ANTIDEPRESSANTS IN EPILEPSY...

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ANTIDEPRESSANTS IN PEOPLE WITH EPILEPSY

1. Depression in epilepsy
   • prevalence
   • presentation
   • models of aetiology

2. Treatment of depression in epilepsy
   • Principles of management
   • Safety of antidepressants
   • Choice of antidepressant
Epilepsy and Psychiatric Disorder: overall perspective

• Most patients with epilepsy do not suffer from psychiatric problems

• Patients with severe epilepsy are at increased risk of psychiatric problems
How common is depression in epilepsy?

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Prevalence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community based studies</td>
<td>4 – 37%</td>
<td></td>
</tr>
<tr>
<td>Hospital based studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Depression – DSM Criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Point prev.</td>
<td>3%</td>
<td>Manchanda, 1996</td>
</tr>
<tr>
<td>Last 12 months</td>
<td>22%</td>
<td>Devinsky, 2005</td>
</tr>
<tr>
<td>Lifetime</td>
<td>24-35%</td>
<td>Victoroff, 1994; Althuler, 1999</td>
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</table>
Is depression more common in epilepsy compared with other disabilities?

Yes ?:-
  • Hospital based studies comparing epilepsy with:-
    • Diabetes
    • migraine
    • Mixed neurological disorders
  • Postal survey of people with disability attending vocational services

No :-
  • Postal survey cf Asthma (Ettinger, 2005)
  • Icelandic Disability-Claimants (Steffansson, 1998)
Is depression in epilepsy atypical?

Up to 50% of depression in epilepsy may be “atypical”

“Interictal Dysphoric Disorder”
- chronic dysthymia *but* with periods of normality
- labile mood
- conspicuous (paroxysmal) irritability with somatic symptoms
- responds to treatment

But:-
- validity
- treatment trials
Depression is often missed in people with epilepsy

Up to 60% symptomatic for 1 year before treatment suggested

1. Patient
   - atypical forms of depression in epilepsy?
   - might assume depression is “normal”

2. Doctor
   - “depression is normal (or understandable)” in epilepsy
   - failure to ask …
   - uncertain about management
Epilepsy and suicide

3 - 5 – fold increased suicide rate in epilepsy

• Major risk factor is psychiatric history.
• also, early onset (<18), and infrequent neurology follow-up.
  (Nilsson, 2002)
Aetiological models of depression in epilepsy

1. Same underlying cause responsible for epilepsy and depression.
   • Eg: alcohol misuse, structural brain pathology, depression → epilepsy?

2. Seizures cause pathogenic physiological changes.
   • Eg: post-ictal depression, post-ictal exacerbation of depression

   • Antiepileptic drugs
   • temporal lobectomy
   • following seizure control (“alternating” psychiatric phenomena)

4. Psychosocial correlates of epilepsy (social class / stigma / family background).
   • Generic factors common to chronic disability
   • Factors specific to epilepsy
     • eg: Unpredictable nature of seizures, stigma

5. (Coincidental)

Multifactorial aetiology  Holistic management
Risk factors for depression in epilepsy

Poorly controlled epilepsy

Jacoby et al, 96; O’Donoghue et al, 99

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Seizures/ month</th>
<th>Depression (HADS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (~55%)</td>
<td>4 - 6%</td>
</tr>
<tr>
<td></td>
<td>&lt;1 (~25%)</td>
<td>10-11%</td>
</tr>
<tr>
<td></td>
<td>&gt;1 (~20%)</td>
<td>21-33%</td>
</tr>
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</table>

TLE cf IGE?
- Probably no association independent of seizure-control

Laterality?
FHx?
General Principles of Psychiatric Management

- Consider neurological, psychological and social factors
- Optimise epilepsy treatment
  - Consider role of AEDs in causing psychiatric presentation
  - Seizure control
  - Consider referral to specialist service
- Treat depression “as usual”
  - Psychological treatment
  - Benefit of specialist service
  - Antidepressants and seizures…?
## Antidepressants in non-epileptic patients

<table>
<thead>
<tr>
<th>Agent</th>
<th>% Seizures with therapeutic use</th>
<th>Seizures after overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclics *</td>
<td>0.3 – 0.5 %</td>
<td>8.4%</td>
</tr>
<tr>
<td>SSRIs</td>
<td>0.1-0.2 %</td>
<td>Uncertain. Lower than cyclics</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>0.3%</td>
<td>uncertain</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0.04%</td>
<td>Uncertain</td>
</tr>
<tr>
<td>MAOIs</td>
<td>V low</td>
<td>Rare reports</td>
</tr>
<tr>
<td>Moclobamide</td>
<td></td>
<td></td>
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</table>

* dose-dependent risk clearly established for cyclic - antidepressants.

eg: **Agent**
- Imiprapine
- Clomipramine
- Bupropion

<table>
<thead>
<tr>
<th>high dose</th>
<th>Seizures (%)</th>
</tr>
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<tbody>
<tr>
<td>&gt;200mg</td>
<td>0.6%</td>
</tr>
<tr>
<td>&gt;300mg</td>
<td>2.1%</td>
</tr>
<tr>
<td>&gt;450mg</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

Alldredge, BK. *Neurology*, 1999, 53 (suppl 2), s68-s75.
But are antidepressants safe in people with epilepsy?

What we need is information about safety in people with epilepsy ....
## ANTIDEPRESSANT TRIALS IN PATIENTS WITH EPILEPSY

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Antidepressant</th>
<th>Effect on Seizure Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson &amp; Trimble, 1985¹⁸</td>
<td>45</td>
<td>amitriptyline, nomifensine</td>
<td>none</td>
</tr>
<tr>
<td>Harmant et al, 1990¹⁹</td>
<td>35</td>
<td>fluvoxamine</td>
<td>none</td>
</tr>
<tr>
<td>Anderssen et al, 1991²⁰</td>
<td>20</td>
<td>paroxetine</td>
<td>none</td>
</tr>
<tr>
<td>Hovorka et al, 2000²¹</td>
<td>24</td>
<td>citalopram</td>
<td>none</td>
</tr>
<tr>
<td>Kanner et al, 2000¹²</td>
<td>97</td>
<td>sertraline</td>
<td>Increase in 1 patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Transient increase in 5</td>
</tr>
<tr>
<td>Kuhn et al, 2003²²</td>
<td>75</td>
<td>citalopram, mirtazapine, reboxetine</td>
<td>none</td>
</tr>
<tr>
<td>Specchio et al, 2004²³</td>
<td>45</td>
<td>citalopram</td>
<td>Overall decrease in seizures</td>
</tr>
<tr>
<td>Thome-Souza et al, 2007²⁴</td>
<td>36 (children &amp; adolescents)</td>
<td>sertraline, fluoxetine</td>
<td>Increase in 2</td>
</tr>
</tbody>
</table>

### Choice of antidepressant

1. Propensity to (possibly) \( \uparrow \) seizures
2. Drug interactions (Look up !)  
3. Side-effect profile …
4. Start low, go slow …

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<th>Antidepressant</th>
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<tbody>
<tr>
<td>Caution (?seizure risk)</td>
<td>Clomipramine, bupropirion, maprotiline, amoxapine</td>
</tr>
<tr>
<td>Caution: interactions</td>
<td>eg: Fluoxetine / phenytoin …</td>
</tr>
<tr>
<td><strong>Good Choice:-</strong></td>
<td>Citalopram, sertraline, venlafaxine, mirtazapine, reboxetine…</td>
</tr>
</tbody>
</table>
Summary

Depression

- common in (severe) epilepsy
- often missed and not treated
- Associated with poor QoL and suicide risk
- Multifactorial aetiology → holistic approach to management

Antidepressants

- Are safe in people with epilepsy
- Start low, go slow …
Depression as a risk factor for epilepsy?

3-6 x ↑ depression before 1st unprovoked seizure

- 3 population-based case/control studies

? Confounding effects

- Non-epileptic seizures
- Alcohol
- Brain-injury etc.
Psychotropics and seizures: overview of data

- 50-fold variability in seizure risk in published reports
- Of drug-induced seizures, commonest cause is psychotropics (35%) (Messing et al 1984).
- Animal studies are an unreliable source of information …
- Best data comes from clinical series …