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Quality of life in children with adverse drug reactions: a narrative and systematic review

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AIMS
Adverse drug reactions are a common problem affecting adults and children. The economic impact of the adverse drug reactions has been widely evaluated; however, studies of the impact on the quality of life of children with adverse drug reactions are scarce. The aim was to evaluate studies assessing the health-related quality of life of children with adverse drug reactions.

METHODS
We conducted a systematic review that included the following electronic databases: MEDLINE, EMBASE and the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Cochrane Controlled Trials Register and the Health Technology Assessment Databases).

RESULTS
Nine studies were included. Four of the studies were conducted in children with epilepsy; the rest of them involved children with chronic viral hepatitis, Crohn's disease, paediatric cancer and multiple adverse drug reactions compared with healthy children. Based on their findings, authors of all studies concluded that adverse drug reactions had a negative impact on the quality of life of children. No meta-analysis was conducted given the heterogeneous nature of the studies.

CONCLUSIONS
To date, there is no specific instrument that measures quality of life of children with adverse drug reactions, and the information available is poor and variable. In general, adverse drug reactions have a negative impact on the quality of life of affected children. For those interested in this area, more work needs to be done to improve tools that help to evaluate efficiently the health-related quality of life of children with adverse drug reactions and chronic diseases.

Introduction

An adverse drug reaction (ADR) is defined as any noxious or unintended reaction to a drug that is administered in standard doses by the proper route for the purpose of prophylaxis (e.g. vaccines), diagnosis (e.g. contrast media) or treatment (e.g. antibiotics) [1, 2]. They can be classified as type A when the reaction results from an exaggeration of the normal pharmacological actions of a medication (i.e. side-effect) and type B when the reaction is an unusual response (i.e. idiosyncratic reaction) [3]. A more descriptive classification is shown in Table 1 [2].

Adverse drug reactions are a common problem and are recognized as an important cause of morbidity and mortality in patients of all ages, notably among hospitalized patients and patients with chronic diseases [4]. The prevalence of ADRs seems to be higher among infants, women and elderly patients. Among both children and adults, some of the risk factors that have been suggested are immaturity or impairment of drug clearance, off-label drug

Table 1
Classification of adverse drug reactions (adapted from [2])

Predictable or reaction that may occur in anyone		Unpredictable or reactions that occur only in susceptible subjects	
Drug Overdose	Toxic reactions linked to excess dose or impaired excretion or both	**Drug intolerance**	A low threshold to the normal pharmacological action of a drug
Drug side-effect	Undesirable pharmacological effect at recommended dose	**Drug idiosyncrasy**	A genetically determined, qualitatively abnormal reaction to a drug related to metabolic or enzymatic deficiency
Drug interaction	Action of a drug on the effectiveness of toxicity of another drug	**Drug allergy**	An immunologically mediated reaction, characterized by specificity, transferability by antibodies or lymphocytes and recurrence on re-exposure
		Pseudo-allergic reaction	A reaction with the same clinical manifestation as an allergic reaction but lacking immunological specificity

use, certain genetic polymorphisms, age, gender, associated illnesses and the number of drugs to which patients are exposed [5–7].

The incidence and prevalence vary greatly depending on the country, age, population and criteria used to classify the ADRs. In 1999, a prospective study of adverse drug reactions in hospitalized children reported a cumulative incidence of ADRs of 16.6% in a 2 year period [8]. Two years later, a systematic review and meta-analysis of prospective studies evaluating the incidence of ADRs in paediatric in- and outpatients showed an overall incidence of ADRs of 9.5% in hospitalized children; 12.9% of them were reported as severe reactions [7]. The overall rate of paediatric hospital admissions due to ADRs was 2%, of which 39.3% of the ADRs were life-threatening reactions. For outpatient children, the overall incidence of ADRs was 1.5%. More recently, diverse authors have reported an overall incidence of ADRs among hospitalized children between 0.7% and 1.6%, whereas in outpatient settings it ranges from 0.3% to 0.5% [9–11]. It is estimated that between 0.4% and 0.5% of all admissions in children result from an ADR [9–11]. However, the incidence might be higher than reported. For example, in Canada, the Department of National Health and Welfare established the Drug Adverse Reaction Reporting Program in 1965 [12]. However, despite this system being in place, health-related accreditation bodies currently estimate that as many as 95% of all adverse drug reactions are not reported [13].

Nevertheless, in spite of the lack of adequate methods of classification and under-reporting of ADRs, the available information is sufficient to support the belief that ADRs represent a substantial healthcare problem with a significant associated healthcare cost [9, 11, 14]. In the USA, the costs due to ADRs represent more than $300 million yearly [5] while other authors report, also in the USA, that the annual cost of managing ADRs among hospitalized adults ranges between $1.6 billion and $4.2 billion [9]. Regarding children, cost implications of ADRs in hospitalized children (New Zealand) had an annual cost of $NZ235 214, with 33% of ADRs potentially resulting in persistent disability [15]. Although numerous studies have evaluated the epidemiological and economic impact of ADRs, there have been very few attempts to assess objectively and accurately the impact of ADRs on health-related quality of life of patients who have suffered an undesirable effect secondary to therapy, in particular among children.

In addition to the economic impact, ADRs can adversely affect the function of patients and negatively impact their life. The World Health Organization and the International League against Rheumatism define quality of life (QoL) as 'the perception of individuals of their own position in life in the context of the culture and value systems of the countries in which they live and in relationship to their goals, expectations, standards and concerns', and health-related quality of life (HRQL) as 'the physical, emotional and social aspects of quality of life influenced by an individual's disease and/or its treatment' [16]. During the last 10 years, there has been a dramatic increase in the development and utilization of paediatric HRQL measures in an effort to improve paediatric patient health and well-being [17]. However, very few studies have measured the impact that ADRs have on the quality of life of children who have received any kind of drug therapy [18–22]. Therefore, the objective of this review was to explore what is known in this area in the paediatric population.

Methods

We conducted a systematic review of studies evaluating quality of life in children presenting ADRs. The search focused on all publications describing or potentially describing a study that evaluated or measured QoL or HRQL in children suffering ADRs. The search included the following electronic databases: MEDLINE, EMBASE (both using the Ovid interface) and the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Cochrane

Controlled Trials Register and the Health Technology Assessment Databases). The search was initially done in March 2012 and updated in April 2014. The terms used were 'children', 'paediatric', 'quality of life', 'health-related quality of life' and 'adverse drug reactions' and were combined using Boolean operators. The strategy is available from the authors upon request. No language or date restrictions were considered. The retrieved references were assessed by one reviewer for possible inclusion on the basis of the evaluation of the title and the abstract, or in full if no abstract was available. A second reviewer independently confirmed the final selection. Disagreements were resolved by consensus. Finally, the bibliographies from the retrieved studies were reviewed manually to identify potential additional references.

We considered for inclusion any study using specific or generic instruments to measure QoL or HRQL in paediatric patients (0–18 years old) with a diagnosis of an ADR in any condition. We excluded studies exclusively including adults, studies evaluating only medical outcomes of the ADRs or studies using nonstandardized measures of QoL, owing to the potential risk for bias if nonstandardized measures are used.

The objective was to describe the general impact of ADRs on the QoL in children using a qualitative synthesis approach. Data for each study were described separately. A formal meta-analysis was not planned given the anticipated heterogeneous nature of the studies.

Results

Search results and characteristics of included studies

The flow diagram of the review is shown in Figure 1. The search indentified 131 records from the databases. Two additional studies were identified through the review of the bibliographies. Seventeen studies were evaluated fully, and seven were excluded for the following reasons: in two studies, the authors described characteristics of the ADRs rather than the effects on the QoL of the patients; in one study the authors evaluated QoL during active chemotherapy but not in relationship to ADRs; and in the rest of the studies the authors failed to use standardized measures of HRQL (e.g. generic subjective assessments of well-being, such as 'good health' or 'poor health'). We finally included nine studies, which were described in 10 references and which included 1269 patients aged 3–18 years (Table 2).

All studies but one were observational. The quality of the studies was not assessed owing to the lack of a validated instrument for this particular type of study. Of the nine studies that were included, six were found as a full text, while three were published only in conference abstracts (one study was reported in two abstracts). Four of the studies were conducted among children with epilepsy; the rest of them evaluated children with chronic viral hepatitis, Crohn's disease, cancer and multiple ADRs compared with healthy children. Regarding the QoL instruments, three were disease specific (USQOLCE, CAVE and QOLIE-AD 48) and four were generic instruments (PedsQL, CHQ-PF-50, Modified Sickness Impact and Rutter Questionnaire). The age of the children among all the studies ranged from 2 to 18 years. Sample sizes of the studies were also diverse, ranging from 16 to 550 patients. Most of the instruments were responded by parents or caregivers, except for the QOLIE-AD 48, which is specifically designed to be answered by children between 11 and 18 years of age, and the studies conducted in adolescents with cancer, in which the PedsQL was used.

Qualitative assessment of study findings

Although the characteristics of patients and the instruments used to measure QoL were heterogeneous, all studies had similar conclusions; regardless of the condition studied or the instrument used, ADRs had a negative effect on the QoL of children. Additionally, several studies suggested that the severity and frequency of ADRs were also associated with poorer QoL. Studies conducted in children with epilepsy constituted the largest group and included the largest number of patients. All studies concluded that ADRs, including side-effects, had a negative impact on the patients' QoL, and one study suggested that the proper selection of anticonvulsants reduced ADRs and thus improved the QoL of children with this condition. Among patients with paediatric neoplasias, the occurrence of chemotherapy-induced side-effects was associated with lower QoL accross several domains of the PedsQL scale. This seemed to be independent of the effects of the cancer itself on QoL, and patients experiencing more severe side-effects had larger detrimental effects of their QoL. The other studies mentioned that ADRs significantly deteriorated the HRQL of children with chronic viral hepatitis undergoing α-interferon treatment, and side-effects of the treatment in children with Crohn's disease are the main concern of their parents or caregivers regarding their children's quality of life. Finally, one study showed that children with multiple ADRs have lower HRQL than children with only one event of ADR.

Discussion

The development of new drug therapies has resulted in increased survival and improved quality of life in adults and children with diseases that were considered fatal or disabling in the past. Unfortunately, highly effective drugs are also associated with the risk of adverse reactions, which can negatively affect QoL. The present study found that studies evaluating HRQL or QoL in children with ADR are very scarce. We were able to retrieve only nine studies that measured HRQL or QoL and its relationship with ADRs

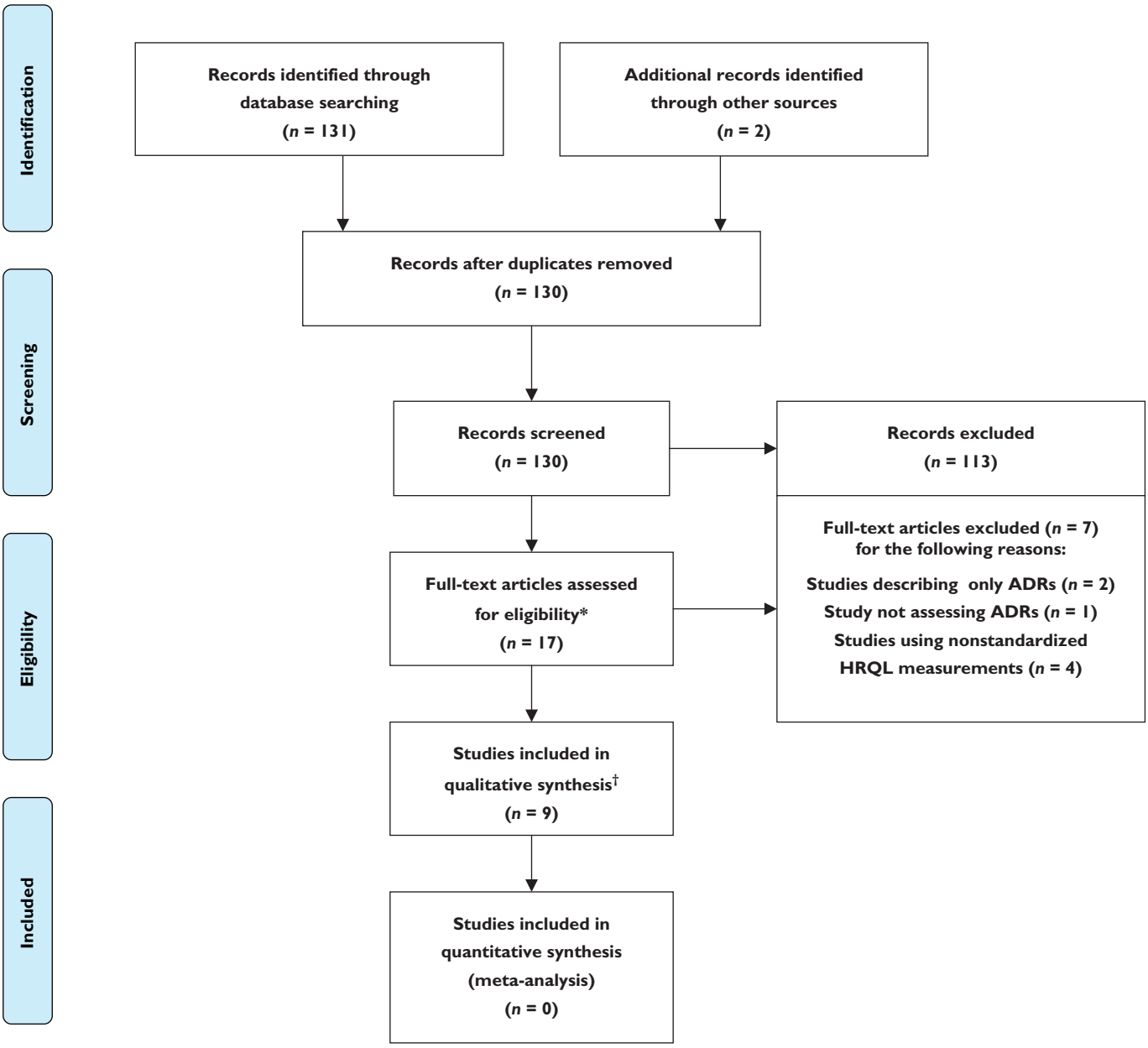

Figure 1

Flow diagram of the systematic review. Abbreviations are as follows: ADRs, adverse drug reactions; HRQL, health-related quality of life. *Four references were available only in abstract form. †The final number of included references was 10, comprising nine studies. One study was reported twice in consecutive years

in paediatric populations. Certainly, this represents only a minute percentage among all studies published in children evaluating either HRQL or ADRs. However, all studies concluded that ADRs result in a lower quality of life in children in different settings.

The interest in HRQL/QoL in children has increased in recent years. Clarke and Eiser [23] reported that QoL is most frequently included in trials in diseases such as asthma, rhinitis and dermatitis (eczema), perhaps because of the high incidence of these conditions, as well as other chronic conditions, such as cancer, epilepsy and diabetes. Interestingly, as we observed in our study, the impact of ADRs among children with epilepsy has been studied slightly more commonly than in other chronic diseases; this may be related to the fact that antiepileptic therapy has been associated with a high incidence of intolerable side-effects and severe ADRs that affect the adherence to treatment [24]. The findings of several studies agree that

Table 2

Studies evaluating quality of life in children with adverse drug reactions

Study, country	Drug involved	Study design	Population studied	HRQL/QoL instrument	Main findings
Rabbett *et al.* (1996), England [34]	Not specified	Randomized cross-sectional study	16 children aged 8–17 years with Crohn's disease	Rutter A Questionnaire	Side-effects of treatment are the parents' main concern regarding their children's QoL. Adverse drug reactions were associated with lower QoL
Iorio *et al.* (1997), Italy [35]	α-Interferon	Prospective cohort	94 children aged 3–14 years with chronic viral hepatitis	Modified sickness impact profile	Health-related quality of life deteriorated significantly during α-interferon therapy
Bellaire *et al.* (2005), Canada [18]	Miscellaneous	Retrospective cohort	42 children aged 5–17 years with one ADR *vs.* multiple ADRs	Parent-Form 50 (CHQ-PF50)	Children with multiple ADRs had a lower HRQL than children with one ADR
Morita *et al.* (2007), USA [25]	Carbamazepine and valproic acid	Prospective cohort	37 children of mean age 7.2 years with new-onset epilepsy	PedsQL and USQOLCE	Severe ADR/side-effects were inversely related to QoL
Virag *et al.* (2010), Slovakia [36]	Carbamazepine and valproic acid and others	Retrospective, prospective cohort	293 children with epilepsy (mean age 12.9 years)	QOLIE-AD-48 (Slovak version)	Adverse effects of antiepileptilc drugs correlated with QoL
Modi *et al.* (2011), USA [26]	Carbamazepine and valproic acid	Longitudinal prospective study	124 children aged 2–12 years with newly diagnosed epilepsy	PedsQL	Side-effects from anticonvulsants were negatively associated with all HRQL domains
Arslan *et al.* (2013), Turkey [37]	Various chemotherapeutic agents	Cross-sectional study	93 children aged 10–18 years with leukaemia, lymphoma or solid tumours	PedsQL 4.0	The occurrence of chemotherapy-related symptoms/side-effects was associated with lower QoL
Erickson *et al.* (2011), USA [38]	Various chemotherapeutic agents	Prospective cohort	20 children aged 12–19 years with leukaemia, lymphoma or solid tumours	PedsQL	Occurrence of chemotherapy-related fatigue was associated with lower QoL
Lara-Herguedas *et al.* (2011, 2013), Spain [39, 40]	Miscellaneous	Observational, cross-sectional, multicentre study	550 children aged <18 years with epilepsy	Quality of life scale CAVE and modified LAEP	Adverse effects of antiepileptics were inversely associated with QoL

Abbreviations are as follows: ADR, adverse drug reaction; CAVE, Quality of Life scale in childhood epilepsy; CHQ-PF50, Child Health Questionnaire; HRQL, health-related quality of life; LAEP, Liverpool Adverse Events Profile; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life; QOLIE-AD-48, Quality Of Life In Epilepsy for Adolescents; USQOLCE, American Quality of Life in Childhood Epilepsy Questionnaire.

more severe antiepileptic drug side-effects are associated with lower quality of life [25–27]. The information regarding HRQL and its relationship with ADRs in other settings or conditions is virtually non-existent. Given that the profile of the adverse reactions varies between drugs, studies evaluating the impact of ADRs in other pathologies are needed.

Interest has been scant among ADR researchers to study the effects of ADRs on the quality of life in children. Even in adults, there are very few studies interested in health-related quality of life and ADRs [28, 29]. In general, studies regarding drug therapies and drug effects related to the quality of life of children would be expected to show an improvement of symptoms or absence of disease. Nevertheless, in some cases when drug therapies produce serious adverse reactions that may affect the quality of life of children, studies focus only on the physical or health impact rather than on the evaluation of all the aspects (physical, emotional and social) of the children's life [30].

Our study has several limitations that need to be noted. First, indexing in databases might be suboptimal for this type of study, because in some of the retrieved studies QoL and HRQL were not the main study outcome. However, we used MeSH terms in our search and we believe that they should have captured the majority of studies. Second, the quality of the studies could not be assessed properly owing to a lack of validated scales for the assessment of this type of study. Scales exist for assessing the quality of observational studies in epidemiology, but their design is focused on other types of outcomes. Third, we were unable to conduct a quantitative analysis of the information owing to the heterogeneity of conditions, instruments and study designs. Furthermore, while all studies concluded that ADRs adversely affected QoL and HRQL, there is no standard measure of effect size, and many studies did not include healthy control subjects. Fourth, QoL and HRQL are also adversely affected by chronic and acute disease, and confounding derived from the underlying

pathologies cannot be excluded entirely. Fifth, the ADRs and side-effects reported in the included studies were widely variable (ranging from fatigue, nausea and vomiting to erythroderma and Stevens–Johnson syndrome) and their impact on QoL is different; however, some studies assessed the severity of the ADRs using validated classifications and concluded that the more severe the ADR, the higher the impact. Finally, the instruments used have inherent limitations to detect changes in HRQL. There are many instruments that help researchers to evaluate quality of life in children [1, 31, 32]. In general, HRQL instruments can be divided into specific and generic. Generic instruments are designed to assess and compare health status in patients with different diseases and may provide valuable information for comparing outcomes between sick and healthy populations; they lack sensitivity to detect small but clinically significant changes in HRQL over time or due to treatment for specific diseases [1, 33]. Disease-specific measures are more suitable for evaluation of clinical trials designed to assess a particular treatment. These measures include items that are likely to be affected by the specific disease or treatment and are therefore more responsive to clinically significant changes [23, 33].

In conclusion, despite recent interest in HRQL, we found that there is very little information about quality of life among children with ADRs. Notwithstanding the considerable economic and epidemiological impact that ADRs have worldwide, there is still low interest shown by physicians and healthcare providers to report common ADRs and also to study objectively their effects on the quality of life of these children and their parents. It is therefore a challenge for those interested in this topic to develop studies and tools to help us increase the knowledge and understanding about ADRs and their consequences, with the final objective of improving methods and strategies for early identification and prevention of ADRs and, in this way, decreasing the morbidity and mortality associated with them.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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