Q12: Should the treatment be similar in individuals with intellectual disability and epilepsy compared to people with epilepsy only?

Background

Cognitively impaired individuals with epilepsy refer to a person with epilepsy and associated intellectual disability or mental retardation or learning disability (as referred to in UK). For sake of convenience, in this document, the term "intellectual disability" would be used for the above spectrum of terms.

The development of epilepsy in a person with intellectual disability is a common occurrence, with an estimated overall prevalence rate of 14 to 44%, with prevalence increasing with severity of the disability (Bowley & Kerr, 2000). A more recent community-based study of epilepsy in intellectually disabled people showed a prevalence of 16%, a significant excess when compared to the general population (Morgan et al, 2003). In those with additional disabilities, such as cerebral palsy or postnatal brain injury, the prevalence of epilepsy can be as high as 75% (Goulden et al, 1991; Shepherd and Hosking 1989). The management of epilepsy in people with an intellectual disability provides special challenges due to a number of factors, including the aetiology and severity of the epilepsy, a limited evidence basefor interventions and difficulties in investigation and communication.

People with intellectual disabilities who also have epilepsy exhibit different types and frequency of seizures; they have a higher frequency of certain epilepsy syndromes, in particular the Lennox-Gastaut syndrome (Mariani,et al, 1993). Furthermore, the underlying cause of the intellectual disability may have an impact on seizure type and outcome, for example tuberous sclerosis is associated with a particular seizure disorder (Webb et al, 1991) as is Down syndrome (Stafstrom 1993).

Rates of behavioural disturbance and psychiatric disorder have been shown to be significantly higher in people with epilepsy compared to the general population and in people with an intellectual disability. There are a number of causes of behavioural disturbances in people with epilepsy and intellectual disability; antiepileptic medication is one of those causes. Conversely, beneficial behavioural effects in response to antiepileptic drugs (AED) have also been reported in people with epilepsy and intellectual disabilities (Beavis et al, 2007). In spite of the high prevalence of epilepsy in people with intellectual disabilities, interventional studies for the treatment of epilepsy are relatively rare. In view of the fact that seizures in intellectually disabled people are often complex and refractory to treatment, and that antiepileptic medication can have a profound effect upon behaviour in this patient group, it is important to assess the AED treatment and whether it should be similar in patients with epilepsy and intellectual disability than in patients with epilepsy only. For the purpose of this review, we would only focus on the standard AEDs (phenobarbital, carbamazepine, valproic acid and phenytoin).

There are a number of psychosocial interventions available to refractory patients which may be used in conjunction with or as an alternative to antiepileptic medication. It is also important to assess the role of psychosocial interventions in this special population group.

Population/Intervention(s)/Comparison/Outcome(s) (PICO)

Population:	individuals with epilepsy and intellectual disability
Interventions:	pharmacologic (standard AEDs) and psychosocial treatments
Comparison:	care as usual
Outcomes:	seizure reduction
	quality of life (QOL)
	adverse effects of AEDs

List of the systematic reviews identified by the search process

Beavis J, Kerr M, Marson AG (2007). Pharmacological interventions for epilepsy in people with intellectual disabilities. *Cochrane Database of Systematic Reviews,* (3).:CD005399. .

Stokes T et al (2004). NICE Clinical Guidelines and Evidence Review for the Epilepsies: diagnosis and management in adults and children in primary and secondary care. London: Royal College of General Practitioners.

Working group of the International Association of the Scientific Study of Intellectual Disability (2001). Clinical guidelines for the management of epilepsy in adults with an intellectual disability. Seizure, 10:401-9.

Search strategy

Cochrane review, NICE/SIGN and BMJ and PubMed MeSH were searched for epilepsy and intellectual disability. The following keywords were used: intellectual disability, mental retardation, cognitive impairment, epilepsy, antiepileptic drugs, carbamazepine, valproate, valproic acid, phenytoin, phenobarbital, phenobarbital, non-pharmacological treatment, surgery, diet, acupuncture.

Inclusion and exclusion criteria

Inclusion criteria: studies in humans, included patients with intellectual disabilities and epilepsy, observational or RCT studies

PICO table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews considered	Comments
	Pharmacological interventions			
I	**Antiepilepsy drug (AED)** (one vs. other AED)	Reduction in seizure frequency Adverse effects QOL	Beavis J, Kerr M, Marson AG (2007). Pharmacological interventions for epilepsy in people with intellectual disabilities. *Cochrane Database of Systematic Reviews,* (3):CD005399.	**Wasn't relevant to the 4 standard AEDs.** Summary: broadly support use of AED in this population, similar side effects (i.e., behavioural side effects). Based on heterogeneous data from 12 studies.
		Adverse effects	Stokes T et al (2004). NICE Clinical Guidelines and Evidence Review for the Epilepsies: diagnosis and management in adults and children in primary and secondary care. London: Royal College of General Practitioners.	Related recommendation not evidence based. Summary: particular attention should be paid to the possibility of adverse cognitive and behavioural effects.
		Reduction in seizure frequency Adverse effects	Working group of the International Association of the Scientific Study of Intellectual Disability (2001). Clinical guidelines for the management of epilepsy in adults with an intellectual disability. Seizure, 10:401-9.	Related recommendation not evidence based. Summary: Ensure that the patient has received appropriate first-line drug treatment for their seizure type and syndrome.
	Non-pharmacological interventions			
	Specialized diet (or	Reduction in seizure frequency	Beavis J, Kerr M, Marson AG	Not relevant for 1st and 2nd levels

	supplementation) ***Ketogenic diet, vitamin and folic acid supplementation***	Adverse effects	(2007). Pharmacological interventions for epilepsy in people with intellectual disabilities. *Cochrane Database of Systematic Reviews,* (3):CD005399.	of health care. no RCTs were included in the review
	Psychological intervention	Reduction in seizure frequency Adverse effects	Beavis J, Kerr M, Marson AG (2007). Pharmacological interventions for epilepsy in people with intellectual disabilities. *Cochrane Database of Systematic Reviews,* (3):CD005399.	No relevant data
	Acupuncture	Reduction in seizure frequency Adverse effects	Beavis J, Kerr M, Marson AG (2007). Pharmacological interventions for epilepsy in people with intellectual disabilities. *Cochrane Database of Systematic Reviews,* (3):CD005399.	No relevant data

Narrative description of the studies

Systematic reviews

Beavis et al, 2007 compared 12 RCTs of eight different pharmacological agents, although **no included studies were relevant to the four standard AEDs (phenobarbital, carbamazepine, valproic acid and phenytoin)**. Meta-analyses were not possible due to the heterogeneity of the study methodologies, design, patient populations and outcome measures. However, this review confirms that the majority of this population obtained a moderate reduction in seizures and occasional seizure freedom with AEDs. Thus, it seems reasonable to say that the pharmacological management of epilepsy in patients with intellectual disabilities has similar effectiveness as in the general epilepsy population. Clinical decision-making will most probably be influenced by possible side-effects, most importantly behavioural exacerbation which can be a major issue in people with complex co-morbidity who are often in supported care environments (Beavis et al, 2007).

Non-systematic reviews

Phenobarbital:

No controlled data is available on the use of phenobarbital in children with epilepsy and intellectual disability. However, in children with epilepsy, a systematic review of 11 RCTs of febrile convulsions and nine RCTs of childhood epilepsy showed no evidence for a difference in antiepileptic efficacy between phenobarbital and any other compared AEDs (Pal, 2006). Reports of cognitive and behavioural side effects are conflicting. Masked studies of phenobarbital in childhood epilepsy have shown no significant differences in behavioural or cognitive adverse effects compared to other AEDs. However, one finding of reduction in cognitive ability associated with phenobarbital treatment for febrile convulsions remains a concern. (Farwell et al, 1990). A prospective RCT from Bangladesh measured seizure control and behavioural side effects in 108 children with generalized tonic-clonic or partial and secondary generalized seizures. They found no significant difference in behavioural side effects with phenobarbital and carbamazepine using objective masked assessments and parental reports (Banu et al, 2007). However, another systematic review details that the most consistent findings with regards to behaviour are the exacerbation of behaviour disorders, mostly hyperactivity, as well as sleep disorders and depression in individuals who already had a predisposition to these problems (Alvarez 1998).

Phenytoin, carbamazepine and valproic acid:

A controlled study compared the social skills of individuals with intellectual difficulties taking monotherapy of carbamazepine (CBZ), valproic acid (VPA) or phenytoin (PHT). Individuals with intellectual disabilities taking either carbamazepine or valproic acid were no different from their matched control groups (with intellectual disability but without epilepsy) in regards to their social skills, whereas those taking phenytoin presented lower positive non-verbal and general positive social skills than their matched control groups (Matson et al, 2004). The study's methodological limitations were mainly the three matched control groups without epilepsy.

Reference	Design	Sample size and demographics	Comparison methods	Limitations	Results

<table>
<tr>
<td>Matson JL, Luke MA, Mayville SB (2004). The effects of antiepileptic medications on the social skills of individuals with mental retardation. Research in Developmental Disabilities, 25:219-28.</td>
<td>Controlled observational study</td>
<td>N=130
(65 patients with epilepsy and intellectual disability receiving either carbamazepine, phenytoin or valproic acid were matched to 65 controls with intellectual disability but without epilepsy)</td>
<td>Social skills measures (questionnaire for individuals with intellectual disability)</td>
<td>Each control group did not have epilepsy</td>
<td>
<table>
<tr><th></th><th>PHT (mean (SD))</th><th>PHT-control (mean (SD))</th><th>p-value</th></tr>
<tr><td>Positive non-verbal</td><td>16.9 (10.9)</td><td>27.0 (11.7)</td><td>.004</td></tr>
<tr><td>General positive</td><td>24.9 (19.2)</td><td>40.3 (18.4)</td><td>.008</td></tr>
</table>
<table>
<tr><th></th><th>CBZ</th><th>CBZ-control</th><th>p-value</th></tr>
<tr><td>Positive non-verbal</td><td>16.0 (12.2)</td><td>19.6 (13.1)</td><td>>.05</td></tr>
<tr><td>General positive</td><td>24.1 (19.9)</td><td>27.3 (20.0)</td><td>>.05</td></tr>
</table>
<table>
<tr><th></th><th>VPA</th><th>VPA-control</th><th>p-value</th></tr>
<tr><td>Positive non-verbal</td><td>20.9 (11.5)</td><td>18.0 (14.5)</td><td>>.05</td></tr>
<tr><td>General positive</td><td>27.2 (19.1)</td><td>25.0 (20.0)</td><td>>.05</td></tr>
</table>
</td>
</tr>
</table>

Monotherapy vs. polytherapy and drug interactions

Individuals with epilepsy and intellectual disability are often treated with various combinations of drugs, such as anticonvulsants and psychotropic drugs. Adverse reactions due to drug interactions, mostly affecting the central nervous system, are common and better seizure control is not always ensured.

Simplifying therapy provides true benefits for some patients in terms of seizure control and reduction of drug toxicity. No controlled data are available but an uncontrolled observational study showed that anticonvulsants are used excessively in patients with epilepsy and intellectual disabilities, since a withdrawal of some anticonvulsant drugs showed no significant worsening of epilepsy, and in some cases improvement in seizure frequency. This was particularly true for patients whose seizures had been controlled for prolonged periods. The proportion of relapse was higher among patients who were being treated with two or more drugs. Individuals with epilepsy and intellectual disabilities often have more complex epilepsy and may well have been more difficult to treat (Beghi et al, 1987).

Methodological limitations

Methodological limitations encountered: paucity of RCT or good quality observational studies in individuals with intellectual disability and epilepsy and role of AEDs and psychosocial interventions.

The Cochrane review (Beavis et al, 2007) on pharmacological treatments was unable to perform meta-analyses due to the heterogeneity of the study methodologies, design, patient populations and outcome measures. No included studies were relevant to the four standard AEDs (phenobarbital, carbamazepine, valproic acid and phenytoin).

No RCT met the inclusion criteria for the Cochrane review on psychosocial interventions.

Directness (in terms of population, outcome, intervention and comparator)

In the absence of direct evidence, indirect comparison of standard AEDs was used for epilepsy and intellectual disability. Furthermore, the two systematic reviews of phenobarbital were conducted in children with epilepsy without any intellectual disability.

Narrative conclusion

People with intellectual disability and epilepsy should have access to the same range of investigations and treatment as the rest of the population (Stokes et al, 2004). The AED treatment of choice in patients with epilepsy and intellectual disabilities should depend on the type of seizure and the standard treatment. It is important to manage seizures (seizure reduction, seizure freedom) in patients with epilepsy and intellectual disabilities in order to avoid additional cognitive impairment from inappropriate AEDs, and since prolonged seizures may cause additional cognitive impairment (Alvarez, 1998).

However, in patients with epilepsy and intellectual disabilities, who are susceptible to balance disturbances and cognitive dysfunction, one may consider trying either valproic acid or carbamazepine instead of phenytoin or phenobarbital due to behavioural adverse effects (Livanainen 1998; Matson et al, 2004). There is

a paucity of good quality data on the choice of pharmacological and psychosocial interventions in this special population group, thus more research (intervention data, behavioural and cognitive safety) is needed in this population.

Reference list

Alvarez N (1998). Barbiturates in the treatment of epilepsy in people with intellectual disability. *Journal of Intellectual Disability Research,* 42 (Suppl 1):16-23.

Banu SH et al (2007). Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial. *British Medical Journal,* 334:1207.

Beavis J, Kerr M, Marson AG (2007). Pharmacological interventions for epilepsy in people with intellectual disabilities. *Cochrane Database of Systematic Reviews,* Issue 3. Art. No.: CD005399. DOI: 10.1002/14651858.CD005399.pub2.

Beghi E et al (1987). Effects of rationalizing drug treatment of patients with epilepsy and mental retardation. *Developmental Medicine & Child Neurology,* 29:363-9.

Bowley C, Kerr M (2000). Epilepsy and intellectual disability. *Journal of Intellectual Disability Research,* 44 (Pt 5):529-43.

Farwell JR et al (1990). Phenobarbital for febrile seizures-effects on intelligence and on seizure recurrence. *New England Journal of Medicine,* 322:364-9.

Goulden KJ et al (1991). Epilepsy in children with Mental Retardation: a cohort study. *Epilepsia,* 32:690-7.

Iivanainen M (1998). Phenytoin: effective but insidious therapy for epilepsy in people with intellectual disability. *Journal of Intellectual Disability Research,* 42(Suppl 1):24-31.

Mariani E et al (1993). Epilepsy in institutionalized patients with encephalopathy: clinical aspects and nosological considerations. *American Journal of Mental Retardation,* 98(Suppl):27-33.

Matson JL, Luke MA, Mayville SB (2004). The effects of antiepileptic medications on the social skills of individuals with mental retardation. *Research in Developmental Disabilities,* 25:219-28.

Morgan CL, Baxter H, Kerr MP (2003). Prevalence of epilepsy and associated health service utilization and mortality among patients with intellectual disability. *American Journal on Mental Retardation,* 108:293–300.

Pal DK (2006). Phenobarbital for childhood epilepsy: systematic review. *Paediatric and Perinatal Drug Therapy,* 7:31-42.

Shepherd C, Hosking G (1989). Epilepsy in school children with intellectual impairments in Sheffield: the size and nature of the problem and the implications for service provision. *Journal of Mental Deficiency Research, 33*(Pt 6):511-4.

Stafstrom CE (1993) Epilepsy in Down syndrome: clinical aspects and possible mechanisms. *American Journal on Mental Retardation,* 98(Suppl):12-26.

Stokes T et al 2004). NICE Clinical Guidelines and Evidence Review for the Epilepsies: diagnosis and management in adults and children in primary and secondary care. London: Royal College of General Practitioners.

Webb DW, Fryer AE, Osborne JP (1991). On the incidence of fits and mental retardation in tuberous sclerosis. *Journal of Medical Genetics,* 28:395-7.

Working group of the International Association of the Scientific Study of Intellectual Disability (2001). Clinical guidelines for the management of epilepsy in adults with an intellectual disability. *Seizure,* 10:401-9.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	*Pharmacological interventions* Cochrane review did not include studies relevant to the four standard AEDs. Stokes et al, 2004, BMJ and a review in Seizure (2001) had related recommendations which were not evidence based. A literature search for any study on AEDs, epilepsy and intellectual disability found a paucity in available data. No controlled data was available on the use of phenobarbital in children with epilepsy and intellectual disability. However, in childhood epilepsy, a systematic review showed no difference in antiepileptic efficacy between phenobarbital and other compared AEDs. Reports of cognitive and behavioural side effects are conflicting. A controlled study compared the social skills of individuals with intellectual difficulties taking monotherapy of carbamazepine, valproic acid or phenytoin. Individuals taking phenytoin presented lower positive non-verbal and general positive social skills than their matched control groups (Matson et al, 2004). The study's methodological limitations were mainly the three matched control groups without epilepsy. An uncontrolled observational study showed that AEDs are used excessively in patients with epilepsy and intellectual disabilities, since a withdrawal of some anticonvulsant drugs showed no significant worsening of epilepsy, and in some cases improvement in seizure control (Beghi et al, 1987). *Psychosocial interventions* No relevant RCT/observational studies found.
Summary of the quality of	No direct evidence available, poor and scarce data. Evidence mainly extrapolated from evidence from people

evidence	with epilepsy without intellectual disability.
Balance of benefits versus harms	Generally, AEDs shown to be effective in the general population are also effective in epilepsy in people with intellectual disability. Extrapolated evidence from phenobarbital and phenytoin studies does suggest a higher risk of behavioural adverse effect in this special population group.
Values and preferences including any variability and human rights issues	Epilepsy and intellectual disability are common comorbidities. This group of population is often vulnerable, neglected and untreated. It is important to manage seizures (seizure reduction, seizure freedom) in patients with epilepsy and intellectual disabilities in order to avoid additional cognitive impairment from inappropriate AEDs, and since prolonged seizures may cause additional cognitive impairment (Alvarez, 1998).
Costs and resource use and any other relevant feasibility issues	People with intellectual disabilities who also have epilepsy exhibit different types and frequency of seizures; they have a higher frequency of certain epilepsy syndromes. They also require investigations to identify the underlying cause of the intellectual disability which may have an impact on seizure type and outcome. Seizures in intellectually disabled people are often complex and refractory to treatment, thus requiring referral to tertiary facilities and supervisory support.
Final recommendation(s) People with intellectual disability and epilepsy should have access to the same range of investigations and treatment as the rest of the population. Strength of recommendation: STRONG The antiepileptic drug treatment of choice in individuals with intellectual disability and epilepsy should depend on the type of seizure and should be individualized. However, in individuals with epilepsy and intellectual disabilities, when available, one may consider either valproic acid or carbamazepine instead of phenytoin or phenobarbital due to lower risk of behavioural adverse effects. Strength of recommendation: STANDARD	

Update of the literature search – June 2012

Antiepileptic drug therapy in individuals with intellectual disability & epilepsy

In June 2012 the literature search for this scoping question was updated. The following systematic review was found to be relevant without changing the recommendation:

Beavis J, Kerr M, Marson AG, Dojcinov I. Non-pharmacological interventions for epilepsy in people with intellectual disabilities. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005502. DOI: 10.1002/14651858.CD005502.pub2.