Original Article

Polypharmacy in Children and Young People With Life-limiting Conditions From 2000 to 2015: A Repeated Cross-sectional Study in England

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Abstract

Context. Polypharmacy is often appropriate for children with life-limiting conditions but is associated with an increase in hospitalizations and inappropriate prescribing, and can affect the quality of life of children and their families as they manage complex medication schedules. Despite this, little is known about polypharmacy in this population.

Objective. To describe the prevalence and patterns of polypharmacy in children with a life-limiting condition in a nationally representative cohort in England.

Methods. Observational study of children (age 0−19 years) with a life-limiting condition in a national database from 2000 to 2015. Common definitions of polypharmacy were used to determine polypharmacy prevalence in each year based on unique medications and regular medications. Hierarchical regression analyses were used to explore factors associated with polypharmacy.

Results. Data on 15,829 individuals were included. Each year 27%−39% of children were prescribed ≥5 unique medications and 8%−12% were prescribed ≥10. Children with a respiratory (OR 7.6, 95%CI 6.4−9.0), neurological (OR 2.8, 95%CI 2.4−3.2), or metabolic (OR 2.2, 95%CI 1.7−2.8) condition were more likely than those with a congenital condition to experience polypharmacy. Increasing age, being diagnosed with a LLC under one year of age, having >1 life-limiting or chronic condition or living in areas of higher deprivation were also associated with higher prevalence of polypharmacy.

Conclusion. Children with life-limiting conditions have a high prevalence of polypharmacy and some children are at greater risk than others. More research is needed to understand and address the factors that lead to problematic polypharmacy in this population. J Pain Symptom Manage 2022;64:213−221.

Key Words

Polypharmacy, Medication, Pediatrics, Child, Life-limiting condition, Life-threatening condition

Key Message

This article describes an observational cohort study reporting prevalence of polypharmacy in children with a life-limiting condition in England. The results show that polypharmacy is common in this population with 27%−39% of children prescribed at least five different medications each year and 8%−12% prescribed at least 10.

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Introduction

Polypharmacy refers to "the concurrent use of multiple medication items by one individual"[1] and is associated with an increased risk of adverse drug-drug and drug-disease interactions,[2] medication errors and adherence problems, medication-related burden, and unnecessary financial cost to the patient and/or provider.[3-5] It is most commonly defined numerically (e.g., referring to five or more medications).[6,7] Although research increasingly distinguishes between "appropriate" and "problematic" polypharmacy, (the latter referring to "the prescribing of multiple medications inappropriately, or where the intended benefit of the medicines are not realized"),[3] there is consistent evidence that polypharmacy itself is associated with inappropriate prescribing and increased hospitalizations.[4]

Polypharmacy research has predominantly focused on older people, who often have multimorbidity (two or more chronic conditions together) and are therefore, likely to be prescribed multiple medications.[4] There is evidence that polypharmacy has increased in this population over recent decades.[8] However, there are growing concerns that younger populations with multimorbidity or medical complexity may also experience the problems associated with polypharmacy.[3,9-13] This includes the rising population of children with life-limiting conditions (those for which there is no reasonable hope of cure and from which children or young people will die, such as Batten disease) and life-threatening conditions (those for which curative treatment may be feasible but can fail, such as cancer), referred to hereafter as life-limiting conditions (LLCs).[14,15]

Children and young people with LLCs often have medical complexity[16] and multimorbidity.[15] They are likely to require several different medications during their illness and these may change over time as their condition worsens (i.e., recurrence of cancer or progression of muscle weakness in neuromuscular conditions) or they experience new symptoms.[9,14] In many cases polypharmacy is therefore, appropriate, but these children may also be at risk of potentially inappropriate, problematic, or excessive polypharmacy because of their changing illness profiles, the complexity of their condition and symptoms, numerous hospitalizations, multiple professionals prescribing different medications, and regular use of "off-label" medicines.[14,17-21] All of these factors may result in children cumulating medicines, experiencing adverse drug events, and problems with adherence and burden, particularly without regular review of medication regimens.[12,13,22-24]

Unfortunately, robust evidence about the prevalence and patterns of polypharmacy in children and young people with LLCs is lacking, limiting opportunities to assess or address problematic polypharmacy.[14,25] A recent scoping review on the prevalence of pediatric polypharmacy,[25] which reported a median prevalence of 39.7% from across the 284 studies identified, found no studies focusing specifically on children with LLCs. One US study that reported the characteristics of 515 pediatric palliative care patients found that children took a mean of 9.1 different medications.[26] Studies from Spain[27] and Israel,[28] which focused on children receiving end of life care, reported median numbers of medications of 4 (n = 164) and 4–6 (n = 90) respectively; and a US study about pediatric intensive care patients reported an average daily exposure to 10 different medications (n = 54,549).[24] In the US study, based in a pediatric intensive care unit, 89% of patients were exposed to five or more distinct medications for at least one day, which is the most commonly applied definition of polypharmacy.[6] Recent children's hospice audits in Wales[29] and Ireland[30] reported similar results, with mean numbers of medications per child of 10 (n = 21) and 8.2 (n = 106) respectively. The Irish study also reported the prevalence of polypharmacy, with 84% of children (n = 106) prescribed >5 medications daily.

These studies suggest that polypharmacy is common in children and young people with LLCs, but robust evidence that focuses specifically on this population is required. This study therefore, aims to describe prevalence and patterns of polypharmacy in children and young people with LLCs in England in a nationally representative cohort. Children in England have access to free at the point of care healthcare via our National Health Service and those with a LLC will receive care from a range of secondary and tertiary specialists (e.g., neurologists, cardiologist, oncologists) with some input from primary care experts (GPs).

Methods

Data Sources

Individual level pseudonymized patient data were obtained from the Clinical Practice Research Datalink (CPRD) GOLD primary care database. The CPRD dataset contains pseudonymized, longitudinal records of primary care from a representative sample of General Practices across the UK (covering approximately 8.5% of the UK population)[31]. Data were linked by CPRD to Index of Multiple Deprivation (IMD) data, Hospital Episode Statistics (HES) Admitted Patient Care (HES APC) data, HES Outpatient (HES OP) data, and death registration data from the Office for National Statistics (ONS).[31] Fig. 1 shows data sources and linkage.

Study Population

The cohort included children and young people (age 0–19 years) with a diagnosed LLC who were registered with a GP practice contributing data to the CPRD

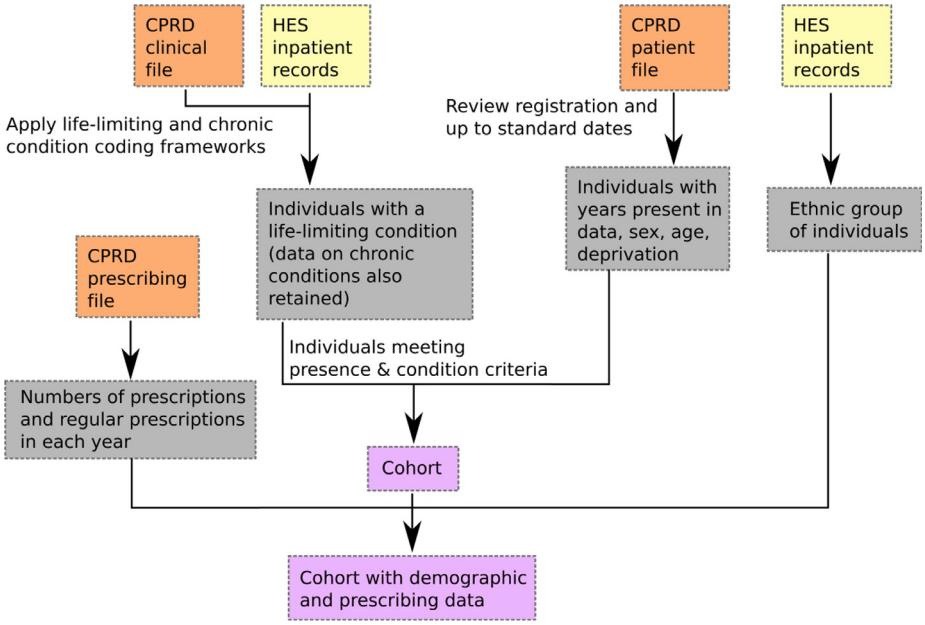

Fig. 1. Cohort construction.

between 2000 and 2015, and who were eligible for HES linkage.

LLCs were identified using a previously developed diagnostic coding framework that uses 777, 4-digit International Classification of Diseases Version (ICD)-10 codes and equivalent Read code diagnoses.[15,32] Diagnostic data recorded in CPRD and HES were used to identify the cohort. Membership into the cohort started at the first recorded diagnosis of a LLC.

Children were grouped into 11 life-limiting diagnostic groups based on the main chapter headings in ICD-10: neurology, hematology, oncology, metabolic, respiratory, circulatory, gastrointestinal, genitourinary, perinatal, congenital, and other (see Supplementary Table 1). Children with more than one LLC were assigned to the diagnostic group that was most commonly recorded during their cohort membership. Children with a perinatal diagnosis only were excluded after the age of 1, and children with an oncology diagnosis only were excluded five years after their first oncology diagnosis.

Age at LLC diagnosis was calculated as the age at the first recorded LLC diagnosis in CPRD or HES data. Other chronic conditions that are not considered to be life-limiting were identified from the primary and secondary care data using a previously defined coding list.[33]

The Index of Multiple Deprivation (2004) is an area-based measure covering seven domains of deprivation[34] which measure relative deprivation or poverty. Index of Multiple Deprivation rankings (Department for Communities and Local Government, 2004b) for the Lower Super Output Areas provided in the data were used to assign each individual to one of five deprivation categories, with approximately 20% of the population of England aged 0–19 years in each category.[34]

Ethnicity was recorded in the HES data according to the 16 groups used in the 2001 Census and was re-categorized into nine groups to reduce risk of disclosure due to small numbers in some of the groups. Where more than one ethnic group was recorded, the most frequently occurring group was assigned.

Medication Counts

All medication prescriptions issued to an individual during their cohort membership were included. Vaccines, anesthetic drugs, emergency treatment of poisoning medications and non-medication items such as blood glucose monitoring equipment were excluded (see Supplementary Table 2 for list of exclusions).[35]

Unique medications were identified by CPRD product code, which represent individual drug formulations.[31] Drawing on previous polypharmacy research using these prescribing data, regular medications were defined as any unique medication that was prescribed in a sequence of at least three prescriptions.[36]

Counts for the number of unique and regular medications prescribed to each individual in each calendar year of their membership in the cohort were calculated.

Polypharmacy Prevalence

Initially we selected ≥2, ≥4, ≥5 and ≥10 medications as key common numeric definitions used in pediatric polypharmacy research[7] and in the wider research and literature on polypharmacy.[3,6] These definitions were often operationalized differently across studies in terms

of whether one-off prescriptions as well as regular medications were included. We sought input on the selected definitions from experts, including parents, young adults with an LLC and healthcare professionals.

Two recommendations were made: 1) that we should use and report the results for several commonly used definitions because together they show the different patterns of polypharmacy in this population; and 2) that we should report polypharmacy for all unique medications as well as for regular medications to capture the potential burden on children and their families.

Definitions in the literature also varied in terms of whether different medications were taken concurrently; however, it was not possible to operationalize this using CPRD prescribing data because of the lack of information about prescription duration and sequencing.

Our final definitions adopted for the study were as follows:

a. ≥5 unique medications − this has been identified by numerous sources as the most commonly applied numeric definition of polypharmacy in research to date.[1,6]
b. ≥10 unique medications − this has been increasingly adopted by research since publication of the King's Fund report on polypharmacy as a definition of excessive polypharmacy.[12,30]
c. ≥2 regular medications − this was identified in a systematic review of definitions used in pediatric polypharmacy as the most commonly applied definition.[7]
d. ≥4 regular medications − this is suggested as the minimum number of regular medications that should be considered as potentially problematic polypharmacy for individuals with key risk factors, which include receiving palliative care or where there is a risk of potentially inappropriate prescribing, e.g., use of off-label drugs.[1]

For each definition, we identified the children who experienced polypharmacy (e.g., for definition a. were prescribed ≥5 unique medications) in each calendar year and reported this as prevalence in that year, i.e. percentage of the total number of eligible children present in the cohort for that year.

Statistical Modelling

We utilized multilevel (hierarchical) logistic regression to account for the repeated (annual) measurement of polypharmacy with individuals at level 2 and year at level 1. Sex, age, ethnic group, deprivation category, main diagnostic category, age at diagnosis of LLC, presence of multiple LLCs (binary variable), and presence of non-LLC chronic comorbidities (binary variable) were all candidate independent variables. Final variable inclusion was guided by the Bayesian Information Criterion (BIC)[37,38] with a reduction in BIC of three or more grounds for retention. Four models were developed, one for each of the polypharmacy definitions employed in the study, but all with the same independent variables.

Data manipulation was undertaken using Microsoft SQL server and STATA version 16 (Stata Corp, College Station, TX) with statistical analysis using STATA. $P < 0.05$ was considered to be statistically significant.

Results

There were 15,829 children and young people (age 0−19 years) with a LLC diagnosis in this cohort (Table 1). There were more males (55.5%) than females and the predominant ethnic group was White (81.5%). The most

Table 1
Sample Characteristics.

	n	%
Median age (yrs) at first LLC diagnosis (IQR)	2.83 (0.35−10.68 yrs)	
Yr of birth		
1980−1984	541	3.4%
1985−1989	1459	9.2%
1990−1994	2239	14.1%
1995−1999	2890	18.3%
2000−2004	3165	20.0%
2005−2009	3244	20.5%
2010−2015	2291	14.5%
Sex (female)	7041	44.5%
Ethnic group		
Bangladeshi	83	0.5%
Black	578	3.7%
Chinese	50	0.3%
Indian	279	1.8%
Mixed	430	2.7%
Other Asian	224	1.4%
Other	319	2.0%
Pakistani	407	2.6%
White	12,897	81.5%
Unknown	562	3.6%
Deprivation group		
Level 1 (least deprived)	3112	19.7%
Level 2	3079	19.5%
Level 3	3018	19.1%
Level 4	3268	20.7%
Level 5 (most deprived)	3338	21.1%
Unknown	14	0.1%
Main LLC diagnostic group		
Circulatory	402	2.5%
Congenital	6245	39.5%
Gastrointestinal	219	1.4%
Genitourinary	714	4.5%
Haematology	828	5.2%
Metabolic	681	4.3%
Neurology	2272	14.4%
Oncology	2586	16.3%
Perinatal	302	1.9%
Respiratory	1395	8.8%
Other	185	1.2%
More than one life-limiting diagnosis	4777	30.2%
Comorbid chronic condition	7760	49.0%

Abbreviations: IQR = interquartile range.

common main diagnostic groups were congenital (39.5%), oncology (16.3%) and neurology (14.4%). The mean age of a first LLC diagnosis was three years old. Nearly a third (30.2%) of children had more than one LLC diagnosis and nearly a half (49%) had a co-morbid chronic condition. More cohort members lived in areas of highest deprivation (21.1%) than in areas of lowest deprivation (19.7%).

The median number of unique prescriptions per year was two with numbers ranging from 0 to 53 (IQR: 1–6). For regular prescriptions, the median number was 0 (range 0–29; IQR 0–2). There was a trend of decreasing numbers of unique and regular prescriptions over time (Fig. 2).

Polypharmacy prevalence varied by definition, but decreased in general over time (Fig. 3). In 2000, 39% of the cohort had five or more unique prescriptions in the year, falling to 27% in 2015. For those with ten or more unique prescriptions, proportions fell from 12% to 8%. For regular prescriptions, 36% had two or more in 2000, falling to 25% in 2015 and 19% had four or more in 2000, falling to 12% in 2015.

The findings from the statistical models were broadly similar across the different definitions of polypharmacy used as outcome variables (Fig. 4, Supplemental Table 1).

There were variations in polypharmacy by age in year, with children under one year having consistently

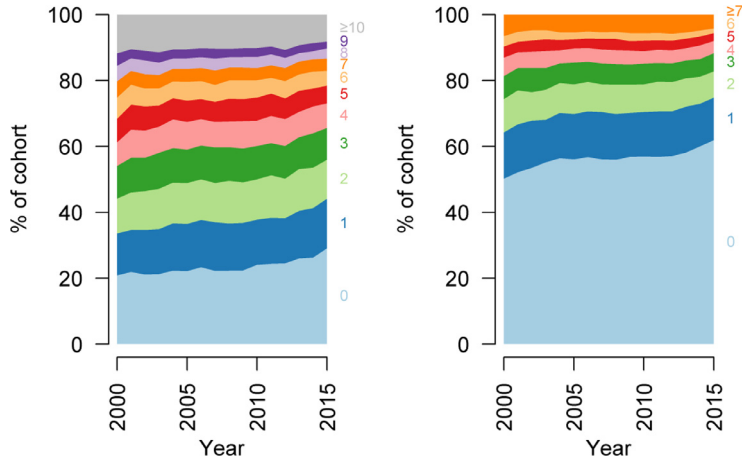

Fig. 2. Numbers, indicated to right of plots, of unique prescriptions (left plot) per person per year and regular prescriptions (right plot) per person per year in the cohort.

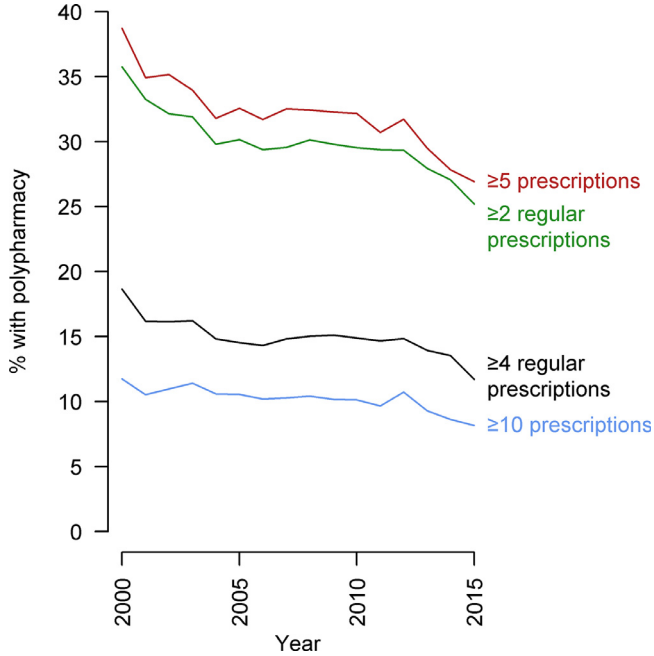

Fig. 3. Proportion of cohort experiencing polypharmacy in each year under the different definitions.

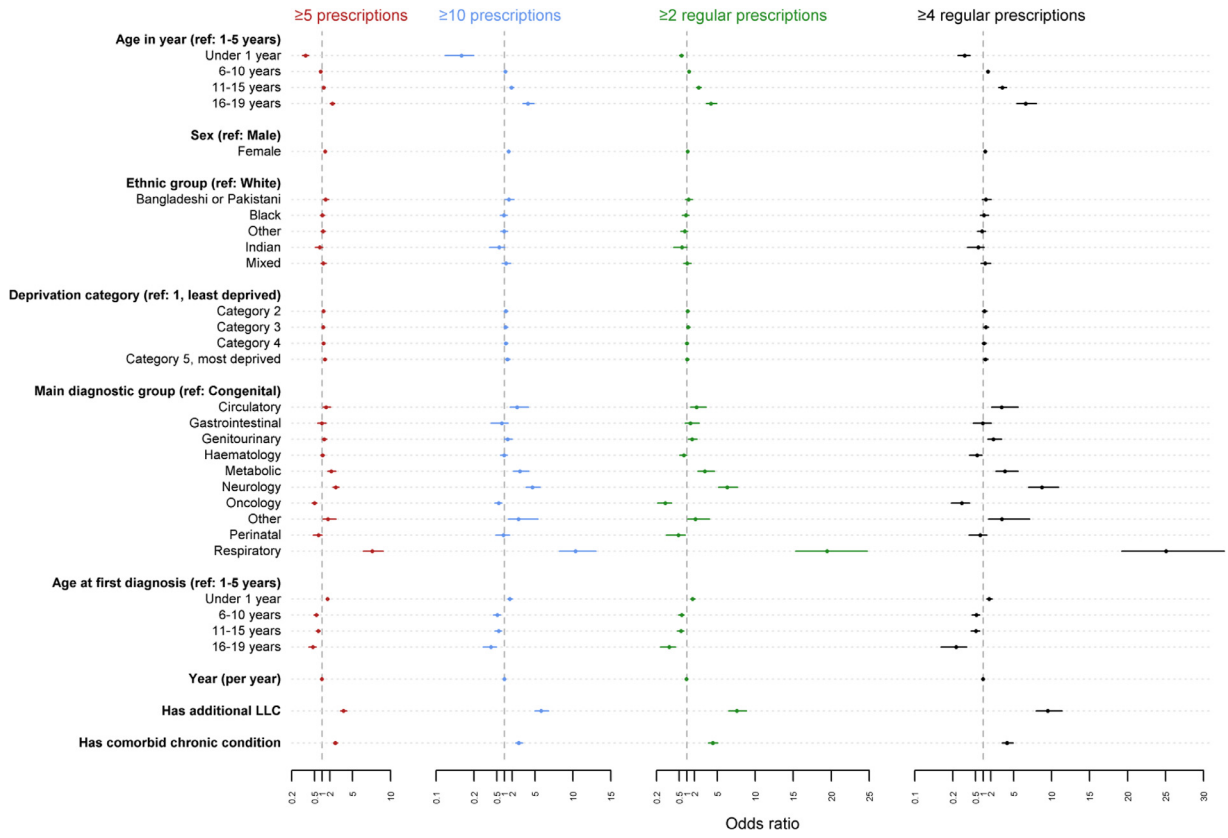

Fig. 4. Odds ratios from logistic regression models for the likelihood of polypharmacy under cohort conditions and demographics. Lines indicate 95% confidence interval.

less polypharmacy than the 1−5 years reference group, with as much as 85% (95%CI: 80%−89%) lower odds of having ≥5 unique prescriptions per year. For all definitions, polypharmacy generally increased with age, with the oldest age group (16−9 years) being up to 6.6 (5.4−8.2) times as likely to experience polypharmacy compared to 1−5-year-olds when defined as ≥4 regular prescriptions per year.

The only significant differences in polypharmacy by ethnic group were for the Bangladeshi or Pakistani ethnic group: risk of polypharmacy compared with the White group was 45% higher (95%CI: 11% −88%) for ≥5 unique prescriptions per year and 57% higher (95%CI: 8%−126%) for ≥10 unique prescriptions per year.

Increasing levels of deprivation were associated with greater levels of polypharmacy with the most deprived category having a 36% (95%CI: 17% −58%) greater likelihood of polypharmacy for ≥5 unique prescriptions per year compared with the least deprived and 38% (95%CI: 11%−72%) greater likelihood for ≥10 unique prescriptions per year. There was no clear gradient for polypharmacy measured by regular prescriptions.

There were large differences in polypharmacy when comparing main diagnostic groups, with those having a respiratory LLC being much more likely to have polypharmacy under all definitions compared to children with congenital conditions. These were by 7.6 (95%CI: 6.4−9.1) times for ≥5 unique prescriptions; 10.4 (95%CI: 8.2−13.0) times for ≥10 unique prescriptions; 19.5 (95%CI: 15.3−24.8) times for ≥2 regular prescriptions and 25.1 (95%CI: 19.2 −32.7) times for ≥4 regular prescriptions. Additionally, children whose main LLC diagnosis was for a circulatory, metabolic, neurology or other conditions also had greater likelihood of polypharmacy, while those with oncology and perinatal conditions had a lower likelihood.

Age at first diagnosis of LLC was also predictive of polypharmacy, with those diagnosed before the age of one the most likely to experience polypharmacy—70% or more likely under all definitions compared to children diagnosed between 1 and 5. Diagnoses at ages older than five years were associated with reduced risk of polypharmacy.

There was a general decrease in polypharmacy each year for most definitions, except for four or more regular prescriptions in a year (here the point estimate still showed a non-significant decrease). Likelihood of polypharmacy decreased by 5% (95%CI: 4%−5%) per year for ≥5 prescriptions per year; 2% (95%CI: 1%−4%) for ≥10 prescriptions and 4% (95%CI: 3%−5%) for ≥2 regular prescriptions.

Presence of multiple LLCs or a comorbid chronic condition were both associated with increased risk of polypharmacy across all definitions. For each additional LLC, the risk increased 3.8 (95%CI: 3.4−4.3) times for ≥5 prescriptions in a year; 5.8 (95%CI: 4.9−6.8) times for ≥10 prescriptions; 7.6 (95%CI: 6.5%−8.8%) times for ≥2 regular prescriptions and 9.5 (95%CI: 8.0−11.4) times for ≥4 regular prescriptions. For a comorbid chronic condition, risks also increased: 2.7 (95%CI: 2.5−3.0) times for ≥5 prescriptions; 3.9 (95%CI: 2.5−3.4) times for ≥10 prescriptions; 4.4 (95%CI: 3.8−5.1) times for ≥2 regular prescriptions; and 4.2 (95%CI: 3.5−4.9) times for ≥4 regular prescriptions.

Discussion

This study confirms that there is great variability in the number of medications prescribed to children and young people with a LLC, but overall polypharmacy is common in this population with 29%−37% of children prescribed ≥5 unique medications each year. Between 8 and 12% of children and young people are exposed to excessive polypharmacy (≥10 unique medications each year), increasing their risk of adverse effects and drug interactions.[2]

The study also provides important insights about which children and young people are most likely to experience polypharmacy. These include children with a main diagnosis of a respiratory, neurological or metabolic life-limiting condition when compared to those with a congenital condition. Unsurprisingly, children with multiple LLCs and other comorbid chronic conditions were also at greater risk of polypharmacy. A recent scoping review showed that much of the existing literature on polypharmacy in children either uses whole population samples or focuses on children with single health conditions e.g., epilepsy,[25] and are therefore, less comparable to the population in the current study. The prevalence of polypharmacy found in the review ranged from 0.9% to 98.4%.[25] However, a nationally representative study of adolescents with disabilities in the US found a prevalence of polypharmacy of 6.4%, although polypharmacy was higher for adolescents with multiple health conditions.[39] Another US study which included a high proportion of children with medical complexity found a similar prevalence to the current study of 35%.[10]

The evidence also suggests that children from Bangladeshi and Pakistani populations and those living in the most deprived areas may be at an increased risk of polypharmacy. Higher prevalence of polypharmacy in children from ethnic minority groups[39] and low-income families[40] has been shown in other studies.

The prevalence of polypharmacy decreased over the time period of this study. This may be a genuine decrease or may be due to an increased in prescriptions for these children being dispensed in secondary and tertiary care and therefore, missed from this dataset. The latter is possible as the changes in National Health Service structure in England over time have resulted in stricter rules on prescribing certain, often high cost, drugs in primary care.

Children with LLCs are known to have a complex health needs and polysymptomatology[41] and therefore, much of the polypharmacy may be appropriate. However, our consultation with parents and professionals indicated that children who were cared for by multiple specialists or who were without a clinician coordinating their care were less likely to receive medication reviews, especially when the child was stable.

Future research needs to address how to identify problematic polypharmacy in children with complex health conditions and the role of medication reviews for these children and families to reduce the risk of adverse effects.[42]

Strengths and Limitations

This is the first nationally representative study to report prevalence of polypharmacy children and young people with LLCs. Identification of such children using diagnostic codes alone is reliant upon high quality coding and the sensitivity and specificity of these codes. This is especially true for the population of children with perinatal life-threatening events who may no longer be considered to have a life-threatening condition. The age of first recording of a diagnoses in these data may be later than first diagnoses if a congenital anomaly was diagnosed at birth and recorded on the maternity dataset. However, this delay is likely to be minimal if a serious congenital anomaly.

This dataset does not contain prescribing data from secondary or tertiary care. This means that some drugs, especially those with specific prescribing requirements e.g., oncology drugs, high costs drugs or those with certain prescribing conditions related to commissioning will be missed. This study is therefore, likely to underestimate polypharmacy for some groups of children and may explain the higher-than-expected proportion of children in these data apparently taking no regular medications. Previous studies in the pediatric palliative care population do, however, also include children not taking any medications.[26]

Conclusion

Children with LLCs are exposed to high rates of polypharmacy with the risk varying according to main diagnosis, age, deprivation level and number of conditions and comorbidities. More research is needed to

understand and address the factors that lead to problematic polypharmacy in this population and to identify appropriate interventions.

Contributions

JT led the study design with contributions from LF, TD and SJ. LF led on the data acquisition. DGS, JT and SJ undertook the analyses and all authors contributed to the interpretations of the findings. JT and LF drafted the manuscript, and all authors revised and approved the final version of the manuscript.

Disclosures

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JT, DGS, AP, TD, VN and MH have no conflicts to declare.

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Supplementary Table 1

ICD-10 Diagnostic Coding Framework Used to Identify and Categorize Children with Life-Limiting Conditions.

Diagnostic Group	ICD-10 Numbers
Neurology	A17 A810 A811 F803 F842 G10 G111 G113 G12 G20 G230 G238 G318 G319 G35 G404 G405 G600 G601 G702 G709 G710 G711 G712 G713 G800 G808 G823 G824 G825 G934 G936 G937
Haematology	B20 B21 B22 B23 B24 D561 D610 D619 D70 D761 D81 D821 D83 D891
Oncology	C D444 D48 (Central Nervous System: C70,C71,C72, D33, D43)
Metabolic	E310 E348 E702 E71 E72 E74 E75 E76 E77 E791 E830 E880 E881
Respiratory	E84 J841 J96 J984
Circulatory	I21 I270 I42 I613 I81
Gastrointestinal	K550 K559 K72 K74 K765 K868
Genitourinary	N17 N18 N19 N258 (Early stage (1-3) renal:N181, N182, N183)
Perinatal	P101 P112 P210 P285 P290 P293 P350 P351 P358 P371 P524 P525 P529 P832 P912 P916 P960
Congenital	Q000 Q01 Q031 Q039 Q040 Q042 Q043 Q044 Q046 Q049 Q070 Q200 Q203 Q204 Q206 Q208 Q213 Q232 Q218 Q220 Q221 Q224 Q225 Q226 Q230 Q234 Q239 Q254 Q256 Q262 Q264 Q268 Q282 Q321 Q336 Q396 Q410 Q419 Q437 Q442 Q445 Q447 Q601 Q606 Q614 Q619 Q642 Q743 Q748 Q750 Q772 Q773 Q774 Q780 Q785 Q792 Q793 Q804 Q81 Q821 Q824 Q858 Q860 Q870 Q871 Q872 Q878 Q91 Q920 Q921 Q924 Q927 Q928 Q932 Q933 Q934 Q935 Q938 Q952
Other	H111 H498 H355 M313 M321 M895 T860 T862 Z515

Supplementary Table 2

Excluded Prescriptions.

The following BNF codes and code stems were excluded	
01.08-	stoma care
03.04.02-	allergen immunotherapy
03.06-	oxygen
06.01.01.03	hypodermic equipment
06.01.06.00	diagnostic and Monitoring devices for diabetes mellitus
07.04.04-	bladder instillations and urological surgery
09.02-	fluids and electrolytes
09.03-	intravenous nutrition
09.04-	oral nutrition
09.05-	minerals
09.06-	vitamins
09.07-	bitters and tonics
10.03.00-	unspecified Drugs for the relief of soft-tissue inflammation and topical pain relief
11.09-	contact lenses
14.—	Vaccinations
15.-	Anaesthesia
16-	Treatment for emergency poisoning
17-	Non-medicinal substances
20	Pseudo chapters (dressings and appliances)

See https://digital.nhs.uk/data-and-information/areas-of-interest/prescribing/practice-level-prescribing-in-england-a-summary/practice-level-prescribing-glossary-of-terms#bnf-classifications