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Factors affecting the patient journey and patient care when receiving an unlicensed medicine: A systematic review

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ABSTRACT

Background: Unlicensed medicines are used across the UK to treat an individual's clinical needs when there are no appropriate licensed alternatives. Patients, carers and parents have reported facing challenges with unlicensed medicines at the points of transfer of care between settings, a key time when medication errors may occur. There is little known about the patient journey as a whole, or the factors affecting patient care when receiving an unlicensed medicine.

Objective: A systematic review of UK literature to better understand factors that affect the entire patient journey from the decision to initiate treatment with an unlicensed medicine to the point at which treatment is supplied through a community pharmacy or ends.

Methods: Scopus, OVID EMCARE, EMBASE, OVID Medline ALL, CINAHL, Web of Science and Joanna Briggs Institute were searched from 1968 (introduction of the Medicines Act) until November 2020, using the PRISMA guidelines. Narrative synthesis of UK studies was employed to analyse descriptive and qualitative data on any reported findings that would impact the patient journey or care related to the use of unlicensed medicines, and any described barriers or enablers.

Results: Forty-five studies met criteria for final inclusion, with high levels of heterogeneity in terms of designs and methods. Specific challenges that were seen to impact the continuity of care across care settings, patient safety and provision of patient-centred care included diversity of clinical needs and impact of patient population age; healthcare professional awareness and acceptability of the use of unlicensed medicines; the hierarchical structure of the NHS; inconsistent doses and formulations with varying bioequivalence; patient/parent/carer/public awareness of unlicensed medicines use and perceived acceptability.

Conclusions: This review identified a clear need for consistent information to be provided to healthcare professional and patients alike to support the safe and effective use of unlicensed medicines across care settings.

1. Introduction

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) are responsible for ensuring all medicines are safe, effective, and (unless exempt) licensed for use.[1] In certain circumstances there may be no appropriate licensed medicine available to meet a patient's individual clinical needs and an unlicensed medicine may be required. Unlicensed medicines encompass many different types of medicines, including off-label and unlicensed 'special' medicines. Off-label medicines are those licensed for a specific use in a specific population but prescribed for use in a way not specified by the marketing authorisation. Unlicensed 'special' medicines do not have a marketing authorisation and are made to meet the clinical needs of an individual patient.[1] Unlicensed 'special' medicines and off-label medicines may be used by patients who suffer from rare diseases,[2] are unable to take a licensed medicine, (e.g., patients with dysphagia),[3] or those who are allergic to specific excipients in a licensed medicine.[4]

Evidence from the UK suggests that parents and carers may face

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difficulties trying to access further supplies of an unlicensed medicine prescribed after being discharged from hospital. Key issues are concerns raised by GPs when asked to continue prescriptions for unlicensed medicines, the cost of the medicines, and an inability of community pharmacies to obtain specific formulations.[5,6] Studies from the UK have explored the views and experiences of those prescribing, supplying and receiving unlicensed medicines, and found concerns from healthcare professionals and the public around the safety of unlicensed medicines.[7,8]

The Word Health Organisation (WHO) have highlighted transfer of care as a key time when medication errors can occur.[9] The WHO also recognises that unlicensed medicines are more commonly used in paediatrics with greater potential for harm as small dosing errors could lead to a more harmful effect in children than adults.[10] Despite the risk of medication errors when patients are transferred across care settings, there is limited evidence on the impact of receiving unlicensed medicines on the patient journey as a whole.

To improve the overall patient experience there is a need to better understand factors that affect the entire patient journey from the decision to initiate treatment with an unlicensed medicine to the point at which treatment is supplied through a community pharmacy or when treatment with the unlicensed medicine ends. Understanding the patient journey could involve collecting information about healthcare professionals' views and decisions to initiate treatment using unlicensed medicines in primary and secondary care, experiences related to the transfer of care across settings, the process and experiences around obtaining or accessing unlicensed medicines by healthcare professionals or patients, and the overall patient care and satisfaction throughout this journey. Patient care relates to the quality of care the patients received, such as the continuity of care across care settings and any potential risks to safety or adverse reactions experienced.

The aim of this systematic review was to explore the patient journey and patient care when receiving an unlicensed medicine in the UK, and to identify the factors that can affect it. To explore this fully, we searched for evidence from the system level (e.g., regulations, guidance, company policies, barriers to supply, perceptions of accessibility and acceptability etc.) and the individual level (e.g., decision making in prescribing and suppling medicines, experiences with prescribing, accessing, supplying and receiving unlicensed medicines, or the views and perceptions around these experiences).

2. Methods

Reporting of this review followed the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) 2009 guidance.[11] A protocol was registered with PROSPERO, CRD42020190201.

2.1. Search strategy

Search terms were developed using an iterative process whereby the lead researcher (AW) conducted multiple scoping searches using combinations of keyword terms, screening the results for relevance, and then refining search terms with a subject librarian (ZY) for further use. Searches were completed in July 2020 and updated in November 2020. No filters were used to limit the search results (individual search strategies presented in Appendix 1). Databases searched for the review included Scopus; OVID EMCARE; EMBASE; OVID Medline ALL; CINAHL (The Cumulative Index to Nursing and Allied Health Literature); Web of Science and Joanna Briggs Institute (JBI). Google Scholar was also searched using keywords to gather any extra data that had not already been identified from the database searches, with the first five pages of results being reviewed to identify any potentially relevant papers. Eligibility criteria can be seen in Table 1.

Table 1
Eligibility criteria for inclusion in the systematic review.

	Inclusion criteria	Exclusion criteria
Population	Healthcare professionals who prescribe, access or supply unlicensed medicines, as well as patients', parents', carers' and the general public. No age or other demographic restrictions or filters were used when including participants.	
Phenomena of interest	The patient journey and care when receiving an unlicensed medicine in the UK.	
Context	UK	Any study not conducted in the UK
Publication type	Original research	
Study designs	Any design	
Language of publication	English	Any study not published in English
Publication date	Published after the introduction of the Medicines Act 1968	Published before the introduction of the Medicines Act 1968

2.2. Study selection

The results of the searches were exported into Mendeley® and deduplicated (using the software and then manually). Titles and abstracts were screened in duplicate by two reviewers using the screening criteria for abstracts (AW and WZ) (See Appendix 2) with any differences discussed and resolved with another reviewer (EM). Two reviewers (AW and EM) screened 25% of the full texts using the screening criteria (Appendix 3) and the remaining full texts were screened by one reviewer (AW) with uncertainties resolved by discussion with another reviewer (EM).

2.3. Data collection process

Descriptive information about each paper was collected. To extract and collect qualitative data, we created a modified data extraction form, based on the JBI-QARI Data Extraction Form for Interpretive and Critical Research[12] and the SURE checklist for identifying barriers and enablers to health systems.[13] For quantitative studies, any quantitative findings reported that would impact the patient journey or care related to the use of unlicensed medicines were recorded, and any described barriers or enablers were noted.

2.4. Data extraction

Data extraction was conducted by two reviewers (AW, WZ) with any uncertainties being discussed with another reviewer (EM). Data included descriptive information about the studies, such as date of publication, area within the UK, number of participants, participant population groups, study methods, unlicensed medicines used (if specified). From qualitative studies, data were considered to be any views or experiences given where the patient journey was affected, or could be affected, using quotations from the text, where available. From quantitative studies, data related to the patient journey or care was collected. For example, prevalence of unlicensed medicine use, number of admissions, errors, adverse drug reactions or survey results of opinions or experiences related to unlicensed medicines if reported as numbers or percentages.

2.5. Quality assessment

Quality assessment was conducted by one reviewer (AW) with around 25% of included studies being verified by another reviewer

(EM). All studies (cohort, case control and qualitative) were appraised for quality using the relevant Critical Appraisal Skills Programme (CASP) checklists and categorized as low (five or more 'can't tell' or 'no' responses), medium (three or more 'can't tell' or 'no' responses) or high quality (Table 2).

2.6. Data synthesis and analysis

As the studies included in the review contained high levels of heterogeneity in terms of designs and methods, a meta-analysis or meta-ethnography was not possible, and the evidence was synthesised using narrative synthesis following the guidance laid out by Popay et al. (2006).[14] The stepwise approach of thematic synthesis by Lucas et al. (2007)[15] was followed, and study commentaries were created before synthesis, highlighting key aspects of the research findings in relation to the research question and the authors conclusions.

3. Results

A total of 2129 documents were initially identified, after deduplication and screening 45 studies met the inclusion criteria and were included in the review (PRISMA flow chart presented in Fig. 1).

3.1. Characteristics of studies included in the review

A total of 45 studies were selected for the full review and narrative synthesis. Table 2 outlines descriptive information about the characteristics of included studies. A mix of designs were included in the review, with a range of focusses, consisting of 36 quantitative papers and 9 qualitative papers. Quality assessment found 39 studies to be of high quality and 6 studies to be of medium quality, with none of the included studies being rated as low quality supporting the strength of the evidence.

3.2. Thematic analysis

Reflexive thematic analysis was conducted to determine factors affecting the different areas of the patient journey and care when receiving an unlicensed medicine in the UK (Fig. 2).

3.3. Theme 1 prescribing of unlicensed medicines

Numerous studies described factors that could impact the prescribing of unlicensed medicines, and these were grouped into studies discussing the diverse clinical needs of the patients and those related to awareness and acceptability of the use of unlicensed medicines among healthcare professionals.

3.3.1. Diversity of clinical needs and impact of patient population age

A total of 19 studies included in the review described the use of, and clinical need for, unlicensed medicines.[18,24–26,29,32,34,39,43–47,49–53,56] This included treatment where there was a lack of a suitable licensed alternatives, or when patients' age and associated limited ability to use the available licensed dosage resulted in prescribing of unlicensed and off-label medicines.

The use of unlicensed and off-label medicines due to a lack of licensed alternatives was highlighted across many care settings including intensive care[47] and palliative care.[52] Other examples included an unlicensed medicine to treat specific conditions such as Ebola (recombinant vesicular stomatitis virus–Zaire Ebola virus vaccine)[24] and a veterinary medicine to treat patients who had severe S. Stercoralis infection.[18] Unlicensed medicines were also required when the available licensed medicines had not been effective for certain patients,[34] or when using a medicine licensed for adults to treat paediatrics.[46]

Some studies explored the use of unlicensed and off-label medicines in specific therapeutic areas such as mental health. The use of psychotropic medicines was highlighted, with a study reporting that 50% of all prescribed medicines were unlicensed or off-label.[29] Two percent and 39% of medicines in new prescriptions from 21 child and adolescent mental health services in a different study were unlicensed and off-label respectively.[50]

Patient age was identified as a key reason to use unlicensed and off-label medicines. Increased use of unlicensed medicines has been reported for adult patients with affective disorders under the age of 65 compared to patients older than 65.[25] However, most studies that highlighted age as a factor for using unlicensed medicines, had a focus in paediatrics, and often in a specific age range. The extend of use varied across studies, from 25% of medicines supplied to children in a children's hospital, for patients aged four days to 20 years,[56] to 0.3% of prescriptions were unlicensed and 10.5% were for off-label medicines for patients aged 12 and under in a primary care study.[51] A similar study reviewing prescriptions from the General Practice Administration System for Scotland found that 20–35% of overall prescriptions for patients aged 0-16-year-olds were for off-label medicines.[43] In a neonatal intensive care unit it was found that during the study period, 90% of patients were prescribed at least one medicine that was unlicensed or off-label.[53] Another study found that 92% of liquid formulations provided to children were available as a marketed solid form, with only 13% of the dispensed liquid formulations not corresponding to a licensed alternative,[32] suggesting potential increased costs for the NHS.

A key finding in relation to the prescribed unlicensed medicines within this age group, was that they accounted for 40% of overall cytotoxic agent prescribing as there were no licensed alternatives for use,[44] showing the use of unlicensed medicines may be higher for specific uses and where there are no licensed alternatives. One study reported that 49% of prescriptions for children within gastroenterology were for unlicensed or off-label medicines,[45] highlighting that only the 'Medicines for Children' formulary contained information on more than half of these, with other formularies lacking information for many paediatric doses. Unlicensed medicines were also found to be used for pain management for children, with off-label medicines accounting for 33% of prescriptions in one study[49] and an increasing use for treating obesity in children outlined by Viner et al. (2009).[39] In the treatment of leukaemia, unlicensed medicines accounted for 19% of prescriptions and off-label medicines made up 26% of prescriptions.[44]

The need for the use of unlicensed medicines in children was also detailed when the licensed medicine was found not to be suitable for the specific patient. One study highlighted the use of mepolizumab in adolescents with eosinophilic asthma who had already tried a licensed alternative which had resulted in allergic reactions or treatment failure.[26]

3.3.2. Healthcare professional awareness of suitable unlicensed medicine use, or licensing status, familiarity with guidance, and perceived acceptability of prescribing

Five studies described different aspects of healthcare professional awareness, including awareness of the licensing status, awareness of suitable uses for unlicensed medicines or guidance available to them. The studies also described prescriber acceptability when prescribing unlicensed medicines and discussed how this could impact prescribing practices.[5,8,17,22,54]

A study exploring the views and practices of obstetric anaesthetists found that 80% of participants thought the Obstetric Anaesthetists' Association (OAA) should issue guidelines on drug practices and the results highlighted the use of an unlicensed medicine for an indication the manufactures had advised against.[54] Interviews with healthcare professionals across primary and secondary care also highlighted a lack of information and training which impacted awareness around the use of unlicensed medicines, with some prescribers reporting that they were not always aware when they were prescribing unlicensed medicines.[17] This lack of awareness and perceived lack of guidance led to some

Table 2
Study characteristics and quality appraisal results of the 45 included studies in the systematic review by design type and recency of publication.

Author/year	Aim	Study design	Sample	Key findings/conclusions	Quality assessment results
Wale, Ireland and Yemm et al. (2020)[16]	To explore the views and experiences of community pharmacy staff on accessing and supplying unlicensed "special" medicines to patients in Wales and the perceived impact of challenges faced on patient care	Qualitative Semi-structured interviews	6 community pharmacy staff	Three main themes: requirement for additional patient responsibilities; influences on the confidence felt by pharmacy staff when accessing and supplying unlicensed "special" medicines; and continuity of supply. Further research is required to see if these views and experiences are representative of community pharmacy staff across the country.	High
Husain, Davies and Tomlin (2017)[6]	To explore the experiences of parents and carers relating to the supply of unlicensed medicines for their child after discharge from hospital	Qualitative Semi-structured interviews	15 parents and carers	Parents and carers experience problems when attempting to obtain unlicensed medicines for their child following discharge from hospital. Problems can occur at the prescribing and dispensing stage and are a source of concern and anxiety for parents and carers.	High
Donovan, Parkin and Brierley-Jones (2016)[17]	To explore the use of unlicensed medicines across primary and secondary care from the perspectives of prescribers, pharmacists and patients	Qualitative Semi-structured interviews	Healthcare professionals and patients	Five main themes: Healthcare professionals' awareness of when they were using an unlicensed medicine and their definition of an unlicensed medicine; perceptions of safety, provision of information; the place of unlicensed medicine use in the clinical management of a patient, including whether licensed alternatives were tried first; and trust as an important aspect in the use of unlicensed medicines. Unlicensed medicines form part of prescribing practice, however, many of the tools that are traditionally available to support clinical decision making and patient use are lacking.	Medium
Barrett, Broderick and Soulsby (2015)[18]	To describe the experience of the successful use of subcutaneous ivermectin in two patients with severe and complicated Strongyloides infection	Qualitative Case studies	2 patients	Both patients were successfully treated with subcutaneous ivermectin, and both recovered completely. Subcutaneous ivermectin has potential as a safe and effective treatment in patients with severe strongyloidiasis, but until there is greater experience of its use in this group, dosing and monitoring remain empirical at best.	High
Haw, Stubbs and Dickens (2015)[19]	To explore mental health nurses' knowledge, attitudes and clinical judgement concerning medicines management in an inpatient setting with a view to enhancing training	Qualitative Semi-structured interviews	50 nurses	Use of clinical vignettes appears to be a useful way of exploring mental health nurses' knowledge, attitudes and experience of medicines management. Many participants appeared unaware of current UK guidance and local medicines policy. The results suggest that mental health nurses require regular refresher sessions on national guidelines and local policies concerned with medicines management.	High
Venables, Stirling and Batchelor et al. (2015)[20]	To explore problems with oral medicines prescribed to paediatric patients from the perspectives of medical practitioners, pharmacists and nurses	Qualitative Focus groups	19 healthcare professionals	Two main themes: sensory and non-sensory. Included within these were taste, texture, colour, smell, size, swallowing, quantity, volume and manipulation with food. Organoleptic and physical properties of medicines were identified as key barriers to medicines administration.	High
Mukattash, Trew and Hawwa et al. (2012)[21]	To explore the views and perspectives of children on the unlicensed/off-label use of medicines in children and on the participation of children in clinical trials	Qualitative Focus groups	123 pupils	Four main themes: Views on the unlicensed use of medicines in children; Informing parents/guardians and children; Clinical trials and willingness to participate; and Illness and participation in clinical trials. Children were able to recognise potential risks associated with the unlicensed use of medicines and felt it is necessary to test and license more medicines in children.	High

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Table 2 (*continued*)

Author/year	Aim	Study design	Sample	Key findings/conclusions	Quality assessment results
Crowe, Tully and Cantrill (2009)[22]	To explore the factors which influence GPs' decision-making process when requested to prescribe specialist drugs	Qualitative Semi-structured interviews	47 healthcare professionals	Six factors were identified: GPs' lack of knowledge and expertise in using specialist drugs; the shared care arrangement; the influence of a locally agreed advisory list; financial and resource considerations; patient convenience and understanding; and GPs' specific areas of interest. The study underlines the importance of increased understanding of GPs' decision-making process for future integration of health care delivery across the primary–secondary care interface.	High
Wong, Basra and Yeung et al. (2006)[5]	To identify the availability of unlicensed and off-label medications for paediatric patients and their carers in primary care, after discharge from a specialist hospital	Qualitative Structured interviews	216 carers	Thirty-three per cent of patients had difficulty obtaining medications in primary care which caused treatment disruption. The main problems were: community pharmacies being unable to supply; and GPs' refusal to prescribe. The results are likely to be applicable to other specialist paediatric hospitals. It is important to identify ways to improve the availability of these medications in primary care.	High
Bagshaw, McCormack and Brooks et al. (2020)[23]	To assess the safety profile and effectiveness of propofol-remifentanil mixtures in the paediatric population undergoing a variety of surgical procedures	Quantitative Service evaluation	873 patients	Anaesthesia using the mixture alone was successful in all but three patients. The commonest nonserious complication was coughing, followed by movement. Serious, related, unexpected adverse events requiring intervention had a low incidence and were largely due to predictable effects of the drugs being administered.	High
Davis, Tipton and Sabir et al. (2020)[24]	To report the use of the rVSV-ZEBOV vaccine given as an emergency intervention to individuals exposed to a patient presenting with a late reactivation of Ebola virus disease	Quantitative Observational follow-up study	26 patients	No severe vaccine-related adverse events were reported. No one exposed to the virus became infected. The vaccine was relatively well tolerated, but a high percentage developed a fever, necessitating urgent screening for Ebola virus, and a small number developed persistent arthralgia.	High
Tiwari and Baldwin (2020)[25]	To examine the demographic and clinical characteristics of patients referred to a regional specialist service to determine the extent of and factors associated with recommendations for unlicensed ('off label') prescriptions	Quantitative Retrospective study	177 patient referrals	Treatment recommendations involving unlicensed applications of medications were common (approximately 50%) in all clusters, but there were no significant differences in measures of illness burden between groups of patients, categorized according to licensed or unlicensed prescriptions. Treatment decisions relating to unlicensed applications appear to be influenced by factors other than overall illness burden.	High
Weir and Paton (2020)[26]	To evaluate Mepolizumab for adolescents with severe eosinophilic asthma who failed on or were ineligible for Omalizumab	Quantitative Retrospective study	7 adolescents	Mepolizumab 100 mg given subcutaneously at monthly intervals was well tolerated in adolescents with severe eosinophilic asthma who were either ineligible for or who had failed on Omalizumab. Mepolizumab reduces exacerbation risk, may improve asthma control and quality of life but does not improve lung function.	Medium
Appleyard, Ashworth and Bedson et al. (2019)[27]	To investigate trends in gabapentinoid prescribing in patients with osteoarthritis	Quantitative Retrospective study	35,031 Prescriptions	Gabapentinoid prescribing in patients with osteoarthritis increased dramatically between 1995 and 2015. In most cases, diagnostic codes for licensed or unlicensed indications were absent. Gabapentinoid prescribing may be attributable to osteoarthritis in a significant proportion but evidence for their effectiveness in osteoarthritis is lacking. Further research to investigate clinical decision making around prescribing these expensive and	High

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Table 2 (*continued*)

Author/year	Aim	Study design	Sample	Key findings/conclusions	Quality assessment results
				potentially harmful medicines is recommended.	
Chua, Richer and Swedrowska et al. (2016)[28]	To measure the release profile of melatonin from Circadin tablets when divided or crushed, and compare this with release from intact tablets	Quantitative evaluation of medicines	7 products 2 UK unlicensed	The prolonged release of melatonin from Circadin tablets was unlike that of any other product tested. When divided into halves, Circadin preserved most of the prolonged-release characteristic, whereas quarter-cut and crushed tablet had a more immediate melatonin release profile. Circadin is significantly less expensive and should be preferred to unlicensed medicines which are not pharmaceutically equivalent and offer less quality assurance.	High
Akram (2015)[29]	To characterise the nature of psychotropic medication prescribed on discharge from a children's psychiatric unit over a 15 year period	Quantitative Retrospective study	234 children	Stimulants and atypical antipsychotics are the most commonly prescribed drugs on discharge from a children's psychiatric ward. Fifty per cent were given an unlicensed medicine or a licensed drug was used in an unlicensed manner, of which risperidone was the most common. Sleep disturbance and tics were most often treated using unlicensed/off label medication. Much of the antipsychotic use is for unlicensed indications or at unlicensed doses.	High
McAuley, Hecht and Barnsdale et al. (2015)[30]	To provide an exploratory descriptive account of drug-related deaths involving novel psychoactive substances recorded by the Scottish National Drug Related Death Database in 2012	Quantitative Exploratory study	36 drug related deaths	In 2012, 36 drug-related deaths were found in Scotland to have novel psychoactive substances recorded within post-mortem toxicology. However, in only 23 of these cases were novel psychoactive substances deemed by the reporting pathologist to be implicated in the actual cause of death. The majority of novel psychoactive substances-implicated drug-related deaths involved Benzodiazepine-type drugs, mainly Phenazepam.	High
Bellis, Kirkham and Nunn et al. (2014)[31]	To examine the impact of off-label and unlicensed prescribing on adverse drug reactions causing unplanned admissions to a paediatric hospital	Quantitative Prospective study	6020 patients	The number of medicines prescribed was a predictor of risk. Off-label and unlicensed medicines were also more likely to be implicated in an adverse drug reaction than authorized medicines, but this was driven by the higher risk of adverse drug reactions to oncology drugs prescribed in an off-label or unlicensed manner than non-oncology drugs.	High
Lajoinie et al. (2014)[32]	To assess the suitability and potential cost savings, from both the hospital and community perspective, of prescribed oral liquid medicine substitution with acceptable solid forms for children over 2 years	Quantitative Prospective study	908 dispensed medicines	Approximately 80% of prescribed liquid formulations could be substituted with a solid form in children aged over 2 years. Considering both dosage and size suitability, half of liquid drugs could be substituted, tablet size being the major limitation for solid form use in children. From both hospital and community perspectives, three quarters of treatment costs may be saved for liquid formulations that could be substituted.	High
Bellis, Kirkham and Thiessen et al. (2013)[33]	To test the hypothesis that off-label and unlicensed status is a risk factor for adverse drug reactions	Quantitative Nested case control study	1388 patients	Off-label and unlicensed medicines are more likely to be implicated in an adverse drug reaction than authorized medicines. The number of medicines administered is a risk factor for adverse drug reactions highlighting the need to use the lowest number of medicines, at the lowest dose for the shortest period, with continual vigilance by prescribers, in order to reduce the risk of adverse drug reactions.	High
Notcutt (2013)[34]	To identify the areas of daily function most affected by the introduction of Sativex, a cannabis-based medicine, and the impact on caregivers and people with multiple sclerosis	Quantitative Survey	124 patients	The majority of respondents and their caregivers reported improvements across a range of daily functional activities, alongside a reduction in the use of concomitant anti-spasticity medication	High

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Table 2 (*continued*)

Author/year	Aim	Study design	Sample	Key findings/conclusions	Quality assessment results
				and in the use of other healthcare resources.	
Bhoday, Conroy and Costa et al. (2012)[35]	To explore the experiences of pharmacists in supplying unlicensed medicines for children.	Quantitative Survey	40 members of the Nottinghamshire and Derbyshire Local Practice Forum of the Royal Pharmaceutical Society	Melatonin, omeprazole and spironolactone were the top three problem medicines highlighted. The most common problems were GPs unfamiliar with the medicine, not being willing or able to prescribe and prescribing errors; parents not informing their GP in time to generate a prescription or their community pharmacist in time to obtain further supplies before they ran out; the price of unlicensed medicines and short shelf lives.	Medium
Chisholm (2012)[8]	To evaluate attitudes towards the use of unlicensed medicines among prescribing doctors and members of the general public	Quantitative Survey	500 members of the public and 249 prescribing physicians	The study suggests pervasive concerns among prescribers over the safety, monitoring, and legal implications of unlicensed prescribing. High levels of concern were expressed among patients and physicians if cost were to become an influential factor when making decisions between licensed and unlicensed medications.	High
Conroy (2011)[36]	To determine whether a relationship exists between medication errors and licence status	Quantitative Prospective study	158 reports	Unlicensed drug use appears to be associated with medication errors in neonates and children. Medication errors causing moderate harm were significantly more likely to be associated with both unlicensed and off label than licensed drugs.	High
Mukattash, Hawwa and Trew et al. (2011)[7]	To investigate the knowledge and views of a range of healthcare professionals (consultant paediatricians, GPs, community pharmacists and paediatric nurses) regarding the use of unlicensed/ off-label medicines in children and the participation of children in clinical trials	Quantitative survey	1212 healthcare professionals	Apart from community pharmacists, most respondents reported having gained their knowledge through personal experience. Even though a large percentage of respondents expressed concerns about the safety (77.8%) or efficacy (87.9%) of unlicensed/off-label prescribing in children, only 30.7% reported informing parents/guardians about such use of medicines in children. In addition, only 56% of respondents believed that unlicensed/off-label medicines should undergo clinical trials in children.	High
Ghosh, Arulrajan and Baldwin (2010)[37]	To evaluate the extent of licensed and unlicensed prescribing for patients undergoing care within a single intellectual disability service led by a consultant psychiatrist	Quantitative Retrospective study	114 patient notes	A total of 66% received licensed drugs for unlicensed applications, principally for aggression, risperidone being the drug most prescribed. Prescribing for unlicensed applications in patients with intellectual disability is common, regardless of degree of disability or place of residence.	High
Mulla, Hussain and Tanna et al. (2010)[38]	To assess the bioequivalence of two liquid preparations against a licensed tablet form	Quantitative Crossover trial	18 healthy adults	Unlicensed liquid captopril formulations have been shown not to be bioequivalent to a licensed tablet form. The practice of prescribing bio-inequivalent formulations interchangeably may contribute to unpredictable drug response and suboptimal therapy. Clinical staff in tertiary care should ideally ensure that children are maintained on the same formulation from the same source for the duration of treatment.	High
Viner, Hsia and Neubert et al. (2009)[39]	To investigate the use of unlicensed anti-obesity drugs (orlistat, sibutramine and rimonabant) in children and adolescents (0–18 years) in the UK	Quantitative Retrospective study	1334 prescriptions for 452 patients	Prescribing of unlicensed anti-obesity drugs in children and adolescents has increased significantly in the past 8 years. Most prescribed anti-obesity drugs in children and adolescents are rapidly discontinued before patients can see clinical benefit, suggesting they are poorly tolerated or poorly efficacious.	High
Johnson (2008)[40]	To compare the performance of three scaling models in predicting	Quantitative evaluation of medicines	Unspecified	Dose scaling should only be used as a last resort for determining a suitable dose in	High

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Table 2 (*continued*)

Author/year	Aim	Study design	Sample	Key findings/conclusions	Quality assessment results
	maintenance doses for children from those used in adults			children. No single method was suitable across the entire paediatric age range.	
Mukattash, Millership and Collier et al. (2008)[41]	To explore awareness and views of the general public on unlicensed use of medicines in children and on the participation of children in clinical trials	Quantitative survey	1000 participants	Participants believed that the use of unlicensed medicines would compromise safety and increase the likelihood of adverse effects. There is limited public knowledge of unlicensed use of medicines in children and a general reluctance to involve children in clinical trials unless the child to be involved has a life-threatening condition.	High
Mulla, Tofeig and Bu'lock et al. (2007)[42]	To ascertain the interhospital constancy of unlicensed liquid captopril formulations used to treat children with heart failure in the UK	Quantitative survey	13 tertiary centres 13 hospitals	This survey shows that paediatric cardiac centres and their referring hospitals use a variety of unlicensed liquid captopril formulations interchangeably. This degree of inconsistency raises issues about optimal captopril dosing and potential toxicity, such that its use may influence paediatric cardiac surgical and interventional outcomes.	Medium
Helms, Daukes and Taylor et al. (2005)[43]	To identify the level and types of such prescribing in the General Practice Administration System for Scotland practices and to establish the level of agreement between the General Practice Research Database and the General Practice Administration System for Scotland for asthma presentations	Quantitative Retrospective study	214 medicines	No unlicensed prescribing was identified. Off-label prescribing due to age was most common among younger and older children. The most common reasons for off-label prescriptions were, in order of frequency, lower than recommended dose, higher than recommended dose, below the recommended age, and unlicensed formulation. The prescribing of off-label medicines to children is common in primary care.	High
Conroy, Newman and Gudka (2003)[44]	To examine the incidence and nature of unlicensed and off label prescribing, in paediatric oncology patients with acute lymphoblastic leukaemia and other malignancies	Quantitative Prospective study	51 patients	All patients received at least one unlicensed or off label drug. Unlicensed preparations were used in 40% of prescriptions for cytotoxic agents, due to a lack of commercially available formulations suitable for the paediatric patient. These drugs included mercaptopurine and methotrexate which have been used in the treatment of paediatric leukaemia for many years, their efficacy having been demonstrated by on-going Medical Research Council trials.	High
Dick, Keady and Mohamed et al. (2003)[45]	To assess the proportion of unlicensed and off-label medications prescribed in a paediatric gastroenterology unit to children discharged to the community and assess adequacy of information about these medications in commonly used British formularies	Quantitative Prospective study	777 prescriptions 308 patients	Use of unlicensed and off-label medications remains a problem in paediatric practice. Of the commonly used formularies, 'Medicines for Children' is the most detailed and comprehensive, and should be available to all general practitioners and pharmacists in the UK.	High
Engelhardt, Steel and Johnston et al. (2003)[46]	To investigate the suitability of tramadol in two different doses in comparison with morphine for pain relief in post tonsillectomy patients	Quantitative Randomised controlled trial	60 patients	Tramadol has similar analgesic properties, when compared with morphine. The various pharmaceutical presentations and the availability as a noncontrolled substance may make it a useful addition to paediatric anaesthesia if it becomes licensed for paediatrician aesthesia in the UK.	High
Shulman and Goldsmith (2003)[47]	To assess the proportion of unlicensed drug use on the intensive care unit of Middlesex Hospital	Quantitative Prospective study	20 drug charts	While they should stay within the boundaries of drug licenses wherever possible, intensive care unit staff may be unaware when a drug is used in an unlicensed manner. Intensive care unit staff are potentially legally responsible for any adverse effects that arise from this use.	High
Wright (2002)[48]	To describe the difficulties faced when administering oral medication to patient with swallowing difficulties in nursing homes, the methods that are used to overcome these difficulties and their appropriateness	Quantitative survey	540 nurses	The crushing or opening of medication results in unlicensed administration. Liability lies solely with the nurse if the action was unauthorised and is shared with the prescriber if it had been authorized. The majority of reported	Medium

(*continued on next page*)

Table 2 (*continued*)

Author/year	Aim	Study design	Sample	Key findings/conclusions	Quality assessment results
				crushing or opening that is taking place is unnecessary. In many instances this is because of prescriber reluctance to change the prescription.	
Conroy and Peden (2001)[49]	To document the incidence and nature of unlicensed and off label analgesic agents in children	Quantitative Prospective study	715 prescriptions	Thirty-three per cent of prescription episodes were licensed medicines used in an off label manner (33%). No medicines were unlicensed. Paracetamol was the most common analgesic used. The industry needs to be aware of the potential for medication errors resulting from the manipulation of preparations designed for adult use.	High
Johnson and Clark (2001)[50]	To collect all instances of new prescribing of medication over the 6-month period	Quantitative Prospective study	478 prescriptions for 411 patients	Of 478 new prescriptions eight were for unlicensed drugs and 188 were for licensed drugs but used in a manner outside of their product licence. This level of unlicensed and outside licence prescribing is similar to levels previously found in studies both within paediatric practice and in adult mental health practice. Anxiety about excessive beyond-lucence prescribing by child mental health services is unlikely to be justified.	Medium
McIntyre, Conroy and Avery et al. (2000)[51]	To determine the incidence and nature of unlicensed and off label prescribing of drugs for children in general practice	Quantitative Retrospective study	3347 prescriptions 1175 children	A significant number of drugs prescribed for children by general practitioners are off label. The reason for this is not hazardous prescribing practices but rather anomalies and inadequacies of product licence information with respect to children.	High
Atkinson and Kirkham (1999)[52]	To review the extent of drug use for unlicensed purposes in a palliative care unit	Quantitative Prospective study	76 patients 689 prescriptions	Fifteen per cent of prescribing events were for unlicensed indications. Drugs are frequently used in the palliative care setting for purposes unsupported by product licences, although usually backed by literature. These drugs are often prescribed for symptoms which are difficult to control.	High
Conroy, McIntyre and Choonara (1999)[53]	To determine the extent of use of drugs that are either not licensed (unlicensed), or are outside the terms of their product licence (off label) in a neonatal intensive care unit	Quantitative Prospective study	455 prescriptions for 70 patients	The use of unlicensed and off label drugs in neonatal intensive care seems to be far greater than other paediatric settings. This highlights the difficulties faced by those trying to ensure safe and effective prescribing for neonates. Urgent action is required to resolve this situation.	High
Howell and Madej (1999)[54]	To collect information from members of the Obstetric Anaesthetists' Association at the 1997 annual meeting about the drug use that is unsupported by the product licence	Quantitative Survey	169 clinicians	Both licensed and unlicensed drugs are widely used in clinical practice outside the limitations imposed by product licence. The commonest types of unlicensed administration in obstetric anaesthetic practice are the use of mixtures and epidural or spinal administration of opioids. Despite widespread awareness of the subject, there appears to be considerable ignorance about the indications for which many commonly used drugs are licensed, even amongst a specialist audience.	High
Turner, Nunn and Fielding et al. (1999)[55]	To determine the incidence of adverse drug reactions to unlicensed and off-label drugs used in paediatric inpatients	Quantitative Prospective study	1046 admissions	Use of drugs in an off-label or unlicensed manner to treat children is widespread. Adverse drug reactions were associated with 3.9% of the licensed drug prescriptions and 6% of the unlicensed or off-label drug prescriptions. Adverse drug reactions are a significant problem following unlicensed or off-label drug prescriptions.	High
Turner, Longworth and Nunn et al. (1998)[56]	To determine the extent of use in children in hospital of drugs that are not specifically licensed for use in children (unlicensed) and of drugs that are used outside the terms of their product	Quantitative Prospective study	609 patients	Thirty-six per cent of patients received one or more courses of an unlicensed or off label treatment in hospital. Use of drugs in an off label or unlicensed manner to treat children is widespread. Drugs are	High

(*continued on next page*)

Table 2 (*continued*)

Author/year	Aim	Study design	Sample	Key findings/conclusions	Quality assessment results
	licence that apply to indication, age, dose, or route of administration (off label)			more likely to be used in an off label manner than in an unlicensed manner.	

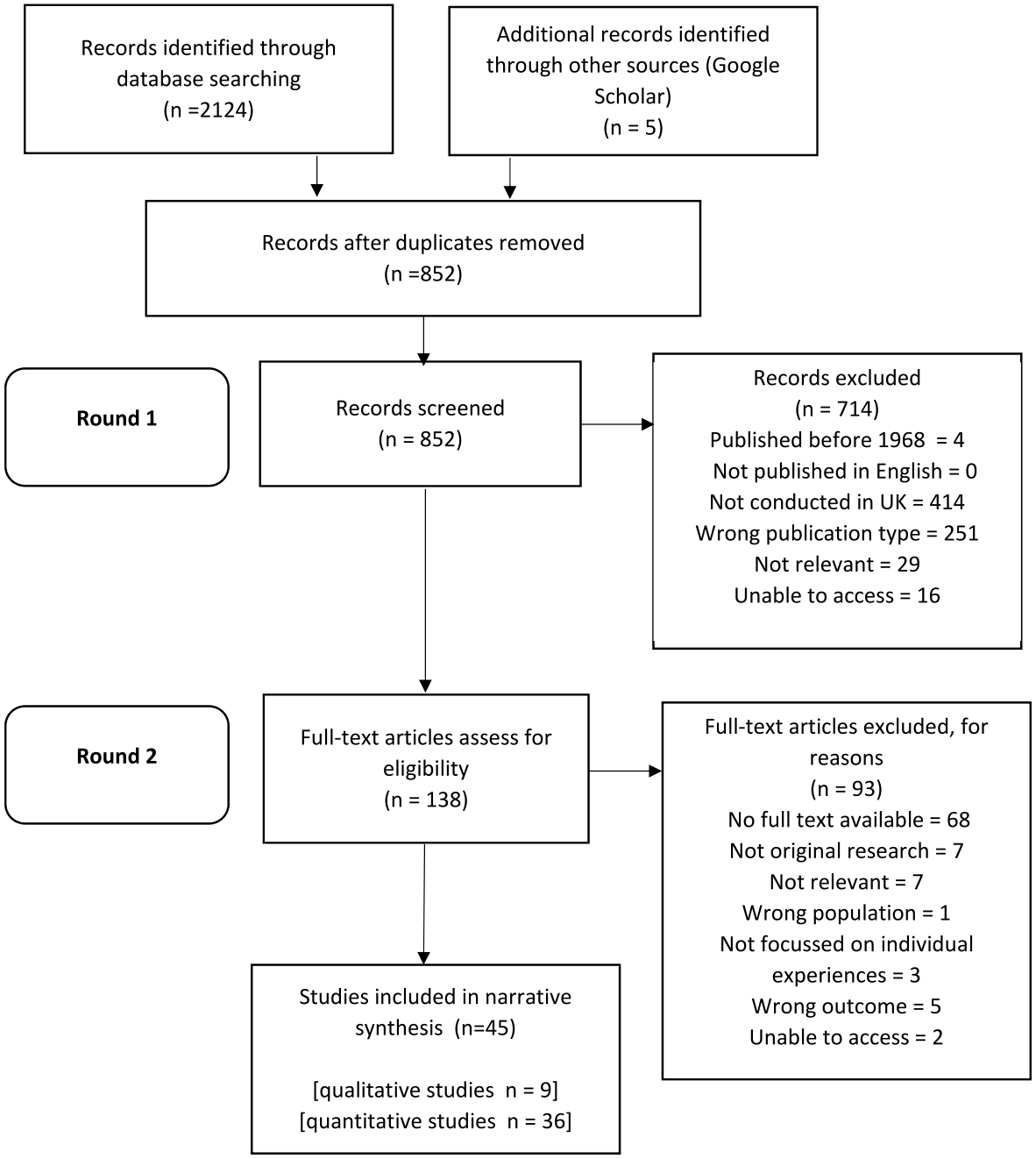

Fig. 1. PRISMA flow diagram with number of studies excluded for each of the screening criteria questions and final number of studies included in the systematic review.

healthcare professionals having concerns. In a questionnaire study, only 14% of prescribers who responded were very familiar with unlicensed medicine guidelines and most prescribers reported concerns around their legal responsibility (76%), and around safety and monitoring of patients receiving unlicensed medicines (71%).[8]

The limited perceived understanding of prescribers and the concerns they held were also seen to affect prescribing practices. Interviews with parents highlighted around a third had faced challenges when trying to access their child's unlicensed medicine after discharge.[5] One reason for this was GPs being unwilling to continue the prescription. GPs reason for this included the medicine being too costly, being outside the prescribing guidance, and a lack of experience or information and concerns

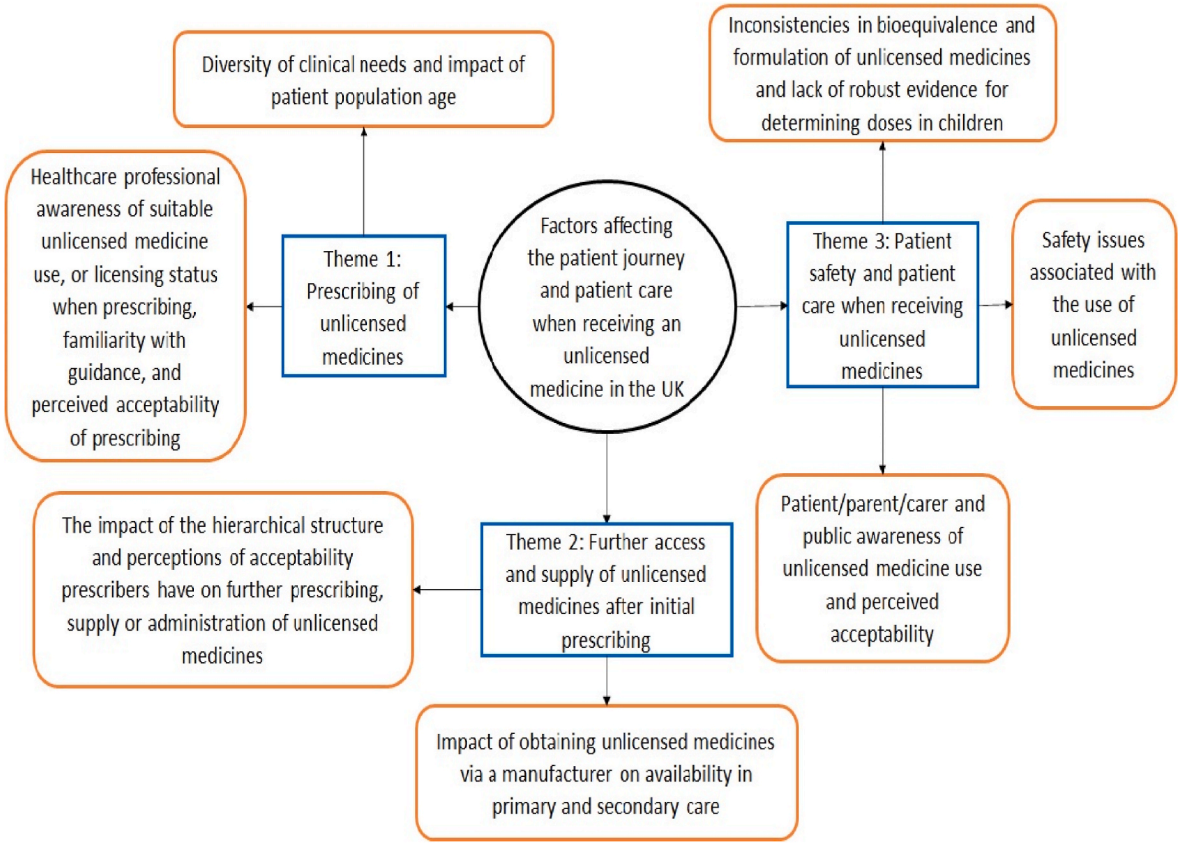

Fig. 2. Overview of the themes and subthemes constructed by systematically reviewing the literature for factors affecting the patient journey and patient care when receiving unlicensed medicines in the UK.

about the additional responsibilities associated with prescribing unlicensed or off-label.[5] However primary care prescribers' acceptability when prescribing or continuing prescriptions for an unlicensed medicine has been found to be impacted by a range of factors including the specific specialist medicine; the level of information they received from secondary care; the work involved and resources needed for shared care arrangements; the cost of the medicines; patient convenience, and their own areas of interest and knowledge along with discussions had with peers in the practice.[22]

3.4. Theme 2 further access and supply of unlicensed medicines after initial prescribing

Two factors were seen to disrupt healthcare professionals when continuing to prescribe previously initiated unlicensed medicines across care settings, or when accessing, supplying, or administering unlicensed medicines: the hierarchical structure and the individual perceptions of acceptability; issues related to accessibility.

3.4.1. The impact of the hierarchical structure within the healthcare system and perceptions of acceptability prescribers have on further prescribing, supply or administration of unlicensed medicines

Four studies provided evidence about the hierarchical structure of the chain of prescribing. Key issues were familiarity and acceptability of the use of unlicensed medicines among the healthcare professionals involved at different levels. This was seen to impact the ability of pharmacists to obtain and supply unlicensed medicines and impact the way unlicensed medicines are administered.[16,19,35,48]

Interviews with community pharmacists[16] highlighted that they were not routinely receiving adequate information on the intended use and indication of the unlicensed medications. In some cases they would contact the original prescriber to confirm whether the medication was clinically appropriate, before agreeing to supplying it. Pharmacists were reassured by the expertise of the original prescriber. Pharmacists also described issues with continuity, with GPs accidently selecting an unlicensed product in their prescribing software, or deciding not to prescribe unlicensed medicines when requested to continue prescriptions originally initiated in secondary care. In another study pharmacists highlighted how issues were experienced with GPs not being familiar with the use of the unlicensed medicine requested, requiring further information, being unwilling to prescribe, prescribing with errors, or the unlicensed medicines required not being listed on the GP computer system.[35] This lack of acceptability subsequently prevented pharmacy staff from being able to supply the medicine to the patients.

The prescribers' views and perceptions of acceptability around the use of unlicensed medicines were also reported to impact the way unlicensed medicines were administered to patients. The unlicensed crushing or opening of medicines was reported by nurses to happen weekly in 80% of nursing homes whose nurses responded to the survey, with 58% of participants suggesting that the prescriber may suggest the crushing of tablets.[48] One of the reasons this was perceived to be preferrable to prescribing unlicensed liquid medicines was the associated high cost involved should unlicensed prescribing take place.[48] Mental health nurses also highlighted the impact of prescribers' actions on how medicines are administered.[19] The nurses' perceptions were reported to impact practice with 20% of participants reporting that they would administer an unlicensed medicine they had no knowledge of, and most participants suggested they would want to know side effects and potential benefits.[19] When discussing off-label medicine prescribing with no clear evidence of benefits, 52% said they would not administer the medicine. However, 8% of nurses suggested they would still provide it rather than challenge the prescribing doctor,[19] highlighting the

influence of the hierarchical structure and the prescribing doctor on the administration of unlicensed medicines.

3.4.2. Impact of obtaining unlicensed medicines via a manufacturer on availability in primary and secondary care

Three studies highlighted issues with the accessibility and availability of unlicensed medicines via an unlicensed medicines manufacturer.[5,16,20] This included difficulties for pharmacists across care settings to find manufacturers to source the medicine.

Nurses, medical practitioners, and pharmacists discussed issues around the use of a specific liquid unlicensed special medicine, omeprazole, reporting difficulties around costing, obtaining, and storing the medicine. Additional issues were short expiry dates and varying bioequivalence of the formulations received, depending on the manufacturer.[20] Community pharmacists also highlighted difficulties accessing unlicensed medicines in another study,[16] such as not being able to access the specific unlicensed medicine required from their regular supplier, having to find other suppliers to source the medicine, or only being able to find a different formulation. In one occasion a manufacturer could not be identified at all. These challenges with accessibility led to longer lead times, treatment delays, and in one case treatment disruption where the patient was referred back to secondary care, but the hospital staff were also unable to access the unlicensed medicine.

The lack of accessibility of unlicensed medicines has also been reported by parents. In one study, a third of the parents had difficulties accessing their child's unlicensed medicine in primary care. Participants explained how the community pharmacies did not store unlicensed medicines due to the often short expiry dates, and how pharmacies were unable to obtain the medicine needed due to not being able to find a manufacturer to provide the medicine, or manufacturers not creating the specific formulations needed.[5]

3.5. Theme 3 – patient safety and patient care when receiving unlicensed medicines

Factors identified that related to patient safety or patient care when receiving unlicensed medicines included inconsistencies in the bioequivalence, formulations or doses of unlicensed medicines supplied, the safety of unlicensed medicines, and the role of patient/public awareness and acceptability of the use of unlicensed medicines.

3.5.1. Inconsistencies in bioequivalence and formulation of unlicensed medicines and lack of robust evidence for determining doses in children

Five studies explored the equivalence of, or inconsistent use of unlicensed medicines.[7,28,38,40,42] This included examination of specific individual medicines, the variation between licensed and unlicensed alternatives and the scaling doses used for determining off-label medicines for children.

One study measured the release profile of melatonin from Circadin® tablets that had been divided or crushed (and therefore rendered unlicensed) compared to intact tablets.[28] Unlicensed melatonin medicines in tablet and capsule forms were also used for comparison. It was found that the unlicensed medicines had a faster release profile and were more expensive than the licensed medicine. The level of melatonin measured showed that unlicensed products had a greater deviation from the label strength compared with the licensed medicines, indicating they may not be bio-equivalent to the licensed medicines or other formulations of the same unlicensed medicines.[28] Another study highlighted the inconsistent bioequivalence of liquid captopril formulations used in children, when compared to other unlicensed formulations or the licensed versions.[38] The range of differing liquid captopril formulations available for children has also been highlighted within the literature with findings showing that of the 13 cardiac centres and associated hospitals studied, only three were using the same liquid formulation, with 10 centres and associated hospitals using different captopril formulations and up to nine different formulations being available in one area of the UK.[42]

The doses determined for children are often based on adult doses using scaling models. One study compared three scaling models in determining doses for children for thirty medicines and found that the scaling models may not accurately predict doses for children and no model was found to be suitable across all paediatric age ranges.[40] This can lead to harm if the correct dose is not provided. There is some evidence that community pharmacists, hospital consultants and paediatric nurses who used off-label medicines for doses lower than recommended in the licence experienced more treatment failures, and those who used off-label for higher than recommended doses experienced more adverse drug reactions (ADRs).[7]

3.5.2. Safety issues associated with the use of unlicensed medicines

Six studies explored the association between the use of unlicensed medicines and safety risks,[23,30,31,33,36,36,55] focusing on medication errors, ADRs, mortality rates and the safety and efficacy of specific unlicensed medicines.

One study suggested that the use of unlicensed medicines in children is significantly associated with medication errors (and subsequent harm) when compared to licensed medicines ($p = 0.003$).[36] However, the results originate from one children's hospital site, and therefore may not be generalisable.

Four studies explored the use of unlicensed medicines in relation to ADRs. One found no significant association between the use of unlicensed and off-label medicines and risk of ADR ($p < 0.106$). However, there was a significant association between the percentage of unlicensed and off-label medicines used and the risk of ADR ($p < 0.0001$).[55] Another study concluded that the use of unlicensed or off-label medicines were more likely to result in an ADR, with the number of medicines being administered also being a risk factor.[33] Not all studies included in the review have shown a significant association between the use of unlicensed medicines and ADRs. One study originally found the use of off-label and unlicensed medicines was reported to be more likely to result in ADRs than compared to licensed medicines. However when oncology medicine results were removed, there was no significant difference in the risk between licensed, off-label or unlicensed medicines.[31] Another study highlighted increased risks of drug related deaths associated with the use of Phenazepam®, an unlicensed benzodiazepine-type medicine[30] suggesting individual medicines may be associated with risk. Evidence has also shown the safe and effective use of unlicensed medicines such as propofol-remifentanil mixtures[23] further highlighting that not all unlicensed medicines may be associated with increased risks and suggests that these risks may be associated with specific unlicensed medicines.

3.5.3. Patient/parent/carer and public awareness of unlicensed medicine use and perceived acceptability

Ten studies reported on the awareness of patients, their parents or carers, and the general public, on the use of unlicensed medicines and described how their perceptions of acceptability could impact the patient journey or care.[6–8,16,17,20,21,35,37,41]

Pharmacists have reported a reluctance to inform patients when unlicensed medicines had been prescribed.[17] Only 30.7% of healthcare professionals reported informing patients when unlicensed medicines were prescribed despite 77.8% of participants reporting concerns around the safety of these medicines.[7] As it is up to the individual healthcare professionals to inform patients, the rates at which patients are informed may vary with results from a single intellectual disability unit showing that the medical notes suggested 80% of patients were informed their medicines was unlicensed.[37]

Awareness when receiving an unlicensed medicine was highlighted as important in terms of being able to access the medicines after discharge. One study found that parents described several actions they felt they had to take to ensure they were able to receive a timely supply, such as increased contact with healthcare professionals, proactively seeking information about the medicine and planning and organising

the process of ordering and receiving.[6] Community pharmacists also emphasized the importance of patient awareness as patients receiving unlicensed medicines were required to take on additional responsibilities to ensure a seamless supply and described how a lack of awareness had led to delays and could potentially lead to treatment disruption.[16] A study exploring the views of pharmacists found that parental issues were reported, with a lack of awareness around the differences in availability and accessibility of unlicensed medicines when compared to licensed medicines, which caused treatment disruption, mainly when parents did not inform the GP in advance of when further supplies were needed.[35]

Acceptability of the use of unlicensed medicines by patients and the general public was explored in four studies. The findings highlighted how sensory issues such as the taste of the medicine impacted paediatric patients' acceptability[20] and how the general public had concerns over the use of unlicensed medicines with 14% of participants stating they would refuse treatment if there was an alternative option.[8] The general public's concerns around the safety of unlicensed medicines for children was seen to increase once being informed about this practice[41] and one study showed that children themselves perceived the use of unlicensed medicines to be unsafe, and that although they would trust their doctor or parent, they still felt it was important for the parent or older children to be informed when prescribed an unlicensed medicine.[21]

4. Discussion

This is the first systematic review to synthesise published research describing factors that affect the patient journey and patient care when receiving an unlicensed medicine in the UK. The findings revealed specific challenges that were seen to impact the continuity of care across care settings, patient safety and provision of patient-centred care.

Multiple instances were highlighted where transfer of care across care settings could be optimised to provide continuity. Continuity of care can be viewed as an ongoing relationship between the patient and a healthcare professional and the organised clinical care that moves smoothly between different care settings.[57] Healthcare professionals in secondary care were found to take different levels of responsibility for overseeing the patient's care, and of ensuring that follow-up arrangements were in place for another suitably qualified prescriber to assume these responsibilities after a patient was discharged from hospital. The General Medical Council (GMC) (2021) describes how for a GP to take on responsibility for further supplies of the unlicensed medicines, they need to be fully informed, provided with all necessary prescribing information or supporting evidence for use, and agree for the patient's care to be transferred to them.[58] It is essential that GPs are provided with sufficient information when required to continue prescriptions for unfamiliar unlicensed medicines. However as there is no consistent content for the undergraduate medical curriculum in the UK,[59] graduates may have varying levels of exposure to the concept of unlicensed medicines and the related issues with respect to patient care. The Royal College of General Practitioners (RCGP) have repeatedly called for GP specialist training to be extended from three years to four years stating that the typical three year programme would not be able to adequately cover all learning outcomes for future GPs.[60,61] Many instances were identified in the report of GPs who were not supported to take on this responsibility, and as a result had concerns over the safety and efficacy of the medicines and their legal responsibility, which in combination with their own perceived lack of knowledge, resulted in reluctance to continuing the supply and therefore disruption of treatment. These prescribing behaviours were shown to be exacerbated by inconsistent information available to healthcare professionals, even around the definitions for what unlicensed medicines are, as reinforced in a study examining the content of 52 guidance documents used within the UK.[62] This wider lack of consistency of definitions within guidance documents and within the literature has been suggested to be potentially confusing to healthcare professionals.[63]

Specific treatment areas such as in intensive care, palliative care or mental health were found to be associated with greater use of unlicensed medicines. However, the main reason for prescribing unlicensed medicines was age, with many studies specifically looking at the use of unlicensed medicines in children, where there is either a lack of available licensed medicines, or the licensed medicines available are not suitable for children who required different doses or formulations for use. A systematic review highlighted that off-label medicines for children are used worldwide with rates from 3.2% to 95%, with reasons classified mainly as age-related, but also related to dose, indication and route.[64] The use of scaling models to determine doses of medicines that are not licensed for children[65] is potentially compromising patient safety, as evidence showed none of the scaling models assessed were suitable for determining doses across the paediatric ages.[40] The ADRs reported in the literature[7,66] may lead to hospital admissions, with incident rates of ADRs causing such admissions in children varying from 0.4 to 10.3%.[67]

It has been suggested that the increased likelihood for children to receive unlicensed and off-label medicines compared to other population groups may partially be attributed to the lack of clinical trials in children,[68] with the associated potential risk on patient safety recognised within the literature for many years.[69,70] There have been initiatives to increase the involvement of children in research, for example the National Institute for Health Research (NIHR) have released a set of standards for public involvement, which places importance on creating inclusive opportunities and working together.[71] The NIHR also highlight the benefits of involving children to improve the design and delivery of clinical research for children,[72] so more medicines can be licensed for use across the different ages.

Many patients have a justified need for the use of unlicensed medicines and the results of this systematic review outlined multiple instances of this, in line with the MHRA guidance[1] that outlines how unlicensed medicines should only be used when there are no suitable licensed alternatives available. In practice, there have been cases where a clinical risk assessment of safety and efficacy justifies the use of unlicensed products over the licensed alternatives, such as the patient safety notice issued in Wales for phenobarbital 50mg/5 ml.[73] The review also outlined many instances whereby the licensed formulation of medicines was altered, for example the crushing of tablets or opening of capsules. The Royal Pharmaceutical Society (RPS) (2011) recognise many risks associated with altering medicines in these ways and suggest in most cases prescribing a ready to use unlicensed medicine, but also outline how uncoated, film-coated or sugar-coated medicines or immediate release medicines may be suitable for crushing if considerations about the medicines are made.[74] Other instances where the license is altered include re-packaging a medicine supplied by the original manufacturer, such as repackaging medicines in a multi-compartment compliance aid, or prepared for a patient in accordance with a prescriber's instructions, such as parenteral nutrition compounding or IV reconstitution. Although not highly associated with patient harm, a literature review highlighted some cases where identified crushing of medicines was found to be associated with problems such as contamination, spillage, and patients not taking the whole dose if crushed into food,[75] which could all impact patient care and the efficacy of the medicine.

In addition to these administration issues, the review described inconsistencies with supply of unlicensed medicines, such as varying formulations across and within care settings. Once a patient's care is transferred to community, there is no requirement for supply from a specific manufacturer, and supply is often determined by cost.[76,77] As unlicensed medicines are made in smaller quantities than licensed medicines, they are often more costly[78] and the possibility of storing them can be limited by short expiry dates and often bespoke nature, resulting in longer lead times for access.[79] Supply is sought from different manufacturers, who produce products with different excipients, contributing further to varying storage needs and expiry dates.[80] Different bioequivalence of these unlicensed products, but also different

bioequivalence between unlicensed formulations and the licensed medicines, can directly impact on patient safety highlighting need for continuity of care across care settings.

The findings highlighted varying practices around how patients were informed of the licensing status of their medicines by prescribers across care settings. Pharmacists were also found reluctant to inform patients who had not previously been informed by their prescriber, even though this is included in their responsibilities when supplying unlicensed medicines in accordance with a prescription, and are professionally accountable for any harm caused that is attributable to their own actions or omissions. These inconsistencies were often attributed to feeling uncomfortable with conflicting official guidance, concerns around patients' perceived safety of these medicines, and associated impact on adherence or acceptance of treatment altogether. For example, some guidance outlines that patients should be informed in all cases[81] whereas others acknowledge the potential of informing patients to lead to concerns and suggest that prescribers may not always want to bring attention to the fact the medicine is unlicensed.[82] However, patient awareness can directly impact on continuity of supply, such as need for understanding of early communication with GPs, increased contact with pharmacy and organising supply to manage extended lead times and short expiry days.

Patient information leaflets are not commonly available for individual unlicensed 'special' medicines.[83] Some examples of more generic leaflets for unlicensed medicines exist but the content is varying and it is unclear how often they are used within practice.[84–86] Consistent information in the form of a patient information leaflet for all patients who receive unlicensed medicines may be a way to support healthcare professionals and patients reach informed decision-making and achieve patient-centred care. Co-creation of any such leaflets with patients and carers is crucial to ensuring the language is appropriate and provides information at the right level, without being frightening.[87,88]

The different factors described in this review might interact to inform or influence the patient journey and patient care when receiving an unlicensed medicine in the UK. For example, patients awareness of unlicensed medicine and perceived acceptability and availability after receipt of the initial prescription may influence their willingness to be prescribed an unlicensed medicine, but we were not able to identify any evidence to directly support this.

Based on the findings of the systematic review the authors are proposing some recommendations to try and mitigate the factors that could disrupt the patient journey when receiving an unlicensed or off-label medicine in the UK, along with some identified key considerations (Table 3).

4.1. Strengths and limitations

The heterogeneity of the included studies made comparison across studies difficult, as some combined data for unlicensed 'special' and off-label medicines and others presented results separately. A number of studies identified throughout the searching process were not available as full report or could not be accessed, potentially preventing valuable evidence from contributing to the review and adding publication bias. To reduce this bias, contact was made with the relevant authors to ask if a full text version of the study was available, and when this was provided, it was screened for inclusion.

However, a robust process was ensured through regular meetings with a subject librarian to strengthen the search strategy, and by using evidence to guide the selection of databases to ensure reliable results. In addition, a thorough quality appraisal process of all studies in the review was conducted using validated checklists.

5. Conclusion

This systematic review explored the patient journey as a whole in relation to the use of unlicensed medicines, and as such provides a

Table 3
Recommendations and key considerations to mitigate the factors that could disrupt the patient journey when receiving an unlicensed or off-label medicine in the UK, based on the findings of this systematic review.

Factor to address	Recommendation made	Considerations
Limited understanding of healthcare professionals (HCPs) around what unlicensed 'special' medicines are – inconsistent terminology.	• Consistent information and terminology to be decided upon by national bodies across the UK. • Guidance document produced to include: o definitions of the different types of unlicensed medicines o clear description of healthcare professionals' responsibilities across the supply chain. • Guidance shared to all HCPs via a key facts update sheet or CPD event.	Multiple participants from within primary, secondary and community pharmacy agreed on the need for further information and training. Increased education and consistent information for health care professionals about the use of unlicensed medicines would help to reduce the need to rely on the expertise of others and increase confidence and understanding. The most effective way to create and disseminate this information would be on a national level.
Limited confidence in when and how to use unlicensed medicines.	• Produce a formulary for unlicensed medicines containing different sections for the different types of unlicensed medicines/specials/off-label/common/less common.	Formularies like the BNF and BNFc are regularly used by prescribers and community pharmacy staff and help to increase the confidence of those prescribing and supplying unlicensed medicines. A formulary for unlicensed medicines could be built using nationwide data of the unlicensed medicines used over the past few years.
Awareness of licensing status when prescribing unlicensed medicines.	• A requirement to state licensing status in discharge letters or medicine requests, or a flagging system to alert other healthcare professionals involved in the patient journey could be enforced that would increase awareness.	This would help increase healthcare professionals' awareness of the licensing status across care settings and could be incorporated into guidance. A standardised template could be created with information to accompany recommendation in secondary care for prescribing of an unlicensed medicine (including specification of the licence status, indication, why a licensed product was not appropriate, expected duration of prescribing, date of review of need for the product). An alternative method to increase prescriber awareness of the licensing status is the addition of a requirement to outline the licensing status, indication and duration of unlicensed medicines within free text boxes in electronic discharge advice letters.
	• Update prescribing software.	GP prescribing software could be updated to ensure medicines are

(continued on next page)

Table 3 (*continued*)

Factor to address	Recommendation made	Considerations
		marked as unlicensed in the drug dictionary when prescribers select a medicine, this would reduce accidental prescribing of unlicensed medicines and help to increase awareness of the licensing status.
Hesitancy of prescribers to inform patients of the licence status of their medicine.	• Prescribers need clearer consistent guidance on when and how to inform patients they are being prescribed an unlicensed medicine, as current guidance varies in this area. • A consistent, standardised information leaflet could be created for patients to be provided with prescriptions for unlicensed medicines, explaining what an unlicensed medicine is, why patients are being prescribed these medicines, cost, shelf-life and an emphasis on the differences in lead times when accessing unlicensed medicines.	The creation of a consistent information leaflet for all patients receiving unlicensed medicines could increase patient awareness of the licensing status while addressing concerns that may arise. This could also help with prescribers' reluctance to discuss unlicensed status as a leaflet can provide information around this. This would also support patients in accessing unlicensed medicines in the community by providing guidance on how to manage extended lead times. The most effective way to create and disseminate this information would be on a national level.
Challenges impacting continuity of care when receiving unlicensed medicines in the community.	• Hospitals could have specific agreements with specials suppliers, we know prescribers make decisions about 'go to' treatments and this could go a step further to include associated suppliers for commonly used unlicensed medicines to ensure consistency of formulations across care settings and reduce the chance of delays or disruption when patients are discharged.	As community pharmacists can choose which suppliers they use, and some chains have specific suppliers already selected this may be impractical to enforce. However, a recommendation could be added to guidance "from a professional perspective you should be trying to ensure continuity of care for your patients". When prescriptions for unlicensed medicines are transferred into the community acceptance and agreements between GPs and community pharmacies could be gained prior to the patient being transferred to reduce risk of disruption during transfer.
Strategies to ensure supply.	• Patients need reassurance around accessing supplies, in cases where delays, disruption or loss of medication occurs, individual advice could be supplied to patients about missing/altering doses and about emergency supply processes.	Healthcare professionals would be in a good position to discuss information with patients. Gaining advice from healthcare professionals could help to increase patient safety if delays or loss of medication occurs. This may also make the patient feel more prepared and supported if supplies are lost and reduce concerns.

unique insight into the factors that can impact on the patient experience, from the decision to prescribe an unlicensed medicine to its administration and supply. Due to the challenges associated with the use of unlicensed medicines and the potential for increased risk, healthcare professionals have an important role in ensuring the medicine prescribed is suitable and in recognising the need for patient-centred care to reduce the chances of errors, delays or harm.

The findings support the recommendation for clear, consistent information to be created and provided to healthcare professionals and patients, so there is a shared understanding of definitions, risks and benefits, and roles and responsibilities; also for clear guidance on managing supply, with approved lists of manufacturers and standardisation of reimbursement for dispensed products. These recommendations can be used internationally to support practice and improve the continuity of care across care settings and patient safety.

Author statement

All co-authors have made substantial contributions to conception, design, or acquisition of data, or analysis and interpretation of data; been involved in drafting and revising the manuscript; given final approval of the version to be published; agreed to be accountable for all aspects of the work.

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Declaration of competing interestCOI

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2023.04.120.

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