Journal of Scientific Research and Studies Vol. 4(12), pp. 345-355, December, 2017
ISSN 2375-8791

http://www.modernrespub.org/jsrs/index.htm

Review

Prophylactic phenobarbitone in very low birth weight babies with unconjugated hyperbilirubinemia: Applying the principles of evidence based medicine

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Accepted 19 November, 2017

Evidence-based medicine (EBM) is the conscientious, explicit and judicious use of current best evidence in making decisions about individual patients. It involves integrating individual clinical expertise with the best available external clinical evidence from systematic research. EBM and evidence based practice (EBP) seek to put together current research evidence and clinical practice, with the understanding of patient values to give the most appropriate care to patients. Although EBP has been in existence for several years and has taken center stage in resource rich countries, it is still relatively infantile in developing countries like Nigeria. EBP helps practitioners to critically review and evaluate the available evidence in other to strengthen or change existing practices or introduce new ones. This is particularly important where resources are limited, and cost and sustainability must be considered before changes in practice are made. The focus on EBP has led to establishment of institutions which develop guidelines to inform health care. Such guidelines are developed to communicate professional medical consensus and to assist in ethical issues in neonatal care. Again there is a dearth of such institutions in some developing countries emphasizing the need for physicians to acquire the skills needed for EBP. This review aims to give healthcare practitioners step by step overview of the EBM process by providing a practical approach to applying the principles to the stated topic. Coming from a resource poor area, it also seeks to justify whether cost and availability are enough to change practice in the light of available evidence.

Key words: Phenobarbitone, jaundice, evidence based medicine.

INTRODUCTION

Evidence-based medicine (EBM) has been defined as the “conscientious, explicit and judicious use of current best evidence in making decisions about individual patients”. This means “integrating individual clinical expertise with the best available external clinical evidence from systematic research” (Sackett et al., 2000a). The aim is to put together current research evidence and clinical practice, with the understanding of patient values to give the most appropriate care to patients (Kheim and Weiss, 2005).

Although evidence based practice (EBP) has been in existence for several years and has taken center stage in resource rich countries, it is still relatively infantile in developing countries like Nigeria. In the same vein, significant steps have been taken toward improving newborn care in modern neonatal-perinatal medicine, but this development is slow in resource poor countries. Some examples of evidence-based medicine in neonatal and perinatal medicine include use of antenatal corticosteroids for promoting lung maturity (Roberts and Dalziel, 2006) and use of surfactant replacement therapy for the treatment and prevention of respiratory distress syndrome (Engle, 2008). Antenatal steroids are in use in many resource limited areas whereas surfactants may be unavailable in many resource-poor settings, cost and availability being determining factors. With advances in care, comes an abundance of available evidence which can sometimes be overwhelming. EBP helps practitioners

to critically review and evaluate the available evidence in other to change existing practices or introduce new ones. In settings like ours where resources are limited, cost and sustainability must also be considered before changes in practice are made.

Again, as neonatal medicine has developed over the years, so has clinical ethics become increasingly relevant (Meadow and Lantos, 2009). Some questions about the ethical issues in neonatal care include "Who deserves access to prenatal and neonatal specialty care?" "Who pays for this care?" "Who decides whether an infant receives care?" "Are the costs of neonatal intensive care acceptable?" among others. Potential for negative iatrogenic effects in much of what is performed in neonatal practice such as side effects of medications must also be recognized. For example, two broad ethical domains are of special relevance in the use of drugs for prophylaxis; well-being and justice. Safety is a critical consideration in prophylactic drug use. Justification for use must be balanced against an array of other threats to the well-being of individuals and communities. (Sugarman and Mayer, 2013).

In order to cater for some of these issues, the focus on EBP has led to establishment of institutions which develop guidelines to inform health care (Graham and Bick, 2010). Such guidelines are developed to communicate professional medical consensus and to assist in ethical issues in neonatal care. Again there is a dearth of such institutions in some developing countries emphasizing the need for physicians to acquire the skills needed for EBP. Recently professional bodies like the Paediatric association of Nigeria, recognizing the need for EBP and standardization of practice have taken up the challenge to begin to produce guidelines (Paediatric Association of Nigeria, 2015). There are challenges in getting physicians to change and begin to use these guidelines bringing to bear the fact noted by some authors that practitioners often tend to maintain conventional methods of practice to which they are comfortable either from reluctance to believe in EBP, cost of adopting new practices or simply resistance to change as part of human nature (Enuku and Igbinosun, 2012).

The aim of the article is to give healthcare practitioners a practical step by step approach to applying the principles of EBM, using the stated topic. Coming from a resource poor area, it also seeks to justify whether cost and availability are enough to change practice in the light of available evidence.

EVIDENCE BASED MEDICINE/PRACTICE TOPIC BACKGROUND

Hyperbilirubinaemia is one of the commonest problems of the newborn and may lead to bilirubin encephalopathy. Premature and low birth weight infants are at high risk for consequential brain damage even with low plasma bilirubin levels (Rubaltelli and Carli, 1971). Accordingly, a number of therapies have been devised to reduce this hyperbilirubinaemia (Carswell et al., 1972). Phototherapy, the commonest treatment, may be unavailable in some settings. In Nigeria, many newborns including preterms are born in places where there are limited or no facilities to manage neonatal jaundice (NNJ). Recent surveys, including a 2011 survey of phototherapy devices in Nigerian hospitals (Owa et al., 2011), have shown that phototherapy (PT) devices for NNJ in these settings frequently deliver suboptimal treatment.

Phenobarbitone, a UDP glucuronyl transferase inducer has been proposed to have some effect on neonatal jaundice (Salle et al., 1977). In the neonate, it induces enzymes in the endoplasmic reticulum of the liver cells, resulting in accelerated conjugation of bilirubin. Its use antenatally for the purpose of inducing hepatic microsomal enzyme system has been documented. This consequently decreases the need for phototherapy or exchange transfusion. However in resource poor areas, in addition to late presentation to hospital negating antenatal use, the high cost of treatment for NNJ makes exploration of postnatal use necessary. Furthermore, phenobarbital is cheap, and easily available and may be a good choice for postnatal prophylaxis and possibly reduce the costs associated with management of NNJ in very low birth weight (VLBW) infants especially in resource limited areas (Valaes and Harvey-Wilkes, 1990). However, several reports on phenobarbitone use in decreasing incidence and/or severity of NNJ were published decades ago, when use of phototherapy was not common and incidence of kernicterus was high in small babies (Trolle, 1968; Vest et al., 1970; Yeung and Field, 1969; Ramboer et al., 1969).

The evidence-based medicine process can be used to help in changing practices or adopting new practices which can sometimes reduce cost. The whole concept of EBM has been summarized in a five-step model (Centre for Evidence Based Medicine, 2009) as shown in Table 1. This review will pay particular attention to the first four.

Step 1: Asking answerable questions

The first step requires the ability to ask answerable, focused questions that are explicit regarding the patient or problem being considered, the intervention being considered, the comparison intervention, and the clinical outcome of interest (Richardson et al., 1995). This is arguably the driving force of the whole EBP process (Fineout-Overholt et al., 2005). Methods available include the PICO, SPICE and PIE. For this review, the PICO model (Richardson et al., 1995, Beecroft et al., 2006), considered appropriate for questions on health interventions has been used (Table 2).

EBP Question: Does prophylactic phenobarbitone

Table 1. 5-step model of EBM.

S/N	Steps
1	Asking answerable clinical questions
2	Searching for the evidence
3	Critically appraising the evidence for its validity and relevance
4	Making a decision, by integrating the evidence with your clinical expertise and the patient's values (Applying the evidence)
5	Evaluating one's performance

Table 2. Using PICO to frame EBP question.

PICO	EBP question
P (Patient/Problem)	Preterm neonates (1000 -<1500 g) with neonatal jaundice
I (Intervention)	Prophylactic phenobarbital given parenterally
C (Comparison)	No prophylactic phenobarbital
O (Outcome)	Reduced duration of phototherapy, reduced serum bilirubin levels

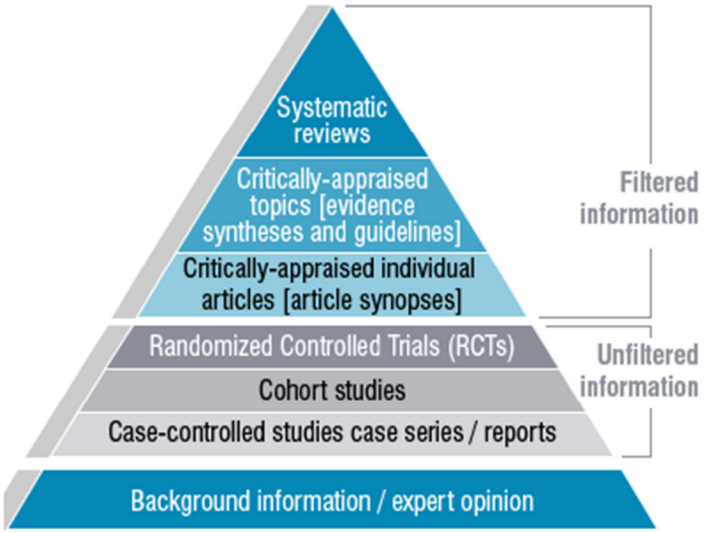

Figure 1. EBM pyramid (Glover et al., 2006)

therapy in the first week of life reduce serum bilirubin levels or duration of phototherapy in preterm very low birth weight neonates who develop unconjugated hyperbilirubinemia?

Step 2: Searching for evidence

This second stage involves looking for available evidence to answer the clinical question. This step helps practitioners search for and evaluate the best evidence on which to base practice. Authors have noted that the best evidence available is not always the best evidence possible. However, most experts agree that the higher up the hierarchy the study design is positioned, the more rigorous the methodology and the more likely it is that the study design can minimize the effect of bias on the results of the study (Guyatt et al., 1993). The quality (strength) of the evidence ranges from systematic reviews and meta-analyses of multiple well-designed randomized, and randomized controlled trials (RCTs) at the top of the hierarchy to expert opinions (based on clinical evidence, descriptive studies, or reports of expert committees) at the bottom (National Health and Medical Research Council, 2009; Hoffman et al., 2013). In the search for evidence-based information, the highest level of evidence possible i.e. SRs or meta-analyses should be targeted. SRs, meta-analyses, and critically-appraised articles have gone through an evaluation process i.e. "filtered." Information that has not been critically appraised is considered "unfiltered." An example of an EBM pyramid is shown in Figure 1.

Table 3. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Preterm babies, very low birth weight,	Term babies, babies < 1000g or ≥ 1500g
Phenobarbitone (intravenous or oral) for prophylactic treatment of neonatal jaundice	Phenobarbitone (intravenous or oral) for treatment of neonatal jaundice
Articles written in English language	Articles not written in English language
Primary sources of evidence (where no systematic review of RCT available)	Secondary review of evidence
Studies that sit on the Hierarchy	

Box 1. Synopsis of Search Results.

Search results
109 combined results
85 potentially relevant
40 excluded due to duplication
37 excluded after applying stringent inclusion and exclusion criteria
3 papers left
One article meeting inclusion and exclusion criteria (Kumar et al., 2002) was also excluded because of inclusion in systematic and meta-analysis paper also chosen
Only two papers were eventually analyzed.

Search terms

There are a variety of traditional and non-traditional sources of evidence that can be searched for relevant literature. For the question, literature search was made especially in the higher order of hierarchy which includes Systematic Reviews and RCTs at the top (Greenhalgh, 2010). A reliable search involves as many sources as possible in other to get as much available evidence as possible. According to Heneghan and Badenoch (2006), there are two main strategies for searching bibliographic databases; Thesaurus and Boolean operators. To search effectively, it is important to combine these strategies.

Both free text and subject headings were used to maximise search results, and truncation used to ensure variations of words were not missed e.g. phenobarb* to include phenobarbitone, phenobarbital, etc. Boolean operators OR and AND were used to combine search results in order to widen or narrow search results. Use of one may lead to missing literature (Beecroft et al., 2006). Sources searched include MEDLINE/PUBMED, COCHRANE Data base and Trip Database, and Google Scholar, as well as primary sources of evidence. This search strategy was done on all the databases, from May – July, 2016. Key words identified were preterm neonates, very low birth weight, phenobarbitone, phototherapy, prevention, prophylactic, neonatal hyperbilirubinemia and neonatal jaundice.

Literature selection

Inclusion and exclusion criteria (Table 3) were applied to identify the papers that best answered the question. A synopsis of the search strategy used can be found in Box 1 whilst the final articles selected are summarized in Table 4. Of these, three papers were identified following the application of stringent inclusion and exclusion criteria. One of the papers seriously considered for inclusion had to be excluded as it was one of the RCTs included in paper 1. From this analysis, the final papers are shown in the Table 4.

Step 3: Critical appraisal and synthesis of the evidence

The third step involves appraising the evidence. Although there is a wealth of research articles available, the quality of these is variable. Putting unreliable evidence into practice could lead to harm being caused or limited resources being wasted (Akobeng, 2005). Critical appraisal can be defined as the process of systematic scrutiny of research to determine its value and relevance

Table 4. Final papers selected for analysis.

Authors	Title	Rationale for choice
Chawla and Parmar (2010)	Phenobarbitone for Prevention and Treatment of Unconjugated Hyperbilirubinemia in Preterm Neonates: A Systematic Review and Meta-analysis	SR and Meta-analysis Evaluated the role of phenobarbitone in the management of unconjugated hyperbilirubinemia during first two weeks of life in preterm neonates
Carswell et al. (1972)	Sequential trial of effect of phenobarbitone on serum bilirubin of preterm infants.	Randomised Controlled Trial Sequential comparison of peak serum bilirubin levels of preterm infants given twice-daily intramuscular doses of Phenobarbitone in a dose of 8 mg/kg per day with randomly matched controls.

within a clinical context (Burls, 2009; Sackett et al., 2000b). It provides a structured but simple method for assessing research evidence in three main areas i.e. validity, importance, and applicability to the patient or patients of interest (Rosenberg and Donald, 1995). Several tools for appraising research articles are available. One of these is developed by the Critical Appraisal Skills Programme (CASP), Oxford, UK which includes tools for appraising RCTs, SRs, case–control studies, and cohort studies. The CASP tools are simple, easy to use, and freely available on the internet (Critical Appraisal Skills Programme, 2004, 2013). However, it is worthy of note that Katrak et al. (2004) in an SR of critical appraisal tools reported no gold standard but stressed on the need for an appropriate tool choice to suit the methodology of the study design (See Appendix 1 for detailed critique and critical appraisal tools used).

Appraisal is discussed under three headings of validity, reliability and applicability, although many areas cut across these categories and may be interwoven.

Validity

Generally, validity is an indication of how sound a research is (Melnyk and Fineout-Overholt, 2011). It applies to both the design and the methods of research. According to Seliger and Shohamy (1989), "Any research can be affected by different kinds of factors which, while extraneous to the concerns of the research, can invalidate the findings." To ensure validity of individual studies in an SR, certain criteria have to be met. The starting point for an SR is a comprehensive search for all relevant studies in major bibliographic databases (e.g., Medline, Cochrane, etc.) and also a search of reference lists from other relevant studies. Language should not be a limitation as relevant articles can easily be missed. This criterion is to a large extent met by Paper 1 (P1) but there was no mention of language barriers. An audit trail is also clearly shown. Auperin et al. (1997) recommends that an outline of rejected studies along with reasons for their rejections should be made readily available.

The inclusion or exclusion of studies in a systematic review should be clearly defined a priori with the eligibility criteria used specifying the patients, interventions or exposures and outcomes of interest (Ciliska et al., 2008). P1 had pre-determined criteria including blinding of randomization and intervention. In addition, the methodological quality of trials was evaluated independently by both authors with one author being blinded to trial authors and institutions. Authors recommend that disagreements, if any, should be resolved through a consensus-building process as was done in this SR (Schlosser, 2007). These help to reduce bias and improve validity (Clarke and Oxman, 2003; O'Mathuna et al., 2011).

In paper 2, which is an RCT, inclusion and exclusion criteria were clearly stated but the addition of babies who were 1.8 kg or less of mothers unsure of their dates on the assumption that they were premature could introduce some bias and heterogeneity to the study as some of these babies could be term.

Allocation concealment and blinding were clearly done in only one of the three papers included in P1. Although, not always possible, randomization of participants reduces the chance of confounding variables, as any factors should be equally distributed between intervention and control groups (Parahoo, 2006; O'Mathuna et al., 2011).

Another way to control the threat to validity is use of blind procedures where certain pieces of information are not disclosed during the experiment to the participant and/or researcher, in order to prevent bias. Studies have shown that certain methodological characteristics, such as poor concealment of treatment allocation or no blinding in studies exaggerate treatment effects (Pildal et al., 2007). In paper 2, there was no mention of blinding. Blinding prevents bias at several stages of a trial and reduces differential assessment of outcomes (Schulz et al., 2002).

In the results section P1, authors clearly state that despite the similarity of subjects enrolled in the individual studies, the results are heterogeneous and discuss possible reasons. These include use of different

strategies and loading doses of phenobarbitone. When heterogeneity is present, the question of whether and how to generalize the results arises (Haidich, 2010). Variability in the intervention effects being evaluated among the different studies in a meta-analysis is known as statistical heterogeneity and arises from clinical or methodological diversity, or both, among the studies. A major limitation of this meta-analysis as stated by the authors is clinical and statistical heterogeneity observed in participants of the included studies. One way to investigate the reasons for heterogeneity are subgroup analysis and meta-regression (Haidich, 2010). Again, authors state that due to non-availability of, or limited data, pre-specified sub-group analysis and analysis of adverse effects could not be carried out. A major decision required when conducting a meta-analysis is whether to use a fixed-effects or a random-effects model. A fixed-effects model assumes that models are homogenous and the sole source of variation in observed outcomes occurs within the study (Stangl and Berry, 2000). In contrast, random-effects models have an underlying assumption that a distribution of effects exists, resulting in heterogeneity among study results. The fixed effects model is not appropriate when statistical heterogeneity is present in the results of studies in the meta-analysis. Studies suggest that comparing the fixed-effects and random-effect models can yield insights to the data (Greenland, 1987). Despite significant statistical heterogeneity observed for peak serum bilirubin, authors used alternate analysis strategies (fixed versus random effect analysis) to show that the observed benefit did not disappear.

Authors in P1 also admit that they did not look for publication bias. An overreliance on only published data gives rise to source selection bias often referred to as publication bias. Rothstein et al. (2000) defined this as “what occurs whenever the research that is published in literature is systematically unrepresentative of the population of completed studies.” Published studies have been consistently shown to have more positive results while unpublished ones show smaller effects or even non-significant findings (Schlosser, 2007). Several methods are available to provide an assessment of publication bias; the most commonly used is the funnel plot (a scatterplot of treatment effect against a measure of study size), which provides a graphical evaluation of the potential for bias (Light and Pillemer, 1984; Egger et al., 1997).

Reliability

Reliability has been described as the accuracy and consistency of study information obtained (Wood et al., 2006; Polit and Beck, 2006). With respect to statistical analysis, statistical tests undertaken, why these tests were used and result should be clearly stated. All participants should also be accounted for (O’Mathuna et al., 2011). Both studies show table of outcomes and 95% confidence intervals were reported for all outcomes in P1. This is expected of a meta-analysis.

In P2, Control and treated infants were compared as they were included in the trial. Only pairs in which both infants survived to at least 8 days of age were considered in the sequential analysis of the difference between the peak bilirubin levels information. Their results were analysed by Bamard's sequential 't' test. Sequential designs are by their nature iterative, requiring the user to take a few samples and enter the results into the program before determining whether further sampling is necessary to meet the sampling objectives (Barnard, 1952). This is clearly shown and represented in a graph showing differences in peak bilirubin levels for matched pairs. Independent statistical analysis ('t' tests) of the peak levels confirmed that there was a significant difference between the peak levels in the two groups of patients. After studying 74 neonates, sequential analysis showed that the treated infants had a significantly lower ($P < 0.05$) peak bilirubin level.

Fisher (1950) proposed significance tests as a means of examining the discrepancy between the data and the null hypothesis. The *p*-value is the probability of results at least as extreme as the actually observed in the clinical experiment, given that the null hypothesis is true (Schervish, 1996). P values used in the analyses in both papers demonstrate that results are statistically significant rather than due to chance (Greenhalgh, 2010), although this does not always translate into clinically significant findings (Nakagawa and Cuthill, 2007).

The difference between statistical significance and clinical importance enables reviewers to translate study findings into clinical practice. P1 acknowledges that phenobarbitone use in preterm very low birthweight neonates reduces peak serum bilirubin and phototherapy requirement but due to paucity of data, further studies are warranted to evaluate adverse effects and neurodevelopmental outcome of this therapeutic strategy. P2 shows that, in Glasgow, administration of phenobarbitone intramuscularly to low birthweight preterm infants reduces the peak serum bilirubin levels. All authors agree that phenobarbitone is a cheap alternative for treatment and prevention of NNJ and would be of use in resource limited settings.

Step IV: Applying the evidence

The fourth step involves applying the evidence. After critical appraisal if evidence is considered valid and important, then decisions on whether that evidence can be applied to our individual patient or population have to be taken. The patient’s own personal values and circumstances, efficacy and risks, costs and availability in addition to consistency with the fundamental principle of

EBM are some of the factors to be considered (Straus and Sackett, 1998).

Applicability assesses the feasibility of providing an intervention in a local setting considering cost-effectiveness, organizational culture and capacity (Buffett et al., 2007). Some considerations are availability of resources and social acceptability. Although the participants were preterms, there different birth weight groups used so transferability may not be feasible. In as much as phenobarbitone would be a ready alternative for resource limited settings like ours, the evidence from the analysis points towards waiting for further studies to clear issues like routes of administration, timing and optimal dosing regimens. Furthermore, race may be an issue in transferring evidence from one group to another. None of the studies were done in Africa.

Transferability assesses the likelihood that the intervention developed and delivered in one setting can achieve the same outcomes when applied in a different local setting. Considerations for transferability include generalizability and community effectiveness (Buffett et al., 2007).

Step 5: Evaluating performance

As EBM gradually becomes part of routine practice, there arises a need for regular evaluations of what is actually being practiced so as to identify areas for improvement in any of the other four steps. There is the need to continually ask if: answerable questions are being formulated, good evidence is retrieved quickly; evidence is appraised effectively; and whether clinical expertise and patient values are integrated in order to provide acceptable management strategies in the best interest of the patient (Straus and Sackett, 1998).

ETHICS

Conduct of research studies within neonatal care raises complex ethical issues which has potential to limit research practice (Carter, 2015). Newborns are a vulnerable group of individuals hence acquisition of evidence for practice is very important. The Declaration of Helsinki (World Medical Association, 2002) documents ethical principles for medical research involving human subjects. The studies gained ethical approval and informed parental consent was sought for each individual study in P1 but in P2, there is no clear documentation of this.

According to Vergnes et al. (2010), the question of ethics in systematic reviews is rarely touched upon. This is not addressed in Paper 1 although it does not breach Cochrane Collaboration Guidelines (Higgins and Green, 2011). The authors in Paper 1 clearly state that due to non-availability of data or limited data, analysis of adverse effects could not be done. Paper 2 shows a list of adverse effects such as increased handling, slightly increased risk of infection and the increased bruising of the treated babies but does not attribute these directly to systemic effects of phenobarbitone. The effect of intramuscular injections in very small babies is also not highlighted. Phenobarbitone is documented to have side effects such as somnolence and an increased need for mechanical ventilation in preterm infants (Dennery, 2002; Whitelaw and Odd, 2007). To change clinical practice, the best interest of the patient including safety must be considered. In as much as cost may be important, resultant adverse effects may on the long run become more expensive to manage. Policies regulating clinical practice should therefore consider whether studies pose greater risks to patients than they would encounter in usual clinical care (Platt et al., 2014).

CONCLUSION

There is some evidence to show that phenobarbitone used in preterm very low birthweight neonates reduces peak serum bilirubin, duration of phototherapy, need of phototherapy. However, the studies have not shown clear cut dosing, routes of administration and adverse effects nor strong evidence that can be used for generalization. Concerning the EBP question therefore, it is apparent that current evidence does not provide clear answers. This demonstrates the fact that the evidence base for many interventions in neonatal care is limited.

Further studies are warranted to evaluate optimal dosing, adverse effects and neurodevelopmental outcome of this therapeutic strategy.

Limitation/Recommendations

The widespread use of phototherapy in prophylaxis and treatment of newborns with NNJ has perhaps shifted attention from newer studies in phenoarbitone use. However, phototherapy still remains unavailable in some resource poor settings and there is need to explore cheaper options.

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Appendix 1. Detailed critique of papers.

Papers	Publication details	Study design/Method	Population and sample size	Data collection and Analysis	Results and statistics
Paper 1 Chawla and Parmar (2010).					
Critical Appraisal tools: abridged Ciliska et al. (2008) and CASP systematic Review checklist (2013)	-Published in the Cochrane Database -Search dates: July 2012 - Two Reviewers. A minimum of two reviewers reduces risk of bias and improves validity of results Editorial Group: Cochrane Neonatal Group Publication bias: Authors admit that they did not look for publication bias. Published studies show more positive results while unpublished ones show smaller effects or even non-significant findings (Schlosser, 2007). -Trials were not excluded based on severity of illness or clinical outcome of enrolled subjects. This also reduces bias	-Cochrane Review systematic review -Full length methodological study - Type of studies included was determined a priori. - included were studies that enrolled preterm neonates and randomized the study subjects into control (placebo or no treatment) and treatment groups (phenobarbitone by oral and/or parenteral route with or without a loading dose; initiated before or after appearance of jaundice). - Review included three randomised controlled trials of efficacy of phenobarbitone (prophylactic and treatment) administration on clinical course of neonatal unconjugated hyperbilirubinemia during first two weeks of life in preterms - few studies may limit generalizability of findings - None of the studies were conducted in Africa - Search method complied with the Cochrane Neonatal Review Group Strategy - Sources searched: Cochrane Controlled Trials Register (online search) and MEDLINE electronic searches plus additional sources from reference lists of retrieved articles. This is important in order not to miss out relevant articles. Ethics: Although not stated, all studies included had ethical approval and informed parental consent. Publication bias not assessed. This gives an allowance for selection bias.	Preterm infants less than 37 weeks gestational age or low birth weight (LBW) with 3 RCTs included. This number is small and may limit generalizability of results 2 studies reported secondary analysis of trials conducted to evaluate efficacy of phenobarbitone in preventing intraventricular hemorrhage while the other conducted a RCT in preterms who were randomized into 3 groups -Group I – babies were given 10 mg/kg loading dose of phenobarbitone on day 1 followed by maintenance 5 mg/kg/day from day 2 to day 5; Group II – neonates were given phenobarbitone in the maintenance dose of 5 mg/kg/day from day 1 to day Birth weight was < 1750 g in all studies There was heterogeneity in the subjects in terms of loading doses and times of administration of phenobarbitone and race.	-Data Collection and Analysis conformed to the Cochrane Neonatal Review Group methods - Pre- determined quality checklist was available. This ensures that the reviewers appraise each study consistently (Ciliska et al., 2008). -Reviews and selection were done independently. This also reduces bias. -Statistical analysis was undertaken following the recommendations of the Cochrane Neonatal Review Group -95% Confidence intervals and odds ratios were used appropriately for statistical analysis - Heterogeneity tests were performed using fixed and random effect models -Forest Plots were given for comparisons to illustrate effect of meta-analysis -No sensitivity analysis was done -Main outcomes sought in the studies were duration of phototherapy (hours), need of exchange transfusion) and survival without major disability at 18-24 months of life.	- For the purpose of meta-analysis, Group I and Group II in the study by Kumar et al. (2002) were combined and compared with placebo or no treatment. -Forest Plots were utilized to demonstrate results of meta- analysis -There was significant statistical heterogeneity for peak serum bilirubin levels. - Appropriate use of OR, RR and CI -Peak serum bilirubin was significantly lower in phenobarbitone group (n=497; mean difference: –1.78 mg/dL, 95% confidence interval: –2.29 to –1.27) -Duration of phototherapy and need of exchange transfusion were reported in two trials (n=396). -Duration of phototherapy was also shorter in the phenobarbitone group (mean difference: –14.75 h, 95% confidence interval: –26.67 to –2.83)

Appendix 1. Contd.

Paper 2 Carswell et al. (1972) Critical Appraisal tools: CONSORT Consolidated Standards Of Reporting Trial (2006) and CASP RCT checklist (2013)	Published several years ago in Archives of Disease in Childhood a high profile journal. A good journal does not always equate to validity of published research More current research would probably give more insight into research findings.	-Randomised Controlled Trial -Full length methodological study A randomised, non-blinded, parallel controlled trial. A single study in a hospital in Glasgow Trial devised to evaluate the efficacy of phenobarbitone in reducing the serum bilirubin levels of preterm infants. The participants were randomly assigned on a 1-1 ratio. -Allocation of participants was randomized. However there was no mention of blinding. This may be a source of bias.	Phenobarbitone was given intramuscularly for the first 7 days of life in a dosage of 8 mg/kg per day in two divided doses to randomly selected infants. Control and treated infants were compared as they were included in the trial. Only pairs in which both infants survived to at least 8 days of age were considered in the sequential analysis of the difference between the peak bilirubin levels. Exclusion of patients who had started the trial may introduce bias.	Inclusion and exclusion criteria stated. Inclusion of babies of mothers with unsure gestational age and the fact that control babies were slightly heavier may introduce heterogeneity -Treated and control groups were randomly assigned, variables such as gestational age, birthweight, etc. were expected by authors to be similarly distributed between the two groups. --Analysis showed that this hypothesis is reasonably valid. This showed some measure of homogeneity.	Sequential analysis showed that the treated infants had a significantly lower (P <0 05) peak bilirubin level. Independent statistical analysis ('t' tests) of the peak levels confirmed that there was a significant difference between the peak levels in the two groups of patients. -Results were analyzed by Bamard's sequential 't' test -Independent statistical analysis ('t' tests) of the peak bilirubin levels confirmed that there was a significant difference between the peak levels in the two groups of patients. -These statistical tests help improve reliability -Phenobarbitone intramuscularly to low birthweight preterm infants reduced peak bilirubin levels they subsequently attain. -Authors conclusion: small reduction in peak serum bilirubin level was produced by phenobarbitone treatment