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Unlicensed "Special" Medicines: Using the Pillar Integration Model to Understand Stakeholder Perspectives Across Care Settings

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Background: The use of unlicensed medicines has been associated with safety concerns, availability and accessibility issues, and lack of integrated care across care settings.

Objective: To understand the interaction between the views and experiences of those who prescribe, those who supply and those who receive unlicensed "special" medicines, so that factors affecting the patient journey and successful treatment can be identified and used to inform areas for change.

Methods: A qualitative, phenomenological approach was adopted, with semi-structured interviews with prescribers, community pharmacy staff and patients. A combination of stratified, purposive, snowball and convenience sampling was used to identify participants. Interviews were analysed using reflexive thematic analysis and the findings were integrated using an adapted model of the Pillar Integration Process.

Results: Three pillars were constructed after synthesising results from interviews with patients (n=4), prescribers (n=5) and pharmacy staff (n=6): the awareness of licensing status; perceptions of patient care and acceptability of unlicensed medicine use; and challenges associated with the accessibility of unlicensed medicines. The varying levels of awareness when unlicensed medicines are prescribed and the varying perceptions of responsibility and acceptability of the use of unlicensed medicines help to explain the challenges faced by participants across the patient journey, Challenges identified included understanding what unlicensed medicines are, awareness of the licensing status when unlicensed medicines are prescribed, managing care across care settings to ensure the patient is effectively treated and ensuring continuity of care for patients in the community.

Conclusion: The results highlight a clear need for more integrated care and support for prescribers to reduce the chances of delays between care settings, and more patient-centred care to ensure that any delays when accessing medicines do not lead to treatment disruption for the patient. The new national guidelines informed by findings of this study can support policy-makers across the globe.

Keywords: unlicensed medicine, off-label medicine, prescriber, patient, community pharmacy, patient experience, qualitative, pillar integration model

Introduction

Unlicensed medicines are used commonly in the UK. The term unlicensed medicine encompasses different types of medicines, including extemporaneous preparations, off-label medicines and unlicensed "special" medicines. Off-label medicines are medicines which have been licensed for a specific use in a specific population but are used in a way not specified by the marketing authorisation in the Summary of Product Characteristics (SPC),[1] and as such, are used in an unlicensed manner. Unlicensed "special" medicines do not have a marketing authorization. In the UK, regulation 167 of the Human Medicines regulation outlines the exceptions in which a medicine can be supplied without a license.[2] Manufactures must hold a manufacturer's "specials" license to produce "specials", and they should only be prescribed when there is no alternative licensed medicinal product available to meet the special clinical needs of an individual

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patient.[1–3] Examples of special clinical needs include patients who suffer from rare diseases,[4] those unable to take a licensed medicine, for example patients with dysphagia,[5] or those who are allergic to specific excipients.[6]

Prescribers have the important role of determining when the use of unlicensed "special" medicines may be necessary, discussing their decision-making with the patients, and deciding together whether to initiate a therapy via prescribing such medicines, or continue prescriptions for products initiated previously by another prescriber. In line with the Medicines and Healthcare products Regulatory Agency's (MHRA) guidance,[7] prescribers should only prescribe an unlicensed medicine if there are no licensed alternatives available to meet the clinical needs of the patient. The MHRA also states that, even though off-label use of medicines is not recommended, it is preferred to use of a "special", if it meets the clinical need of the patient.[1] However, evidence has shown that the guidance available to healthcare professionals can be confusing and can contain inconsistent information about what unlicensed medicines are,[8] which inevitably impacts on prescribers' attitudes towards initiating or maintaining therapy with an unlicensed medicine.

Community pharmacy is the first point of contact for patients and community pharmacists have a vital role in ensuring unlicensed medicines can be accessed. The role of a community pharmacist has evolved overtime from checking and dispensing medicines to a more patient-focussed role, such as assisting patients in self care of minor conditions or running successful interventions, such as smoking cessation services.[9,10] Difficulties for community pharmacy staff accessing unlicensed medicines relate to the cost, storage and often short expiry dates. The available literature from within the UK has highlighted that patients have experienced issues when accessing their unlicensed medicines after discharge, with pharmacy staff being unable to find a supplier or manufacturer for a certain product or specific formulation,[11,12] although this was reported from the patient perspective.

Wale et alconducted a systematic review to better understand factors affecting the patient journey and patient care when receiving an unlicensed "special" medicine, highlighting 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.[13] No studies were identified whereby the views and experiences of prescribers, pharmacists and patients were triangulated using an appropriate framework, to obtain a holistic perspective. By obtaining an insight into the views and perceptions of those who prescribe, supply or receive unlicensed medicines, factors affecting the patient journey and successful treatment can be identified and used to inform areas for change, while supporting previous evidence or highlighting findings specific to patients in different localities. As such, the aim of this study was two-fold: to first explore the views and experiences of prescribers, in primary and secondary care, who have experience of initiating or maintaining therapy with unlicensed "special" medicines, pharmacists in the community who obtain and supply unlicensed "special" medicines, and patients (or the parents and carers of those) who receive unlicensed "special" medicines in the community; to then understand the interaction between prescriber, pharmacist and patient views as well as the impact on patient care.

Methods

A qualitative phenomenological approach was taken involving semi-structured interviews of three stakeholder groups involved in the patient's journey: prescribers in primary and secondary care, community pharmacists, and patients or parents and carers of those who receive unlicensed medicines. This paper is based on the thesis of Wale, A.[14] An inductive thematic analysis of interviews with the community pharmacy sample has been published elsewhere,[15] but for the purpose of this study all findings were re-analysed with an adapted version of the Pillar Integration Process[16] in order to triangulate the findings from the different population groups involved.

Sample

A combination of stratified, purposive, snowball and convenience sampling was used to identify participants. The sampling frame included patients and the parents/carers of patients who were currently being prescribed an unlicensed "special" medicine and were receiving this in the community in Wales (this sample will hereto be referred to as the patient group); prescribing clinicians working in primary and secondary care in Wales, with experience in prescribing unlicensed "special" medicines; community pharmacy staff with experience ordering and supplying unlicensed "special" medicines. Eligibility criteria for the interviews can be seen in Table 1.

Table 1 Eligibility Criteria for the Interviews with the Three Stakeholder Groups in the Sampling Frame: Patients and the Parents/Carers of Patients; Prescribing Clinicians Working in Primary and Secondary Care; Community Pharmacy Staff

Eligibility Criteria	Patient/Guardian/Carer	Community Pharmacy Staff*	Prescribers
Inclusion criteria			
Population	Individuals or carers/parents of individuals who have been initiated or on maintenance therapy with an unlicensed "special" medicine; Individuals who access unlicensed "special" medicines through a community pharmacy, (as new or maintenance therapy) or will be discharged from secondary care and have been initiated on an unlicensed "special" medicine; Over the age of 16.	Registered Pharmacists or pharmacy technicians currently working at the selected chain of community pharmacies; Assumed over the age of 18 due to their profession.	Individuals who work in primary or secondary care with the role of prescribing medicines.
Experiences	Individuals who have been initiated or on maintenance therapy with an unlicensed "special" medicine in primary or secondary care; Individuals who have accessed an unlicensed "special" medicine from a community pharmacy at least one time.	Experience (≥ 1 year) procuring and dispensing unlicensed "special" medicines in a community pharmacy.	A minimum of 1 years' experience prescribing medicines; Experience prescribing unlicensed "special" medicines.
Communication	Can communicate effectively in English (does not have to be first language), to be assumed upon response to the information booklet; Ability to provide informed consent.	Can communicate effectively in English (does not have to be first language); Assumed capable of giving informed consent due to their profession and, in the case of pharmacists, annual declarations to the General Pharmaceutical Council (GPhC).	Ability to provide informed consent assumed due to the professional registration required of prescribers in the UK (ie the General Medical Council).
Exclusion Criteria			
Population	Individuals or carers/parents of individuals who are no longer being treated with an unlicensed "special" medicine and have current prescriptions for licensed medicines only; Under 16 years of age.		
Experience	Individuals with limited experience in procuring and dispensing unlicensed "special" medicines, despite ≥ 1 year exposure	Individuals who have no experience prescribing unlicensed "special" medicines.	
Communication	Ability to provide informed consent could not be verified by the lead researcher at the time of the interview.		

Notes: * An inductive thematic analysis of transcribed interviews with the community pharmacy sample has been published elsewhere [15], but for the purpose of this study all findings were re-analysed with an adapted version of the Pillar Integration Process.

Recruitment

Participants in the patient group were recruited in a number of ways including online advertisements, through community pharmacies and within secondary care. The lead author (AW) contacted HealthWise Wales (an online platform with a register of members of the public who have agreed to be informed about research).[17] The study advert was disseminated in a newsletter through email to their members across Wales. Patients were also recruited directly through their community pharmacy after the lead author had disseminated the study documents to multiple community pharmacies. When recruiting from secondary care, some gatekeepers from the different organisations responsible for planning and providing health and wellbeing services (health boards) where the hospitals were based agreed to disseminate the study information directly to individuals within the departments that were reported by stakeholders[14] as using unlicensed medicines more frequently (paediatrics, dermatology and gastroenterology), while others provided contact details for key hospital staff who would act as gatekeepers themselves, for the lead author to reach out to directly.

Community pharmacy staff were recruited from a small chain of community pharmacies in South Wales. One pharmacist agreed to act as a gatekeeper in recruiting other pharmacists and pharmacy technicians. The gatekeeper was sent a personalised email invitation containing all relevant study information and disseminated this information by email to all other pharmacists and pharmacy technicians who fit the eligibility criteria.

Prescribers were recruited from primary and secondary care. Health board facilitators were asked to provide contacts within gastroenterology, dermatology and paediatric departments who could act as gatekeepers for the study. Where the health board facilitator agreed to act as a gatekeeper, the lead author sent the study information directly to them to be disseminated to potential participants. Where contacts were provided, the author then contacted the individuals and sent them the study information asking them to act as a gatekeeper for the study and to disseminate the study documents to potential participants.

All participants were self-selected; participants were provided with a cover letter and an information sheet with the contact details of the research team. If a participant wished to take part in an interview, they were asked to contact the research team directly, the lead author then contacted the participants and arranged a suitable time to conduct the interview.

Data Collection

Semi-structured interviews were conducted to allow participants to address individual experiences or perceptions that may not have been identified in the existing literature. Topic guides for the interviews were informed by literature and finalised in collaboration with external stakeholders, part of the study's steering group. Further details about the interview schedules and an in-depth description of the methods used has been published elsewhere.[14] Using the principles of information power,[18] it was estimated that between 4–5 participants from all different populations would be needed to gain valuable data across Wales, to account for a representative sample. Interviews were conducted by the lead author (AW), either in person or online, lasting between 10–40 minutes. Data collection for community pharmacy staff was conducted between September 2018 until January 2019. Data collection for prescribers and patients was conducted during the COVID-19 period between November 2020 and continued until June 2021. All interviews were audio-recorded, with consent, either via Microsoft Teams™ or a recorder and transcribed *verbatim*, with audio recordings being deleted directly after transcription. Informed consent included the publication of anonymised responses and direct quotes.

Data Analysis

Data was first analysed for the three qualitative samples using reflexive thematic analysis with an inductive approach, following the method suggested by Braun and Clarke.[19] Even though the data was only qualitative, it came from three sources and a robust and transparent process for integrating findings was sought. An adapted model of the Pillar Integration Process was developed to allow for data from the three separate qualitative studies to be integrated, based on the four stages of integration outlined by Jonson et al.[16] The qualitative data gained from prescribers was analysed first, followed by the qualitative data gained from community pharmacy staff and patients/carers.

One member of the research team (EM) was a pharmacist. To minimise any risk of bias in the data analysis, transcribing was completed initially by the other member of the team (AW), and checked by EM. Mapping against the PIP was conducted independently by both researchers and any identified differences were discussed and resolved.

Ethical Considerations

When recruiting community pharmacy staff, the community pharmacy chain approved the research within their company. Approvals were also sought from Cardiff University's School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee and ethical approval was granted on the 9th of August 2018. For the recruitment of prescribers and patients full Health Research Authority and Health and Care Research Wales approvals were granted on 23rd December 2019. This report has been based on the Standards for Reporting Qualitative Research (Supplementary File 1).[20]

Results

Qualitative Analysis for Prescribers

A total of five participants took part in an interview, four were primary care prescribers and one was a secondary care prescriber. Reflexive thematic analysis of transcribed interviews was used to construct three themes: understanding of what unlicensed "special" medicines are, acceptability of their use and awareness of licence status when prescribing; factors influencing the confidence and decision to prescribe unlicensed "special" medicines; and patient interactions and perceived patient awareness of licensing status and acceptability of the therapy received.

Qualitative Analysis for Community Pharmacy Staff

A total of six participants took part and completed an interview, five pharmacists and one pharmacy technician. Reflexive thematic analysis of transcribed interviews revealed 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.

Qualitative Analysis for Patients

A total of four patients took part and completed an interview, two were patients receiving unlicensed "special" medicines themselves and two were parents accessing unlicensed "special" medicines for their child. Through reflexive thematic analysis three themes were constructed: awareness of licensing status and acceptability of receiving an unlicensed "special" medicine; patient perceptions of healthcare professionals impacted by issues experienced; and strategies adopted by patients to ensure timely access and continuity of supply when receiving unlicensed "special" medicines.

Integration of Qualitative Results

The results were synthesised together using an adapted version of the Pillar Integration Process. After integration three main pillars were constructed; the awareness of licensing status; perceptions of patient care and acceptability of unlicensed medicine use; and challenges associated with the accessibility of unlicensed medicines (Tables 2, 3 and 4).

Pillar One: Awareness of Licensing Status

Qualitative findings from the prescriber and patient groups revealed varying levels of understanding around the licensing status of medicines. Prescribers reported differing definitions for what an unlicensed "special" medicine is, and the term off-label was often used interchangeably with "special" medicine, reiterating the confusion around the terminology and definition around unlicensed medicines. They highlighted how, when they were asked to continue in primary care prescriptions that originated in secondary care, it may not be adequately noted when a medicine is unlicensed. This led to a lack of awareness of the licensing status on the part of some GPs, with one GP explaining how they had looked through the repeat prescriptions they had signed in preparation for the interview, and discovered they had been prescribing unlicensed medicines without realising. The lack of awareness of the licensing status when prescribing unlicensed medicines was not only due to the lack of information provided across care settings, but also as a result of the prescribing software not effectively alerting prescribers when unlicensed medicines were selected.

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Table 2 Pillar One of the Adapted Pillar Integration Model, Constructed After Integration of Results from the Three Qualitative Studies

Pillar Building Themes	Qual Categories (Prescribers)	Qual Codes (Prescriber)	Qual Categories (Community Pharmacy Staff)	Qual Codes (Community Pharmacy Staff)	Qual Categories (Patients)	Qual Codes (Patients)
Pillar one: Awareness of licensing status	**Understanding of the definition of unlicensed "special" medicines**	"I do not know really much about it, I always think of unlicensed medicines as stuff where, they are, they are [sic] sort of, they are to be used for certain things, but if you use them for outside of that, those specifications, then that's what I think of as unlicensed" [INT 1.3]	**Understanding of the definition of unlicensed "special" medicines**	"[An unlicensed "special" medicine is] something that's being used away from the product license, meds that are licensed for one use and then used for different conditions" [INT 2.3].	**Understanding of the definition of unlicensed "special" medicines**	"What I think, [an unlicensed "special" medicine is] it has not been approved in UK, but still if, someone needs it, doctor you know, loads of doctors review it, it's not, you know will not do any harm, they will just help that person you know they will prescribe it" [INT 3.4].
		"My understanding, again, very limited, is that it's a medication that has to be made up specifically for a patient, because they have specific requirements" [INT 1.4].				"[An unlicensed "special" medicine is] something that is not. available via the official NHS prescription, via the GP surgery. yeah, an-and it's issued by a special lab, sort of a private lab and. they are medications which are specifically made up for the individual patient" [INT 3.2].
	Awareness of the licensing status when prescribing medicines	"Pretty much everything we use is unlicensed, (laughs) I don't even know what is licensed, 'cause [sic] I think most of it isn't licensed" [INT 1.5]	**Awareness of the justification for the use of an unlicensed "special" medicine when supplying unlicensed "special" medicines**	"What the hospitals have been doing recently is actually been giving me a back sheet, with some indications of why this is being prescribed, that's really valuable" [INT 2.1].		

		"If they're initiated in secondary care, we may not notice their licensing use, if that makes sense, so we continue prescribing but we might not notice, y'know [sic], it might not be highlighted that it's unlicensed use" [INT 1.2].		"It took a call to the surgery, a call to the hospital and a call to the patient, whereas if I'd had that information with the prescription, 'this is an unlicensed medicine, the dose has been checked by a kidney specialist, the patient has been on it for years and years, well, and it goes on, that would probably have saved me a bit of time" [INT 2.4].		
	Attitudes towards sharing information related to treatment with an unlicensed "special" medicine with patients and nature of interactions	"I just have that discussion with them [the patient] about that, it's unlicensed, has not been formally kind of tested in, in [sic] a trial to be to, to, [sic] assess it, but it's standard practice and we use this on a regular basis, that kind of will be my discussion" [INT 1.4].				
	Perceptions of need of informing patients of the licensing status of the medicine and reported hesitancy	"I'd have to honestly say I suspect [patients] do not [have awareness their medicine is unlicensed], and I suspect, it may be, it probably is an important part of the ethics of prescribing, when you are [prescribing unlicensed "special" medicines], but the problem when you start saying things like 'this is an unlicensed or off label' [medicine] is it creates panic" [INT 1.1]	**Perceptions of need of informing patients of the licensing status of the medicine**	"[Patients need] an understanding that [unlicensed "special" medicines are] not something that we can just take off the shelf, that, we need a little bit of warning, that we cannot order it in advance without having the prescription…and they need to allow us enough lead time" [INT 2.2].	**Lack of consistent methods used to inform patients they were receiving an unlicensed "special" medicine and impact on patient awareness of what unlicensed "special" medicines are**	"Oh yes, yes, yes, [the prescriber] explained that [the medicine was unlicensed], and she gave me a leaflet explaining what. unlicensed medicines are" [INT 3.2].

(*Continued*)

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Table 2 (Continued).

Pillar Building Themes	Qual Categories (Prescribers)	Qual Codes (Prescriber)	Qual Categories (Community Pharmacy Staff)	Qual Codes (Community Pharmacy Staff)	Qual Categories (Patients)	Qual Codes (Patients)
		"If I'm going to start a child on an unlicensed medication, I don't actually, because most of it is, I don't actually say it's unlicensed or licensed because I think it's really confusing term" [INT 1.5].		"[Patients are aware their medicine is unlicensed] once we have told them (laughs) you do get occasional, it tends to be the walk-in ones, and it's the first time they have ever had it, and they will sort of come in and go 'oh I'll try somewhere else then' and I will go 'well you're not going to get It anywhere actually'" [INT 2.2].		"It's literally only from you [the invitation to the study] that I realised it's unlicensed, there was all- you know, I could give them [the pharmacy] the prescription, and I'd always know that it would have to be ordered, so I'd say I will pick it up in a couple of days, but no one ever mentioned that it was unlicensed, I just assumed it was not something they had in stock, so they'd have to just order it, I did not know that was why" [INT 3.3].

Table 3 Pillar Two of the Adapted Pillar Integration Model, Constructed After Integration of Results from the Three Qualitative Studies

Pillar Building Themes	Qual Categories (Prescribers)	Qual Codes (Prescriber)	Qual Categories (Community Pharmacy Staff)	Qual Codes (Community Pharmacy Staff)	Qual Categories (Patients)	Qual Codes (Patients)
Pillar two: Perceptions of patient care and acceptability of unlicensed "special" medicine use	**Interprofessional interactions, dynamics and accepting expertise of other healthcare professionals**	"If it's licensed or unlicensed, I guess. the- The [sic] specialist has made that prescribing decision so. like I said, as long as there's an explicit, that reason, rationale, duration, and dose, then I would, would [sic] usually add it to the repeat prescription" [INT 1.4].	**Interprofessional interactions, dynamics and accepting expertise of other healthcare professionals**	"If the dose is unlicensed, then the first thing I would do is speak to the prescriber [GP], Just to get a bit of context, and a bit of background, obviously they've got access to a lot more notes than I have" [INT 2.4].		
				"[Unlicensed "special" medicines], well, they're prescribed from upon recommendation from the consultant, so I guess we all just have trust in the consultant that they've recommended something that's suitable" [INT 2.3].		
	Perceptions of role and acceptability of prescribing unlicensed "special" medicines	"I don't think GPs should be prescribing unlicensed medicines… I mean as GPs, we can't know about all the studies and all the ins and outs of the treatment for specific conditions, and so I, I do feel that should be a specialist prescription really" [INT 1.3].	**Perceptions of role and acceptability of supplying unlicensed "special" medicines**	"Well, I guess, it's more sort of a dangerous feel to sort of mess about with children and elderly patients, so, yeah I would not really, it's probably not the safest thing to experiment with unlicensed meds in children…. But then I guess then (pause), the prescribers then (pause) sort of assessing the risk benefit, depending on the child's size, might be a big child, small child, so yeah, I guess" [INT 2.3].	**Patient perceptions of how their care, and the responsibility for it, is managed by healthcare professionals**	"So it feels like the GP, liability wise, is just saying 'as long as I have blood on file it's OK' and it does not matter what that blood says, 'cause [sic], and I suppose that's a bit concerning, 'cause [sic] if I was, you know, if I was miss-medicating, or if you know, anything could have happened to me and I don't think the GP would pick it up at all, it's like they do not care which is odd" [INT 3.1]

(*Continued*)

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Table 3 (Continued).

Pillar Building Themes	Qual Categories (Prescribers)	Qual Codes (Prescriber)	Qual Categories (Community Pharmacy Staff)	Qual Codes (Community Pharmacy Staff)	Qual Categories (Patients)	Qual Codes (Patients)
		"I would never perceive my role being to prescribe unlicensed medicines, my role is to obviously, y'know [sic], patient-centered, trying to address their. concerns and perceived needs and, come to a shared decision about how best to do that, so as long as I feel that, and, and the patient feels that we have discussed their concerns, the benefits and the potential drawbacks or risks, adverse effects associated with the medication, and they are comfortable and confident in the medication, I feel that I have properly discharged my role and responsibility in prescribing that unlicensed medication" [INT 1.1]		"Well I think [the role of accessing and supplying unlicensed "special" medicines is], part of my job, it's y'know [sic] we should be, if a patient has been prescribed an item, (pause) within reasonable grounds we should be able to supply it" [INT 2.1].		
	Patient attitudes towards, and acceptability of, receiving unlicensed "special" medicines	"I think that's what [patients] they are most worried about, you know, 'what do I do if I miss it', or 'what if they have too much', 'what are the side effects', and [I have to] answer those questions, I do not think they are, too worried about the licensing [status of the medicine]" [INT 1.5].	**Perception of patient attitudes**	"One of the common discussions I will have [with parents is] well you know, 'is this really necessary?' and the other thing is "is my child being used as an experiment?" [INT 2.1].	**Acceptability of the use of unlicensed "special" medicines**	"I, I was. low in energy and much more tired and I feel much better now, so I'm very happy with the. the extra. unlicensed medicines, and I intend to continue with them" [INT 3.2].

		"So generally, I think most patients I've spoken to and said it's unlicensed, I don't think they're particularly concerned about it, well, have not at least voiced their concerns when I've had those discussions" [INT 1.4].		"Often patients are a little wary, you know because they realise that this is a "special" medication, and sometimes they will have talked with a consultant and they have been told that perhaps, it's the first time it's being used" [INT 2.1].		"I think it's just that unlicensed label on it that you kind of think, or what is that? Why? Why is that? Why, it kind of makes you wonder if it's safe" [INT 3.3]
	Personal experience prescribing unlicensed "special" medicines	"my experience, generally, the ones that I've given, I'm not aware of any, any [sic] problems or, or [sic] safety concerns at this stage" [INT 1.4].			**Limitations imposed by the use of unlicensed "special" medicines on patients' personal and professional life**	"It is quite distressing I suppose, 'cause like if I was to consider for work, there is opportunities for me to work abroad and I actually have to think about how would I get my drugs. because you can't post them so it has held me back career wise" [INT 3.1].

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Table 4 Pillar Three of the Adapted Pillar Integration Model, Constructed After Integration of Results from the Three Qualitative Studies

Pillar Building Themes	Qual Categories (Prescribers)	Qual Codes (Prescriber)	Qual Categories (Community Pharmacy Staff)	Qual Codes (Community Pharmacy Staff)	Qual Categories (Patients)	Qual Codes (Patients)
Pillar three: Challenge associated with the accessibility of unlicensed "special" medicines	**Decision making processes when prescribing unlicensed "special" medicines**	"If you are deciding that [an unlicensed "special" medicine is] what the patient needs, then often, and there is no other option, which is. more. financially sort of, sensible, then you have to, you have to take that decision anyway" [INT 1.2].				
	Unwillingness to prescribe unlicensed "special" medicines	"I definitely have the sensation of refusing [to prescribe unlicensed medicines in the past]…. yeah just that feeling that it I do not, I do not [sic] have the expertise or the knowledge about the drug or, or [sic] perhaps the condition to, to [sic] prescribe it and take responsibility for it, or know what checks I should be doing or what reviews I should be doing" [INT 1.3].	**Issues faced**	"I mean we had some last year, with the flu vaccination and two of the [GP] surgeries I think, or it might even have been three of the surgeries, picked the "specials" liquid for the anti-viral by mistake, instead of the licensed one" [INT 2.2]	**Issues faced by patients during their journey from being prescribed to obtaining regular supplies**	"Sometimes when I phone [the GP] to order the medicines, they did not wanna [sic] give it to me, so then I got to go back to my son's paediatrician [in secondary care] and he had to send a letter that [my son] is on that medicine so they would give him that, so I had few problems with that" [INT 3.4].

		"Whether it was licensed or unlicensed…if it [the request to prescribe] wasn't clear in terms of the dose, the duration, and the rationale then yes, I probably would refuse to, to [sic] prescribe it" [INT 1.4]		"The issue that I still find a little irksome, is when we have an ADHD child, whose been prescribed a drug by their hospital paediatrician and their GP has refused to do the follow on… it's known as shared care, and there's generally an agreement between the two, and it does not happen as often as it used to. but it still happens" [INT 2.1].		"The flow of information between paediatrician clinic and GPs, 'cause there is a delay in it, I know the letters should be sent and the letter has been sent, but sometimes they say they has not [sic]" [INT 3.4].
			Strategies taken to ensure supply	"We had a word with the surgery, got a new prescription and did that one…that probably causes more time than actually having a "special" prescription" [INT 2.2].	**Adopting different channels of communication with different healthcare professionals**	"[The GP] They said it's unlicensed medicines they cannot prescribe, I said you know he's [my son] being prescribed, but he, by his paediatrician, he cannot go without it, so then [you have to] go back to paediatrician, they had to send the letter again [to the GP]" [INT 3.4].

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Table 4 (Continued).

Pillar Building Themes	Qual Categories (Prescribers)	Qual Codes (Prescriber)	Qual Categories (Community Pharmacy Staff)	Qual Codes (Community Pharmacy Staff)	Qual Categories (Patients)	Qual Codes (Patients)
				"We do not tend to order [unlicensed "special" medicines] automatically because it varies, (pause) you know in theory it should run out at this time, but it seems with [short] expiry dates and with liquids especially, especially if it's being administered and the nurses are pouring it, it does not always last as long as you'd expect it to" [INT 2.2].		
			Managing supplies	"[The suppliers] didn't have a solution they only had a suspension so, we couldn't use them in the end for that for that item. we had to go to someone else to order it… and then that wasn't as straight forward" [INT 2.6].	**Managing and storing supplies**	"What I have done is I have bought a couple of months' [supply of the unlicensed medicine] privately on the quiet just so I am not short because quite often I go to collect it and it's not ready, they are [the pharmacy are] only ordering it then, or they are only reminding the GP then, and there's a lag so it would not be unusual for like for a month prescription I actually have to make it last five or five and a half weeks". [INT 3.1].

As some prescribers described not being confident in their understanding of the terminology around unlicensed medicines, this impacted their decision to inform patients, with some prescribers suggesting that informing patients would lead to concerns or that it was simply too confusing. This was supported from findings from the patient interviews where again differing definitions were provided for what an unlicensed "special" medicine is, with one patient not being aware they were receiving an unlicensed "special" medicine for their child until they were invited to participate in the study. However, the importance of patients being aware when receiving unlicensed "special" medicines was highlighted by community pharmacy staff who stated that due to the short expiry dates and cost of unlicensed "special" medicines, they could not be ordered in advance and stored in the pharmacy. As such, patients were required to order further supplies of their unlicensed "special" medicines in advance, and that if they were not aware of this, the delay in ordering could lead to a delay in accessing the medicine and could lead to treatment delays or disruption.

Pillar Two: Perceptions of Patient Care and Acceptability of Unlicensed "Special" Medicine Use

Qualitative findings from participants in all groups showed varying perceptions of patient care and acceptability of unlicensed "special" medicine use. While some prescribers viewed the use of unlicensed "special" medicines as a last resort and therefore the only available option for the patient, others felt that prescribing of unlicensed "special" medicines should be the responsibility of secondary care prescribers due to their perceived expertise and familiarity with their uses. Pharmacy staff viewed prescribers as having increased expertise and this resulted in a level of trust that, when the medicine had been prescribed, it was suitable Patients also viewed secondary care prescribers as being more responsible, giving as examples how they experienced secondary care prescribers having to repeatedly contact primary care prescribers to ensure the medicine would be supplied. One patient described the primary care prescribers as being "less caring" and "not understanding the patient condition", which caused the patient concerns about the quality of care they were receiving. This was a direct result of the care they had received, as their GP had decided against prescribing the unlicensed "special" medicine on numerous occasions, which resulted in delays for the patient when accessing their medicine, negatively impacting the doctor-patient relationship. This was coupled with the secondary care doctor having to write letters to repeatedly ask the GP to continue the prescription. It was requested that a note would be added on the medicine box stating "as prescribed by the endocrinologist", which was interpreted by the patient as the GP only having the administrative role of signing a new prescription, and not being clinically or legally responsible for the continuation of the treatment.

Despite some concerns when prescribing unlicensed "special" medicines all prescribers felt that patients were accepting when prescribed an unlicensed medicine, and they stated they were not aware of any issues after prescribing the medicine. Pharmacy staff on the other hand highlighted specific concerns patients receiving unlicensed "special" medicines occasionally raised, such as the perceived safety of the medicine. During patient interviews, some patients did state that the term "unlicensed" had caused them some concerns about the safety of the medicine, and that needing an unlicensed "special" medicine actually impacted their day to day life, with one patient describing feeling that they could not move away for career opportunities as they did not feel confident they would be able to access their medicine elsewhere. However, overall, patients' acceptability of receiving an unlicensed "special" medicine was mainly impacted by a cost-benefit analysis between the perceived need for the medicine and the potential risks. Patients described the risk of not receiving the medicine as being more important than the risk of potential side effects. The most frequent concern described by patients was being unable to access their medicines, rather than any safety implications.

Pillar Three: Challenge Associated with the Accessibility of Unlicensed Medicines

Prescribers reported how, when they had experienced more integrated care, such as good quality information transfer between settings or the use of shared care protocols, their confidence in their own practice increased. Similarly, pharmacy staff also reported their confidence increasing when information about the medicine itself and the clinical need for the specific patient was provided to them by the original prescriber. Patients also highlighted the need for further integrated working citing many of the issues with access they had experienced being related to differences in acceptability among healthcare professionals in different care settings or a lack of communication across care settings.

Qualitative findings from pharmacy staff and patients showed how, when prescribers were uncomfortable with, or unwilling to, continue prescriptions for unlicensed "special" medicines, this led directly to challenges for pharmacy staff who were then unable to obtain and supply the medicines and for patients trying to access their medicines. To mitigate this pharmacists reported having to contact GPs and hospital prescribers on behalf of the patients, to ensure the prescription could be accessed, and in some cases having to wait until a different member of the prescribing team who was willing to continue the prescription became available. Patients described having to adopt multiple methods to handle these challenges as well, such as having increased communication with healthcare professionals and managing and ordering supplies to ensure continuity of care. While prescribers in primary care shared their own concerns and reasons that would lead them to be unwilling to prescribe or continue a prescription for an unlicensed "special" medicine initiated in secondary care, pharmacy staff and patients described the impact of this on patient care. As unlicensed "special" medicines require ordering in advance patients described some potentially dangerous methods to ensure continuity of treatment, such as syringing the medicine off the floor when dropped, or buying supplies privately and using the medicine out of date to manage the delays they often experienced with accessing further supplies in the community.

Discussion

This study uses a formal integration tool to triangulate findings from interviews with three key stakeholder groups directly involved throughout 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. Overall, results build the body of evidence showing varying levels of awareness around what unlicensed medicines are, varying perceptions of how patient care is managed and varying perceptions of acceptability around the use of unlicensed "special" medicines in general. The findings also suggest that prescribers in primary care may not only be unaware of the challenges patients face when trying to access their unlicensed "special" medicine in the community, but may inadvertently cause challenges to patients and pharmacy staff when being uncomfortable with, or unwilling to continue a prescription that was initiated in secondary care.

Prescribers reported varying levels of understanding around what unlicensed "special" medicines are, often using the term interchangeably with off-label medicines, which could reflect the varying definitions provided in guidance documents for healthcare professionals,[8] with the lack of consistency in terminology leading to confusion.[21] Prescribers in primary care also reported that when unlicensed medicines were initiated in secondary care, they may be unaware of the licensing status, exacerbated by the prescribing software not effectively alerting them when unlicensed medicines were selected. Similar findings were reported by Donovan et al,[22] where prescribers also acknowledged that the prescribing software may not alert them to the licensing status when unlicensed medicines are selected. Issues have also been reported in the wider literature that show other types of alerts on prescribing software are not effective and can sometimes be viewed by prescribers as irrelevant.[23] This suggests there needs to be a more effective way to alert prescribers when unlicensed medicines have been selected. Varying levels of understanding and awareness about what unlicensed medicines are have been reported across countries, with many studies highlighting that doctors may be prescribing off-label medicines unknowingly.[24] If prescribers are not aware when they have prescribed unlicensed medicines, they would be unable to effectively inform patients of the licensing status of the medicine. This could explain why one of the patients interviewed in this study was unaware their child was receiving an unlicensed "special" medicine and could explain the varying rates in how often patients were informed of the licensing status when prescribed an unlicensed medicine described within the wider literature.[25,26]

Prescribers also reported varying perceptions of acceptability when prescribing unlicensed "special" medicines, with some primary care prescribers suggesting this should be the responsibility of secondary care prescribers. This view has been reported in previous literature, where GPs have expressed concerns around taking on the legal and clinical responsibility for specialist prescribing that was initiated by another doctor in secondary care, feeling as though they should not be held responsible for someone else's prescribing decision, especially in an area where they have little experience.[27] However, concerns around the safety of unlicensed medicines as well as the legal responsibility have also been reported by secondary care prescribers within the international literature.[28–30] This concern arises as prescribers are

legally responsible for any prescription they sign and are recommended not to sign a prescription for an unlicensed medicine unless they feel comfortable that the medicine is the most suitable option and has enough evidence to support its use.[31] However, when disagreements occur over the responsibility to prescribe, this can leave patients without the medicine they need.[32]

Transfer of care across settings had been recognised as an area where medication errors often occur.[33] Within the literature doctors have expressed the need for integration between primary and secondary care in the UK, believing that the barriers faced between care settings can negatively impact on the quality of care provided to patients.[34] The findings from the patient interviews show how the lack of integration between primary and secondary care can directly result in delays or disruptions when trying to access unlicensed "special" medicines in the community, further exacerbating patient concerns around accessibility. The lack of integrated care was also described by community pharmacy staff, who shared examples where primary care prescribers did not feel comfortable to continue a prescription for an unlicensed "special" medicine, and gave examples of prescriptions sent directly by secondary care prescribers where patient-specific information was not provided with the prescription. This led to an increased workload for community pharmacy staff, who had to take steps to access the prescription for the patient, and to try to confirm the clinical need for the medicine. Some of the issues experienced arise as pharmacists are not usually provided with information about discharge medicines.[35] Experiencing delays and disruption in this way led to one patient to perceive GPs as less caring and less responsible. The perception of GPs just being responsible for signing the prescription has been reported within the literature by other patients receiving unlicensed medicines.[12] This could also reflect the general public's perception with previous literature suggesting GPs are viewed as "the middle man" and that care would be of higher quality in hospitals.[36,37] The findings highlight the importance of informing patients about GP roles and responsibilities so that patients can appreciate when valid concerns arise, and the GP-patient relationship can be improved.

Despite some concerns when prescribing unlicensed "special" medicines, all prescribers felt that patients were accepting of unlicensed "special" medicines when needed. Results from the patient and pharmacy staff interviews highlighted that concerns existed, showing that prescribers may be unaware of concerns patients held and the impact receiving an unlicensed "special" medicine had on the patients' lives. Despite these concerns, all patients felt like they needed their unlicensed medicine, so much so that the most frequent concern described by patients was being unable to access their medicines. This is in line with the necessity-concerns framework,[38] showing that patients perform a cost benefit analysis between the perceived need and the potential risks.

Patients and pharmacy staff highlighted how those who receive unlicensed "special" medicines are required to take on increased responsibilities, and manage access across care settings. Patients taking on specific strategies to manage the ordering of and access to unlicensed medicines has also been reported in England.[12] The evidence from this study and the wider literature has shown that patients across the UK may be faced with a need to manage access to unlicensed medicines across care settings, or else put themselves at risk of delays or treatment disruption. This finding further emphasises the importance that patients are informed not only of the licensing status of their medicines, but also the implications this has on accessibility.

Internationally, a range of guidance documents exist around the use of unlicensed medicines, all of which have similar requirements related to the justification of using unlicensed medicines, however their content varies.[39,40] In response to the issues across the patient pathway highlighted by this study, the All Wales Medicines Strategy Group engaged further with stakeholders and have created updated national guidance on understanding unlicensed medicines to support those involved in the access or supply of unlicensed medicines and the patients who receive them.[41] This guidance, which can be used by policy-makers internationally, covers the entire patient journey and provides a supportive framework for stakeholders across all care settings, including prescribers, community pharmacists and community pharmacy staff, clarifying everyone's role in the supply chain and ensuring awareness of challenges at different stages that could increase the lead time that is often required when accessing and supplying unlicensed medicines. In turn, this could help to reduce treatment delays or disruptions and improve both patient safety and the patient experience. The guidance also includes a patient information leaflet that can be provided to patients and carers to ensure they are aware of the licensing status what this means and the potential challenges with accessibility in the community. Further research could be conducted to see how this updated guidance is perceived by prescribers, pharmacists and patients and conducted overtime to see how well

the guidance is utilised by those involved. Further research could also be conducted to compare the content and utilisation of guidance documents for unlicensed medicines internationally.

Limitations

Data collection for this study overlapped with the COVID-19 period, with increased workplace pressures in primary and secondary care. We mitigated against the anticipated impact on recruitments by using principles of information power to determine sample size, so that the final sample included different types of prescribers, and patients recruited from both primary and secondary care. The desirable minimum sample size was reached, but the final number of participants was small, with sample populations not homogenous in some instances (eg, only one secondary care prescriber), which may mean that results may not be fully representative. Despite this, we collected rich data from all the different sample populations, giving an insight into their experiences. To the authors' knowledge, none of the included patients were treated by the prescribers or accessed their medicines from the community pharmacists included in this study. In this way the individual populations may have had largely differing experiences. Further research could follow patients through their medical journey and interview the patients and the healthcare professionals they interact with at different stages, in order to observe how one stage and the decisions of those involved could directly affect another.

Conclusion

The results of this study highlight that there are varying levels of awareness among healthcare professionals and patients when unlicensed "special" medicines are prescribed. This, coupled with the varying perceptions of responsibility and acceptability of the use of unlicensed "special" medicines among healthcare professionals led to a range of challenges experienced by participants in this study. These include managing care across care settings to ensure the patient is effectively treated, and ensuring continuity of care for patients in the community to reduce the chance of treatment delay or disruption. Further evidence is needed to validate and expand on these findings. There is a clear need for more support for healthcare professionals to increase awareness when unlicensed "special; medicines are used, and to ensure consistent understanding about each healthcare professional"s role in the supply chain. There is also a clear need for integrated and patient-centred care to ensure that any delays experienced when accessing unlicensed medicines do not lead to treatment disruption or harm for the patient. New national guidance developed as a result of the findings can be used by policy-makers internationally to support a reflective review of their own systems and processes.

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