label medication is commonplace since more beneficial treatments for children are often not available, while trials for many medicines intended for children have in fact not been carried out (Wong et al., 2003).

Prior studies have attempted to gain some understanding of the opinions and experience of healthcare professionals with regards to the phenomena of off-label prescriptions for children (Ekins-Daukes et al., 2005; McLay et al., 2006; Mukattash et al., 2011a, 2011b; Stewart et al., 2007). It has been found that healthcare professionals have a moderate level of awareness of this issue, which they obtained through their profession experience and development, as well as through their undergraduate and post-graduate education and training.

The research presented in this work was designed to build upon previous literature and to examine the knowledge and attitudes towards the prescription of off-label medication in Jordan. The importance of this arises from the fact that most previous work dealing with the prescription of off-label medicines has been undertaken in the USA, the United Kingdom and other European countries (McLay et al., 2006; Mukattash et al., 2011a; Mukattash et al., 2008; Stewart et al., 2007). In fact, this paper represents the first study of these issues, from a pharmaceutical perspective, with the entire Middle East.

The objective of this study is to examine the perceptions and attitudes of Jordanian hospital pharmacists towards the dispensing off-label medicines to pediatric patients.

2. Methodology

2.1. Questionnaire development

Following a review of the literature, a questionnaire was developed which, while focusing mainly on the use of off-label pediatric medicines, also looked into the role of hospital based pharmacists in terms of giving information to parents about the use of off-label medicines in pediatric patients. The questionnaire was mainly based on those previously used to explore the views, attitudes, knowledge, and perceptions of different healthcare professionals towards the use of unlicensed and off-label medicines in pediatric patients (Ekins-Daukes et al., 2005; McLay et al. 2006; Stewart et al. 2007; Mukattash et al. 2011a; Mukattash et al. 2011b). Most of the questions had pre-formulated answers, except for those where a reason for the participant’s answer was required. The resulting questionnaire consisted of a total of 27 questions.

The questionnaire was divided into four sections addressing different topics of interest. The first section (questions 1–9) focused on the area of medicine use in pediatric patients and on the use of off-label medicines for pediatrics. The second part (questions 10–13) was concerned with the involvement of parents in deciding what medicine will be prescribed to their child. The third section (questions 14–16) dealt with issues surrounding the dosages recommended when dispensing off-label medicines to pediatric patients. The fourth and final section (questions 17–27) involved collecting the participants’ details and relevant demographic information in order to assess any variability in the responses as a function of these factors. As part of the questionnaire, information about the off-label use of medicines in pediatric patients, including definitions and relevant examples, was provided to assist those participants who may not have been familiar with the employed terminology.

The questionnaire was first issued to a small sample of pharmacist (n = 20) working at the School of Pharmacy of the Jordan University of Science and Technology. These participants informed the authors that the questionnaire was clear and easily understood. Note, while these questionnaires were not included in the final analysis, they nonetheless showed similar results as those making up the rest of the study.

2.2. Data collection

The final questionnaire was distributed to a selection of pharmacists working in a list of randomly chosen hospitals. Hospitals were randomly selected from a list including all hospitals in Jordan. Before data collection, a letter was sent to pharmacy departments of all hospitals who were selected to take part in the study. The letters were sent to the head of each pharmacy department to ask them if they were willing to have their pharmacists take part in this study and if this was the case, they were also asked to indicate the number of questionnaires that would be required in each unit. Twelve hospitals agreed to take part in the study, seven public hospitals, four private hospitals, and one university hospital. In August and September 2014, questionnaires were provided to those departments who had agreed to take part in the study, asking that they complete it within four weeks. Those who had not completed the questionnaire within four weeks were allowed another two-week period before the questionnaire was collected again.

2.3. Ethical approval

The study received ethical approval from the Institutional review board at King Abdullah University Hospital in May 2014 (REF: 73-2014). The study was undertaken following the ethical methods and standards outlined in the guidelines provided by the World Medical Association Declaration of Helsinki (Association, 2013).

2.4. Data analysis

After collecting the completed questionnaires, the responses were transcribed and entered into SPSS for Windows, version 21, for statistical analyses. The main descriptive analysis was carried out using the derived mean and standard deviations (SD) for the continuous parameters, and percentages for the qualitative variables.

3. Results

3.1. Demographics

The questionnaires were distributed to a total of 250 randomly selected pharmacies based in hospitals distributed throughout Jordan. A response rate of 60% (n = 150) was obtained after two visits. The majority of participants were female (62%, n = 93). Regarding their experience years, 70% (n = 105), had been working as hospital pharmacists for more than ten years and the majority of participants (80%, n = 120) reported more than 20 h per week of direct patient contact. The majority of participants (60%, n = 90) reported that pediatric prescriptions formed more than 20% of their
dispensing workload. Only 20% (n = 30) of participants reported that they had postgraduate education and only 16% (n = 24) reported that they gained their pharmacy degree from universities abroad. The demographic characteristics of the study participants are summarized in Table 1.

### 3.2. Off-label dispensing

Less than half the participants taking part in the study (44%, n = 66) stated that they were aware of off-label dispensing. Of those who were familiar with it, 65.2% (n = 43) said that they had learned of this through their dispensing experience as opposed to their undergraduate (13.6%, n = 9) or postgraduate education (21.2%, n = 16).

Within their own practice, 36% (n = 54) of participants admitted that they had knowingly dispensed off-label prescriptions meant for pediatric patients. Meanwhile, 22% (n = 33) denied undertaking any such actions, while 42% (n = 63) were unsure if they had or hadn’t, as indicated in Fig. 1.

Of those participants who admitted that they had dispensed off-label medicines meant for children, 30% (n = 45) reported failures in the prescribed treatment. Furthermore, 14% (n = 21) reported adverse drug reactions arising when dispensing such medicines for children. The most common reasons the dispensed medicines were being described as off-label were; the child’s age was younger than recommended (88%, n = 132), a higher than recommended dose was prescribed (70%, n = 105), and different indication (42%, n = 63) (see Fig. 2).

Among the participants, 18% had major concerns with regards to the effectiveness of the off-label medicines prescribed to pediatric patients (n = 37), while 64% had minor concerns (n = 96), with only 12% (n = 18) of participants having no concerns.

The participants also often had concerns about the safety of off-label prescriptions for children. A minority (32%, n = 48) of participants had major concerns, 66% (n = 99) had minor concerns, while 2% (n = 3) had no concerns.

Concerns about how safe was the dispensing of off-label medicine use in children was again raised in a question that examined if participants felt that the use of off-label medicines in children may increase the likelihood of adverse drug reactions (ADRs). It was found that the majority of participants (88%, n = 132) were concerned that the prescription of off-label medicines to children may increase the chance of ADRs occurring.

A majority (94%, n = 141) of participants said that they had rechecked the doses of the medicines being prescribed to the Pediatric patients when a calculation was required in determining the required dosage. Interestingly, 48% (n = 72) of the participants had encountered an error in the dosage of a pediatric prescription during their professional career. When asked about their personal roles in the dispensing of pediatric off-label medicines, the majority of the participants (78%, n = 117) agreed or strongly agreed that the pharmacist had a duty to inform the prescriber that they were prescribing medicines in an off-label manner, while 60% (n = 90) agreed or strongly agreed that the pharmacist also had a duty to inform the parents and guardians of the children to whom the medicines were being prescribed, that the medicines were off-label. However, only 24% (n = 36) of the participants reported actually informing the children’s parents and guardians that such medicines were off-label, and no one requested written or verbal consent to dispense medicines in an off-label manner to their children.

Unfortunately, respondents’ perceptions of off-label dispensing were not significantly affected by an of demographic parameters nor practice patterns in this study. This could be explained by the lack of awareness of such dispensing in pediatric patients.

### 4. Discussion

The role of pharmacists is growing in importance in terms of ensuring the safe use of medication. This in turn requires a thorough understanding of the issues that surround the dispensing of

---

**Table 1**

Demographic data of respondents.

| Variable                  | Results |
|---------------------------|---------|
| Gender                    | Male 40% Female 60% |
| Experience years (years)  | N = 150 |<5 12% 5–9 18% 10–14 32% 15–19 23% |
| Patient contact per week (hours) | N = 150 |<10 9% 10–19 11% 20–29 24% 30–39 40% >39 16% |
| Pediatric dispensing workload, % | N = 150 |<10 13% 10–19 15% 20+ 60% Don’t know 12% |
| Graduation country        | N = 150 |Jordan 84% Abroad 16% |
| Highest degree obtained   | N = 150 |BSc 80% MSc 20% PhD 0% |
| Work place                | N = 150 |Private hospital 20% Public hospital 62% University hospital 18% |

N: The total number of respondents.
off-label medications, especially to pediatric patients. The findings of the present study are very important in term of their contribution to the development of appropriate education and training schemes for pharmacists, as well as for policy development regarding pharmaceutical care for pediatrics. In addition to the fact that a majority of the participants were not actually familiar with the concept of off-label prescribing, most of those claimed to have obtained their knowledge through their professional experience rather than via their undergraduate or postgraduate training, which was similar to that presented by studies that dealt with general practitioners, community pharmacists, pediatric consultants, and nurses (Ekins-Daukes et al., 2005; McLay et al., 2006; Mukattash et al., 2011a; Mukattash et al., 2011b; Stewart et al, 2007). This response, together with the finding that more than half of the participants were unfamiliar with off-label dispensing of medication, highlights a serious deficiency in the undergraduate and postgraduate education and training of pharmacy students (Mukattash et al., 2017).

Although the off-label dispensing of medicines to children is common in secondary and tertiary care situations (Mukattash et al., 2016), with up to 90% of the involved children being affected, only 36% of the participants to this survey admitted to knowingly dispensing such medicines, which suggests the possible failure of the participants to actually recognize off-label prescriptions. It should be noted that in a survey of UK-based general practitioners, while 74% were aware of the issue of off-label prescriptions, only 40% admitted to prescribing such medicines themselves (Ekins-Daukes et al., 2005). Furthermore, similar results were found in studies carried out in Northern Ireland (Mukattash et al., 2011a), and Scotland (McLay et al., 2006), where participants reported different levels of awareness of off-label prescribing but a minority of participants in all the studies admitted to prescribe, dispense or administer medicines in an off-label manner (Mukattash et al., 2011b).

The most common forms of off-label prescription given by the participants were: the children for whom the medicine was intended were younger than that recommended age, and dispensing a dose higher than recommended. These responses were similar to those provided by studies in Scotland and Northern Ireland (McLay et al., 2006; Mukattash et al., 2011a), but differing from the results of the above mentioned community-based study in the UK dealing with general practitioners, where lower doses than that recommended was reported to be the most frequent form of off-label prescription, while younger age than recommended was one of the least frequent reasons (Ekins-Daukes et al., 2005). By contrast, in a study of pediatricians in Jordan, the most common form of off-label prescription was for a different indication (Mukattash et al., 2011b). This raises questions about the real liaison between pediatricians and pharmacists in hospitals, though pediatricians have previously reported an important role for clinical pharmacists in pediatric wards (Mukattash et al., 2011a, 2011b).

Despite the high levels of concern regarding safety and efficacy of off-label prescribing, only two thirds of the participants said that they would always contact the prescriber in order to confirm the prescribed dosage. The reason for pharmacists not contacting the prescriber, however, is not clear. It may reflect a need to improve communications, especially important when one consider that hospital-based pharmacists and the prescribing pediatricians in fact work in the same location (Liu et al, 2016). The majority of the participants also believed that they had a role in informing parents and guardians when their child’s medicine was off-label, which is consistent with the current transform the pharmacy profession is undergoing (Mukattash et al., 2008). However, the provision of such information may disturb the parent or guardian, potentially undermining confidence in both the pediatrician and the pharmacist having negative effects of drug adherence among pediatric patients (DiMatteo, 2004).

Regarding their own practices and professional experience, less than a quarter of the participants reported that they informed the parents when they dispense off-label medicines, which was similar to findings in previous studies (Mukattash et al., 2011.). This emphasizes the need to improve communications between parents and healthcare professionals in situations when off-label prescriptions are being issued (Khdour et al., 2012). For example, a public survey study dealing with off-label prescriptions to children found that most of the participants believed that parents should be informed about such prescriptions (Mukattash et al., 2008).

It is well understood that pediatric patients should be prescribed medicines that are safe and effective, and that are dispensed and administered by well-trained professionals who are up-to-date in terms of their professional knowledge and who are competent to work with children (Roberts et al., 2003). Pharmacists are encouraged to participate in the development and provision of high-quality, informative material for parents and children (Zhang et al., 2012), in particular in discussing unlicensed and off-label medicines, while at the same time involving parents in the prescription of medication to their children, allowing them some measure of choice when possible (Gilroy et al., 2004). Ensuring the provision of the most reliable and appropriate pediatric medication requires sound communications between the prescriber pediatrician and the pharmacist. However, without agreed-upon standards and protocols, the situation may arise where either parties could see the other as questioning their competence and authority given the situation of off-label prescriptions (Bergman et al., 2016).

Research on the use of off-label medicine in children is still at its early stages, not only in Jordan, but in all the Middle East. In addition to this study, the views of Jordanian pediatricians have been sought previously regarding their experience and attitudes towards the use of off-label medicines in children.

It is recommended that more research on the attitudes and views of other healthcare professionals, pharmacy students, medical students, and the general public towards unlicensed and off-label medicine use in pediatric patients should take place. The issue of treatment efficacy and safety should also be addressed.

Furthermore, it is important to review the curricula and training programs of medical and pharmacy students to include important issues such as this in relation to treating pediatric patients.

4.1. Study limitations

Self-report questionnaires naturally are limited with regards to accurately assess prescription, dispensing and medicine administration practices. While the participants may give “socially desirable” answers to the questions, it is hoped that the anonymity of the questionnaire will encourage honesty in their answers. This is an exploratory study that depends of respondents’ memory in reporting practice-related issues, further studies should explore the nature and prevalence of off-label medicine use in pediatric patients retrospectively through reviewing prescriptions of prospectively through following up inpatients and outpatient pediatric patients.

5. Conclusion

This survey sought the perceptions and attitudes of hospital-based pharmacists towards the dispensing of off-label medicines to children. Although, as in other studies, it was reported what people ‘say they do’ rather than ‘what they actually do’, the following general conclusions can be drawn: The majority of participants...
were not familiar with the concept of off-label medicines. For those that did know about this issue, while reporting to have gained their knowledge from their professional experience, only a minority of participants reported that they knowingly dispensed off-label medicines for pediatric patients. Participants indicated that manufacturing more appropriate formulations for pediatric patients would reduce such practices in this population. Having concerns regarding the efficacy and safety of off-label medicines used for pediatric patients, participants felt that the use of off-label medicines would increase the likelihood of adverse drug reactions (ADRs). Finally, the participants felt that the practice of prescribing and dispensing should receive parental consent.

Funding

This project was generously funded by the Deanship of Research at the Jordan University of Science and Technology (REF: 20140101).

Conflicts of Interests

None to declare.

References

Association, W.M., 2013. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. Jama 310, 2191.
Bergman, A.A., Jaynes, H.A., Gonzalez, J.D., Hudson, K.S., Frankel, R.M., Kobylnski, A.L., Zillich, A.J., 2016. Pharmaceutical role expansion and developments in pharmacist–physician communication. Health Commun. 31 (2), 161–170.
Conroy, S., Choonara, I., Impicciatore, P., Mohn, A., Arshell, H., Rane, A., Knoopel, C., Seyberth, H., Pandolfini, C., Raffaelli, M.P., 2000. Survey of unlicensed and off-label drug use in paediatric wards in European countries. Brmj 320, 79–82.
DiMatteo, M.R., 2004. The role of effective communication with children and their families in fostering adherence to pediatric regimens. Patient Educat. Counsel. 55 (3), 339–344.
Ekins-Daukes, S., Helms, P.J., Taylor, M.W., McLay, J.S., 2005. Off-label prescribing to children: attitudes and experience of general practitioners. British J. Clin. Pharmacol. 60, 145–149.
Gilroy, K., Winch, P.J., Daawara, A., Swedberg, E., Thiero, F., Kane, M., Daou, Z., Berthe, Z., Bagayoko, A., 2004. Impact of IMCI training and language used by provider on quality of counseling provided to parents of sick children in Bougouni District Mali. Patient Educ. Couns. 54 (1), 33–44.
Liu, W., Gerdzit, M., Manias, E., 2016. Creating opportunities for interdisciplinary collaboration and patient-centred care: how nurses, doctors, pharmacists and patients use communication strategies when managing medications in an acute hospital setting. J. Clin Nursing 25 (19–20), 2943–2957.
McLay, J.S., Tanaka, M., Ekins-Daukes, S., Helms, P.J., 2006. A prospective questionnaire assessment of attitudes and experiences of off label prescribing among hospital based paediatricians. Arch. Dis. Childhood 91, 584–587.
Mukattash, T.L., AlHdzawi, N.Y., Farha, R.K.A., Jarab, A.S., Hämenn-Anttila, K., Vainio, K., Gammoh, O.S., 2017. An audit on parental attitudes towards medicines used in children. Saudi Pharm. J.
Mukattash, T., Jawwa, A.F., Trew, K., McElnay, J.C., 2011a. Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials. Europ. J. Clin. Pharmacol. 67, 449–461.
Mukattash, T., Millership, J., Collier, P., McElnay, J., 2008. Public awareness and views on unlicensed use of medicines in children. British J. Clin. Pharmacol. 66, 838–845.
Mukattash, T.L., Wazaify, M., Khouri-Boulos, N., Jarab, A., Jawwa, A.F., McElnay, J.C., 2011b. Perceptions and attitudes of Jordanian paediatricians towards off-label paediatric prescribing. Internat. J. Clin. Pharm. 33, 964–973.
Mukattash, T.L., Hayajneh, W.A., Ibrahim, S.M., Ayoub, A., Ayoub, N., Jarab, A.S., Khdour, M., Almaaytah, A., 2016. Prevalence and nature of off-label antibiotic prescribing for children in a tertiary setting: a descriptive study from Jordan. Pharm. Pract. (Granada) 14 (3).
Pandolfini, C., Bonati, M., 2006. A literature review on off-label drug use in children. Europ. J. Pediat. 164, 552–558.
Khdour, M., J Jarab, A., O Adas, H., Z Samaro, E., L Mukattash, T. and O Hallak, H. Identification of drug-related problems: a prospective study in two general hospitals Current Clin. Pharmacol. 7 4 2012 276 281.
Roberts, R., Rodriguez, W., Murphy, D., Crescenzi, T., 2003. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. Jama 290 (7), 905–911.
Stewart, D., Rouf, A., Snaith, A., Elliott, K., Helms, P.J., McLay, J.S., 2007. Attitudes and experiences of community pharmacists towards paediatric off-label prescribing: a prospective survey. British J. Clin. Pharmacol. 64, 90–95.
Turner, S., Nunn, A., Fielding, K., Choonara, I., 1999. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatri. 88, 965–968.
Wong, I., Swes, D., Cope, J., Florence, A., 2003. Paediatric Medicines Research in the UK. Drug Safety 26, 529–537.
Zhang, C., Zhang, L., Huang, L., Luo, R., Wen, J., 2012. Clinical pharmacists on medical care of pediatric inpatients: a single-center randomized controlled trial. PLoS One 7 (1), e30856.