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Improving epilepsy control among children with cerebral palsy in rural Bangladesh: A prospective cohort-based study

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ABSTRACT

Objective: To define the prevalence and seizure subtypes among children with cerebral palsy (CP) in rural Bangladesh and explore barriers to optimum epilepsy control.

Design: Prospective cohort study

Setting: The study was conducted in Shahjadpur, a rural subdistrict of Bangladesh.

Participants: Children (<18 years) with CP and epilepsy identified using the Bangladesh CP Register in the study site.

Methods: Assessments were conducted in three focused epilepsy clinics overseen by a pediatric neurologist between December 2016 - January 2018, with intervening phone and video-conference follow-ups. Details of event type, frequency and medication compliance were collected. Antiepileptic drugs (AED) were prescribed based on seizure type, family income, comorbidity and medication availability.

Results: 23.4% (170/726) of the BCPR cohort had a clinical diagnosis of epilepsy of whom 166 were assessed. Following the focused epilepsy clinics, 62.0% (103/166) children were clinically determined to have ongoing epileptic seizures. 62.1% (64/103) had generalized tonic clonic seizures, 27.2% (28/103) had focal seizures with altered awareness and 10.7% (11/103) had other seizure types. None of the children with prolonged seizures (31/103) had an emergency seizure management plan. Non-epileptic events were being pharmacologically treated as seizures in 18.1% (30/166) children. Financial constraints were the main reason for non-compliance on follow up.

Conclusions: Gaps in optimum epilepsy management in rural Bangladesh are amenable to improvement anchored with local health care workers. Training and clinical care focused on recognition of common seizure types, seizure mimics and rationalizing use of available AEDs can be facilitated by better referral pathways and telehealth support.

Key Words: Epilepsy, cerebral palsy, Bangladesh, CP

Strengths and limitations of this study

- Children with CP and epilepsy identified through an ongoing population-based surveillance.
- Specialist clinical assessments were conducted overseen by a pediatric neurologist.
- Phone and video-conference follow-ups were conducted.
- The study provided opportunity for continuing local capacity building.
- The clinical diagnoses relied on clinical impression and were not corroborated by investigations.

INTRODUCTION

Cerebral palsy (CP) is a term that defines a heterogenous group of early-onset, non-progressive, neurodevelopmental disorders secondary to injury to the developing brain [1]. Studies show that epilepsy is associated with greater impairment of cognitive function, poorer motor outcomes, more profound behavioral and psychological problems, and poorer quality of life among children with CP, all of which collectively contribute to a greater burden of disability and care [2]. Children with CP and epilepsy tend to have early onset of seizures which can often be difficult to control [3].

Recent estimates from a population-based study in Bangladesh showed a high burden of CP with an estimated prevalence of 3.4 per 1000 children [4]. Bangladesh is one of the most densely populated and under resourced countries in the world [5]. The World Health Organization (WHO) classified Bangladesh as one of the countries with severe shortages of health workers. There is inequity in the skill mix and distribution of health workers between urban and rural Bangladesh [6]. One of the four axes of the value-based framework for global health delivery highlights the need for alignment of care delivery to the local context [7].

Resources for the diagnosis and management of neurologic disorders such as epilepsy are often limited in low and middle-income countries (LMICs) such as Bangladesh [8]. Several aspects of epilepsy management that may be considered routine in tertiary or specialist settings are not applicable to community-based settings [9]. There is a substantial epilepsy treatment gap in low resource settings owing to a wide spectrum of factors including shortage of doctors particularly in the rural areas,[6] lack of available investigation and inpatient treatment facilities as well as decreased service utilization due to the stigma around a disability diagnosis.[10]

We aimed to define the prevalence, clinical phenotypes and barriers to optimum epilepsy control among children with CP in a community-based setting in Bangladesh.

METHODS AND ANALYSIS

Cohort compilation

We used the Bangladesh CP Register (BCPR); a prospective population-based surveillance of children with CP in Shahjadpur a northern subdistrict of Rajshahi division in Bangladesh for identification of children with CP and epilepsy. Detailed account of the BCPR study protocol and findings have been described in previous publications [4]. During previous BCPR camps, a diagnosis of epilepsy had been

based on history of one or more unprovoked seizures in the previous 3 months recorded by medical practitioners and review of any available medical records [4].

Clinical assessment of epilepsy

Children with CP and epilepsy identified via the BCPR were clinically reviewed in three focused epilepsy clinics held for three days each time at three different locations within the BCPR study site. Specialist clinical assessments at the clinics were overseen by a pediatric neurologist from Australia who travelled to Bangladesh for the focused epilepsy clinics during the study period. Diagnoses of epilepsy and seizure like events were reviewed during assessment in the clinics. Details of seizure/event type, frequency, medication use and compliance were collected according to a predesigned standard proforma (Appendix A). Workflow during the clinic is outlined in Figure 1.

Local capacity building

Two physicians were trained by the pediatric neurologist in classifying seizure types according to the 2017 International League Against Epilepsy (ILAE) guidelines [11], demonstration of clinical signs during the epilepsy clinics, and discussions around seizure mimics and drug choice (Appendix B). One community worker based in the study area was also trained to conduct phone follow ups of the children on antiepileptic drugs (AED).

Selection of antiepileptic drugs

Before the clinics, the community worker collected information on availability and cost of AED in local pharmacies within the study area between December 2016 and January 2018. A dose equivalence table was drawn up for easy prescription in the clinic along with notes on important side effects and interactions. During the clinics, AED were prescribed based on seizure type, medication availability and family income. The approach undertaken for shared decision making in AED prescription is outlined in Figure 2.

Telehealth supported follow up and clinics

Phone follow up

Targeted phone follow ups of the children on AED were conducted by the trained community health worker every three months during the study period, following the initial specialist assessment at the focused epilepsy clinics. The phone follow ups were semi-structured. The design, conduct and the outcome measures for the follow ups were additionally informed by the study team's experience

and input from the primary caregivers (Appendix C). Seizure control was documented during phone follow ups. In our study seizure control was defined as no reported seizure since the last follow up.

Telemedicine clinics

Telemedicine clinics were initiated in May 2018 and held on a monthly basis using Skype as part of ongoing capacity building to improve epilepsy control among the study cohort. The local trained physician saw the patients face to face in the study site and used a handheld, internet connected tablet to videoconference with the pediatric neurologist in Australia. Patient interview for new and follow up patients followed a set format (Appendix C). New patient data from the telemedicine clinics are not included in this paper.

Patient and Public Involvement

This work was informed by the priorities, experience and preferences of the primary caregivers of the children with CP and epilepsy who participated in the study. The design and implementation of the follow ups, including outcome measures important to the study participants, relied on feedback from families of children with CP and epilepsy. Baseline information was communicated to the primary caregivers by the study team. This informed shared decision making related to the treatment and follow up for their children. Furthermore, the follow ups and telemedicine clinics were conducted by a local community worker and local physician, which enhanced community involvement during and beyond the study.

Statistical analysis

Descriptive analyses were carried out. All statistical analysis was conducted using SPSS version 24 (IBM Armonk, NY, USA).

Ethics

This study was conducted as part of the Bangladesh Cerebral Palsy Register Study which has been approved by the Bangladesh Medical Research Council (BMRC) Human Research Ethics Committee (Ref no. BMRC/NREC/2013–2016/1267) in Bangladesh, and by the Cerebral Palsy Alliance NHRMC Human Research Ethics Committee (Ref no.2015–03-02) in Australia. Written informed consent was taken from the primary caregiver/parents/guardian of the children with CP.

RESULTS

Prevalence and basic demographic characteristics

726 children with CP were registered into the BCPR between January 2015 and December 2016, 23.4% (170/726) of whom had a clinical diagnosis of epilepsy. 166 of these children attended the three focused epilepsy clinics between December 2016 and January 2018 and form the study cohort. 55 (33.1%) were female. The mean age of the children was 6 years 10 months (SD: 4 years 5 months) years.

After the focused epilepsy clinics, 62.0% (103/166) children were clinically determined to have ongoing epileptic seizures based on review of their history, existing medical records and specialist clinical evaluation (Figure 3). Therefore, the revised prevalence of epilepsy among the BCPR cohort during the study period was 14.3%.

Seizure subtypes

62.1% (64/103) had generalized tonic clonic seizures (GTCS), 27.2% (28/103) had focal seizures with altered awareness and 5.8% (6/103) had other seizure types (focal seizures with preserved awareness, epileptic spasms, myoclonic seizures and tonic seizures). Data on seizure type was unclear on history for 4.9% (5/103). At the time of first assessment, seizures were already controlled with AED in 5.8% (6/103) children. 30.1% (31/103) of children had a history of prolonged seizures (>30 minutes) and none of these patients had an emergency seizure plan. Their caregivers tended to wait at home till the seizures settled and did not seek emergency medical assistance due to geographical or financial constraints.

Barriers to optimum epilepsy control

Non-epileptic events among children with CP

Non-epileptic events were determined to have been mislabeled as seizures in 18.1% (30/166) children which included extremity clonus (n=7), dystonic postures (n=6), spasticity related spasms (n=4), breath holding spells (n=3), mannerisms (n=3), sleep related myoclonic jerks (n=2), startles (n=2), stereotypies (n=2) and rhythmic movement disorders in sleep (n=1). 23.3% (7/30) of these children were being treated with AED.

Epilepsy control

Of the 103 children with seizures, 62 were already on AEDs at the time of our clinical review. Polypharmacy with more than two concurrent AED was commonly observed and AED changes were made for the majority of them. Advised AED changes consisted of dose alteration in 54.8% (34/62) and medication change in 17.7% (11/62). 27.4% (17/62) were advised to continue treatment already

initiated by various providers. We initiated treatment for 39/41 children not previously on AED who were clinically determined to still be having epileptic seizures; 2/41 only had short seizures once or twice a year and were not put on AED.

Telehealth supported follow up and clinics

Phone follow up

We were able to review 75.8% (78/90) children with epileptic seizures on follow up during the study period. On follow-up (median 6.0 months), 69.2% (54/78) were taking prescribed medications as advised. Among them 75.9% (41/54) showed improvement in seizure control (>50% seizure reduction), including 14 children who became seizure free. 30.8% (24/78) families had discontinued the advised treatment due to affordability (8/24, 33.3%), excessive drowsiness (7/24, 29.2%), development of a rash (4/24, 16.7%), no perceived benefit with medication and lack of understanding behind the use of regular medications (2/24, 8.3%). Three (3/24, 12.5%) children who discontinued medications were reported to be seizure free. None of the families reported any adverse effects that led to reported cardiorespiratory compromise, hospital presentation or death.

Two children from our cohort died during the follow up period, one due to meningitis and the other due to a lower respiratory tract infection. Their cause of death was determined by verbal autopsy conducted as part of a separate study [12].

Telemedicine

Five telemedicine clinics undertaken in 2018 contributed to patient follow up and clinical capacity building. During these clinics 47 patients were seen by a local medical practitioner with internet-based videoconference support from the pediatric neurologist in Australia. Each clinic was of three hours duration during which patient interview was undertaken in the same manner as in the focused epilepsy clinics. Thirty minutes were marked during each clinic for discussion regarding clinical signs, history taking and AED choice. Clinical details for new patients reviewed during telemedicine clinics were not included in this cohort.

DISCUSSION

Epilepsy is a significant comorbidity in some individuals with CP. Previous studies have described a prevalence of 15-90% epilepsy in CP cohorts [13,14]. Overall, epilepsy contributes more significantly to the global burden of disease in resource poor settings as evident from the 2015 Global burden of disease studies. We found an initial prevalence of epilepsy of 23.4% in our cohort. Interestingly,

following reassessment in our clinics, as described, this was revised to 14.3%. Previous studies have also noted such discrepancy between determination of a clinical diagnosis of epilepsy between specialist and community-based settings with a misdiagnosis of epilepsy being made in as many as 25% of cases [15]. This has flow on impacts as we noted in terms of incorrect, often excessive use of medications. Epilepsy poses substantial economic burden on families [16]. When families devote a significant proportion of their finances, attention, time or all of these towards one aspect of their child's management, other aspects of care such as physical therapy, nutrition, pain and musculoskeletal management are likely to be neglected, more so in resource poor settings [17].

As demonstrated by recent innovative projects in neighbouring Nepal, education of community level workers and general medical practitioners can lead to more consistent clinical diagnosis of epilepsy [18]. In our experience, rationalisation or cessation of medications after focused clinical assessments led to changes in family finances diverted towards medication use. We envision that the development of simplified print and multimedia based educational resources for health care workers and medical practitioners hold the potential to improve epilepsy diagnosis in resource scarce settings such as our study site.

Polypharmacy with more than two concurrent AEDs is unlikely to contribute significantly to seizure control [19]. In countries like Bangladesh with a mismatch of clinical care practices between urban and rural areas, the use of less conventional or alternative medications is very likely to be encountered.

AED availability is very limited in rural Bangladesh [20]. Medications need to be purchased by families and hence, cost per month for AEDs is a significant consideration when choosing medications for chronic use to ensure good compliance. The cheapest and most readily available AEDs are phenobarbitone, clobazam and sodium valproate. If a diagnosis of CP is very likely based on clinical evaluation and history, earlier use of sodium valproate or clobazam in this setting is a viable option for transitioning from phenobarbitone which is most commonly prescribed in infancy. As outlined in our methods and Figure 2, AED choice can be rationalized based not only on the seizure type but also existing comorbidity as some AEDs can help improve comorbid psychiatric symptoms or sleep disturbance.

Our experience highlighted a gap in the recognition and management of prolonged seizures in settings like ours compared to conventional management in urban and resource rich settings.

Benzodiazepines are the mainstay of out of hospital, particularly health worker or parent led management of prolonged seizures. However, midazolam or lorazepam are not available at all in rural Bangladesh. Diazepam is only available in glass ampoules through restricted prescriptions in some pharmacy outlets. In our and wider reported experience caregivers are often reluctant to use glass ampoules or follow several steps in medication administration to a child at home [21]. Other readily available benzodiazepines are cheap (clobazam: 0.042 USD per 10 mg tablet and clonazepam: 0.048 USD per 1 mg tablet; prices mid 2018) but there is very little evidence regarding their use in the setting of prolonged seizures [22,23]. Status epilepticus can significantly add to the burden of cumulative brain injury and therefore warrants a solution [24]. This may be in the form of a per-rectal, oral or, alternative routes for delivery of well-established medications for status epilepticus such as phenobarbitone, valproate or midazolam. Alternatively, the use of medications such as clonazepam drops via open label trials requires urgent exploration for such settings.

Our model has demonstrated that immediate positive impact on epilepsy management and reduction in burden of care on families can be achieved through structured assessments by medical and allied personnel who are trained to assess children for epilepsy and use available medications according to a structured framework. This can be achieved for a population base such as in our study area with limited personnel and without additional investigation or formalized health care facilities, though these would be desirable to further improve patient outcomes. We piloted the use of videoconference-based telemedicine clinics after initial face to face clinics. With some prior training in the use of a structured clinical approach, this method can be very time-efficient in reviewing patients led by a non-specialist medical practitioner/community worker and supported by a specialist. In our experience, this not only provided continuity of clinical support with existing personnel but also provided an opportunity for continuing professional development and capacity building. We hope that in the post-COVID era, implementation and incorporation of telemedicine should be easier and more acceptable to providers, policymakers and the community.

We summarize the key barriers identified and proposed or already implemented solutions in Table 1. Development of multimedia or mobile application-based resources that may simply illustrate clinical assessment of children with epilepsy, examples of non-epileptic events and emergency seizure management will provide convenient means for translation of our findings to the wider population in Bangladesh and, with language translation, to similar resource poor settings across the world.

We have engaged with tertiary paediatric neurology centres in Bangladesh to support some families with requisite investigations or more frequent specialist review. However, this will always be limited to financial and logistic constraints of rural families.

Study limitations

We did not systematically collect baseline investigation information for this cohort as a small proportion had any previous tests such as electroencephalography (EEG) or neuroimaging. The clinical diagnosis of seizures and non-epileptic events were not corroborated by investigations as they were unavailable in this resource limited setting. We had to rely on the clinical impression of a limited number of observers. Although we utilized standard criteria to assess seizure reduction, the collection of the follow up data was based on reporting by the primary caregiver which may have been a source of potential bias.

CONCLUSION

Epilepsy is prevalent among children with CP in rural Bangladesh and the various gaps in optimum epilepsy management are lack regular follow-up, recognition of common seizure types and non-epileptic seizure mimics, familiarization with commonly available, affordable AED and availability of guidelines for prolonged seizure management. These gaps are amenable to proposed low cost, educational interventions. Health care workers can improve epilepsy management with regular follow-up, education on common seizure types, seizure mimics, use of commonly available, affordable AED and guidelines for prolonged seizure management.

AUTHORS' CONTRIBUTION

All listed authors meet the appropriate authorship criteria, and nobody who qualifies for authorship has been omitted. GK and SM conceptualized and established this research study. They also contributed to study design, development of the study materials and overall conduct of the study supported by TK. SM, TK and MCD were responsible for assessment of study participants and data collection. SM, GK and MM provided specialist advice in this study. TK, SM and GK completed data analysis, interpretation of the data and drafted the initial and revised manuscript with input from all the co-authors. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST DISCLOSURES

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

No additional data are available.

REFERENCES

[1] Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, et al. Proposed definition and classification of cerebral palsy, April 2005. Developmental Medicine & Child Neurology. 2005;47(8):571-6.

[2] Mesraoua B, Ali M, Deleu D, Al Hail H, Melikyan G, Haddad N, Alalamy O, Athanasios C, Asadi-Pooya AA. Epilepsy and Cerebral Palsy. Neurodevelopment and Neurodevelopmental Disorder 2019 May 8. IntechOpen.

[3] Singhi P, Jagirdar S, Khandelwal N, Malhi P. Epilepsy in children with cerebral palsy. Journal of Child Neurology. 2003;18(3):174-9.

[4] Khandaker G, Muhit M, Karim T, Smithers-Sheedy H, Novak I, Jones C, et al. Epidemiology of cerebral palsy in Bangladesh: a population-based surveillance study. Developmental Medicine & Child Neurology. 2019 May;61(5):601-9.

[5] National Institute of Population Research and Training (NIPORT), ICF International. Bangladesh Demographic and Health Survey. Dhaka, Bangladesh; 2014.

[6] Ahmed SM, Hossain MA, RajaChowdhury AM, Bhuiya AU. The health workforce crisis in Bangladesh: shortage, inappropriate skill-mix and inequitable distribution. Human Resources for Health. 2011;9(1):3.

[7] Kim JY, Farmer P, Porter ME. Redefining global health-care delivery. The Lancet. 2013;382(9897):1060-9.

[8] Bearden DR. Pediatric Neurology in Resource-Limited Settings: a Systematic Review. Current Pediatrics Reports. 2018;6(1):34-9.

[9] Kim JY FP, Porter ME. A global health delivery framework approach to epilepsy care in resource-limited settings. Journal of the Neurological Sciences. 2015;358(1-2):263-5.

[10] Patel P, Baier J, Baranov E, Khurana E, Gambrah-Sampaney C, Johnson A, et al. Health beliefs regarding pediatric cerebral palsy among caregivers in Botswana: A qualitative study. Child: Care, Health and Development. 2017;43(6):861-8.

[11] Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522–530

[12] Jahan I, Karim T, Das MC, Muhit M, Mcintyre S, Smithers-Sheedy H, Badawi N, Khandaker G. Mortality in children with cerebral palsy in rural Bangladesh: a population-based surveillance study. Developmental Medicine & Child Neurology. 2019 Nov;61(11):1336-43.

[13] Aicardi J. Epilepsy in Brain-Injured Children. Developmental Medicine & Child Neurology. 2010;32(3):191-202.

[14] Aksu F. Nature and Prognosis of Seizures In Patients With Cerebral Palsy. Developmental Medicine & Child Neurology. 2008;32(8):661-8.

[15] National Clinical Guideline Centre. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. http://www.nice.org.uk/nicemedia/live/13635/57784/57784.pdf (accessed March 2021)

[16] Allers K, Essue BM, Hackett ML, Muhunthan J, Anderson CS, Pickles K, Scheibe F, Jan S. The economic impact of epilepsy: a systematic review. BMC neurology. 2015 Dec 1;15(1):245.

[17] Nuri RP, Aldersey HM, Ghahari S. Needs of families of children with cerebral palsy in Bangladesh: A qualitative study. Child: Care, Health and Development. 2018;45(1):36-44.

[18] Rajbhandari H, Joshi S, Malakar S, Paudel P, Jain P, Uppadaya K, et al. Epilepsy field workers, a smartphone application and telephone telemedicine: Safe and effective epilepsy care in rural Nepal. Seizure. 2019;64:54-8.

[19] Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. The Lancet Neurology. 2003;2(6):347-56.

[20] Hussain ME. Burden of Epilepsy in Bangladesh: Current Approach. Journal of Current and Advance Medical Research. 2018;4(1):1-2.

[21] Chiang LM, Wang HS, Shen HH, Deng ST, Tseng CH, Chen YI, Chou ML, Hung PC, Lin KL. Rectal diazepam solution is as good as rectal administration of intravenous diazepam in the first-aid cessation of seizures in children with intractable epilepsy. Pediatrics & Neonatology. 2011 Feb 1;52(1):30-3.

[22] Shangguan Y, Liao H, Wang X. Clonazepam in the treatment of status epilepticus. Expert Review of Neurotherapeutics. 2015;15(7):733-40.

[23] Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus. New England Journal of Medicine. 1998;339(12):792-8.

[24] Kwong KL, Wong SN, So KT. Epilepsy in children with cerebral palsy. Pediatric Neurology. 1998;19(1):31-6.

Table 1: Barriers to epilepsy control and suggested interventions

Barriers	Suggested interventions
AED availability	Selection of locally available medications for management through a structured guideline
Lack of skilled personnel for epilepsy management and follow up locally	Capacity building and engagement of local medical practitioners and community health workers Development of multimedia or mobile application-based resources Telemedicine
Affordability	Rationalization of drugs
Poor treatment compliance	Rationalization of drugs Training and engagement of health workers for follow up Caregiver education
Prolonged seizure management	Development of guideline and resources for management of prolonged seizure for training of local health workers
Misidentification of non-epileptic episodes as seizures	Development of video resources describing seizures and non-epileptic events
Lack of parental understanding regarding epilepsy treatment	Parent education on epilepsy treatment

Figure 1: Clinical assessment of epilepsy in children with CP in Shahjadpur

Bangladesh Cerebral Palsy Register
Population-based surveillance of children with cerebral palsy in Shahjadpur

↓

Dates for epilepsy clinics decided

↓

Children with CP having epilepsy identified from the BCPR cohort

↓

Families of the children informed of the clinic date and location by phone by community worker

↓

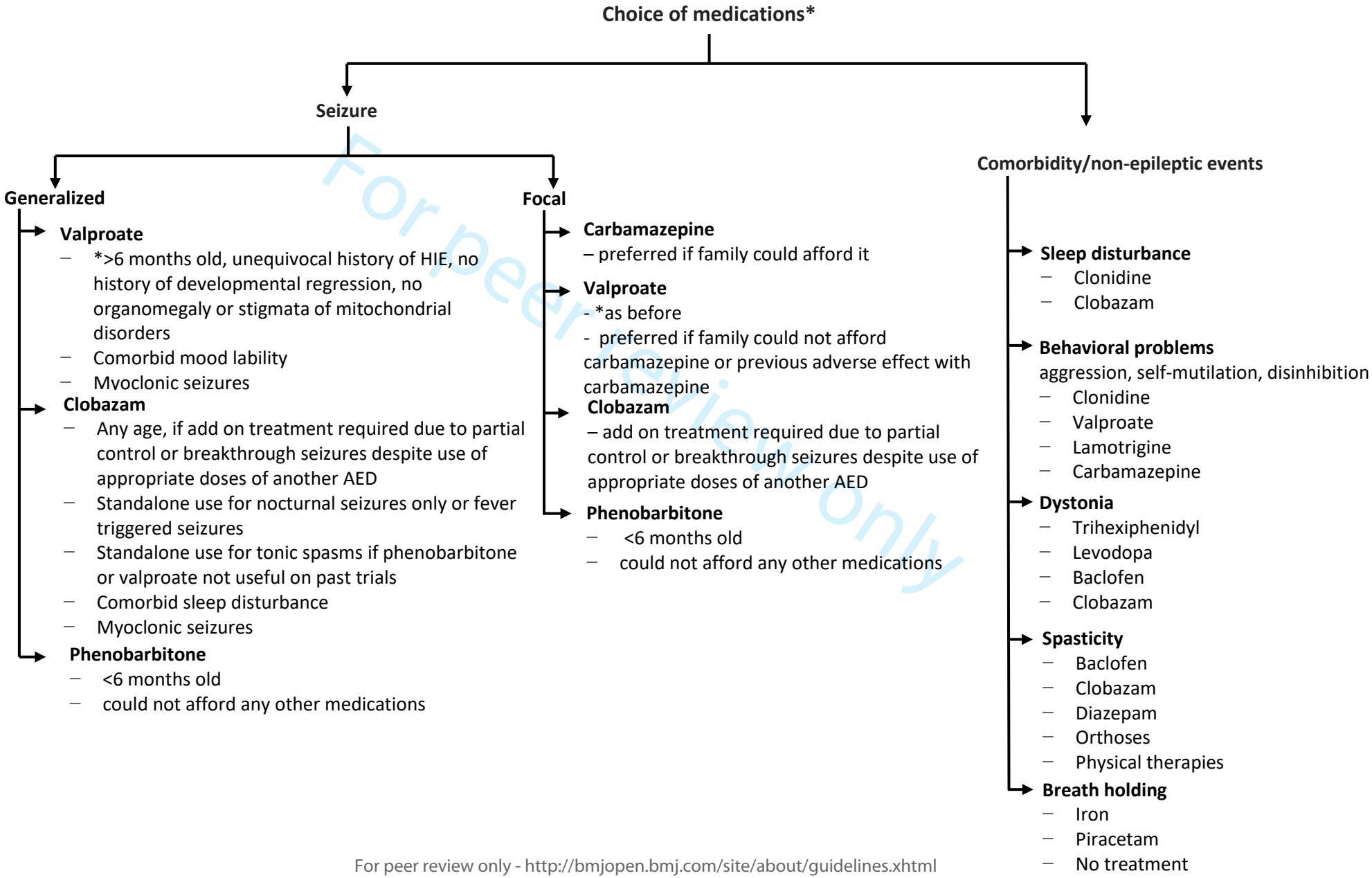
Epilepsy clinics held at 3 sites in Shahjadpur

- Structured proforma populated and anthropometric measurement taken by community workers
  10 minutes per patient

- Clinical review by local medical practitioners overseen by pediatric neurologist from Australia and review of relevant medical records
  15 minutes per patient with interpretation

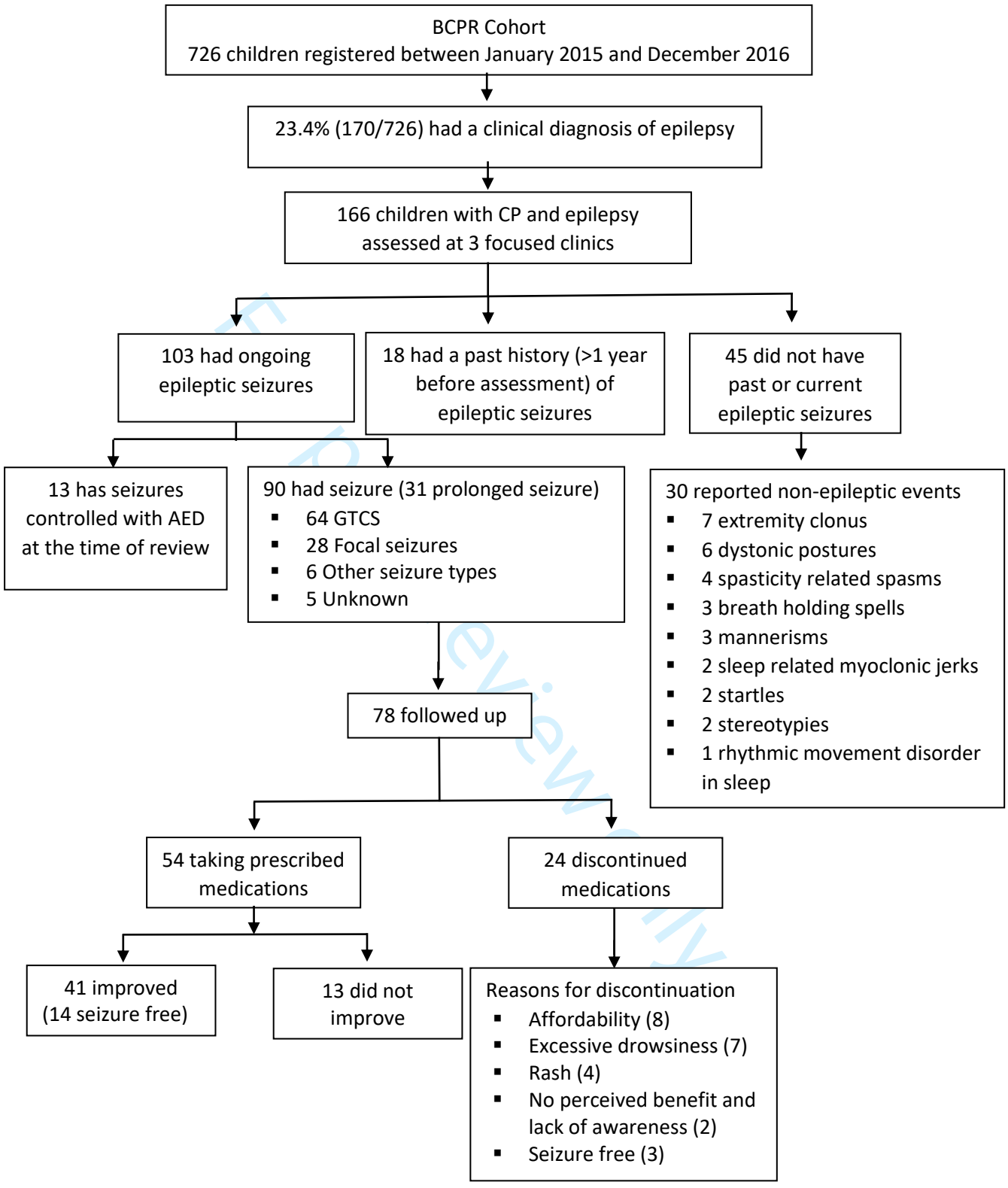
- Medications explained by community worker
  5 – 10 minutes per patient

Figure 2: Suggested considerations in choice of medications for seizures and comorbidity in children with cerebral palsy



*All medications are listed in order of preference for management

Figure 3: Study diagram



Appendix A: Clinic proforma used during focused epilepsy clinics

ASSESSMENT DETAILS		
ID NUMBER:	**SERIAL NUMBER:**	
ASSESSMENT LOCATION:	**ASSESSMENT DATE:** DD / MM / YYYY	
CHILD'S DETAILS		
NAME:	**GENDER:** ☐ M ☐ F	**DOB:** DD / MM / YYYY
HEAD CIRCUMFERENCE (cm):	**WEIGHT (kg):**	**LENGTH/HEIGHT (cm):**
FATHER'S DETAILS		
NAME:	**DOB:** DD / MM / YYYY	**OCCUPATION:**
EDUCATION ☐ Illiterate ☐ Primary ☐ Secondary ☐ Higher secondary ☐ Graduation ☐ Post-graduation ☐ Diploma/other trade qualification		
MOTHER'S DETAILS		
NAME:	**DOB:** DD / MM / YYYY	**OCCUPATION:**
EDUCATION ☐ Illiterate ☐ Primary ☐ Secondary ☐ Higher secondary ☐ Graduation ☐ Post-graduation ☐ Diploma/other trade qualification		
CONTACT DETAILS		
DISTRICT:	**SUB-DISTRICT:**	
UNION:	**VILLAGE:**	
POST CODE:	**PHONE NO.:**	
TYPE OF CASE (select one): ☐ New ☐ Follow-Up		
SEIZURE CONTROL: ☐ Same ☐ Better ☐ Worse	**SEIZURE FREE ON TREATMENT:** ☐ Yes ☐ No	
COMPLIANT: ☐ Yes ☐ No	**IF NO, REASON FOR NON-COMPLIANCE:**	
REASON FOR POOR SEIZURE CONTROL:		
MAIN CONCERN:		
HISTORY AND EXAMINATION FINDINGS		
BIRTH HISTORY:		
SEIZURE		
FIRST:	**LAST:**	
HISTORY OF PROLONGED SEIZURE (> 5 mins): ☐ Yes ☐ No		
CURRENT FREQUENCY: _____ times per ☐ day ☐ week ☐ month ☐ year		
TYPE:		
DURATION OF SEIZURE:	**DESCRIPTION:**	
PREVIOUS MEDICATION & INVESTIGATION		

Appendix B: Guideline for drug choice at clinics

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MEDICATIONS FOR SEIZURE MANAGEMENT

PHENOBARBITONE

Dose range

- 1–6 mg/kg daily in 1 or 2 doses; start at the lower end of range and increase slowly if required.

Seizure types useful for

- For generalized seizures and focal seizures.
- Recurrent febrile seizures
- Neonatal seizures
- Less likely to help blank staring "absence" seizures

Adverse effects

- Allergic rash, rarely can cause extreme hypersensitivity reaction
- Hyperactivity
- Sedation

Comment

- Generally, a good medication to continue unless it is not working or the side effects are not tolerable
- Do not stop suddenly and wean over several weeks if patient has been on it for more than 3 months

SODIUM VALPROATE

Dose Range

- 20–40 mg/kg daily in 2 divided doses; start at 5-10 mg/kg/day and increase slowly to 20 mg/kg/day. Then increase further if required.

Seizure types useful for

- For all seizure types

Adverse effects

- Hyperactivity
- Liver dysfunction
- Caution with use in children with developmental delay less than two years or older who are likely to not have true CP. Valproate can cause fatal liver dysfunction in those with a history of mitochondrial disorders. This is suggested by a history of developmental regression eg. A child who was able to sit before can no longer do so.

Comment

- Valproate is likely to work for most seizure types and cause less sedation than phenobarbitone
- Valproate works synergistically with clobazam and lamotrigine.
- Lamotrigine should be introduced very cautiously if someone is already on valproate

CLOBAZAM

Dose Range

- Start at 1-2 mg/dose once a day. Can increase as required to
  - 2.5-5 mg BD in children <2 years
  - 5-10 mg BD in children 2-10 years
  - 10 mg TDS in older children
  - maintenance 0.3-1 mg/kg/day in 2 divided doses
- The above doses are a guide and higher doses can be used in younger children if tolerated and if thought to be beneficial for seizure control

Seizure types useful for

- For all seizure types
- Also helpful for dystonia management in some cases

Adverse effects

- Sedation
- Hyperactivity
- Hallucinations
- Drooling

Comment

- Useful monotherapy or add on medication
- Start at small doses like 1 mg BD and grade up
- Can crush tablet and suspend in water to make up small doses if liquid not available
- If difficult for family to understand use quarter tablet / half tablet instead of dissolving
- Wean very slowly similar to phenobarbitone if patient has been taking Clobazam for more than 3 months
- Children can sometimes get used to benzodiazepines. If seizures break through after a few months of good control, then consider swapping over to another benzodiazepine like Nitrazepam.

NITRAZEPAM

Dose Range

- Start at 1 month – 2 years: 0.25mg/kg twice daily, up to 0.5mg/kg twice daily
- The above doses are a guide and higher doses can be used in younger children if tolerated and if thought to be beneficial for seizure control

Seizure types useful for

- For all seizure types
- Infantile spasms

Adverse effects

- Sedation
- Drooling

Comment

- Useful monotherapy or add on medication
- Start at small doses like and grade up
- Wean very slowly similar to phenobarbitone if patient has been taking Nitrazepam for more than 3 months
- Children can sometimes get used to benzodiazepines. If seizures break through after a few months of good control, then consider swapping over to another benzodiazepine like Clobazam.

CARBAMAZEPINE

Dose Range

- 10–20 mg/kg daily in 2-3 divided doses; start at 2.5-5 mg/kg/day and increase slowly to 10 mg/kg/day. Then increase further if required. Some patients can respond to low doses 5-10 mg/kg/day and can be maintained on these doses without further increasing unless required

Seizure types useful for

- Focal seizures only
- Avoid for generalized, absence and febrile seizures

Adverse effects

- Hyperactivity
- Liver dysfunction

Comment

- Useful drug for focal seizures, e.g. With hemiplegic CP

MEDICATIONS FOR DYSTONIA/SPASTICITY MANAGEMENT

TRIHEXIPHENIDYL/BENZHEXOL

Dose Range

- Start at 0.25 mg once a day and gradually increase to 0.25 mg tds.
- If tolerated, can trial up to 2 mg – 4 mg tds
- In older children, higher doses can be used if benefit is noted

Symptoms useful for

- Mainly for dystonia management. Can also help drooling due to its anticholinergic properties

Adverse effects

- Dry mouth, eyes
- Constipation
- Confusion
- Double vision

- Irritability

Comment

- About 25-50% efficacy for dystonia management if side effects are not a problem. Some children can benefit remarkably more
- Avoid other anticholinergic medications or if any of the adverse effects are already a clinical problem
- If not benefit after maximum doses for 3-4 weeks, then discontinue as delayed benefit is unlikely to occur.

BACLOFEN

Dose Range

- **2-7 y** -10-40 mg/day divided in three to four doses/day. Start: 2.5-5 mg twice a day, may increase by 5-15 mg/day every 3-4 days, Max: 40 mg/day.
- **8-11 y -** Dose: 10-60 mg/day divided in three to four doses/day. Start: 2.5-5 mg twice a day, may increase by 5-15 mg/day every 3-4 days; Max: 60 mg/day.
- **12 y and older -** Dose: 20-80 mg/day PO divided in three to four doses/day. Start: 5 mg twice a day, may increase by 15 mg/day every 2-3 days; Max: 80 mg/day.

Start Symptoms useful for

- Mainly for spasticity management.

Adverse effects

- Hypotonia
- Drooling
- Sedation

Comment

- Baclofen is a good medication for high tone which is due to spasticity
- It is not so good when there is dominant or mixed dystonia
- Relatively high doses may be needed in some patients making side effects intolerable, these have to be balanced with dose
- Other sedative medications will add to sedative effects and drooling – benzodiazepines, phenobarbitone
- Taper and stop slowly over few weeks if patient has been taking Baclofen for more than 3 months.

LEVODOPA/CARBIDOPA

Dose Range

- 1-4 mg/kg/day (levodopa component). Start slowly at 1 mg/kg/day divided in 2 doses and increase to target 4 mg/kg/day in 3 divided doses.
- Can increase further if focal but clear benefit.

Symptoms useful for

- Dystonia management
- Can be very helpful when dystonia shows a trend of worsening as the day progresses or is exercise induced

Adverse effects

- Nausea

Comment

- About 25% efficacy for dystonia management in cerebral palsy but a safe drug to try
- Very useful in genetic dopamine responsive dystonia which can mimic CP but is rare.
- Some preparations are available as Levodopa/Benserazide. Dose guide is same for levodopa component

MEDICATIONS FOR BEHAVIOUR MANAGEMENT

CLONIDINE

Dose Range

- Start at 25 micrograms at night for sleep management
- Can increase to 25-100 microgram three times a day for behavior management

Start Symptoms useful for

- Management of hyperactive or aggressive behavior. e.g. biting, inattentive in school, disturbs other children, fidgety, can't sit still (these symptoms have to be sufficiently severe to be disruptive to daily home or school life to be considered for treatment)
- Also helpful for episodic management of severe dystonia in patients who get periodic worsening. Doses up to 100 micrograms 4-6 times per day can be helpful for short bursts of 3-4 days. Then wean back to baseline doses or stop

Adverse effects

- Sedation
- Sometimes postural dizziness due to postural hypotension – more likely at lower doses

Comment

- Wean slowly over a week if patient has been on clonidine for more than 3 months
- Average efficacy for ADHD, stimulants are better

RISPERIDONE

Dose Range

- 0.25mg – 5 mg/day in children. Try to manage on least efficacious dose

Symptoms useful for

- Management of hyperactive or aggressive behaviour.

Adverse effects

- Increased appetite
- Weight gain
- Metabolic disturbance – hyperlipidemia after years of use
- Extrapyramidal effects like rigidity

Comment

- Try clonidine first
- Can be quite useful if behavioral issues are really disruptive for daily life.

MEDICATIONS FOR EMERGENCY MANAGEMENT

DIAZEPAM

Dose Range

- 0.5 mg/kg <6 y/o; 0.3mg/kg 6-11 y/o; 0.2mg/kg >11y/o

Symptoms useful for

- Management of prolonged seizures >5 min at home.

Adverse effects

- Sedation
- Respiratory depression and arrest
- Local injury

Comment

- Only prescribe if family have received education on use and understand the administration process
- If a child is having a seizure in which he/she is convulsing or is unconscious, it is important to follow simple first aid measures ie. protection from injury, positioning on their side to assist breathing.
- Materials needed
    - a 25ml bottle of diazepam mixed with a stabilizing solution, containing 1mg of diazepam in each 1ml (or alternative concentration)
    - a reusable 10ml syringe
    - a reusable soft plastic tube to attach to the syringe for drawing up and injecting the diazepam
    - a sachet of lubricant jelly

REFERENCES

- Australian Medicines Handbook
- MIMS Australia
- Epocrates
- www.rch.org.au
- www.dhs.winsconsin.gov

Appendix C: Follow up questionnaire

Child's Name:				Gender:	□ Male □ Female
Weight in kg:		Phone No:		DOB:	DD/MM/YYYY
Mother's Name:			Father's Name:		
Assessment Location:				Assessment Date:	DD/MM/YYYY

Check before phone call/follow up clinic:

□ Medications and doses the child is on □ Was there a change made in the last clinic

Phone Call: ☎

1. Is your child taking the prescribed medication regularly?

□ **No**, is your child taking any other medication? □ **Yes** → *Fill up table below* □ **No** → *Go to **3***

□ **Yes**, *(Fill up table below)* Has there been any improvements? □ **Yes** → *Go to **2*** □ **No** → *Go to **2***

Name of Medication	**Formulation**	**Dose**	**Daily Dose Frequency**
□ Valproic acid *[Valex/Epilim/Epilim/Valpro]*	□ Syrup □ Tablet	□ ___ ml/___spoon □ ___ mg, ___ tabs	□ 1 □ 2 □ 3 □ 4
□ Phenobarbitone *[Barbit/Berdinal/Emer/Epinal/Pheno/Phenoba/Phenoson]*	□ Syrup □ Tablet	□ ___ ml/___spoon □ ___ mg, ___ tabs	□ 1 □ 2 □ 3 □ 4
□ Epinephrine *[Adrinor/Adrenaline/Adrin]*	□ Injection □ IV	□ ___ ml □ ___ mg	□ 1 □ 2 □ 3 □ 4
□ Benzodiazepine *[Clonazepam/Clobazam/Alsium/Clob/Clobam/Epson/ Frisium /Epiclon/Epnil/Leptic/Myotril/Rivotril/Rivo]*	□ Syrup □ Tablet	□ ___ ml/___spoon □ ___ mg, ___ tabs	□ 1 □ 2 □ 3 □ 4
□ Clonidine *[Catapres 0.1/Clonipres 0.1]*	□ Syrup □ Tablet	□ ___ ml/___spoon □ ___ mg, ___ tab	□ 1 □ 2 □ 3 □ 4
□ Piracetam *[Neurolep/Neuratam/Piratam/Juvain/Piramax]*	□ Syrup □ Tablet	□ ___ ml/___spoon □ ___ mg, ___ tabs	□ 1 □ 2 □ 3 □ 4
□ Baclofen *[Flexifen/Bacofen/Mylofen/Axant/Beclovan]*	□ Syrup □ Tablet	□ ___ ml/___spoon □ ___ mg, ___ tabs	□ 1 □ 2 □ 3 □ 4
□ Trihexyphenidyl *[Hexinor/Trihexy]*	□ Syrup □ Tablet	□ ___ ml/___spoon □ ___ mg, ___ tabs	□ 1 □ 2 □ 3 □ 4
□ Other*(write)*	□ Syrup □ Tablet	□ ___ ml/___spoon □ ___ mg, ___ tabs	□ 1 □ 2 □ 3 □ 4

2. Is your child seizure free at current dose?

□ **Yes** → *End*

□ **No**, Frequency of seizure: _____ per day / week / month / year

Average duration of seizure _____ minutes/hours

For those **not taking any medicine now**:

3. Has the medicine caused any problem? □ **Yes** → *Fill up table below and end.* □ **No** → *Go to **4**.*

	Problem	**Immediate action on the phone**
□	Extensive rash developed on medication	Stop the medication and need to review urgently
□	Child too drowsy to feed safely on medication	Reduce to older dose/previous medication
□	Other Problem:	

4. Specify any other reason for not taking prescribed medication regularly:

_____

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-6
		(b) Give reasons for non-participation at each stage	Figure 3
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Figure 3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11-12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Improving epilepsy control among children with cerebral palsy in rural Bangladesh: A prospective cohort-based study

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Improving epilepsy control among children with cerebral palsy in rural Bangladesh: A prospective cohort-based study

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ABSTRACT

Objective: To define the prevalence and seizure subtypes among children with cerebral palsy (CP) in rural Bangladesh and explore barriers to optimum epilepsy control.

Design: Prospective cohort study

Setting: The study was conducted in Shahjadpur, a rural subdistrict of Bangladesh.

Participants: Children (<18 years) with CP and epilepsy identified using the Bangladesh CP Register in the study site.

Methods: Assessments were conducted in three focused epilepsy clinics overseen by a pediatric neurologist between December 2016 - January 2018, with intervening phone and video-conference follow-ups. Details of event type, frequency and medication compliance were collected. Antiepileptic drugs (AED) were prescribed based on seizure type, family income, comorbidity and medication availability.

Results: 23.4% (170/726) of the BCPR cohort had a clinical diagnosis of epilepsy of whom 166 were assessed. Following the focused epilepsy clinics, 62.0% (103/166) children were clinically determined to have ongoing epileptic seizures. 62.1% (64/103) had generalized onset tonic clonic seizures, 27.2% (28/103) had focal onset seizures with impaired awareness and 10.7% (11/103) had other seizure types. None of the children with prolonged seizures (31/103) had an emergency seizure management plan. Non-epileptic events were being pharmacologically treated as seizures in 18.1% (30/166) children. Financial constraints were the main reason for non-compliance on follow up.

Conclusions: Gaps in optimum epilepsy management in rural Bangladesh are amenable to improvement anchored with local health care workers. Training and clinical care focused on recognition of common seizure types, seizure mimics and rationalizing use of available AEDs can be facilitated by better referral pathways and telehealth support.

Key Words: Epilepsy, cerebral palsy, Bangladesh, CP

Strengths and limitations of this study

- Children with CP and epilepsy identified through an ongoing population-based surveillance.
- Specialist clinical assessments were conducted overseen by a paediatric neurologist.
- Phone follow-ups were conducted.
- The study provided opportunity for continuing local capacity building.
- The clinical diagnoses relied on clinical impression and were not corroborated by investigations.

INTRODUCTION

Cerebral palsy (CP) is a term that defines a heterogenous group of early-onset, non-progressive, neurodevelopmental disorders secondary to injury to the developing brain [1]. Studies show that among children with CP epilepsy is associated with greater impairment of cognitive function, poorer motor outcomes, more profound behavioral and psychological problems, and poorer quality of life, all of which collectively contribute to a greater burden of disability and care [2]. In comparison to children with epilepsy only, children with CP and epilepsy tend to have early onset of seizures which can often be difficult to control [3].

Recent estimates from a population-based study in Bangladesh showed a high burden of CP with an estimated prevalence of 3.4 per 1000 children [4]. Bangladesh is one of the most densely populated and under resourced countries in the world [5]. The World Health Organization (WHO) classified Bangladesh as one of the countries with severe shortages of health workers. There is inequity in the skill mix and distribution of health workers between urban and rural Bangladesh [6]. One of the four axes of the value-based framework for global health delivery highlights the need for alignment of care delivery to the local context [7].

Resources for the diagnosis and management of neurologic disorders such as epilepsy are often limited in low and middle-income countries (LMICs) such as Bangladesh [8]. Several aspects of epilepsy management that may be considered routine in tertiary or specialist settings are not applicable to community-based settings [9]. There is a substantial epilepsy treatment gap in low resource settings owing to a wide spectrum of factors including shortage of doctors particularly in the rural areas,[6] lack of available investigation and inpatient treatment facilities as well as decreased service utilization due to the stigma around a disability diagnosis.[10]

We aimed to define the prevalence, clinical phenotypes and barriers to optimum epilepsy control among children with CP in a community-based setting in Bangladesh.

METHODS AND ANALYSIS

Cohort compilation

We used the Bangladesh CP Register (BCPR); a prospective population-based surveillance of children with CP in Shahjadpur a northern subdistrict of Rajshahi division in Bangladesh for identification of children with CP and epilepsy.

Medical assessment camps are conducted on a regular basis in the surveillance sites for BCPR. A multidisciplinary medical assessment team including a paediatrician, a physiotherapist, and a counsellor conduct detailed assessment for data collection for the BCPR. Data on the presence of associated impairments including epilepsy are also documented based on review of limited available medical records, report by the parents or primary caregivers of the children with CP, and clinical assessment by the medical assessment team. Detailed account of the BCPR study protocol and findings have been described in previous publications [4].

During the BCPR medical assessment camps preceding this study, a diagnosis of epilepsy had been based on history of one or more unprovoked seizures in the previous 3 months recorded by medical practitioners and review of any available medical records [4].

Clinical assessment of epilepsy

Children with CP and epilepsy identified via the BCPR were clinically reviewed in three focused epilepsy clinics held for three days each time at three different locations within the BCPR study site. Specialist clinical assessments at the clinics were overseen by a pediatric neurologist from Australia (SM) who travelled to Bangladesh for the focused epilepsy clinics during the study period. Diagnoses of epilepsy and seizure like events were reviewed during assessment in the clinics. Details of seizure/event type, frequency, medication use, and compliance were collected according to a predesigned standard proforma (Appendix A). Workflow during the clinic is outlined in Figure 1.

Local capacity building

Two physicians (TK and MCD) were trained by the pediatric neurologist in classifying seizure types according to the 2017 International League Against Epilepsy (ILAE) guidelines [11], demonstration of clinical signs during the epilepsy clinics, and discussions around seizure mimics and drug choice (Appendix B). One community worker based in the study area was also trained to conduct phone follow ups of the children on antiepileptic drugs (AED).

Selection of antiepileptic drugs

Before the clinics, the community worker collected information on availability and cost of AED in local pharmacies within the study area between December 2016 and January 2018. A dose equivalence table was drawn up for easy prescription in the clinic along with notes on important side effects and interactions. During the clinics, AED were prescribed based on seizure type, medication

availability and family income. The approach undertaken for shared decision making in AED prescription is outlined in Figure 2.

Telehealth supported follow up and clinics

Phone follow up

Targeted phone follow ups of the children on AED were conducted by the trained community health worker every three months during the study period, following the initial specialist assessment at the focused epilepsy clinics. The phone follow ups were semi-structured. The design, conduct and the outcome measures for the follow ups were additionally informed by the study team's experience and input from the primary caregivers (Appendix C). Seizure control was documented during phone follow ups. In our study seizure control was defined as no reported seizure between the clinic and follow up.

Patient and Public Involvement

This work was informed by the priorities, experience and preferences of the primary caregivers of the children with CP and epilepsy who participated in the study. The design and implementation of the follow ups, including outcome measures important to the study participants, relied on feedback from families of children with CP and epilepsy. Baseline information was communicated to the primary caregivers by the study team. This informed shared decision making related to the treatment and follow up for their children. Furthermore, the follow ups were conducted by a local community worker and local physician, which enhanced community involvement during and beyond the study.

Statistical analysis

Descriptive analyses were carried out. All statistical analysis was conducted using SPSS version 24 (IBM Armonk, NY, USA).

Ethics

This study was conducted as part of the Bangladesh Cerebral Palsy Register Study which has been approved by the Bangladesh Medical Research Council (BMRC) Human Research Ethics Committee (Ref no. BMRC/NREC/2013–2016/1267) in Bangladesh, and by the Cerebral Palsy Alliance NHRMC Human Research Ethics Committee (Ref no.2015–03-02) in Australia. Written informed consent was taken from the primary caregiver/parents/guardian of the children with CP.

RESULTS

Prevalence and basic demographic characteristics

726 children with CP were registered into the BCPR between January 2015 and December 2016, 23.4% (170/726) of whom had a clinical diagnosis of epilepsy. 166 of these children attended the three focused epilepsy clinics between December 2016 and January 2018 and form the study cohort. 55 (33.1%) were female. The mean age of the children was 6 years 10 months (SD: 4 years 5 months) years.

After the focused epilepsy clinics, 62.0% (103/166) children were clinically determined to have ongoing epileptic seizures based on review of their history, existing medical records and specialist clinical evaluation (Figure 3). Therefore, the revised prevalence of epilepsy among the BCPR cohort during the study period was 14.3%.

Seizure subtypes

62.1% (64/103) had generalized onset tonic clonic seizures (GTCS), 27.2% (28/103) had focal onset seizures with impaired awareness and 5.8% (6/103) had other seizure types (focal onset aware seizures, epileptic spasms, generalized onset myoclonic seizures and generalized onset tonic seizures). 11.6% (12/103) had multiple seizure types. Data on seizure type was unclear on history for 4.9% (5/103). At the time of first assessment, seizures were already controlled with AED in 5.8% (6/103) children. 30.1% (31/103) of children had a history of prolonged seizures (>30 minutes) and none of these patients had an emergency seizure plan. Their caregivers tended to wait at home till the seizures settled and did not seek emergency medical assistance due to geographical or financial constraints.

Barriers to optimum epilepsy control

Non-epileptic events among children with CP

Non-epileptic events were determined to have been mislabeled as seizures in 18.1% (30/166) children which included extremity clonus (n=7), dystonic postures (n=6), spasticity related spasms (n=4), breath holding spells (n=3), mannerisms (n=3), sleep related myoclonic jerks (n=2), startles (n=2), stereotypies (n=2) and rhythmic movement disorders in sleep (n=1). 23.3% (7/30) of these children were being treated with AED. AED was stopped for all seven of them. At follow up none of them worsened, thereby, further confirming the misdiagnosis of epilepsy and unnecessary administration of AED to these children.

Epilepsy control

Of the 103 children with seizures, 62 were already on AEDs at the time of our clinical review. Polypharmacy with more than two concurrent AED was commonly observed and AED changes were made for the majority of them. Advised AED changes consisted of dose alteration in 54.8% (34/62) and medication change in 17.7% (11/62). 27.4% (17/62) were advised to continue treatment already initiated by various providers. We initiated treatment for 39/41 children not previously on AED who were clinically determined to still be having epileptic seizures; 2/41 only had short seizures once or twice a year and were not put on AED.

Telehealth supported follow up and clinics

Phone follow up

We were able to review 75.8% (78/90) children with epileptic seizures on follow up during the study period. On follow-up (median 6.0 months), 69.2% (54/78) were taking prescribed medications as advised. Among them 75.9% (41/54) showed improvement in seizure control (>50% seizure reduction), including 14 children whose seizures were controlled. 30.8% (24/78) families had discontinued the advised treatment due to affordability (8/24, 33.3%), excessive drowsiness (7/24, 29.2%), development of a rash (4/24, 16.7%), no perceived benefit with medication and lack of understanding behind the use of regular medications (2/24, 8.3%). Three (3/24, 12.5%) children who discontinued medications were reported to no longer have seizures. None of the families reported any adverse effects that led to reported cardiorespiratory compromise, hospital presentation or death.

Two children from our cohort died during the follow up period, one due to meningitis and the other due to a lower respiratory tract infection. Their cause of death was determined by verbal autopsy conducted as part of a separate study [12].

DISCUSSION

Epilepsy is a significant comorbidity in some individuals with CP. Previous studies have described a prevalence of 15-90% epilepsy in CP cohorts [13,14]. Methodological differences in identification of children with CP (population-based vs institutional based recruitment) and use of variable definitions of epilepsy in studies contribute further to the reported differences in rates of epilepsy among children with CP. The Australian CP register defined epilepsy as “two or more afebrile seizures

before age 5 years; excluding neonatal seizures" while other definitions for epilepsy used across the literature include use of AED, insurance claims and parent reported diagnosis [15]. As one of the most common associated impairments of CP, we recommend the use of a harmonized definition i.e., the ILAE definition for description of epilepsy within CP registers to enable accurate estimation of rates of and meaningful comparisons.

The rate of epilepsy observed among children with CP in our study is consistent with rates reported in other low resource settings such as Indonesia where 13.5% of children with CP had epilepsy [16]. The Australian CP Register reports that epilepsy was more common amongst children with post-neonatally acquired CP compared to pre/perinatally acquired CP (50% vs 30%). This eludes into the potential role of antecedents of CP on the proportion of children with epilepsy in CP cohorts. There is a growing body of evidence on the differences in the prevailing risk factors and timing of acquisition of CP among children in low resource settings compared to high income countries [4,16,17]. These factors are often associated with varied likelihood of having epilepsy, therefore, further contribute to the wide-ranging reported rates of epilepsy among children with CP globally.

Overall, epilepsy contributes more significantly to the global burden of disease in resource poor settings as evident from the 2015 Global burden of disease studies. We found an initial prevalence of epilepsy of 23.4% in our cohort. Interestingly, following reassessment in our clinics, as described, this was revised to 14.3%. Previous studies have also noted such discrepancy between determination of a clinical diagnosis of epilepsy between specialist and community-based settings with a misdiagnosis of epilepsy being made in as many as 25% of cases [18]. This has flow on impacts as we noted in terms of incorrect, often excessive use of medications. Epilepsy poses substantial economic burden on families [19]. When families devote a significant proportion of their finances, attention, time or all of these towards one aspect of their child's management, other aspects of care such as physical therapy, nutrition, pain and musculoskeletal management are likely to be neglected, more so in resource poor settings [20].

As demonstrated by recent innovative projects in neighbouring Nepal, education of community level workers and general medical practitioners can lead to more consistent clinical diagnosis of epilepsy [21]. In our experience, rationalisation or cessation of medications after focused clinical assessments led to changes in family finances diverted towards medication use. We envision that the development of simplified print and multimedia based educational resources for health care workers

and medical practitioners hold the potential to improve epilepsy diagnosis in resource scarce settings such as our study site.

Polypharmacy with more than two concurrent AEDs is unlikely to contribute significantly to seizure control [22]. In countries like Bangladesh with a mismatch of clinical care practices between urban and rural areas, the use of less conventional or alternative medications is very likely to be encountered.

AED availability is very limited in rural Bangladesh [23]. Medications need to be purchased by families and hence, cost per month for AEDs is a significant consideration when choosing medications for chronic use to ensure good compliance. The cheapest and most readily available AEDs are phenobarbitone, clobazam and sodium valproate. If a diagnosis of CP is very likely based on clinical evaluation and history, earlier use of sodium valproate or clobazam in this setting is a viable option for transitioning from phenobarbitone which is most commonly prescribed in infancy. As outlined in our methods and Figure 2, AED choice can be rationalized based not only on the seizure type but also existing comorbidity as some AEDs can help improve comorbid psychiatric symptoms or sleep disturbance.

Our experience highlighted a gap in the recognition and management of prolonged seizures in settings like ours compared to conventional management in urban and resource rich settings. Benzodiazepines are the mainstay of out of hospital, particularly health worker or parent led management of prolonged seizures. However, midazolam or lorazepam are not available at all in rural Bangladesh. Diazepam is only available in glass ampoules through restricted prescriptions in some pharmacy outlets. In our and wider reported experience caregivers are often reluctant to use glass ampoules or follow several steps in medication administration to a child at home [24]. Other readily available benzodiazepines are cheap (clobazam: 0.042 USD per 10 mg tablet and clonazepam: 0.048 USD per 1 mg tablet; prices mid 2018) but there is very little evidence regarding their use in the setting of prolonged seizures [25,26]. Status epilepticus can significantly add to the burden of cumulative brain injury and therefore warrants a solution [27]. This may be in the form of a per-rectal, oral or, alternative routes for delivery of well-established medications for status epilepticus such as phenobarbitone, valproate or midazolam. Alternatively, the use of medications such as clonazepam drops via open label trials requires urgent exploration for such settings.

Our model has demonstrated that immediate positive impact on epilepsy management and reduction in burden of care on families can be achieved through structured assessments by medical and allied personnel who are trained to assess children for epilepsy and use available medications according to a structured framework. This can be achieved for a population base such as in our study area with limited personnel and without additional investigation or formalized health care facilities, though these would be desirable to further improve patient outcomes.

We piloted the use of videoconference-based telemedicine clinics after initial face to face clinics. Telemedicine clinics were initiated in May 2018 and held on a monthly basis using Skype as part of ongoing capacity building to improve epilepsy control among the study cohort. The local trained physician saw the patients face to face in the study site and used a handheld, internet connected tablet to videoconference with the pediatric neurologist in Australia. Patient interview for new and follow up patients followed a set format (Appendix C). New patient data from the telemedicine clinics are not included in this paper. Five telemedicine clinics undertaken in 2018 contributed to patient follow up and clinical capacity building. During these clinics 47 patients were seen by a local medical practitioner with internet-based videoconference support from the pediatric neurologist in Australia. Each clinic was of three hours duration during which patient interview was undertaken in the same manner as in the focused epilepsy clinics. Thirty minutes were marked during each clinic for discussion regarding clinical signs, history taking and AED choice. Clinical details for new patients reviewed during telemedicine clinics were not included in this cohort. These clinics created mentoring opportunity for the local team which is a substantial contribution towards for long term sustainability. Unfortunately, this process was interrupted due to limited local team and patient mobility in 2020 and 2021 due to the pandemic therefore limiting structured data from this phase. We aim to resume this approach to maintain a sustainable model for ongoing care.

With some prior training in the use of a structured clinical approach, this method can be very time-efficient in reviewing patients led by a non-specialist medical practitioner/community worker and supported by a specialist. In our experience, this not only provided continuity of clinical support with existing personnel but also provided an opportunity for continuing professional development and capacity building. We hope that in the post-COVID era, implementation and incorporation of telemedicine should be easier and more acceptable to providers, policymakers and the community.

We summarize the key barriers identified and proposed or already implemented solutions in Table 1. Development of multimedia or mobile application-based resources that may simply illustrate clinical

assessment of children with epilepsy, examples of non-epileptic events and emergency seizure management will provide convenient means for translation of our findings to the wider population in Bangladesh and, with language translation, to similar resource poor settings across the world.

We have engaged with tertiary paediatric neurology centres in Bangladesh to support some families with requisite investigations or more frequent specialist review. However, this will always be limited to financial and logistic constraints of rural families.

Study limitations

We did not systematically collect baseline investigation information for this cohort as a small proportion had any previous tests such as electroencephalography (EEG) or neuroimaging. The clinical diagnosis of seizures and non-epileptic events were not corroborated by investigations as they were unavailable in this resource limited setting. We acknowledge that there is a potential for having underdiagnosed seizures if they had last occurred several months prior to our assessment and also being dependent on parental recall and description. We had to rely on the clinical impression of a limited number of observers. Although we utilized standard criteria to assess seizure reduction, the collection of the follow up data was based on reporting by the primary caregiver which may have been a source of potential bias.

CONCLUSION

Epilepsy is prevalent among children with CP in rural Bangladesh and the various gaps in optimum epilepsy management are lack regular follow-up, recognition of common seizure types and non-epileptic seizure mimics, familiarization with commonly available, affordable AED and availability of guidelines for prolonged seizure management. These gaps are amenable to proposed low cost, educational interventions. Health care workers can improve epilepsy management with regular follow-up, education on common seizure types, seizure mimics, use of commonly available, affordable AED and guidelines for prolonged seizure management.

AUTHORS' CONTRIBUTION

All listed authors meet the appropriate authorship criteria, and nobody who qualifies for authorship has been omitted. GK and SM conceptualized and established this research study. They also contributed to study design, development of the study materials and overall conduct of the study supported by TK. SM, TK and MCD were responsible for assessment of study participants and data collection. SM, GK, NB and MM provided specialist advice in this study. TK, SM and GK completed

data analysis, interpretation of the data and drafted the initial and revised manuscript with input from all the co-authors. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST DISCLOSURES

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

No additional data are available.

REFERENCES

[1] Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, et al. Proposed definition and classification of cerebral palsy, April 2005. Developmental Medicine & Child Neurology. 2005;47(8):571-6.

[2] Mesraoua B, Ali M, Deleu D, Al Hail H, Melikyan G, Haddad N, Alalamy O, Athanasios C, Asadi-Pooya AA. Epilepsy and Cerebral Palsy. Neurodevelopment and Neurodevelopmental Disorder 2019 May 8. IntechOpen.

[3] Singhi P, Jagirdar S, Khandelwal N, Malhi P. Epilepsy in children with cerebral palsy. Journal of Child Neurology. 2003;18(3):174-9.

[4] Khandaker G, Muhit M, Karim T, Smithers-Sheedy H, Novak I, Jones C, et al. Epidemiology of cerebral palsy in Bangladesh: a population-based surveillance study. Developmental Medicine & Child Neurology. 2019 May;61(5):601-9.

[5] National Institute of Population Research and Training (NIPORT), ICF International. Bangladesh Demographic and Health Survey. Dhaka, Bangladesh; 2014.

[6] Ahmed SM, Hossain MA, RajaChowdhury AM, Bhuiya AU. The health workforce crisis in Bangladesh: shortage, inappropriate skill-mix and inequitable distribution. Human Resources for Health. 2011;9(1):3.

[7] Kim JY, Farmer P, Porter ME. Redefining global health-care delivery. The Lancet. 2013;382(9897):1060-9.

[8] Bearden DR. Pediatric Neurology in Resource-Limited Settings: a Systematic Review. Current Pediatrics Reports. 2018;6(1):34-9.

[9] Kim JY FP, Porter ME. A global health delivery framework approach to epilepsy care in resource-limited settings. Journal of the Neurological Sciences. 2015;358(1-2):263-5.

[10] Patel P, Baier J, Baranov E, Khurana E, Gambrah-Sampaney C, Johnson A, et al. Health beliefs regarding pediatric cerebral palsy among caregivers in Botswana: A qualitative study. Child: Care, Health and Development. 2017;43(6):861-8.

[11] Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522–530

[12] Jahan I, Karim T, Das MC, Muhit M, Mcintyre S, Smithers-Sheedy H, Badawi N, Khandaker G. Mortality in children with cerebral palsy in rural Bangladesh: a population-based surveillance study. Developmental Medicine & Child Neurology. 2019 Nov;61(11):1336-43.

[13] Aicardi J. Epilepsy in Brain-Injured Children. Developmental Medicine & Child Neurology. 2010;32(3):191-202.

[14] Aksu F. Nature and Prognosis of Seizures In Patients With Cerebral Palsy. Developmental Medicine & Child Neurology. 2008;32(8):661-8.

[15] Report of the Australian Cerebral Palsy Register Birth years 1995-2012, November 2018

[16] Jahan I, Al Imam MH, Karim T, Muhit M, Hardianto D, Das MC, Smithers-Sheedy H, Badawi N, Khandaker G. Epidemiology of cerebral palsy in Sumba Island, Indonesia. Developmental Medicine & Child Neurology. 2020 Dec;62(12):1414-22.

[17] Karim T, Dossetor R, Huong Giang NT, Dung TQ, Son TV, Hoa NX, Tuyet NH, Van Anh NT, Chau CM, Bang NV, Badawi N. Data on cerebral palsy in Vietnam will inform clinical practice and policy in low and middle-income countries. Disability and Rehabilitation. 2021 Jan 9:1-8.

[18] National Clinical Guideline Centre. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care.

http://www.nice.org.uk/nicemedia/live/13635/57784/57784.pdf (accessed March 2021)

[19] Allers K, Essue BM, Hackett ML, Muhunthan J, Anderson CS, Pickles K, Scheibe F, Jan S. The economic impact of epilepsy: a systematic review. BMC neurology. 2015 Dec 1;15(1):245.

[20] Nuri RP, Aldersey HM, Ghahari S. Needs of families of children with cerebral palsy in Bangladesh: A qualitative study. Child: Care, Health and Development. 2018;45(1):36-44.

[21] Rajbhandari H, Joshi S, Malakar S, Paudel P, Jain P, Uppadaya K, et al. Epilepsy field workers, a smartphone application and telephone telemedicine: Safe and effective epilepsy care in rural Nepal. Seizure. 2019;64:54-8.

[22] Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. The Lancet Neurology. 2003;2(6):347-56.

[23] Hussain ME. Burden of Epilepsy in Bangladesh: Current Approach. Journal of Current and Advance Medical Research. 2018;4(1):1-2.

[24] Chiang LM, Wang HS, Shen HH, Deng ST, Tseng CH, Chen YI, Chou ML, Hung PC, Lin KL. Rectal diazepam solution is as good as rectal administration of intravenous diazepam in the first-aid cessation of seizures in children with intractable epilepsy. Pediatrics & Neonatology. 2011 Feb 1;52(1):30-3.

[25] Shangguan Y, Liao H, Wang X. Clonazepam in the treatment of status epilepticus. Expert Review of Neurotherapeutics. 2015;15(7):733-40.

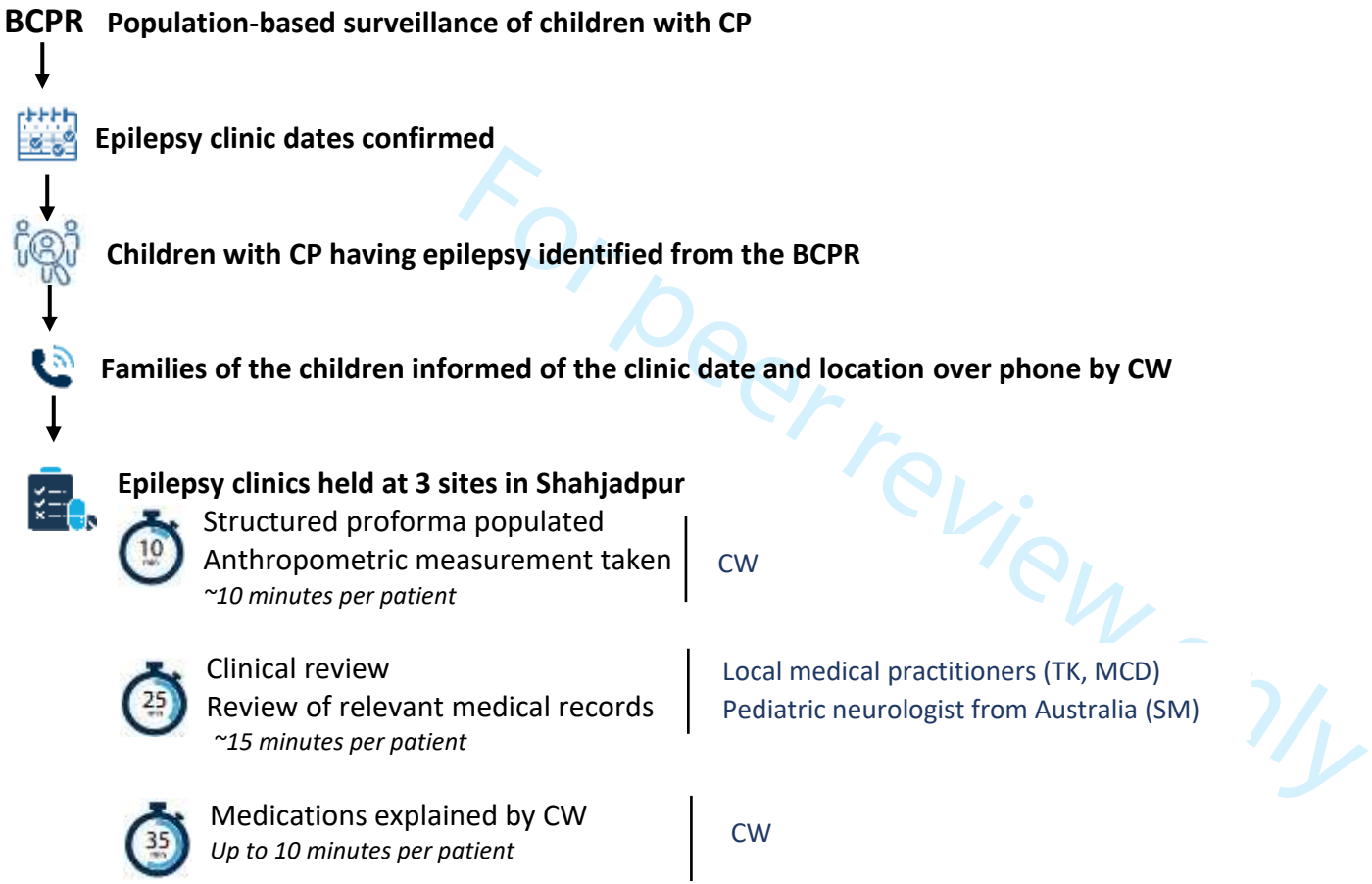
[26] Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus. New England Journal of Medicine. 1998;339(12):792-8.

[27] Kwong KL, Wong SN, So KT. Epilepsy in children with cerebral palsy. Pediatric Neurology. 1998;19(1):31-6.

Table 1: Barriers to epilepsy control and suggested interventions

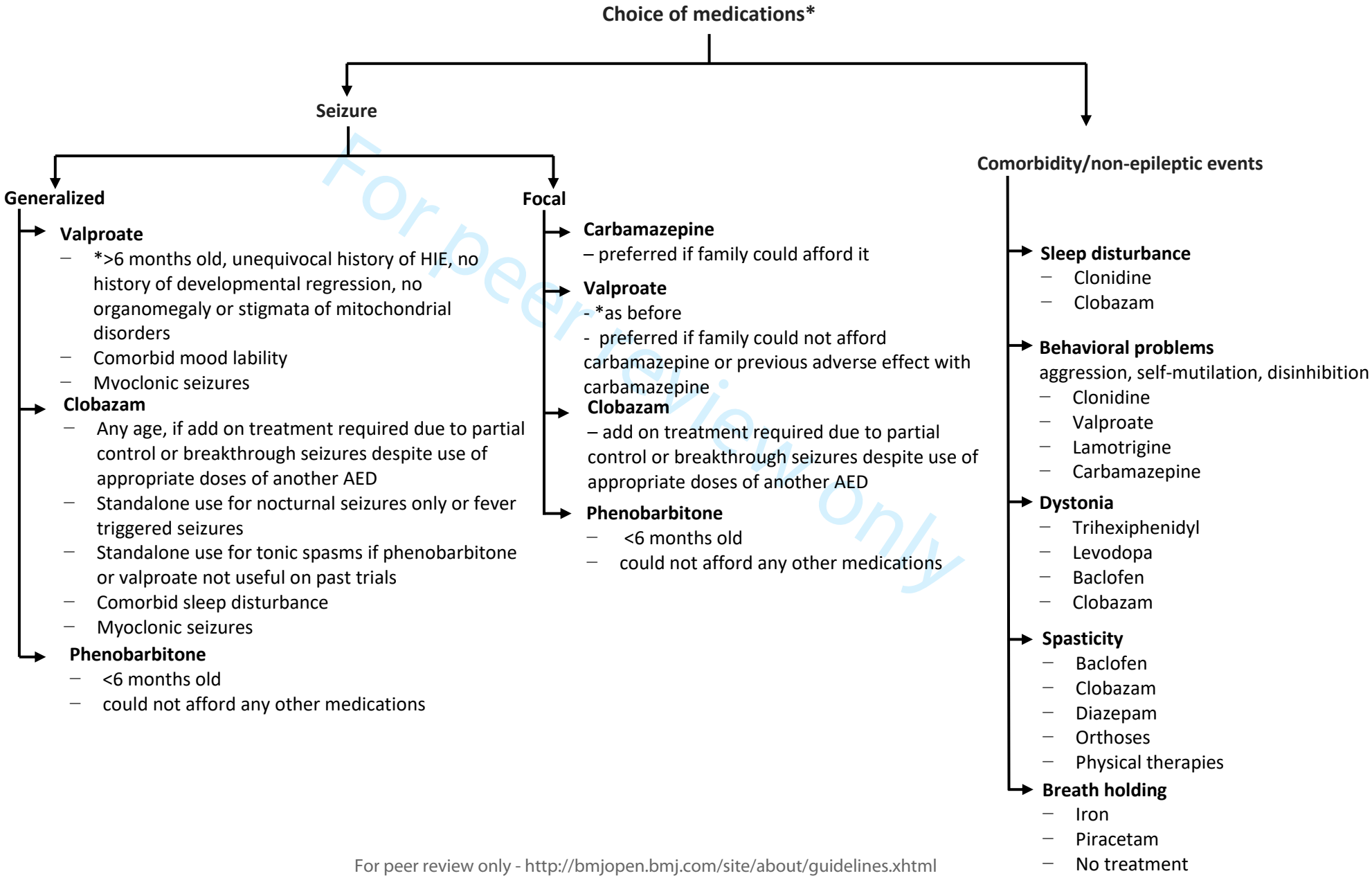
Barriers	Suggested interventions
AED availability	Selection of locally available medications for management through a structured guideline
Lack of skilled personnel for epilepsy management and follow up locally	Capacity building and engagement of local medical practitioners and community health workers Development of multimedia or mobile application-based resources Telemedicine
Affordability	Rationalization of drugs
Poor treatment compliance	Rationalization of drugs Training and engagement of health workers for follow up Caregiver education
Prolonged seizure management	Development of guideline and resources for management of prolonged seizure for training of local health workers
Misidentification of non-epileptic episodes as seizures	Development of video resources describing seizures and non-epileptic events
Lack of parental understanding regarding epilepsy treatment	Parent education on epilepsy treatment

Figure 1: Clinical assessment of epilepsy in children with CP in Shahjadpur



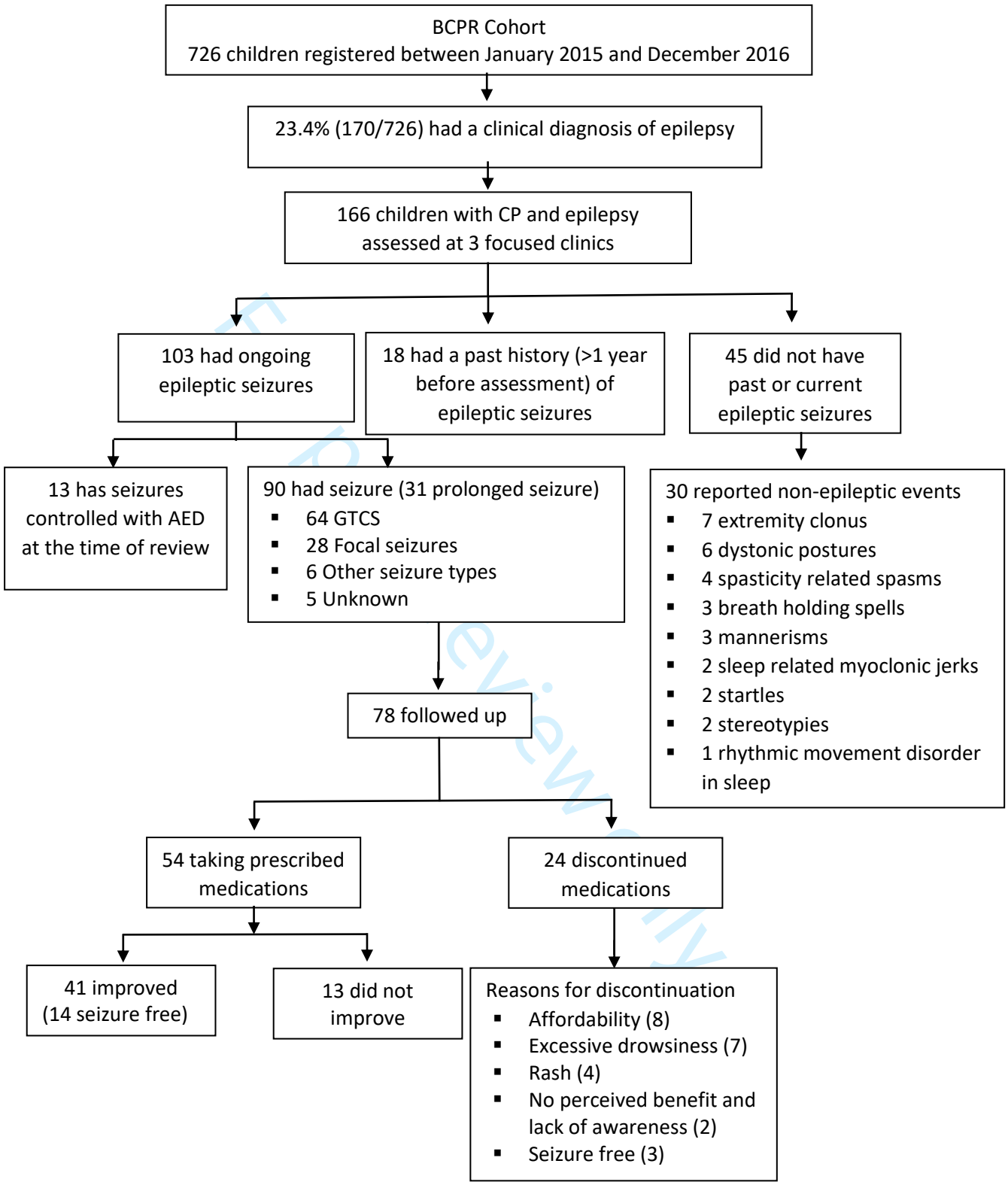
CP: cerebral palsy, BCPR: Bangladesh Cerebral Palsy Register, CW: community worker

Figure 2: Suggested considerations in choice of medications for seizures and comorbidity in children with cerebral palsy



*All medications are listed in order of preference for management

Figure 3: Study diagram



Appendix A: Clinic proforma used during focused epilepsy clinics

ASSESSMENT DETAILS		
ID NUMBER:		**SERIAL NUMBER:**
ASSESSMENT LOCATION:		**ASSESSMENT DATE:** DD / MM / YYYY
CHILD'S DETAILS		
NAME:	**GENDER:** ☐ M ☐ F	**DOB:** DD / MM / YYYY
HEAD CIRCUMFERENCE (cm):	**WEIGHT (kg):**	**LENGTH/HEIGHT (cm):**
FATHER'S DETAILS		
NAME:	**DOB:** DD / MM / YYYY	**OCCUPATION:**
EDUCATION ☐ Illiterate ☐ Primary ☐ Secondary ☐ Higher secondary ☐ Graduation ☐ Post-graduation ☐ Diploma/other trade qualification		
MOTHER'S DETAILS		
NAME:	**DOB:** DD / MM / YYYY	**OCCUPATION:**
EDUCATION ☐ Illiterate ☐ Primary ☐ Secondary ☐ Higher secondary ☐ Graduation ☐ Post-graduation ☐ Diploma/other trade qualification		
CONTACT DETAILS		
DISTRICT:		**SUB-DISTRICT:**
UNION:		**VILLAGE:**
POST CODE:		**PHONE NO.:**
TYPE OF CASE (select one): ☐ New ☐ Follow-Up		
SEIZURE CONTROL: ☐ Same ☐ Better ☐ Worse		**SEIZURE FREE ON TREATMENT:** ☐ Yes ☐ No
COMPLIANT: ☐ Yes ☐ No	**IF NO, REASON FOR NON-COMPLIANCE:**	
REASON FOR POOR SEIZURE CONTROL:		
MAIN CONCERN:		
HISTORY AND EXAMINATION FINDINGS		
BIRTH HISTORY:		
SEIZURE		
FIRST:		**LAST:**
HISTORY OF PROLONGED SEIZURE (> 5 mins): ☐ Yes ☐ No		
CURRENT FREQUENCY: _____ times per ☐ day ☐ week ☐ month ☐ year		
TYPE:		
DURATION OF SEIZURE:		**DESCRIPTION:**
PREVIOUS MEDICATION & INVESTIGATION		

Appendix B: Guideline for drug choice at clinics

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MEDICATIONS FOR SEIZURE MANAGEMENT

PHENOBARBITONE

Dose range

- 1–6 mg/kg daily in 1 or 2 doses; start at the lower end of range and increase slowly if required.

Seizure types useful for

- For generalized seizures and focal seizures.
- Recurrent febrile seizures
- Neonatal seizures
- Less likely to help blank staring "absence" seizures

Adverse effects

- Allergic rash, rarely can cause extreme hypersensitivity reaction
- Hyperactivity
- Sedation

Comment

- Generally, a good medication to continue unless it is not working or the side effects are not tolerable
- Do not stop suddenly and wean over several weeks if patient has been on it for more than 3 months

SODIUM VALPROATE

Dose Range

- 20–40 mg/kg daily in 2 divided doses; start at 5-10 mg/kg/day and increase slowly to 20 mg/kg/day. Then increase further if required.

Seizure types useful for

- For all seizure types

Adverse effects

- Hyperactivity
- Liver dysfunction
- Caution with use in children with developmental delay less than two years or older who are likely to not have true CP. Valproate can cause fatal liver dysfunction in those with a history of mitochondrial disorders. This is suggested by a history of developmental regression eg. A child who was able to sit before can no longer do so.

Comment

- Valproate is likely to work for most seizure types and cause less sedation than phenobarbitone
- Valproate works synergistically with clobazam and lamotrigine.
- Lamotrigine should be introduced very cautiously if someone is already on valproate

CLOBAZAM

Dose Range

- Start at 1-2 mg/dose once a day. Can increase as required to
  - 2.5-5 mg BD in children <2 years
  - 5-10 mg BD in children 2-10 years
  - 10 mg TDS in older children
  - maintenance 0.3-1 mg/kg/day in 2 divided doses
- The above doses are a guide and higher doses can be used in younger children if tolerated and if thought to be beneficial for seizure control

Seizure types useful for

- For all seizure types
- Also helpful for dystonia management in some cases

Adverse effects

- Sedation
- Hyperactivity
- Hallucinations
- Drooling

Comment

- Useful monotherapy or add on medication
- Start at small doses like 1 mg BD and grade up
- Can crush tablet and suspend in water to make up small doses if liquid not available
- If difficult for family to understand use quarter tablet / half tablet instead of dissolving
- Wean very slowly similar to phenobarbitone if patient has been taking Clobazam for more than 3 months
- Children can sometimes get used to benzodiazepines. If seizures break through after a few months of good control, then consider swapping over to another benzodiazepine like Nitrazepam.

NITRAZEPAM

Dose Range

- Start at 1 month – 2 years: 0.25mg/kg twice daily, up to 0.5mg/kg twice daily
- The above doses are a guide and higher doses can be used in younger children if tolerated and if thought to be beneficial for seizure control

Seizure types useful for

- For all seizure types
- Infantile spasms

Adverse effects

- Sedation
- Drooling

Comment

- Useful monotherapy or add on medication
- Start at small doses like and grade up
- Wean very slowly similar to phenobarbitone if patient has been taking Nitrazepam for more than 3 months
- Children can sometimes get used to benzodiazepines. If seizures break through after a few months of good control, then consider swapping over to another benzodiazepine like Clobazam.

CARBAMAZEPINE

Dose Range

- 10–20 mg/kg daily in 2-3 divided doses; start at 2.5-5 mg/kg/day and increase slowly to 10 mg/kg/day. Then increase further if required. Some patients can respond to low doses 5-10 mg/kg/day and can be maintained on these doses without further increasing unless required

Seizure types useful for

- Focal seizures only
- Avoid for generalized, absence and febrile seizures

Adverse effects

- Hyperactivity
- Liver dysfunction

Comment

- Useful drug for focal seizures, e.g. With hemiplegic CP

MEDICATIONS FOR DYSTONIA/SPASTICITY MANAGEMENT

TRIHEXIPHENIDYL/BENZHEXOL

Dose Range

- Start at 0.25 mg once a day and gradually increase to 0.25 mg tds.
- If tolerated, can trial up to 2 mg – 4 mg tds
- In older children, higher doses can be used if benefit is noted

Symptoms useful for

- Mainly for dystonia management. Can also help drooling due to its anticholinergic properties

Adverse effects

- Dry mouth, eyes
- Constipation
- Confusion
- Double vision

- Irritability

Comment

- About 25-50% efficacy for dystonia management if side effects are not a problem. Some children can benefit remarkably more
- Avoid other anticholinergic medications or if any of the adverse effects are already a clinical problem
- If not benefit after maximum doses for 3-4 weeks, then discontinue as delayed benefit is unlikely to occur.

BACLOFEN

Dose Range

- **2-7 y** -10-40 mg/day divided in three to four doses/day. Start: 2.5-5 mg twice a day, may increase by 5-15 mg/day every 3-4 days, Max: 40 mg/day.
- **8-11 y -** Dose: 10-60 mg/day divided in three to four doses/day. Start: 2.5-5 mg twice a day, may increase by 5-15 mg/day every 3-4 days; Max: 60 mg/day.
- **12 y and older -** Dose: 20-80 mg/day PO divided in three to four doses/day. Start: 5 mg twice a day, may increase by 15 mg/day every 2-3 days; Max: 80 mg/day.

Start Symptoms useful for

- Mainly for spasticity management.

Adverse effects

- Hypotonia
- Drooling
- Sedation

Comment

- Baclofen is a good medication for high tone which is due to spasticity
- It is not so good when there is dominant or mixed dystonia
- Relatively high doses may be needed in some patients making side effects intolerable, these have to be balanced with dose
- Other sedative medications will add to sedative effects and drooling – benzodiazepines, phenobarbitone
- Taper and stop slowly over few weeks if patient has been taking Baclofen for more than 3 months.

LEVODOPA/CARBIDOPA

Dose Range

- 1-4 mg/kg/day (levodopa component). Start slowly at 1 mg/kg/day divided in 2 doses and increase to target 4 mg/kg/day in 3 divided doses.
- Can increase further if focal but clear benefit.

Symptoms useful for

- Dystonia management
- Can be very helpful when dystonia shows a trend of worsening as the day progresses or is exercise induced

Adverse effects

- Nausea

Comment

- About 25% efficacy for dystonia management in cerebral palsy but a safe drug to try
- Very useful in genetic dopamine responsive dystonia which can mimic CP but is rare.
- Some preparations are available as Levodopa/Benserazide. Dose guide is same for levodopa component

MEDICATIONS FOR BEHAVIOUR MANAGEMENT

CLONIDINE

Dose Range

- Start at 25 micrograms at night for sleep management
- Can increase to 25-100 microgram three times a day for behavior management

Start Symptoms useful for

- Management of hyperactive or aggressive behavior. e.g. biting, inattentive in school, disturbs other children, fidgety, can't sit still (these symptoms have to be sufficiently severe to be disruptive to daily home or school life to be considered for treatment)
- Also helpful for episodic management of severe dystonia in patients who get periodic worsening. Doses up to 100 micrograms 4-6 times per day can be helpful for short bursts of 3-4 days. Then wean back to baseline doses or stop

Adverse effects

- Sedation
- Sometimes postural dizziness due to postural hypotension – more likely at lower doses

Comment

- Wean slowly over a week if patient has been on clonidine for more than 3 months
- Average efficacy for ADHD, stimulants are better

RISPERIDONE

Dose Range

- 0.25mg – 5 mg/day in children. Try to manage on least efficacious dose

Symptoms useful for

- Management of hyperactive or aggressive behaviour.

Adverse effects

- Increased appetite
- Weight gain
- Metabolic disturbance – hyperlipidemia after years of use
- Extrapyramidal effects like rigidity

Comment

- Try clonidine first
- Can be quite useful if behavioral issues are really disruptive for daily life.

MEDICATIONS FOR EMERGENCY MANAGEMENT

DIAZEPAM

Dose Range

- 0.5 mg/kg <6 y/o; 0.3mg/kg 6-11 y/o; 0.2mg/kg >11y/o

Symptoms useful for

- Management of prolonged seizures >5 min at home.

Adverse effects

- Sedation
- Respiratory depression and arrest
- Local injury

Comment

- Only prescribe if family have received education on use and understand the administration process
- If a child is having a seizure in which he/she is convulsing or is unconscious, it is important to follow simple first aid measures ie. protection from injury, positioning on their side to assist breathing.
- Materials needed
    - a 25ml bottle of diazepam mixed with a stabilizing solution, containing 1mg of diazepam in each 1ml (or alternative concentration)
    - a reusable 10ml syringe
    - a reusable soft plastic tube to attach to the syringe for drawing up and injecting the diazepam
    - a sachet of lubricant jelly

REFERENCES

- Australian Medicines Handbook
- MIMS Australia
- Epocrates
- www.rch.org.au
- www.dhs.winsconsin.gov

Appendix C: Follow up questionnaire

Child's Name:				Gender:	☐ Male ☐ Female
Weight in kg:		Phone No:		DOB:	DD/MM/YYYY
Mother's Name:			Father's Name:		
Assessment Location:				Assessment Date:	DD/MM/YYYY

Check before phone call/follow up clinic:

☐ Medications and doses the child is on ☐ Was there a change made in the last clinic

Phone Call: ☎

1. Is your child taking the prescribed medication regularly?

☐ **No**, is your child taking any other medication? ☐ **Yes** → *Fill up table below* ☐ **No** → *Go to **3***

☐ **Yes**, *(Fill up table below)* Has there been any improvements? ☐ **Yes** → *Go to **2*** ☐ **No** → *Go to **2***

Name of Medication	**Formulation**	**Dose**	**Daily Dose Frequency**
☐ Valproic acid *[Valex/Epilim/Epilim/Valpro]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Phenobarbitone *[Barbit/Berdinal/Emer/Epinal/Pheno/Phenoba/Phenoson]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Epinephrine *[Adrinor/Adrenaline/Adrin]*	☐ Injection ☐ IV	☐ ___ ml ☐ ___ mg	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Benzodiazepine *[Clonazepam/Clobazam/Alsium/Clob/Clobam/Epson/ Frisium /Epiclon/Epnil/Leptic/Myotril/Rivotril/Rivo]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Clonidine *[Catapres 0.1/Clonipres 0.1]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tab	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Piracetam *[Neurolep/Neuratam/Piratam/Juvain/Piramax]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Baclofen *[Flexifen/Bacofen/Mylofen/Axant/Beclovan]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Trihexyphenidyl *[Hexinor/Trihexy]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Other*(write)*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4

2. Is your child seizure free at current dose?

☐ **Yes** → *End*

☐ **No**, Frequency of seizure: _____ per day / week / month / year

Average duration of seizure _____ minutes/hours

For those **not taking any medicine now**:

3. Has the medicine caused any problem? ☐ **Yes** → *Fill up table below and end.* ☐ **No** → *Go to **4**.*

	Problem	**Immediate action on the phone**
☐	Extensive rash developed on medication	Stop the medication and need to review urgently
☐	Child too drowsy to feed safely on medication	Reduce to older dose/previous medication
☐	Other Problem:	

4. Specify any other reason for not taking prescribed medication regularly:

_____

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-6
		(b) Give reasons for non-participation at each stage	Figure 3
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Figure 3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11-12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.