Identifying and prioritising epilepsy treatment uncertainties

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Identifying and prioritising epilepsy treatment uncertainties

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Abstract

Objective

To identify and prioritise uncertainties regarding epilepsy treatment from people with epilepsy, their carers and from epilepsy clinicians.

Background

Failure to acknowledge and address genuine treatment uncertainties has caused unnecessary iatrogenic harm. We define an uncertainty as a question that cannot be sufficiently answered by a systematic review of the literature. The database of the uncertainties of the effects of treatment (DUETs) is a collection of 'known unknowns' that enables patient-prioritised research.

Design and Participants

We organised five separate focus groups (two consisting of clinicians, three of patients and carers) to garner questions on epilepsy treatment uncertainties; these yielded 398 potential research questions. Participants were asked to rank the questions in terms of importance. We then performed a thematic analysis.

Results

Patients rated questions concerning cognitive drug side-effects, managing the consequences of side-effects and improving public awareness about the treatment of epilepsy through improved services as most important. For clinicians, the most important themes were

treatment programmes for non-epileptic attack disorder (NEAD), concerns about side-effects *in utero* and uncertainties regarding prescribing in pregnancy.

Conclusions

Patient uncertainties were often focussed on very practical considerations – how to take prescribed medication, access to services and how to minimise drug side effects. Clinicians' questions were also practical but clustered around 'the challenging consultation' e.g. NEAD, sudden unexplained death in epilepsy (SUDEP) and prescribing in pregnancy. We have published the research questions on NHS Evidence, and are working with them to identify those questions which represent genuine uncertainties. We encourage other clinicians to seek patient and carers' priorities in order to shape their research agenda.

Introduction

It is often unclear how research topics are chosen and prioritised. Industry-sponsored projects may be selected to display their product to advantage[1,2] and availability of time, money and personnel may determine topics chosen for independent investigation.[3] Grant committees rightly ask applicants to consider patients' views when submitting an application, but this is difficult without knowledge of exactly *what is uncertain* and which topics are patient priorities. Do funded research questions address the priorities of people with epilepsy? [4] Do they even reflect the uncertainties prioritised by clinicians?

When prescribing for certain groups, e.g. people with epilepsy and learning disability, we often work in an evidence vacuum, extrapolating from relevant studies of related patient groups. Our comfort with uncertainty and our acceptance of this 'grey area' has unwittingly promoted a climate where immeasurable harm is perpetrated through labelling situations as "uncertain" where there is already sufficient evidence to make them certain; e.g.,

corticosteroids in head injury,[5] caffeine for neonates[6] or prophylactic anti-arrhythmics after myocardial infarction.[7] The James Lind Initiative aims to promote "identification of the most important gaps in knowledge about the effects of treatments" through developing a database of uncertainties of treatments (DUETs), published on-line at NHS Evidence.[8] As part of this project we facilitated people affected by epilepsy and its treatment (patients, carers, clinicians and scientists) to create and prioritise treatment uncertainties.

Methods

Using qualitative methodology based upon the consultations in rheumatoid arthritis,[9] we arranged five separate focus groups: three with patients and carers and two with clinicians and health professionals. The sequence of meetings was Cardiff professionals, Cardiff patients, Swansea professionals, Swansea patients and Cardiff patients; beyond geographical convenience there was no attempt to place people in specific focus groups for balance. Patients were invited from several sources: clinic appointments, previous involvement in local projects with the Wales Epilepsy Research Network (WERN), and membership of local charity groups. Involvement was voluntary and unpaid; meetings lasted 90 to 120 minutes. We did not discourage anyone from attending who expressed an interest in doing so. Participants were invited to try to ensure a balance of adult and paediatric, oligoepilepsy and refractory epilepsy, pre- and post-surgical candidates, people with learning disability, parents and children, carers and support workers (see Box 1).

Box 1. Focus group participants

	Professionals (n=16)	**Patients and carers** (n=25)	
Sex	Male (8)	**Sex**	Male (8)
Role	Adult neurology consultant (4) Paediatric neurology consultant (2) Learning disability consultant (1)	**Role**	Patients (19) Carers (6)

	Neurology registrar (3) General Practitioner (1) Epilepsy nurse specialist (4) Genetic counsellor (1) Dietician (1)	**Mean Age** **Age Range**	Patients (46.6 years) Carers (50.8 years) Patients(23-69 years) Carers (34-69 years)

Each meeting had the same agenda and two of us were present to write the questions onto an overhead projector and to chair the discussion. The focus groups were asked to identify questions addressing treatment uncertainties; therefore we excluded questions exclusively addressing diagnosis, service complaints or the natural history of epilepsy. When facilitating the meetings we encouraged each participant to consider all patient-groups and possible treatments, and offer questions on the topic. So as to maintain participation we did not attempt (during the consultation) to answer any of the questions posed, or suggest that the answers may already be known. Each participant then ranked the questions created in their meeting only, enabling us to identify the most important potential research questions.

Thematic Analysis

Using an interpretive phenomenological approach to analysis we used not only the text of the question produced but our knowledge of who asked the question and the context it was created in to better understand what was being asked. Blinded to the ranking, CH and RT grouped the questions into themes to allow us to compare professionals' and patients' questions both in content, number and relative ranking. Some sub-categories involving special groups (e.g. people with learning disability or children) were teased out from the main themes for comparison (Box 2). The themes were developed both individually and in group work until it was agreed that the identified themes were all-encompassing and useful. We did not limit the number of questions that could be posed over the course of a meeting and therefore to compare the relative rank we must adjust for the number of questions. We standardised each prioritised question as a value on a scale between 1 and 100; the lower the standardised rank score, the more important its rating. In order to test the significance

of the differences between focus groups or themes, we examined the most highly ranked questions. We identified, for every participant, the number of questions from each theme ranked in the top quartile. We performed the Mann Whitney U test, using asymptotic significance, to identify differences between the focus groups, or between the themes, with statistical significance taken as $p<0.05$. We identified both differences between the two groups and the similarities: the shared priorities. Finally, a database of unique uncertainties was produced for publication in the UK DUETs database.[6]

Box 2. Thematic groupings

Who should be treating epilepsy?

Prescribing Uncertainties

- Special groups – Children, older people and pregnancy
- Financial Influence
- Ongoing therapeutic monitoring
- Uncertainties about drug action (such as drug interactions)
- **Drug Side Effects**
  - Recognition and acknowledgement of side effects
  - Management of drug side effects
  - Specific side effects – mood, fertility, bone health, cognitive side effects and side effects *in utero*
  - Learning disability
- **Acute treatments**
  - Oxygen and midazolam
  - Status and non convulsive status epilepticus
- **Drug Withdrawal**
  - Including withdrawal in non epileptic attack disorder

How best to take prescribed medications

- Adherence with prescribed medications

Epilepsy Surgery

- Choice and pre-surgical considerations
- Uncertainties following surgery

Non-drug treatments of epilepsy that are supervised by a professional

- Nutritional support

Considering the patient as an individual

- Special groups – Pregnancy, older people, learning disability
- Non epileptic attack disorder
- **The effect of lifestyle on seizures**
  - Drugs, alcohol and diet
  - Complementary therapies and stress management
- **Epilepsy co-morbidities**
  - Depression, cognitive problems and sudden unexplained death in epilepsy
- **Information based epilepsy management**
  - Patient centred-services
  - Public awareness of seizure management

Results

The meetings produced 188 questions from 25 patients and carers and 210 questions from 17 professionals. Despite the repetition of research themes, patients and clinicians posed

only eleven identical questions. Box 3 shows the top two prioritised questions from each group.

Box 3. Highest ranked research questions

Both groups prioritised practical uncertainties affecting the greatest number of people ahead of esoteric questions or single issue, minority group uncertainties.

Patients and carers

"Should you take a forgotten dose as soon as you remember or skip a dose and take your next dose as normal?

"What training should teachers and school nurses have about epilepsy and treatment of seizures?"

Clinicians

"What are the neuro-developmental effects of exposure to each of the AEDs in pregnancy?"

"How is the choice of second monotherapy influenced by the seizure type/syndrome?"

Patients and carers

Patients' and carers' highest-ranked themes were: cognitive drug side-effects (mean standardised rank 13.3, n=5); managing the consequences of any side-effect from an AED (25.7, n=5); improving public awareness about the treatment of epilepsy and seizures through services (26.2, n=8) and non-medical treatment of cognitive problems (28.1, n=2). Patients rated information-based management (such as improving public awareness) a consistently higher priority than did clinicians (p=0.001).

Clinicians

The highest-ranked uncertainties concerned the following themes: individual differences in the treatment of non-epileptic attack disorder (mean rank 10.2, number of questions=3); antiepileptic drugs (AEDs) side effects; AEDs exposure *in utero* (11.5, n=3); prescribing in pregnancy (14.2, n=50; treatment of depression in epilepsy (17.8, n=3) and AED mood side effects (19.1, n=5). Box 4 illustrates key questions from the themes. Clinicians rated

prescribing uncertainties (including for older people, children and in pregnancy) as more important than patients did ($p<0.0001$). In contrast AED side-effects were more important to patients and carers ($p<0.0001$).

Box 4. Example questions from key themes

Patients and Carers

Managing the consequences of any AED side effect

"How frequently should we test or look for side effects of AEDs?"

Improving public awareness about the treatment of epilepsy and seizures through services

"Would rapid access to epilepsy specialists improve treatment for people with epilepsy?"

Clinicians

Considering individual differences in the treatment of non epileptic attack disorder

"What is the best treatment programme for non-epileptic attacks?"

Individual differences in the treatment of depression in epilepsy

"What is the optimal support for those with depression and epilepsy?"

Shared priorities

Cognitive drug side effects

Patients – "Do different epilepsy medications affect people differently? Are the problems reversible?"

Clinicians – "Are certain people more likely to develop cognitive side effects and can they be predicted?"

Improving epilepsy control by improving public awareness of epilepsy

Patients – "What advice should be given to all schools about epilepsy and how would this improve epilepsy control for school children?"

Clinicians – "Can better education about epilepsy improve quality of life for people with epilepsy by reducing stigma?"

Shared prioritisation	MSR	Clinicians' questions	Clinicians - top quartile	Patients' questions	Patients - top quartile
Cognitive drug side effects	21.4	**4**	3	**5**	4
Public awareness	25.4	**1**	0	**8**	3
Mood side effects	26.3	**5**	3	**1**	0
Prescribing in pregnancy	27.3	**5**	4	**2**	0
Treatment of depression as a co-morbidity	30.1	**3**	2	**2**	1
Drug withdrawal	34.1	**10**	2	**1**	0
Adherence	35.2	**10**	0	**2**	0
In utero side effects	35.9	**3**	2	**6**	2
Information and self-management	36.2	**3**	0	**3**	1
Recognition and acknowledgment of side effects	37.8	**3**	1	**9**	2
Management of side effects	37.9	**3**	0	**5**	4
Pre-surgical choices	38.3	**10**	4	**4**	2

Table 1. Top 12 shared priorities. MSR – Mean Standardised ratio – the smaller the number the more important the theme, **Clinicians' questions** – number of questions in this theme produced from clinicians' meetings, **Top quartile** – number of questions about that theme which are ranked in the top quartile **Patients' questions** - number of questions in this theme from patients and carers.

Shared priorities

There was a great deal of consensus between the groups concerning the themes that were important to both. The most important shared priority was research into the cognitive side-effects of AEDs. Five of the top 12 shared priorities concerned AED side-effects, two pregnancy priorities and two mood disorders uncertainties. Themes that dealt with starting AEDs were more of a priority than AED withdrawal ($p<0.001$).

Discussion

This study demonstrates that patients and clinicians have different agendas when asked independently to produce and prioritise lists of treatment uncertainties. We recognise some limitations including that the presence of a doctor at the three patient meetings may have introduced an observer bias and that there were no newly-diagnosed patients in those groups. The uncertainties generated by our participants are certainly not exhaustive, in part

because we concentrated on treatment rather than natural history, causation and investigation. Our list of epilepsy therapeutic uncertainties needs to be supplemented by 'fresh' prospectively gleaned uncertainties by scouring recent Cochrane and other systematic reviews, and clinical guidelines. Furthermore, the database, no matter how dynamic, is redundant if we do not attempt to confirm whether the questions posed (by both clinicians and patients) are genuine uncertainties, i.e. 'known unknowns'. The first sixty questions have been scrutinised via systematic review and the outcomes published on the DUETs website of NHS Evidence: the majority have remained uncertainties following review.[8] This project provides the framework and content which can be used by professionals in targeting genuinely patient-focussed research and we welcome validation of these results from other cohorts and geographical areas.

Practical considerations

We might have expected patients to focus more on their individual needs regarding epilepsy treatment; however the qualitative and statistical analysis does not generally support this. Not only did epilepsy professionals produce an equal number of questions under the theme of *"considering the patient as an individual"* (n=14) but they ranked these uncertainties as more important than patients did. Both groups prioritised practical considerations that were specific to them.

Fifteen questions produced exclusively by patients and carers focused on how to take prescribed medication, (theme 'how best to take AEDS' Box 2). Four questions were raised about the general practitioner's role in epilepsy: all came from patients and carers, including two questions about repeat prescription access. Strikingly, not only did patients and carers generate 8 of the 9 questions regarding public awareness of epilepsy and seizures, but three of these questions were in the patients and carers' top quartile.

Clinicians also prioritised practical considerations *from their viewpoint,* all of which clustered around 'the challenging consultation'. Clinicians posed all the questions about treatment of non-epileptic attack disorder (NEAD) (n=6, 2 were highly rated). Clinicians also accorded side effects *in utero* and prescribing issues in pregnancy greater importance than patients and carers did. However, half of the patients were 45 years or older and as a result may not have rated prescribing in pregnancy as a priority. Patients and carers did not volunteer any of the questions about prevention of sudden unexpected death in epilepsy (SUDEP) (n=3); clinicians produced all ten questions focussing on older people's needs (6 regarding prescribing AEDs, 4 focussing on more general therapeutic needs); clinicians asked most of questions on the considerations before starting treatment (8/9), medication adherence (10/11) and nutritional support (11/12).

Priorities

When discussing uncertainties about epilepsy treatment, we expected to receive questions about 'curing epilepsy' and achieving life-long seizure freedom: such questions were conspicuous by their absence. Patients asked two questions and epilepsy professionals eleven, regarding how best to *manage* seizure freedom – most of these questions were about safe drug withdrawal. Does this mirror pragmatism (as opposed to idealism) represented in the important priorities? Epilepsy is not necessarily life-long – several participants had achieved seizure freedom, both with surgery and medication.

We are still at an early stage in promoting an environment which engenders genuine patient involvement in posing questions and developing outcomes that matter [10], and in mapping mismatches between researchers' and patients' priorities. For patients with rheumatoid arthritis, the priority treatment outcome is not pain reduction, but control of fatigue and

sleep quality.[9,11,12,13] The James Lind Alliance has identified patient research uncertainties in several other conditions including schizophrenia[14] and urinary incontinence.[15] A key theme from their priority setting partnership for incontinence mirrors the practical considerations of people with epilepsy: people with continence difficulties want more public toilets.

Conclusion

We encourage researchers in other disciplines to engage with patients and carers to help people with a personal experience of a condition to express their research priorities and condition-specific uncertainties. We would welcome any group keen to address an epilepsy uncertainty or to undertake a systematic review to consult DUETs. We will need the help of the epilepsy community in both continuously updating the uncertainty database and answering the questions that are raised. 'Uncertainties' is an occasional BMJ feature [16,17] that is supported by editors of BMJ Knowledge, BMJ Clinical Evidence, and BMJ Point of Care. We would like to encourage authors and editors to consider explicitly the *uncertainties* apparent in a body of work, in addition to the areas that they directly address.

What is already known on this topic?

Patients are seldom asked to identify important research questions; surprisingly neither are health care professionals.

Failure to identify areas where current knowledge is deficient—'uncertainties'—can have serious negative effects on patient care.

What this study adds

The epilepsy research agenda has not been prioritised in this way before.

This study identifies research topics that are highly valued by both patients and clinicians.

Practical questions are prioritised by people with epilepsy suggesting that simple pragmatic projects would most closely meet their needs.

Ethics

This study involves patients and professionals as partners in a consultancy about research and as such no one is considered a participant in research.[18]

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Conflicts of interest

All authors declare that the answer to the questions on your competing interest form are all 'no' and therefore have nothing to declare.

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