



## Comparative neuropsychology of Lewy body and Alzheimer's dementia

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EDITORIAL

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## New drug treatments for epilepsy

After the introduction of valproate in 1973, excluding benzodiazepines, there was a 19 year gap before the introduction of vigabatrin, the first in a series of new antiepileptic drugs to be developed and licensed. At the time of writing gabapentin, lamotrigine, oxcarbazepine, tiagabine, and topiramate have a licence in the United Kingdom. Zonisamide and levetiracetam are licensed in some countries outside the United Kingdom. In this article, we review some of the evidence for the effectiveness and tolerability of these new drugs. We also attempt to draw attention to lessons learned and the conflict between the needs of the pharmaceutical industry, the clinician, and the patient.

### New antiepileptic drugs as add-on treatments

#### DRUG REFRACTORY LOCALISATION RELATED EPILEPSY

New antiepileptic drugs are licensed as add-on treatments in the first instance, efficacy and safety having been demonstrated in randomised placebo controlled add-on trials, with additional safety data predominantly derived from follow on studies. Results from follow on studies are often difficult to interpret because comparisons are no longer randomised.

#### Efficacy of new drugs as add-on therapy

Drug	Dose (mg/day)	50% or greater reduction in seizures	
		Proportion/dose (95% CI)	Odds ratio (95% CI) across range of doses
Gabapentin	0 (placebo)	9.9 (7.2-13.5)	
	600	14.4 (12.0-17.3)	
	900	17.3 (14.6-20.3)	
	1200	20.6 (17.1-24.6)	
	1800	28.5 (21.5-36.7)	
	600-1800		2.29 (1.53-3.43)
Tiagabine	0 (placebo)	6.2 (3.9-9.7)	
	16	9.8 (4.5-20.1)	
	30-32	21.6 (17.7-26.0)	
	56	29.8 (19.4-42.8)	
	16-56		3.03 (2.01-4.58)
Topiramate	0 (placebo)	11.6 (8.0-16.6)	
	200	26.7 (15.8-41.3)	
	400-1000	45.7 (41.3-50.1)	
	200-1000		4.07 (2.87-5.78)
Vigabatrin	0 (placebo)	13.8 (9.7-19.2)	
	1000 or 2000	22.8 (14.5-34.0)	
	3000 or 6000	45.9 (39.5-52.5)	
	1000-6000		3.67 (2.45-5.51)
Lamotrigine	200-500		2.32 (1.47-3.68)
Levetiracetam	1000-3000		3.81 (2.78-5.22)
Oxcarbazepine	600-2400		3.35 (2.32-4.83)
Remacemide	300-1200		1.63 (0.92-2.87)
Zonisamide	500		2.72 (1.74-4.25)

Proportion/dose shows the estimated proportion of patients with a 50% or greater reduction in seizure frequency.

Trials usually recruit patients with drug refractory partial seizures. Patients are first of all observed during a prerandomisation baseline period of 8-12 weeks duration. Provided they have a sufficient a number of seizures (usually four a week), they are randomised to have either active drug or placebo added to their regime, and are followed up for 12-16 weeks. Efficacy is assessed by comparing individual patient's seizure frequency during the treatment period with the baseline period. Median reduction in seizure frequency and the number of patients with a 50% or greater reduction in seizure frequency (responders) are usually reported as efficacy outcomes.

The table summarises the results of intention to treat analyses from a systematic review of placebo controlled add on studies investigating gabapentin, lamotrigine, tiagabine, topiramate vigabatrin, and zonisamide in patients with drug refractory localisation related seizures,<sup>1 2</sup> and in addition shows data for levetiracetam (UCB Pharma) and remacemide (AstraZeneca Pharmaceuticals) and oxcarbazepine (Novartis). For gabapentin, tiagabine, topiramate, and vigabatrin, the table shows estimated proportion of 50% responders/dose derived from regression models. For lamotrigine, levetiracetam, and zonisamide, the table shows odds ratios for a 50% reduction in seizures compared with placebo across a range of doses.

Regression models were not able to distinguish between doses of 400-1000 mg/day of topiramate, suggesting a plateauing of therapeutic response. Results were similar for vigabatrin, where regression models were unable to distinguish between doses of 3000-6000 mg/day. Results for gabapentin and tiagabine show no plateauing of therapeutic response and for gabapentin in particular, it is likely that optimal doses have not been tested. For remacemide, estimates of efficacy are low, and an odds ratio across doses shows no significant effect. A significant effect was found for higher doses (800-1200 mg/day)

#### DRUG REFRACTORY GENERALISED EPILEPSY

There is some evidence for efficacy of topiramate against generalised tonic clonic seizures in drug refractory patients,<sup>3</sup> but a trial comparing 1200 mg/day of gabapentin with placebo found no significant difference between treatment groups.<sup>4</sup> There is no evidence from randomised clinical trials to support or refute the efficacy of the other new drugs in drug resistant generalised epilepsies, other than in Lennox-Gastaut syndrome (see below). It is therefore surprising that in the absence of such evidence, lamotrigine is considered by some to be a first choice add-on

treatment for patients with generalised epilepsy syndromes such as juvenile myoclonic epilepsy.

#### LENNOX-GASTAUT SYNDROME

There is some evidence of efficacy of lamotrigine<sup>5</sup> and topiramate<sup>6</sup> for patients with this difficult epilepsy syndrome; however, trials have been of short duration (16 weeks), and treatment effects small. For example, in a trial comparing lamotrigine with placebo, 33% of the lamotrigine versus 16% of the placebo group had a 50% or greater reduction in seizure frequency.

#### Limitations of existing evidence for add-on use of new antiepileptic drugs

Gowers warns, when discussing evidence for the efficacy of bromides, that: "Indications for special treatment in epilepsy is a subject of greatest importance. There is no point in therapeutics however more open to fallacy, or on which more generalisations have been published, which subsequent observation has proved inaccurate."<sup>7</sup>

His comments are still of relevance today. Although these trials were predominantly undertaken for the purpose of getting a license for add-on use, care is needed when trying to use these results in clinical practice, and many important clinical questions remain unanswered:

#### WHAT DOES A 50% REDUCTION IN SEIZURE FREQUENCY MEAN TO THE INDIVIDUAL PATIENT?

There is convincing evidence that reducing a patient's seizure frequency is the most important contributor to a change in quality of life.<sup>8</sup> However, the true meaning of a 50% reduction in seizure frequency to the individual patient is difficult to put into context. One hundred per cent reduction in seizure frequency (seizure freedom) would be easier to interpret; however, this is an unrealistic outcome for existing treatments, given that seizure free rates in these trials are typically less than 10%, and there are no magic bullets on the horizon.

#### HOW DO THESE DRUGS COMPARE WITH EACH OTHER?

To choose between these drugs, the clinician needs to know how they compare with each other, and ideally needs the results of head to head randomised clinical trials that have used clinically meaningful outcomes. However, few comparative trials have been undertaken, and those that have lack the power to inform clinical practice.<sup>9</sup>

For drug refractory partial seizures, indirect comparisons can be made using the results of the systematic review already quoted.<sup>1-2</sup> Overlapping confidence intervals around summary estimates indicate that no significant differences were found; however, the existence of important therapeutic differences has not been excluded either. Others have used these data to infer that significant differences do exist, but have used flawed methods.<sup>10-11</sup>

#### WHICH DRUG SHOULD BE USED FOR WHICH EPILEPSY SYNDROME?

The trials reviewed and hence any meta-analysis included a heterogeneous population of patients with localisation related epilepsy, and the trials and meta-analysis provide overall estimates of effect for this heterogeneous population. It may be that certain drugs will be more effective for certain epilepsy syndromes, but current data do not provide evidence to support or refute this hypothesis. Any evidence to support this hypothesis from existing trials would need to come from subgroup analyses. However, the trials and meta-analyses are of insufficient size to allow reliable results from subgroup analyses and this issue will also need to be considered in future head to head trials.

#### ARE ANY PARTICULAR COMBINATIONS OF ANTIEPILEPTIC DRUGS MORE EFFECTIVE THAN OTHERS?

Rational polytherapy is currently in vogue for the treatment of epilepsy.<sup>12</sup> The theory is that combining drugs with differing mechanisms of action (for example, combining drug with a sodium channel action and a GABAergic drug) will be more effective and cause fewer side effects than combining drugs with similar modes of action. There is, however, no hard evidence from randomised control trials to support this approach.

#### WHAT IS THE LONG TERM EFFICACY OF THESE DRUGS?

Although a significant proportion of patients benefit in the short term, the proportion achieving long term benefit remains uncertain. Longer term follow up studies indicate continued benefit, but their interpretation is difficult as they are no longer dealing with a randomised comparison, and are confounded by selective drop out of non-responders.

A significant proportion of patients have these drugs withdrawn in the long term, despite responding in the short term. For example, an audit of patients recruited into placebo controlled add-on studies with lamotrigine or vigabatrin showed that 86% of those still alive had had the trial drug withdrawn after 6–8 years.<sup>13</sup> This is despite 21%–31% of patients in the original trials having a 50% or greater reduction in seizure frequency. A clinic based audit of less refractory patients found that 45% of patients treated with add-on topiramate had had this drug withdrawn at 12 months.<sup>14</sup>

#### WHAT IS THE EFFECT OF THESE DRUGS IN CHILDREN?

Although some studies have been conducted in children,<sup>15-17</sup> the great majority of trials have been conducted in adults. Even for children with the same epilepsy syndromes as adults recruited into individual studies, great caution is needed when trying to extrapolate results from adults to children. In addition, children present with a unique range of epilepsy syndromes that need to be investigated in randomised controlled trials. One example is infantile spasms, for which there is evidence for the efficacy of vigabatrin,<sup>18</sup> which has become the treatment of choice for this condition.

#### HARM

As most reported trials of new antiepileptic drugs are of relatively short duration, they are unable to inform us about long term toxic effects. They are also unable to inform us of the risks of rare side effects such as aplastic anaemia, a side effect that led to the withdrawal of felbamate in the United Kingdom shortly after it was given a licence. For example, if the incidence of aplastic anaemia on a drug were one in 5000, a total of 15 000 patients would need to be exposed to that drug to give a 95% chance of seeing a single case.<sup>19</sup> However, nowhere near this number of patients are exposed to new antiepileptic drugs before they are marketed. A rigorous system of postmarketing surveillance is required to pick up these rare but life threatening side effects as soon as possible; however, no such system is in place in the United Kingdom or elsewhere.

The visual side effects of vigabatrin are another example of a serious side effect picked up after marketing. The first reports were in 1997<sup>20</sup> and authors report concentric visual field constriction with relative temporal sparing. In 1995, Kalviainen *et al*<sup>21</sup> reported a monotherapy study comparing carbamazepine and vigabatrin. They have recently revisited this cohort and found that 41% of the vigabatrin group had concentric visual field abnormalities, compared with none in the carbamazepine group.<sup>22</sup> These visual field abnormalities seem irreversible, and have persisted despite vigabatrin withdrawal.

As a result, vigabatrin cannot be recommended other than a treatment of last resort for patients with drug refractory partial seizures, but may still be given as monotherapy for children with infantile spasms. Hoechst-Marion-Rousselle (maker of vigabatrin) recommends that visual fields be assessed before starting treatment for any patient with a developmental age of 9 or older. Fields should then be reassessed at 6 monthly intervals for 3 years and annually thereafter. Static perimetry (Humphrey or Octopus), or kinetic perimetry (Goldmann) are recommended (Hoechst letter). This is more problematic for patients with a developmental age of less than 9, as there is no established method for detecting visual field abnormalities in this group, and is a particularly difficult issue for those managing children with infantile spasms for whom vigabatrin may be the treatment of choice.

### Monotherapy

Monotherapy licenses for new antiepileptic drugs tend to lag behind licenses for add-on treatment. This is due to the general agreement that monotherapy studies should only be undertaken once there is proof of efficacy as add-on.<sup>23</sup>

#### MONOTHERAPY TRIAL DESIGN

In view of the fact that head to head monotherapy trials have failed to find convincing evidence for differences in efficacy of antiepileptic drugs, it is worth considering whether future trials should be designed to detect a difference or equivalence.<sup>24</sup> In 1998, The Commission on Antiepileptic Drugs of the International League Against Epilepsy<sup>25</sup> concluded that comparative monotherapy trials should be designed to detect equivalence. In other words, trials should be designed to generate confidence intervals around efficacy estimates that are narrow enough to exclude the possibility of important differences existing. This of course needs an a priori definition of the smallest important clinical difference. The Commission also suggests that a new drug could be considered a first line agent if it is shown to have equivalent efficacy to but is better tolerated than a standard drug. A new drug showing equivalent efficacy and tolerability to a standard drug would be considered a second line treatment.

For regulatory purposes, European authorities are willing to accept evidence of equivalence as adequate for licensing an antiepileptic drug for monotherapy. The Food and Drug Administration (FDA) in the United States, however, will not accept evidence of equivalence in epilepsy trials, and demand that trials show a statistical difference, and the arguments for such a stance are outlined by Leber.<sup>26</sup> This stance has resulted in a considerable divergence in the needs of the pharmaceutical industry and the needs of the clinician. To gain a licence, the industry is required to design and undertake trials that demonstrate that their product is better than something. The resulting trials that use placebo or pseudoplacebo comparisons do little to inform clinical practice, and raise a number of ethical concerns. One approach is to compare monotherapy with a high dose of a new drug with a low dose (sometimes referred to as a pseudoplacebo) in patients who continue to have seizures despite conventional antiepileptic drug therapy.<sup>27</sup> This trial does not consider a useful clinical question, and there are ethical concerns about giving low dose monotherapy to patients whose seizures have not been controlled by standard antiepileptic drugs. A more worrying trial design uses what has been called the surgical paradigm.<sup>28-30</sup> Patients undergoing seizure recording as part of a surgical work up, who have had their antiepileptic drugs withdrawn are randomised to receive either placebo or new antiepileptic drugs. Admittedly, these trials are undertaken in controlled environments, in which patients

are monitored continuously, and the duration of the trials is short with patients protected by exit criteria. However, the questions answered by this type of trial are of no clinical relevance, and the potential risk to the patients from status epilepticus cannot be ignored.

#### RESULTS OF MONOTHERAPY TRIALS

##### *Lamotrigine*

Lamotrigine is licensed for monotherapy in the United Kingdom, and has been compared with carbamazepine in three randomised clinical trials.<sup>31-33</sup> The largest of these recruited 260 patients with partial onset seizures or generalised tonic-clonic seizures, and was of 42 weeks duration. Lamotrigine fared significantly better than carbamazepine for the global outcome time to treatment withdrawal, and significantly more patients had carbamazepine withdrawn due to side effects. There was no difference, however, for the efficacy outcome "proportion of patients seizure free in the last 24 weeks of the study". The study, however, lacked the power to exclude the possibility of important differences in efficacy existing, the duration of the trial was short given that epilepsy is a chronic condition, and the efficacy outcomes have marginal clinical meaning and lack statistical power.

##### *Gabapentin*

Gabapentin and carbamazepine have been compared in one head to head monotherapy trial recruiting patients with partial seizures.<sup>34</sup> This trial was designed primarily to meet the licensing needs of the pharmaceutical industry and was of 24 weeks duration, with 292 patients randomised in a 1:1:1:1 ratio to 600 mg/day carbamazepine, 300 mg/day gabapentin, 900 mg/day gabapentin, and 1800 mg/day gabapentin. The primary outcome was time to exit and reasons for exit included a single tonic-clonic seizure, three complex partial seizures, and status epilepticus. For this outcome, no statistical difference was found between carbamazepine and 900 or 1800 mg gabapentin/day. Adverse events were more common in the carbamazepine group. Although this trial has met the regulatory needs of the pharmaceutical industry by finding a difference in efficacy between differing doses of gabapentin, the protocol deviates significantly from everyday clinical practice, and the results do little to inform clinicians

##### *Vigabatrin*

Vigabatrin has been compared with carbamazepine in three monotherapy trials.<sup>21 35 36</sup> The largest of these trials recruited 459 patients who were randomised to vigabatrin or carbamazepine, and was of 52 weeks duration. The trial was double blind, and treatment dose was increased to meet clinical need in an attempt to mirror clinical practice. The results showed no significant difference between drugs for the primary end point time to treatment failure, or for the outcome time to 6 month remission. However, confidence intervals around these estimates failed to meet the authors' generous definition of equivalence. Patients taking vigabatrin had significantly earlier first seizures post-randomisation, and were significantly more likely to have vigabatrin withdrawn due to lack of therapeutic effect, whereas carbamazepine was significantly more likely to be withdrawn because of side effects. This trial failed to find evidence to support the use of vigabatrin as monotherapy, and in view of the associated visual field abnormalities, it is unlikely that it will ever gain a monotherapy licence.

##### *Topiramate*

As already mentioned, topiramate has been tested in a monotherapy trial comparing 100 and 1000 mg/day.<sup>27</sup> Although this trial provides evidence of efficacy as monotherapy, it does not inform us how topiramate compares with standard treatments.

### Oxcarbazepine

Oxcarbazepine has recently been licensed for monotherapy in the United Kingdom. Initial monotherapy trials of oxcarbazepine compared it with carbamazepine<sup>37</sup> and due to the results of these trials and its chemical similarity to carbamazepine, oxcarbazepine was licensed in the 1990s for monotherapy in some European and Scandinavian countries. Close scrutiny of these trials, however, shows that they do not provide firm evidence on which to recommend oxcarbazepine for use as monotherapy. Although no therapeutic difference was found between oxcarbazepine and carbamazepine, these trials lacked the power to exclude the possibility of important differences existing. Also, results of the largest trial were confounded by the exclusion of 70 of the 235 randomised patients from efficacy analyses.<sup>37</sup>

More recently oxcarbazepine has been compared with phenytoin in two<sup>38 39</sup> and valproate in one<sup>40</sup> monotherapy randomised controlled trial. All three trials were of similar design and of 56 weeks duration. Primary efficacy outcomes were the proportion of patients seizure free, and the primary tolerability outcome was time to withdrawal due to side effects. None of these three trials found a difference between oxcarbazepine and its comparators in the proportion of patients seizure free, and no difference was found when compared with valproate for time to treatment withdrawal due to side effects.<sup>40</sup> When compared with phenytoin, oxcarbazepine fared significantly better for time to treatment withdrawal due to side effects in both adults<sup>38</sup> and children.<sup>39</sup> Although no difference was found for the primary efficacy outcomes, these trials also lacked the power to exclude the possible existence of important difference, and do not prove equivalence.

### LESSONS LEARNED AND FUTURE TRIALS

In this article, we have drawn attention to evidence pertaining to the efficacy and tolerability of some of the new antiepileptic drugs. Most of this evidence comes from randomised clinical trials, but with the growing culture of evidence based medicine, it is important to realise that the randomised controlled trial is not the only vehicle that provides valuable information about treatments. Other sources may be more appropriate, particularly for long term safety, and picking up rare but important adverse events.

The pharmaceutical industry has been the major driving force in generating data from randomised clinical trials, and most of the those referenced in this editorial were sponsored by the industry. The prime aim of the industry, however, is to provide data that satisfy the requirements of the licensing bodies. These requirements and particularly those of the Federal Drug Administration (FDA) have resulted in the serious schism between trials that satisfy licensing authorities and those that inform clinical practice. We find this position difficult to reconcile, and urge the licensing authorities to ensure that their requirements better reflect the needs of the clinician and patient.

We clearly need reliable evidence on which to base our choice of antiepileptic drugs, particularly for monotherapy, given that up to 70% of patients are managed on monotherapy. Given the increasing number of published randomised clinical trials, there is a clear need for systematic reviews of existing trials, a task being addressed by the Cochrane Epilepsy Group.<sup>41</sup> However, as we have highlighted in this article, much of the evidence regarding the new antiepileptic drugs has been acquired from trials that do not reflect day to day clinical practice, or use clinically meaningful outcomes. There is therefore a clear need for pragmatic trials comparing new antiepileptic drugs with each other and with standard drugs. In response to this need, NHS Health Technology Assessment Programme has

funded the Standard And New Antiepileptic Drugs (SANAD)<sup>42</sup> trial which is a pragmatic trial comparing carbamazepine, gabapentin, lamotrigine, topiramate and valproate.

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## EDITORIAL COMMENTARIES

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# Building an evidence base for multiple sclerosis management: support for physiotherapy

The recent debate in the United Kingdom over whether or not  $\beta$ -interferon and glatiramer acetate should be prescribed on the National Health Service for people with multiple sclerosis has focused the attention of the media, health services, and the business community in a way never previously experienced. However, the use of drugs which have a partial effect on disease activity is just one component of the active management of this complex disease. Multiple sclerosis has wide ranging physical and psychosocial consequences, which may have an enormous long term impact on almost every aspect of the daily lives of people with the disease and their families. In providing an adequate service it is therefore crucial to focus not only on the role of immunomodulatory drugs, but also on the many rehabilitation strategies which aim to improve the quality of life of people with multiple sclerosis. Drug therapy and rehabilitation strategies should be viewed as partners rather than competitors in the allocation of resources. Evidence based medicine requires resources to be allocated to interventions of proved effectiveness. It is therefore timely that the paper by Wiles *et al* in this issue (pp 174–179)<sup>1</sup> provides evidence of the effectiveness of a very commonly used rehabilitation intervention, physiotherapy.

Given that physiotherapy is so commonly used in multiple sclerosis, it is perhaps difficult to understand why such a paucity of scientific evidence exists to either support or refute its effectiveness. In part, this is because studies of this type are difficult to plan and to implement. This controlled randomised cross over study by Wiles *et al*<sup>1</sup> shows that rigorous methodology is possible. Of importance, it provides evidence to support the widely held belief (by both clinicians and patients) that specialist neurological physiotherapy helps to improve mobility in people with multiple sclerosis. The next step is to understand the mechanism by which these strategies work.

Physiotherapy is just one component within the comprehensive model of care designed to improve the quality of life of people with multiple sclerosis. It is encouraging that in the past few years two randomised controlled studies have been published to demonstrate the positive impact that multidisciplinary packages of care can have on the daily life of the person with multiple sclerosis.<sup>2,3</sup> While recognising that scientifically credible studies remain few in number, it is hoped that this gradual accumulation of evidence will help to reduce the negative preconceptions, which have tended to persist about the effectiveness and validity of rehabilitation in multiple sclerosis; and will positively influence the allocation of funds to these areas.

A review of the allocation of resources for the management of multiple sclerosis is clearly needed. A recent study investigating the level of community services in the United Kingdom showed that the provision of services seemed to be simply a matter of chance, providing support for the often expressed dissatisfaction by people with multiple sclerosis about the services they receive.<sup>4</sup> It is hoped that national guidelines and standards of care will help to improve this situation. Currently guidelines for the management of multiple sclerosis are being drafted by the National Institute for Clinical Excellence. Their development and the future allocation of resources will depend heavily on the available evidence base. Further rigorous evaluation of rehabilitation interventions such as physiotherapy is therefore clearly necessary. In undertaking such evaluation there is a need to broaden the research methodologies used, to tap the experience and views of people with multiple sclerosis, their families, and clinicians who work within this field. The “New NHS” claims to positively promote user involvement in the development of health services. This is a golden opportunity for this principle to be put into action; to provide the much needed impetus to improve the

provision of services to people with multiple sclerosis. We await to see whether this is an opportunity seized...or one that is lost.

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## Comparative neuropsychology of Lewy body and Alzheimer's dementia

The occurrence of Lewy bodies has a prevalence rate of 2%–9% in elderly people<sup>1</sup> and dementia with Lewy bodies (DLB) accounts for 12%–27% of cases previously diagnosed as dementia of the Alzheimer type (DAT).<sup>2,3</sup> The core features of DLB are fluctuating cognition with pronounced variation in attention and alertness, recurrent visual hallucinations, and spontaneous parkinsonian signs; probable DLB requires two of these features. There is considerable overlap between DLB and DAT,<sup>4</sup> but there have been only a few comparative neuropsychological studies. Various neuropsychological issues were addressed in the papers by Lambon Ralph *et al*<sup>5</sup> (this issue, pp 149–156) and Calderon *et al*<sup>6</sup> (this issue, pp 157–164) who disclosed some valuable insights that merit closer inspection. Clinicians and researchers will also find a useful tabulation of recent findings in the paper by Lambon Ralph *et al*<sup>5</sup>.

Previous studies have suggested that visuoperceptual problems are salient in DLB, but this evidence came from measures that represent a complex of abilities. The papers here report that basic figure-ground discrimination was worse in one DLB sample, whereas the other DLB sample instead had problems identifying silhouettes of real versus non-real objects. More complex visual tasks produced similar deficits in both DLB and DAT groups. Perhaps the most interesting finding was that the DLB groups in both studies showed marked impairments when identifying fragmented letters. This task has minimal cognitive load, and was unaltered in the DAT samples, so it may be especially promising for differential diagnosis and treatment evaluations.

Attention may be a second area of weakness in DLB<sup>3</sup> which, together with the related areas of working memory and executive function, influences adaptive functioning and performance on formal tests. Calderon *et al*<sup>6</sup> have confirmed that patients with DLB show widespread difficulties in this domain. Whereas patients with DAT showed set shifting, letter fluency, and selective attention deficits, the DLB group had additional problems in sustained and divided attention tasks.

The third contribution made by these two papers concerns long term episodic memory and semantic

memory, two major hallmarks of DAT. One important finding is that delayed recall represents one of the apparently few areas in which patients with DAT have a disproportionately greater weakness than their DLB counterparts, even though the patients with DLB do show substantial deficits on recall and recognition tasks. Category fluency and picture naming were also substantially but equally impaired in both dementias, so semantic memory itself does not distinguish these two disorders. The more marked visuoperceptual problems in patients with DLB seem, however, to exacerbate their semantic memory performance in some tests when presentation uses the visual modality.

Calderon *et al*<sup>6</sup> also make the interesting point that visual hallucinations in DLB may be related to the combination of impaired visuoperception and fluctuating attention. Cholinergic deficits are more profound in DLB and this too may be associated with both attentional difficulties and hallucinations. These ideas, and the various lines of evidence presented, will undoubtedly guide future research on the behavioural and neurobiological sequelae of the DLB syndrome.

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