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SPECIAL REPORT

The challenges and practical considerations with optimizing neonatal pharmacotherapy

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ABSTRACT

Introduction: Optimal neonatal pharmacotherapy requires the implementation of high-quality information about medicines.

Areas covered: High quality information about medicines needs carefully designed programs that are centered on the needs of people affected by neonatal conditions, delivered using appropriate dosage forms, based on good pharmacometrics, and built around causal pathways reflected in study eligibility criteria and endpoints. Implementation of information about medicines requires multidisciplinary effort that is rooted in family integrated care (or similar approaches) and rigorously evaluated. Collaboration promotes effective work to generate high-quality information and to implement it.

Expert opinion: A range of contemporary approaches can be applied to neonatal medicines development but need strong underpinning research supplemented by clear research questions that target specific contexts of use. Appropriate prescribing, administration, and monitoring of medicines to neonates depend on well-resourced Clinical Pharmacists who implement evidence-based approaches to their work and are embedded in a team centered on the baby and family.

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KEYWORDS
Neonates; drug development; pediatric extrapolation; clinical pharmacy; family integrated care

1. Introduction

Each year, 132 million babies are born globally [1] and can be classified as 'neonates' until 28 days after the date they were due to be born on [2]. All neonates deserve prophylaxis for at least one condition (e.g. Intraventricular Hemorrhage (Vitamin K), Respiratory Syncytial Virus, Hepatitis B etc.) and so should receive at least one medicine or vaccine. Around 10% of neonates are admitted to a neonatal unit and need medication to manage infection, prematurity, congenital anomalies or other illnesses that arise at the time of birth. Sick neonates often need support for multiple body systems, so medicines are used for many reasons beyond the presenting complaint.

Neonatal care has been improved in several ways. One approach is to conduct a series of large randomized controlled trials (RCTs). However, the uncritical use of RCTs is not the best way to develop or refine knowledge about neonatal pharmacotherapy. For example, more than 350,000 babies have been randomized in trials of probiotics and we still don't know which probiotics to give, how much probiotics to give, or how long to give them for [3].

Optimal neonatal pharmacotherapy needs medicines that are: a) prescribed and monitored in the light of information that is relevant to neonates about dosing, efficacy, and safety; b) available in an age-appropriate formulation and dispensed and administered appropriately; c) managed as part of a holistic package of care that meets the needs of babies, family members, and health care systems. Addressing these challenges and practical considerations benefits from integrated work by multiple disciplines in addition to families.

Neonates have some characteristics and illnesses that are shared with other populations and some features and conditions that are specific to this age group. Pharmacotherapy needs to be adapted to the neonatal population while taking account of knowledge gained in other age groups and specific research, innovation, and service improvements that are conducted in this population. Neonatal pharmacotherapy occurs in several settings including neonatal intensive care, other hospital settings, and at home: prescribing, monitoring, dispensing, and administration need to be appropriate for the setting as well as the indication for the medicine. Some of the issues with medicines development and use have been discussed in the recent Lancet Child and Adolescent Health Commission on the Future of Neonatology [4]. This paper aims to give an overview for a general audience of the specific efforts needed to optimize the use of medicines in neonates through the integration of research and implementation of good practice.

2. Challenges

The challenges with optimizing neonatal pharmacotherapy are summarized in Table 1 which includes some suggestions about how to address these challenges and illustrates the work of the research community and their efforts to support optimized neonatal pharmacotherapy. The challenges are related to a) lack of underpinning information to support medicines use in general and b) lack of condition- or medicine-specific information. Each of these challenges needs

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Article highlights

- Optimal neonatal pharmacotherapy is centered on the baby and family inpractice and research.
- Challenges include the need for underpinning information about diseaseprogression and neonatal pharmacometrics.
- The application of contemporary approaches to medicines development to neonates willadvance the field.
- Practical issues include compatibility, safety, therapeutic drug monitoring,and avoidance of errors.
- Robust evidence to support neonatal clinical pharmacy practice needs to be developed in multicentre networks for practice and research.

research, innovation, and enhanced approaches to service delivery. Underpinning work would benefit from an integrated approach to understanding the course of neonatal conditions, for example a study similar to a neonatal Framingham Study. Ideally work on these challenges will be integrated between settings in order to promote sharing of data and experience. Successful approaches to the practical considerations of neonatal pharmacotherapy depend on clinical pharmacy. Much research about neonatal clinical pharmacy practice has been single-centered. Innovations are often piloted and evaluated in single centers but need to be evaluated across multiple centers. Networks of health care professionals and sites promote effective clinical pharmacology and pharmacy practice and research.

The development of medicines requires information about disease progression and the targets of medicines (pharmacodynamic targets, clinically outcomes, and surrogate endpoints). Pharmacodynamic targets are biological entities, such as receptors, that are responsible for the actions of a medicine. The neonatal pharmacodynamic target may be the same as it is in adults or different due to ontogeny. The relationship between concentration in the appropriate body compartment and the desired physiological effect of the medicine is of central importance, even if the precise molecular mechanism is not known, so that studies of pharmacokinetics in neonates are essential. Clinical outcomes are endpoints 'that describe or reflect how an individual feels, functions or survives' [11]. Clinical outcomes are used to define whether a medicine is useful or not, e.g. whether a medicine should have a Marketing Authorization. These outcomes need to: reflect the causal pathway of the targeted condition; capture the effect of the medicine on the causal pathway; be measurable consistently and precisely in relevant clinical environments; and be meaningful to families and people with lived experience of ill-health during the neonatal period. Identification of such outcomes is an urgent goal for almost all the conditions that affect sick and premature neonates. The use of clinically convenient and familiar outcomes that do not

Table 1. Challenges with optimizing neonatal pharmacotherapy.

Challenge	Description	Solution	References
Lack of knowledge to support prescribing	Insufficient understanding of indication, dosage form, dosage regimen, efficacy and safety (including drug-drug interactions and compatibility), and adaptations to special situations such as therapeutic hypothermia	Research targeted at information gaps (that may be part of drug development programmes to supporting licensing on-label or off-label but on-evidence) Systematic research on compatibility	[5] [6]
Lack of knowledge to underpin development and use of medicines	Insufficient information about ontogeny of PK and PD including metabolism of medicines, relevant physiology, systems biology, and endpoints for assessments of efficacy and safety and for implementation of therapeutic drug monitoring (TDM)	Research targeted on information gaps, e.g. disease progression models (perhaps similar to the Framingham study in adults) and information to support TDM Microdosing is a useful technique to probe metabolic pathways and provide qualitative and quantitative information about those pathways	[7] [8]
Insufficient application of existing knowledge and innovation	Poor diffusion of evidence. Poor uptake. Poor preparation of research for implementation	Effective implementation based on appropriate planning that is built into research and innovation. Education and training. This is likely to be an increasing problem given the potential importance of methods not previously used in neonates. Need for systematic approach to implementation, deployment, and adoption as research and innovation are extended	
Insufficient resource for research and innovation	Research and innovation needs to generate value for money to public and private funders (including health care providers).	Improved markers of clinical effects that support Health Technology Assessment decisions. Improved information about what health care systems are willing to pay for improved therapies. Clear understanding of market size and scope to promote investment by industry	
Insufficient attention to needs and preferences of families and people with lived experience of neonatal care	Professionals make decisions or assumptions with paying attention to the needs and preferences of families or people with lived experience	Work with families and people with lived experience of neonatal illness to identify problems and develop solutions	[9] [10]
Specific features of research and innovation in neonates	Small samples needed. Sampling matrices may not have been developed. Recruitment during emergency settings, including consent, are sometimes needed	Small, opportunistic samples at the same time as clinically indicated samples with appropriate planning Phased consent	
Limited willingness/ability to do the work, despite pockets of excellence	High quality work to develop and implement best practice is not generalized. Insufficient research sites, resources, adoption are partly responsible but skills and willpower can play a role	Enhanced training and personal development	

have the necessary characteristics may not capture the effects of a medicine.

Surrogate endpoints predict 'clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence,' are often biomarkers, and need to reflect the causal pathway and be measurable consistently and precisely in relevant clinical environments [11]. Studies that report associations between 'biomarkers' and clinically reported outcomes are not sufficient to support their use in studies that will support approval by regulatory agencies. Consensus about which variables to include in clinical studies does not, in itself, meet the need for useful outcomes during medicines development. The quality of clinical outcomes and surrogate endpoints is important given the extent to which neonatal pharmacotherapy will rely on extrapolation, modeling, and small trials.

Therapeutic Drug Monitoring (TDM) is essential to adapt dosing to different circumstances but is underused in neonates. TDM allows the use of medicines that might otherwise be harmful and can adapt therapy to stages of illness, for example variations in fluid and renal status during an episode of neonatal sepsis. TDM benefits from the same information as medicines development: the necessary underpinning information includes ontogeny of renal and hepatic function which can be expressed in maturation charts for individual organs [12] or through integrated descriptions of neonatal physiology [13].

A comprehensive agenda for medicines research in neonates needs to consider Marketing Authorization (licensing) as a base case for the most important uses of a medicine. Marketing Authorization (licensing) requires a degree of rigor and stringency that may not be familiar to clinicians. The content of Summary of Medicinal Product Characteristics (SmPC) (label) needs to be supplemented by information that allows on-evidence, professionally assured off-label use if on-label use is not possible for commercial or other reasons. When medicines are widely used, the burden of research after Marketing Authorization (licensing) needs to be proportionate to the benefits to the neonatal population of the results of the research [14]

These challenges require advocacy for optimal pharmacotherapy, training in medicines optimization for the multidisciplinary team (MDT), standards for services, and collaboration.

3. Practical considerations

Practical issues with optimizing neonatal pharmacotherapy are summarized in Table 2 which is intended as an overview of the topics a neonatal health care team may want to address when aiming to optimize pharmacotherapy. In principle, addressing these issues requires adapting strategies that are well-developed in other settings to neonates. In practice, the adaptation of existing information to neonatal settings is not well-developed and will benefit from strong team working in each unit and between units to promote benchmarking and best practice.

Surveillance and systems for prevention, recognition and management of medicine-related problems are needed. These systems can be implemented and evaluated ideally with robust methodologies such as randomized controlled trials [17]. Clinical pharmacy has a central role embedded in the MDT. Each unit that seeks to optimize pharmacotherapy needs to adopt one of the many explicit and well-characterized approaches to altering the way the unit works (so-called 'change management') including establishing a vision to guide change and metrics to assess the success of efforts to achieve change which requires collaboration and can take significant amounts of time to accomplish. Systems and surveillance for prevention, recognition and management of problems with medicines include the use of neonate-specific formularies, administration instructions, technology (e.g. programmable syringe pumps), and regular clinical pharmacy rounds [18]. As noted above, networks of health care professionals and institutions can promote high quality practice.

Drug-drug interactions should be avoided or minimized during neonatal pharmacotherapy. Neonates are vulnerable because of their immature and evolving enzymatic pathways, transporter ontogeny, altered protein binding, saturable metabolic routes, and lack of knowledge about these aspects of medicines disposition in general and when interactions are possible. There is a paucity of tools to identify drug-drug interactions that have been validated for neonates, although machine learning may provide some opportunities [19].

Medication errors are common in neonates and their impact and prevention have been reviewed recently [20]. There are multiple potential contributions to medication errors including dose calculation (exacerbated by frequent changes in the bodyweight of weight), dilution, infusion programming, small volumes of doses. Many formulations are used-off label in neonates so that appropriate procedures to assure pharmaceutical quality in this context have not been followed. Surveillance by the multidisciplinary team is essential and can be supported by machine-learning models incorporating both pharmacotherapy and workload variables [21]. In addition, system-level interventions can have an impact including smart pumps, standardized concentrations, and clinical decision support. As noted, the effective implementation of system-level interventions requires buy-in and effort from the whole clinical team.

The journey of each neonate includes several transitions – between levels of care and from hospital to home. Each of these transitions involves medicines so the need for continuity of purpose for each medicine needs to be reconciled with adaptation to the new environment taking account of resources in each environment and the needs and expectations of parents. Accordingly. transitions between health care facilities need to be planned carefully. Discharge from hospital is a particularly important transition which has a major effect on families who are often not supported adequately. Discharge needs to be supported with targeted parent education and integrated community pharmacology services [9].

Information sources that support the use of medicines in neonates need to be evidence based and transparent [22]. The Kinderformularium is a good example [23] that includes specific neonatal doses [24] and has been deployed across multiple countries. Advice for specific situations is useful. For example, advice about what to do if a neonate vomits shortly

Table 2. Practical considerations with optimizing neonatal pharmacotherapy.

Consideration	Description	Neonatal specificities	Action	References
Polypharmacy	Multiple medicines with risks of DDIs and ADRs	Uncertainty about benefits and risks of each medicine	Reduce prescriptions or deprescribing, ideally systematically	
Safety	Unintended effects that harm or add burdens to patients	Uncertainty whether medicines cause adverse events in the presence of multiple comorbidities	Systems and surveillance for prevention, recognition and management that are fit-for-purpose in neonatal settings	[15]
Adaptation to concurrent conditions	Evidence based modifications of dosage regimens to prevent or adapt to intercurrent conditions including acute kidney injury and acute or chronic hepatic injury	Lack of understanding of intercurrent conditions, including the best biomarkers to use for illness severity	Systems and surveillance for prevention, recognition and management of relevant intercurrent illnesses that are fit-for-purpose in neonatal settings	
Medication errors	An unintended failure in the medicine treatment process that leads to, or has the potential to lead to, harm to the patient. Mistakes in the prescribing, dispensing, storing, preparation and administration of a medicine are the most common preventable cause of undesired adverse events in medication practice	Complexity of medicines administration (see text)	Systems and surveillance for prevention, recognition and management that are fit-for-purpose in neonatal settings	[16]
Avoidance of preventable drug drug interactions (DDIs)	Avoiding alteration to a medicine's effect by the concomitant administration of another medicine based on information that is clinically relevant to neonates	See text	Systems and surveillance for prevention, recognition and management that are fit-for-purpose in neonatal settings	
Medication non-adherence	Lack of compliance with prescribed medications. prescribed medicines.	Can be related to inaccurate delivery systems, e.g. administration of intravenous medicines using suboptimal pumps or tubing or related to limits on family capacity to administer	Systematic research on optimal delivery systems	
Size of patients	Ensure that products can be used conveniently and accurately	Need age-appropriate formulations and delivery devices	Careful procurement; work sharing to specify and obtain appropriate products	
Challenges with the transitions of care	Move from level of care within neonatal unit, between neonatal and other units, at discharge from hospital.		Systems and surveillance for prevention, recognition and management that are fit-for-purpose in neonatal settings. Focus on needs of families	
Costs of medications	Can a health care facility or system afford medicines?	Difficulties with decision-making approaches, such as Health Technology Assessment relating to nature and duration of outcomes that are not addressed comprehensively by existing methodologies	Careful justification based on health economic assessments that are appropriate for neonates; advocacy by families and staff	
Lack of access to healthcare	Absolute lack of access due to lack of appropriate medicines; relative lack of medicines – some people do not have access to medicines that others have access to.	Lack of evidence to support neonatal access Lack of equity for neonates	Careful justification; advocacy; attention to equity and fairness	
Emergence and management of antimicrobial resistance	Presence of infectious agents that are, or are likely to be, resistant to anti-infective agents.	High risk situation (e.g. invasive lines and tubes) Repeated exposure to antibiotics – often empirically in situations with low likelihood of infection	Systems and surveillance for prevention, recognition and management that are fit-for-purpose in neonatal settings	

after taking a medicine has recently become available [25]. Lactation during administration of medicines to mothers is in principle safe for almost all medicines but clinical practice needs to account for maternal preferences and individual circumstances such as: the risks of stopping maternal medication; the likely extent of absorption of medicine from breast milk (taking account of data about transfer of the medicine into breast milk); and the likelihood that the mother will be able to respond to a problem in the infant due to lactation (for example if a maternal psychotropic medicine causes drowsiness in some babies does the mother's mental state allow her to recognize the infant's drowsiness and alert health care professionals appropriately)

4. Expert opinion

Most of the issues with optimizing neonatal pharmacotherapy can be addressed using existing knowledge and technology, particularly if approaches used in other age groups are applied effectively [26]. Optimization of neonatal pharmacotherapy needs good organization and generalization of good practice across facilities and topics while taking account of clinical reality. While RCTs have a place in neonatal medicines development, RCTs need to be part of a coherent plan that starts from existing information and uses appropriate study designs to answer questions about dosing and safety as well as efficacy [5].

Optimizing use of medicines requires communication across the MDT, with key family members at the center of communication and decision-making (Figure 1). Optimizing medicines needs to be built into Family Integrated Care (FICare) and similar approaches which are hallmarks of good neonatal care [27]. Families need to be included in research as leaders and contributors.

In the past, the standard approach to generate information about medicines would be to do a series of studies in each population that would use a medicine such as Phase 1, 2, and 3 prior to marketing authorization for a product followed by large, strategic trials to establish the role of the product in clinical care. The contemporary paradigm for generation of evidence about new and existing medicines is different and is based on the need to gather information about specific information gaps rather than follow a standardized, comprehensive approach [5]. Modeling and simulation can improve the efficiency of information gathering and reduce the burden on study participants but requires significant amounts of underpinning information. Some information can be borrowed from other populations (pediatric extrapolation is important for neonates in selected circumstances). It is crucial to recognize that these approaches will also be central to neonatal clinical practice in future. Neonatal health care professionals will need to understand modeling and simulation and pediatric extrapolation in order to select which medicine to use but also in order to use medicines wisely. For example, TDM should be at the center of neonatal pharmacotherapy but needs a good understanding of pharmacometrics among members of the neonatal team.

Artificial Intelligence (AI) is likely to play a role in neonatal pharmacotherapy as summarized in a scoping review that found examples relating to the hemodynamic effects of NSAIDS on PDA, optimization of the dosage of caffeine and medicines eliminated by the kidney, and prediction of medication errors and drug-drug interactions [28]. As in other contexts, it is essential to make sure the learning set is appropriate, including inclusivity, generalizability, and relevance (taking account of the characteristics of datasets from individual neonatal units: small size, unbalanced, and heterogeneous); that the AI model is fit for purpose, useful, and cost-effective in the intended context of use; and that the

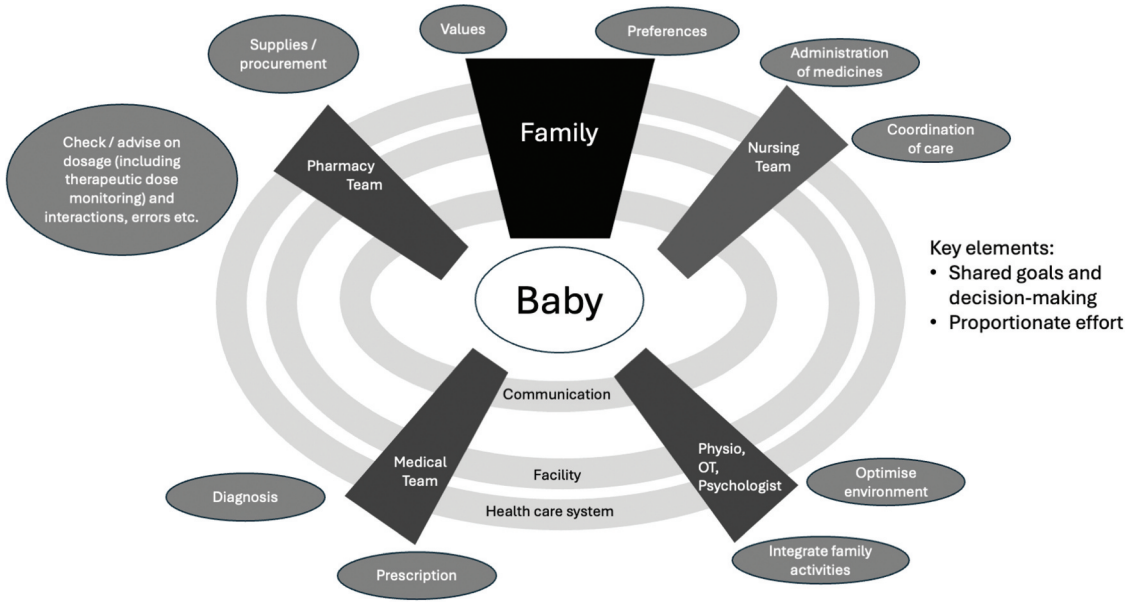

Figure 1. Model for optimizing neonatal pharmacotherapy.

The baby is at the center of discussion. The family are important contributors to the discussion informed by links with each member of the health care team. Each member of the health care team brings specific skills to the discussion.

implementation of AI respects the need for privacy and consent (which can pose specific ethical issues in the neonatal context), environmental responsibility, and is supported by a structured approach to implementation/change management including appropriate training for health care professionals. The EMA has reported its experience with AI in the medicines lifecycle and their reflection paper includes a useful list of points to consider when developing and deploying AI models to support pharmacotherapy [29]. For example, validation of each AI model is important: according to one systematic review, fewer than 30% of published neonatal applications of AI reported validation for accuracy [30].

Real-world data (RWD) can also contribute to the development and use of neonatal medicines. The extent and value of RWD depends on data quality and relevance to the questions being answered by RWD. For example, the use of RWD as a source of external controls requires that the data source captures the same information about safety and concurrent medicines as a clinical trial would gather and that the group captured by RWD experiences the same standard of care as the group given a medicine under investigation. Co-development with families and people with lived experience of neonatal care for AI and RWD is needed building on meaningful involvement of families and people with lived experience in the selection and leadership of projects and listening to the voices of families and people with lived experience as tools are developed and deployed; work with advocacy groups to find and support relevant people is essential [10].

In conclusion, tools for optimizing neonatal pharmacotherapy are available and feasible. Support for practical issues when medicines are administered to neonates can be improved by good information about medicines that will be the result of addressing the challenges listed here. A roadmap to optimizing neonatal pharmacotherapy could include: establishing a mission mentality that promotes a shared set of goals; mobilizing resources; underpinning work; study design and conduct; regulatory approval; and effective implementation of good practice through clinical pharmacy and MDT work.

In practice, there will continue to be trade-offs between the ideal situation of developing and using regulatory grade evidence, the real-world situation of relying on useful evidence that supports off-label but on-evidence use of medicines, and the worst case of following informed opinion. These trade-offs will benefit from the scientific curiosity and dedication that characterizes neonatal health care supplemented by meaningful involvement of families and people who have experienced health care during the neonatal period.

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