ASSESSMENT OF PICTOGRAM USE IN PEDIATRIC ORAL LIQUID MEDICATION LABELING AT SULTANAH BAHIYAH HOSPITAL, ALOR SETAR, KEDAH, MALAYSIA

by

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LIST OF ABBREVIATIONS

ADE	Adverse drug event
CI	Confidence interval
Cm	Centimeters
FGD	Focus group discussion
FTFI	Face-to-face interview
HIS	Hospital Information System
mL	Milliliters
MREC	Medical Research Ethics Committee
MeSH	Medical Subject Headings
NMRR	National Medical Research Register
NVS	Newest Vital Sign
OHME	Out-of-hospital medication error
OR	Odds ratio
OTC	Over-the-counter
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
REALM	Rapid Estimate of Adult Literacy in Medicine
SD	Standard deviation
TOFHLA	Test of Functional Health Literacy in Adults
US	The United States
UK	The United Kingdom
vs.	Versus

LIST OF SYMBOLS

Φ	Phi coefficient
$\geq$	Equal or greater than
$<$	Less than

PENILAIAN KEGUNAAN PIKTOGRAM DALAM PERLABELAN UBAT CECAIR ORAL KANAK-KANAK DI HOSPITAL SULTANAH BAHIYAH, ALOR SETAR, MALAYSIA

ABSTRAK

Cecair adalah bentuk dos oral yang lazimnya diberikan kepada kanak-kanak. Secara umumnya, penggunaan piktogram untuk menyampaikan arahan ubat-ubatan dianggap sebagai satu pendekatan yang munasabah tetapi maklumat tentang keberkesanannya dalam perubatan pediatrik masih terhad. Tesis ini merangkumi tiga kajian dengan rekabentuk berlainan yang pada akhirnya mencetuskan penghasilan label baru yang menggabungkan penggunaan piktogram dan teks. Satu ulasan sistematik dijalankan terlebih dahulu untuk mengkaji keberkesanan intervensi-intervensi yang menggunakan piktogram bagi membantu penjaga kanak-kanak dalam administrasi ubat cecair. Pangkalan data elektronik (*MEDLINE, CINAHL, PsycINFO, Cochrane Library, Scopus* dan *ScienceDirect*) telah digunakan untuk mengenalpasti artikel yang diterbitkan sehingga Februari 2015. Lima kajian berbentuk intervensi dengan jumlah seramai 962 subjek melaporkan keputusan yang positif untuk sekurang-kurangnya satu titik akhir yang disasari termasuk ketepatan dos, kefahaman dan ingatan terhadap arahan ubat-ubatan serta tahap kepatuhan kanak-kanak terhadap rawatan. Kemudian, satu soal selidik (n=208) telah dijalankan di Hospital Sultanah Bahiyah, Alor Setar untuk menilai literasi kesihatan dan kesukaran membaca label ubat di kalangan penjaga. Literasi kesihatan mereka diukur dengan menggunakan versi Melayu *Newest Vital Sign* (NVS-M) yang telah divalidasi dan keputusannya menunjukkan hanya 5.8% daripada mereka mempunyai literasi kesihatan yang mencukupi. Penjaga dengan tahap pendidikan primer

atau sekunder sahaja (nisbah odds [OR] terlaras: 34.44; 95% selang keyakinan [CI]: 6.2, 214.08; $p<0.001$) dan pendapatan bulanan di bawah ambang kemiskinan, iaitu RM 830 (OR terlaras: 11.12; 95% CI: 1.13, 109.75; $p=0.039$) lebih cenderung untuk mempunyai literasi kesihatan yang terhad. Menurut keputusan soal selidik ini, lebih daripada 80% penjaga juga melaporkan kesukaran membaca label pada tahap tertentu. Kesukaran membaca label didapati berhubungkait secara signifikan dengan literasi kesihatan yang terhad di kalangan penjaga ($\varphi=0.46$; $p<0.001$). Seterusnya, satu kajian kualitatif yang melibatkan 18 ahli farmasi telah dijalankan di Hospital Sultanah Bahiyah, Alor Setar untuk mengenalpasti kelemahan perlabelan ubat cecair. Perbincangan kumpulan fokus, temubual individu dan pemerhatian tapak telah digunakan untuk mengumpul data. Empat tema utama telah dihasilkan daripada analisa kandungan termasuk format label, persembahan arahan ubat-ubatan, kekurangan maklumat dan keperluan terhadap alat membantu eksternal serta pendidikan. Peserta-peserta telah membuat beberapa cadangan, contohnya untuk menebalkan huruf dan membesarkan saiz font maklumat utama, menyampaikan arahan penting melalui piktogram serta menggunakan “empat waktu” untuk menggambarkan waktu administrasi. Sebagai kesimpulan, tesis ini telah memberikan penekanan terhadap bidang-bidang yang berpotensi untuk diintervensi bagi meningkatkan keberkesanan komunikasi arahan ubat-ubatan dengan penjaga. Sebagai gerak balas terhadap hasil penemuan ini, satu label yang menggabungkan penggunaan piktorgram dan teks telah direkabentuk dan ia bersedia untuk diuji di dalam pusat-pusat kesihatan yang sebenar.

ASSESSMENT OF PICTOGRAM USE IN PEDIATRIC ORAL LIQUID MEDICATION LABELING AT SULTANAH BAHIYAH HOSPITAL, ALOR SETAR, KEDAH, MALAYSIA

ABSTRACT

Liquids are commonly the preferred form of oral medication delivery for children. Generally, using pictograms to illustrate medication instructions is viewed as a feasible approach to improve communication, but limited information is available on its usefulness in pediatric medicine. This thesis consists of three studies with different designs, eventually leading to the construction of a pictogram-plus-text label for pediatric liquid medications. First, a systematic review was conducted to determine the effectiveness of pictographic interventions introduced to assist children's caregivers in liquid medication administration. Electronic databases, including MEDLINE, CINAHL, PsycINFO, the Cochrane Library, Scopus and ScienceDirect, were searched for articles published up to February 2015. Five interventional studies with a total of 962 subjects reported positive results for at least one of the targeted endpoints, including dosing accuracy, comprehension and recall of medication instructions, and children's adherence to treatment. Thereafter, a survey (n=208) was undertaken in the Sultanah Bahiyah Hospital, Alor Setar, to assess health literacy and difficulty in reading the medication labels among caregivers. Their health literacy was measured by using the validated Malay version of the Newest Vital Sign (NVS-M), and results showed that only 5.8% of them had adequate health literacy. Caregivers who had only primary or secondary educational levels (adjusted odds ratio [OR]: 34.44; 95% confidence interval [CI]: 6.2,

214.08; $p<0.001$) and monthly incomes below the poverty threshold of MYR830 (adjusted OR: 11.12; 95% CI: 1.13, 109.75; $p=0.039$) were more likely to have limited health literacy. Results of this survey also showed that more than 80% of caregivers reported certain levels of difficulty in reading medication levels, which was associated with the limited health literacy ($\varphi=0.46$; $p<0.001$). Subsequently, a qualitative study involving 18 pharmacists was conducted in the Sultanah Bahiyah Hospital, Alor Setar, to identify weaknesses of the existing labeling of pediatric liquid medications. Focus group discussions, face-to-face interviews, and onsite observation were used for data collection. Four major themes emerged from the content analysis, including format of labels, presentation of medication instructions, insufficiency of information, and the need for external aids and education. Participants made several recommendations, such as to bold and enlarge the font sizes of key information, to illustrate important instructions via pictograms, and to use "four-time periods" to denote administration times. In conclusion, this thesis has highlighted the potential areas for interventions to improve the communication of medication instructions with caregivers. In response to the findings, a pictogram-plus-text label was constructed and is ready to be tested in real health care settings.

CHAPTER 1

GENERAL INTRODUCTION

1.1 The Use of Oral Liquid Dosage Form in Pediatric Medicine

Children and adults are subject to many of similar ailments and diseases that may respond to the same drug treatment (Mennella & Beauchamp, 2008; Mennella, Pepino, & Beauchamp, 2003; Stephenson, 2005). However, the well-worn phrase "children are not just little adults" simply emphasizes the special need in pediatric medicine (Gillis & Loughlan, 2007; Klassen, Hartling, Craig, & Offringa, 2008; McGrath, 2005). One of the major challenges in administering an oral medication to children is its poor palatability, as mounting evidence has suggested that children's ability to differentiate tastes is already developed at birth (Baguley, Lim, Bevan, Pallet, & Faust, 2012; Beauchamp & Mennella, 2011; Lipchock, Reed, & Mennella, 2012; Matsui, 2007; Mennella, Jagnow, & Beauchamp, 2001; Mennella et al., 2003; Ventura & Worobey, 2013; Winnick, Lucas, Hartman, & Toll, 2005). Lin et al. (2011) reported that more than one-third of children in Canada failed to adhere to antiretroviral drugs because of intolerable tastes. In a recent qualitative study among parents of liver and kidney transplant recipients in Belgium, "bad tastes of medications" was also collectively viewed as one of the major barriers to adherence to immunosuppressants (Claes, Decorte, Levtchenko, Knops, & Dobbels, 2014). Liquids are therefore the preferred form of oral medication delivery for infants and children, as such formulations are often combined with pleasant-tasting excipients and easier to swallow (Davies & Tuleu, 2008; Mennella, Spector, Reed, & Coldwell, 2013).

Differences in drug responses and pharmacokinetic profiles between children and adults are also well established. The vulnerability of children due to immature organ systems and metabolic functions has been highlighted (Anderson & Lynn, 2009; Fernandez et al., 2011; Ivanovska, Rademaker, van Dijk, & Mantel-Teeuwisse, 2014; Stephenson, 2005; Strolin Benedetti & Baltes, 2003). Thus, access to a smaller dosage is crucial for pediatric patients. Dosing based on weight, age, body surface area and clinical conditions is common in pediatric medicine nowadays (Aseeri, 2013; Benavides, Huynh, Morgan, & Briars, 2011; Robinson, Siu, Meyers, Lee, & Cash, 2014; Wong, Ghaleb, Franklin, & Barber, 2004). Tablet splitting is frequently performed but often leads to mass deviations, loss in drug content and inaccuracy in dosing (Elliott, Mayxay, Yeuichaixong, Lee, & Newton, 2014; Rosenberg, Nathan, & Plakogiannis, 2002; van Santen, Barends, & Frijlink, 2002). Within this context, solutions, syrups, suspensions and emulsions have advantages over solid dosage forms, as the doses can be personalized using special measuring devices (Wening & Breitkreutz, 2011).

1.2 Unsafe Use and Mishandling of Pediatric Medications in the Household – Why the Concern?

There is a growing concern over drug safety in the pediatric population, as a comprehensive nationwide study in the United States (US) recently revealed that one child experienced an out-of-hospital medication error (OHME) every eight minutes over the past 10 years, and more than 80% of these errors involved oral liquid preparations (Smith et al., 2014). Of all OHMEs reported to the US National Poison Data System,

more than 30% occurred in children below six years of age (Shah & Barker, 2009; Smith et al., 2014). Antipyretics, analgesics, cough and cold preparations, antihistamines, antibiotics, antineoplastic agents, and psychotropic agents are among the high-risk medications that have been causing OHMEs and the subsequent adverse drug events (ADEs) (Bourgeois, Shannon, Valim, & Mandl, 2010; Cote, Karl, Notterman, Weinberg, & McCloskey, 2000; Gunn, Taha, Liebelt, & Serwint, 2001; Hermanns-Clausen et al., 2009; Neuspiel & Taylor, 2013; Ogilvie, Rieder, & Lim, 2012; Smith et al., 2014; Walsh et al., 2013; Walsh, Stille, Mazor, & Gurwitz, 2008; You, Nam, & Son, 2015). The resultant hospitalization had unavoidably led to increased annual health care cost, as more than 70,000 children in the US were brought to the emergency departments for ADEs, especially those of overdosing (Budnitz & Salis, 2011). A number of these errors, particularly those involving children below one year of age, required intensive care or were even fatal (Smith et al., 2014). However, there is still a lack of awareness of the potential harm due to ADEs among children's caregivers (You et al., 2015).

Notwithstanding the fact that the risk of excessive use of medications in children has been frequently underscored, suboptimal treatment outcomes attributable to underdosing and non-adherence are equally of concern (Anabousi, 2013; Goldman & Scolnik, 2004; Matsui, 2007; Sawyer & Aroni, 2003; Walsh et al., 2013). Underdosing of acetaminophen in the household has been related to inadequate management of children's fever, increased stress level among caregivers and overutilization of health care facilities (Anabousi, 2013; Goldman & Scolnik, 2004). At a more serious level, Walsh et al. (2013) reported a child's death in the US because of underdosing, whereby a parent only administered 50% of the prescribed dose of trimethoprim-

sulfamethoxazole for *Pneumocystis* prophylaxis. On top of that, non-adherence to medications is associated with life-threatening therapeutic failures in children, including uncontrolled diabetes mellitus, relapse in leukemia, organ graft failure, and exacerbation of cardiovascular diseases (Matsui, 2007). Poor adherence to certain medications, such as antimalarial and antiretroviral agents, also increases risk of drug resistance (Arage, Tessema, & Kassa, 2014; White, 2004).

Proper handling of pediatric medications in the household is also crucial. Ideal storage conditions for medications are important due to the temperature-dependent stability (Crichton, 2004). Liquid preparations, in particular those reconstituted from powder or extemporaneously compounded, are stable for a longer duration under refrigerated storage conditions (DiGiacinto, Olsen, Bergman, & Hoie, 2000; Peace, Olubukola, & Moshood, 2012). Besides, a number of commonly-used pediatric medications are available in suspension form, which needs to be shaken well before use to ensure dose uniformity (Zajicek et al., 2013). Moreover, mistakenly co-administering medications with or without food could yield clinically-relevant interactions; for example, fluoroquinolones tend to form complex with metal ions of food that reduces the bioavailability (Bushra, Aslam, & Khan, 2011). Supplying liquid medications in unreconstituted form to caregivers would also be expected to cause more errors, as more knowledge and techniques are required along the process of administration (Hu et al., 2013).

1.3 Caregiver-related Safety Issues Surrounding Liquid Medication Administration

1.3.1 Dosing Errors

While liquid medications are widely used in the household, dosing errors have been prevalent, with a considerable proportion of caregivers (5-90%) measuring the doses incorrectly (Alves, Cardoso Neto, Almeida, & Almeida, 2007; Angalakuditi & Sunderland, 2003; Frush, Luo, Hutchinson, & Higgins, 2004; Ravikiran & Shivarajashankara, 2011; Ryu & Lee, 2012; Sobhani, Christopherson, Ambrose, & Corelli, 2008; Wallace, Keenum, DeVoe, Bolon, & Hansen, 2012; Yin et al., 2008; Yin et al., 2010; Yin et al., 2011). One of the major issues of concern is the unstandardized use of measuring devices (Honey, Condren, Phillips, & Votruba, 2013). Overall, the use of calibrated oral syringes caused fewer errors compared with other devices such as dosing cups, household spoons and droppers (Beckett, Tyson, Carroll, Gooding, & Kelsall, 2012; Madlon-Kay & Mosch, 2000; Neuspiel & Taylor, 2013; Ravikiran & Shivarajashankara, 2011; Ryu & Lee, 2012; Sobhani et al., 2008). Nevertheless, Yin et al. (2010) found that approximately one-fourth of caregivers in New York, irrespective of devices used, still measured liquid medications with deviations larger than 40% from prescribed doses, resulting in either underdosing or overdosing. To explain such a phenomenon, dosing errors were also related to caregivers' confusion as to medication concentrations and measurement units, including "milliliters (mL)", "teaspoons", "tablespoons" and "cups" (Bailey et al., 2014; Farooqi, Seifert, Kunkel, Johnson, & Benson, 2009; Madlon-Kay & Mosch, 2000; Ogilvie et al., 2012; Rood et al., 2014;

Shah R., Blustein, Kuffner, & Davis, 2014; Walsh et al., 2008). Furthermore, their uncertainty about doses presented in fractions and multiple decimal points had caused tenfold errors, which constituted about 1% of the pediatric OHMEs in the US (Smith et al., 2014).

1.3.2 Poor Comprehension of Medication Instructions

Although a great majority of caregivers claimed that they read the instructions prior to administration (Bushby, Anderson, & Braund, 2010; Dawood, Ibrahim, & Palaian, 2010; Eiland, Salazar, & English, 2008), 10 to 60% of them still had difficulty to indicate the correct dosing frequency and time intervals for liquid medications (Alomar, Alenazi, & Alruwaili, 2011; Bailey et al., 2009; Madlon-Kay & Mosch, 2000; Wallace et al., 2012). In fact, inadvertently giving medications twice or too close together to children contributed to more than 30% of common administration errors in the household (Smith et al., 2014). Furthermore, a study of drug handling in Palestine showed that nearly half of the mothers did not store reconstituted antibiotics in refrigerators. More than 20% of them were also found not following instructions for the selection of diluents, measuring devices to use and methods of adding diluents during reconstitution (Anabousi, 2013). In addition, Saidum and Pratheepawanit (2010) expressed concern that one-third of caregivers in Thailand were unaware of the need for shaking the bottles of suspensions before administration. Moreover, Hu et al. (2013) revealed that approximately 35% of the Taiwanese caregivers were unsure of whether or

not liquid medications should be administered to their children with food despite the instructions provided.

1.3.3 Lack of Knowledge and Commitment in Supporting Children's Adherence

Medication adherence in children lies with the caregivers' knowledge of diseases, beliefs about the benefits of treatment and long-term commitment (Goodfellow et al., 2015; Guilfoyle, Goebel, & Pai, 2011; Hebert, Polotskaia, Joober, & Grizenko, 2013; Kalyango et al., 2013; Landier, 2011; Matsui, 2007; Naar-King et al., 2013; Santer, Ring, Yardley, Geraghty, & Wyke, 2014). According to the published literature over the past five years, children's adherence to oral medications widely ranged from 20 to 100% (Arage et al., 2014; Bagenda et al., 2011; Biressaw, Abegaz, Abebe, Taye, & Belay, 2013; De & Dalui, 2012; Eticha & Berhane, 2014; Goodfellow et al., 2015; Haberer et al., 2012; Hommel, Franciosi, Hente, Ahrens, & Rothenberg, 2012; Hong et al., 2013; Kalyango et al., 2013; Lennon, Amin, & Colreavy, 2013; Mghamba, Minzi, Massawe, & Sasi, 2013; Pelajo et al., 2012; Sebunya, Musiime, Kitaka, & Ndeezi, 2013; Shah et al., 2013; Vreeman et al., 2014). A number of these studies had relied solely on self-reports of caregivers. However, evidence has shown that self-reporting measures tend to overestimate adherence compared with other methods of assessment, including counting pills, checking pharmacy refill records and measuring plasma levels (Bagenda et al., 2011; Biressaw et al., 2013; Haberer et al., 2012; Mghamba et al., 2013). There are very few studies specifically examining adherence to liquid medications. Nonetheless, two

studies addressing this issue showed that adding liquid medications to a pediatric treatment regimen significantly reduced adherence (Bagenda et al., 2011; Haberer et al., 2012). Generally, medication adherence in children also decreases over the treatment period (Winnick et al., 2005).

1.4 Significance of the Study

Mishandling of pediatric medications and poor adherence have often been associated with ineffective communication between health care providers and caregivers (Neuspiel & Taylor, 2013; Samuels-Kalow, Stack, & Porter, 2013; Winnick et al., 2005; Yin et al., 2008; Yin, Dreyer, et al., 2014). The use of pictograms to illustrate medication instructions is generally deemed as a feasible approach to improve communication (Houts, Doak, Doak, & Loscalzo, 2006; Katz, Kripalani, & Weiss, 2006), but its effectiveness in pediatric medicine has yet to be comprehensively studied. In addition, labels have been utilized as the source of medication-related information by most of the Malaysian caregivers (Dawood et al., 2010). However, very little is known about the caregivers' health literacy, and their ability to read, interpret and use such information. Furthermore, insufficiencies of text-only labels used among the Malaysian public health care centers were reported, yet interventions made to improve labeling practice had focused mainly on adult patients with chronic health conditions (Chan & Hassali, 2014).

1.5 Study Objectives

The study objectives were as follows:

(i) To assess the effectiveness of pictographic interventions to facilitate communication of instructions for liquid medication administration in the household.

(ii) To determine the health literacy and difficulty to read the existing labels among children's caregivers visiting the Sultanah Bahiyah Hospital, Alor Setar.

(iii) To assess the need for improving labeling of pediatric liquid medications in the Sultanah Bahiyah Hospital, Alor Setar, by incorporating pictograms into written instructions.

1.6 Outline of the Thesis

This thesis is organized in the following sequence to address three study objectives:

(i) Chapter 2 depicts a systematic review of published literature on the usefulness of pictogram-based instructions in improving dosing accuracy, caregivers' comprehension of instructions and children's adherence to liquid medications.

(ii) Chapter 3 describes a survey of caregivers' health literacy and difficulty to read the existing labels in the Sultanah Bahiyah Hospital, Alor Setar.

(iii) Chapter 4 reports a qualitative study which summarized pharmacists' recommendations on how to improve the labeling of liquid medications in the

Sultanah Bahiyah Hospital, Alor Setar. A new label using pictograms to illustrate several key instructions is also proposed in this chapter.

(iv) Chapter 5 concludes the major findings of this study, contributions, limitations and recommendations for future studies.

1.7 Ethics Approval

The study protocol was registered with the National Medical Research Register (NMRR), Malaysia, under the protocol number NMRR-14-1324-23088. It was also approved by the Medical Research Ethics Committee (MREC), Malaysia.

CHAPTER 2

EFFECTIVENESS OF PICTOGRAMS TO IMPROVE COMMUNICATION OF INSTRUCTIONS FOR LIQUID MEDICATION ADMINISTRATION IN THE HOUSEHOLD: A SYSTEMATIC REVIEW

2.1 Introduction

Communication to build a therapeutic relationship between health care providers and recipients of information, either patients or their caregivers, is inherently challenging (Ha & Longnecker, 2010; Yee & Ross, 2006). Although the initial comprehension of patients or caregivers could be high, more than 50% of verbal instructions conveyed during clinical encounters will be forgotten shortly after they leave the health care centers (Martin, Williams, Haskard, & DiMatteo, 2005; McCarthy et al., 2012). In addition, the use of medical terminology and jargons among health care providers could further impede their comprehension and retention of information (Graham & Brookey, 2008; Martin et al., 2005). Therefore, written instructions, such as labels, package inserts, and patient information sheets, are the most important and readily-available source of medication-related information in the household. However, such materials have still been criticized mainly for their poor readability, substandard design and incomprehensible text (Al-Ramahi, Zaid, Kettana, Sweileh, & Al-Jabi, 2012; Leat, Ahrens, Krishnamoorthy, Gold, & Rojas-Fernandez, 2014; Luk, Tasker, Raynor, & Aslani, 2010). For that reason, health care providers are obliged to improve

communication of written instructions with the aims to strengthen comprehension of readers, and to subsequently reduce medication errors and enhance adherence (Yin et al., 2008; Yin et al., 2009).

Research indicates that humans generally have a cognitive preference for pictures rather than for words, the so-called "picture superiority effect" (Whitehouse, Maybery, & Durkin, 2006). The widely-used phrase "a picture is worth a thousand words" suggests that graphics could be deployed to improve communication and modify people's health behaviours (Fagerlin, Wang, & Ubel, 2005). In fact, the use of pictograms has been proven helpful in improving attention, comprehension and recall of medical instructions, health intentions, adherence and satisfaction, particularly of adult patients with limited health literacy (Adepu & Swamy, 2012; Choi, 2011; Dowse & Ehlers, 2005; Houts et al., 2006; Katz et al., 2006; Mansoor & Dowse, 2006; Mohan, Riley, Boyington, & Kripalani, 2012; Zeng-Treitler, Kim, & Hunter, 2008; Zerafa, Zarb Adami, & Galea, 2011). To avoid misinterpretation, a number of studies also highlighted the need for using pictograms in conjunction with text in written instructions (Choi, 2011; Houts et al., 2006; Katz et al., 2006; Roberts, Ghiassi, & Partridge, 2008). Nevertheless, the impact of pictographic intervention has not been well investigated in pediatric medicine. Given that liquid formulations had contributed to the majority of OHMEs in children and increased risk of non-adherence to treatment (Bagenda et al., 2011; Haberer et al., 2012; Smith et al., 2014), this systematic review was designed specifically to confirm the effectiveness of pictograms to improve communication of instructions for liquid medication administration.

2.2 Methods

2.2.1 Literature Search

A proposal of search strategies was developed by one of the investigators (Chan) and approved by all the co-investigators. Electronic databases, including MEDLINE, CINAHL, PsycINFO, the Cochrane Library, Scopus and ScienceDirect, were searched for articles published from database inception until January 2015. The second search was then conducted in February 2015 to capture updated articles. There were no search limiters placed on document type, language and study design. Search strategies were slightly different across databases but mainly involved five groups of the Medical Subject Headings (MeSH), thesauruses and keywords combined using the Boolean operators (Table 2.1). Bibliographies and the Google Scholar search engine were also used to identify additional articles which were related to the included studies.

Table 2.1: Literature search strategies

Databases	Search Strategies
MEDLINE	1. (Pictogram OR picture OR pictograph OR pictorial OR cartoons [MeSH] OR visual OR illustration OR graphics OR diagram OR chart OR image) AND 2. (Caregivers [MeSH] OR parents [MeSH]) AND 3. ("Medication adherence" [MeSH] OR "patient compliance" [MeSH] OR comprehension [MeSH] OR knowledge [MeSH] OR "health literacy" [MeSH] OR "medication errors" [MeSH] OR measurement) AND 4. (Medicine [MeSH] OR pharmacy [MeSH] OR "administration, oral" [MeSH] OR medication OR pill OR drug) AND 5. (Child [MeSH] OR pediatrics [MeSH]).
CINAHL	1. (Pictogram OR picture OR pictograph OR pictorial OR cartoons OR visual OR illustration OR graphics [MeSH] OR diagram OR chart OR image) AND 2. (Caregivers [MeSH] OR parents [MeSH]) AND 3. ("Medication compliance" [MeSH] OR "patient compliance" [MeSH] OR comprehension OR knowledge [MeSH] OR "health literacy" OR "medication errors" [MeSH] OR measurement) AND 4. (Medicine [MeSH] OR pharmacy OR "administration, oral" [MeSH] OR medication OR pill OR drug) AND 5. (Child [MeSH] OR pediatrics [MeSH]).
PsycINFO	1. (Pictogram OR picture OR pictograph OR pictorial OR cartoons OR visual OR illustration OR graphics OR diagram OR chart OR image) AND 2. (Caregivers OR parents) AND 3. ("Treatment compliance" OR comprehension OR knowledge OR "health literacy" OR "medication errors" OR measurement) AND 4. ("Drug therapy" OR pharmacy OR "oral administration" OR medication OR pill OR drug) AND 5. (Child OR pediatrics).
The Cochrane Library	1. (Pictogram OR picture OR pictograph OR pictorial OR cartoons [MeSH] OR visual OR illustration OR graphics OR diagram OR charts [MeSH] OR image) AND 2. (Caregivers [MeSH] OR parents [MeSH]) AND 3. ("Medication adherence" [MeSH] OR "patient compliance" [MeSH] OR comprehension [MeSH] OR knowledge [MeSH] OR "health literacy" [MeSH] OR "medication errors" [MeSH] OR measurement [MeSH]) AND 4. ("Pharmaceutical preparations" [MeSH] OR pharmacy [MeSH] OR "administration, oral" [MeSH] OR medicine OR medication OR pill OR drug) AND 5. (Child [MeSH] OR pediatrics [MeSH]).

Table 2.1: Continued

Databases	Search Strategies
Scopus	1. (Pictogram OR picture OR pictograph OR pictorial OR cartoons OR visual OR illustration OR graphics OR diagram OR chart OR image) AND 2. (Caregivers OR parents) AND 3. ("Medication adherence" OR "patient compliance" OR comprehension OR knowledge OR "health literacy" OR "medication errors" OR measurement) AND 4. (Medicine OR pharmacy OR "administration, oral" OR medication OR pill OR drug) AND 5. (Child OR pediatrics). 6. Limited to the following subject areas: "Medicine", "Nursing", "Health Professions", and "Pharmacology, Toxicology and Pharmaceutics".
ScienceDirect	1. (Pictogram OR picture OR pictograph OR pictorial OR cartoons OR visual OR illustration OR graphics OR diagram OR chart OR image) AND 2. (Caregivers OR parents) AND 3. ("Medication adherence" OR "patient compliance" OR comprehension OR knowledge OR "health literacy" OR "medication errors" OR measurement) AND 4. (Medicine OR pharmacy OR "administration, oral" OR medication OR pill OR drug) AND 5. (Child OR pediatrics). 6. Limited to the following subject areas: "Medicine and Dentistry", "Nursing and Health Professions", and "Pharmacology, Toxicology and Pharmaceutical Science".
MeSH: Medical Subject Heading.	

2.2.2 Inclusion and Exclusion Criteria

To be included in this review, a study had to (i) be published in a peer-reviewed journal and reported original findings; (ii) be designed as an interventional, cross-sectional, cohort or case-control study; (iii) recruit caregivers of children below 12 years of age; (iv) use pictograms to facilitate communication of instructions for liquid medication administration; and (v) measure at least one of the three selected endpoints, including dosing accuracy, comprehension or recall of medication instructions, and children's adherence. Studies introducing pictographic interventions which were directly delivered to children or provided only general medication information, such as common side effects, were excluded.

2.2.3 Article Selection and Review

All records retrieved from databases were exported to the EndNote version X7 (Thomson Reuters, New York). Duplicates were removed, followed by evaluation of the titles and abstracts. Articles which were clearly irrelevant to the aims of this review were excluded. Thereafter, two investigators (Chan & Tan) independently appraised the remaining articles, determined the eligibility of studies, and extracted the following information from the included studies into an evidence table: (i) study identification (authors and year); (ii) design (study design and setting, study period, medications tested); (iii) participants (inclusion and exclusion criteria, sample size,

sociodemographics of both caregivers and children); (iv) intervention (details of pictographic intervention); (v) assessment (methods, instruments, time points and endpoints); (vi) findings; and (vii) strengths and limitations of study claimed by the authors. Any discrepancies between two investigators were reconciled by consensus.

2.2.4 Methodological Quality Assessment

Two investigators (Chan & Tan) independently assessed methodological quality of the included studies using the Cochrane Collaboration's tool (Higgins et al., 2011). Agreement on the outcomes of assessment was subsequently achieved by consensus between two investigators. Risk for bias in each study was rated as "unclear", "high" or "low" based on the following criteria: (i) sequence generation (selection bias); (ii) allocation concealment (selection bias); (iii) blinding of participants and personnel (performance bias); (iv) blinding of outcome assessment (detection bias); (v) incomplete outcome data (attrition bias); (vi) selective reporting (reporting bias); and (vii) other bias.

2.2.5 Data Analysis

Statistical pooling of data was not performed due to the variations of studies in designs, outcome measures, medications tested and instruments used. Rather, findings of the included studies were summarized qualitatively.

2.3 Results

2.3.1 Literature Search

Figure 2.1 depicts the process of study selection using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Liberati et al., 2009). The literature search yielded a total of 1363 records (228 from MEDLINE, 48 from CINAHL, 22 from PsycINFO, 753 from the Cochrane Library, 290 from Scopus, 15 from ScienceDirect, and seven from other resources). After removing the duplicates (n = 237), 1126 titles and abstracts were screened. Eleven original studies introducing new interventions to improve communication of instructions for liquid medication administration were retained for full review. A total of five interventional studies met the inclusion criteria, as listed in Table 2.2 (Hu et al., 2013; Patel, Eisemon, & Arocha, 1990; Tork, 2013; Yin et al., 2008; Yin et al., 2011). Of six studies excluded, two did

not assess the impact on caregivers (Ajayi, Oladepo, Falade, Bamgboye, & Kale, 2009; Hameen-Anttila, Kemppainen, Enlund, Bush Patricia, & Marja, 2004), two used marked syringes (Angalakuditi & Sunderland, 2003; McMahon, Rimsza, & Bay, 1997), one used colour coding (Frush et al., 2004), and one used text-based pamphlets (Bertsche et al., 2010).

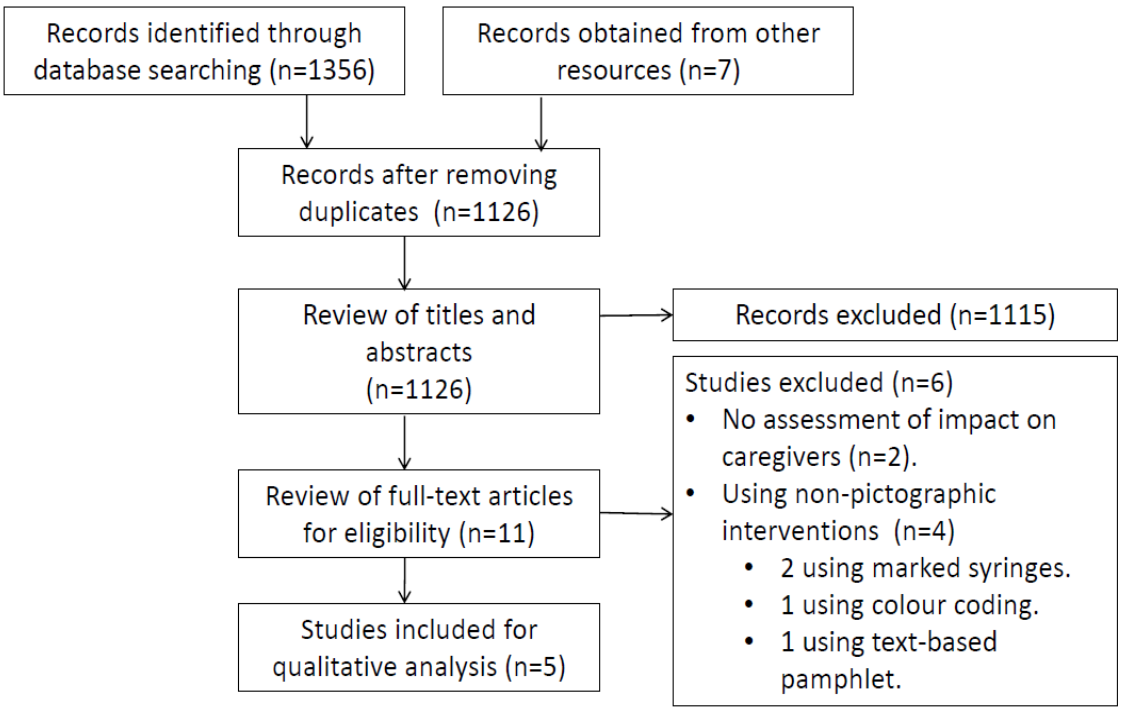

Figure 2.1: PRISMA flow diagram for study selection

Table 2.2: Studies included in the review (n=5)

Authors (year)	Participants	Interventions	Controls
Patel et al. (1990)	Kenyan mothers (n=18)	Pictograms with revised text (n=9)	Pictograms with original text in the commercial products (n=9)
Yin et al. (2008)	US parents and caregivers (n=245)	Medication counseling with a pictogram-based instruction sheet (n=124)	Standard medication counseling (n=121)
Yin et al. (2011)	US parents and caregivers (n=299)	Text-plus-pictogram dosing instructions (n=155)	Text-only dosing instructions (n=144)
Hu et al. (2013)	Taiwanese parents and caregivers (n=150)	First group: Pictogram-based educational sheet (n=50); Second group: Medication counseling with the pictogram-based educational sheet (n=50).	Standard package inserts in two commercial products (n=50)
Tork (2013)	Egyptian parents and caregivers (n=250)	Pictogram-based medication counseling (n=129)	Standard medication counseling (n=121)
US: The United States.			

2.3.2 Overview of the Selected Studies

The majority of studies identified were published over the past 10 years. Aside from one study in early 1990s (Patel et al., 1990), there were no publications that pre-dated 2008 (Hu et al., 2013; Tork, 2013; Yin et al., 2008; Yin et al., 2011). Two studies took place in the US (Yin et al., 2008; Yin et al., 2011), followed by one each from Taiwan (Hu et al., 2013), Kenya (Patel et al., 1990) and Egypt (Tork, 2013). Four studies recruited caregivers who presented to the hospitals (Hu et al., 2013; Tork, 2013; Yin et al., 2008; Yin et al., 2011), while one was designed as a community-based trial (Patel et al., 1990). Three studies tested the use of pictogram-based materials with prescription medications (e.g. antibiotics, steroids, antihistamines) (Hu et al., 2013; Tork, 2013; Yin et al., 2008), whereas two focused on over-the-counter (OTC) products (e.g. antipyretics, oral replacement treatment) (Patel et al., 1990; Yin et al., 2011). Only one study targeted both the medications taken daily and as needed (Yin et al., 2008). Five included studies enrolled a total of 962 participants (range, 18–299).

One study involved only mothers aged between 18 and 35 years (mean, 25 years) (Patel et al., 1990), while the other four included both parents and non-parent caregivers, with mean ages ranging from 29.6 to 38.9 years (Hu et al., 2013; Tork, 2013; Yin et al., 2008; Yin et al., 2011). Four studies reported mean ages of children, ranging from 2 to 3.7 years (Hu et al., 2013; Tork, 2013; Yin et al., 2008; Yin et al., 2011). While three Asian and African studies addressed the local populations (Hu et al., 2013; Patel et al., 1990; Tork, 2013), two US studies focused primarily on the ethnic minorities and

immigrants (approximately 80%) (Yin et al., 2008; Yin et al., 2011). Three studies also assessed caregivers' health literacy by using either the Test of Functional Health Literacy in Adults (TOFHLA) or the Newest Vital Sign (NVS), and 13.2 to 69.9% of them were found to have limited health literacy (Tork, 2013; Yin et al., 2008; Yin et al., 2011).

Details of the targeted endpoints, methods of measurement and data collection instruments are summarized in Table 2.3. Two studies compared the usefulness of pictograms with that of text-based instructions (Patel et al., 1990; Yin et al., 2011), whereas three utilized pictogram-based materials to facilitate medication counseling (Hu et al., 2013; Tork, 2013; Yin et al., 2008). Endpoints and methods of assessment used widely varied across studies. Three studies examined dosing accuracy (n = 794) (Tork, 2013; Yin et al., 2008; Yin et al., 2011), four assessed comprehension or recall of medication instructions (n=663) (Hu et al., 2013; Patel et al., 1990; Tork, 2013; Yin et al., 2008), and only one measured children's adherence to treatment (n=245) (Yin et al., 2008).

Table 2.3: Targeted endpoints, methods of measurement, data collection instruments and findings of the included studies (n=5)

Authors (year)	Endpoints	Methods of measurement	Instruments	Findings
Patel et al. (1990)	Recall of medication instructions	Structured interview	A 5-item questionnaire	Very little text-based information was recalled in both groups (10% vs. 7% of propositional information), but all participants completely remembered a sequence of directions illustrated with pictures.
Yin et al. (2008)	Dosing accuracy	Direct observation	The measuring device chosen or brought by a participant	Intervention group made fewer dosing errors for both the medications taken daily (5.4% vs. 47.8%; $p<0.001$) and as needed (15.6% vs. 40%; $p=0.003$).
	Comprehension of medication instructions	Structured interview	Not reported	Intervention group made fewer errors for the questions with regard to dosing frequency (0% vs. 15.1%; $p=0.007$) and preparation of both medications taken daily (10.9% vs. 28.3%; $p=0.04$) and as needed (21.5% vs. 43%; $p=0.006$).
	Adherence	Self-reporting	Not reported	Children of intervention group had a lower non-adherence rate (9.3% vs. 38%; $p=0.002$).