The Role of the Glutamate System in OCD

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Introduction to the Glutamate system

• Established and effective medications for OCD target two neurotransmitters (brain chemicals): serotonin and dopamine

• Over the last 8 years there has also been research into the role of another neurotransmitter, glutamate, in OCD
Introduction to the Glutamate system

• Glutamate = most abundant excitatory neurotransmitter in the brain

• It is essential for communication of nerve cells in almost every circuit in the Nervous System

• Abnormally high level of glutamate can lead to neuron damage.

• Glutamate has been studied in conditions such as CVAs
Glutamate and OCD

Neuroimaging and studies of CSF in OCD patients suggest abnormalities in Glutamate in various areas of the brain in people with OCD
Studies demonstrating Glutamate Abnormalities in OCD

• 21 OCD patients who were unmedicated (and had not received psychotropic meds) compared with Normal Controls
• CSF Glutamate levels were significantly higher in OCD patients
• Gender, age, duration of illness, YBOCS score, or CGI-S score had no effect on CSF glutamate level
Glutamate modulates Neurotransmitters and is Neuroexcitatory

Glutamate

Neurone → Glial Cell

Neurone

Neurotransmitters (eg serotonin)
Genetic Studies, Glutamate and OCD

• High Glutamate in the brain of people with OCD does not demonstrate causation. It may be the effect of OCD.

• Genetic studies, however, seem to suggest a causative effect of glutamate imbalance in at least some cases of OCD.
Genes, Glutamate and OCD

- Two independent research groups in 2006 reported abnormalities in the protein which transports glutamate in the brain (SLC1A1 Glutamate Transporter Gene:
  - Stewart SE et al, 2007
  - Arnold PD et al, 2006
Genes, Glutamate and OCD

Mice have been genetically modified so that they do not have the SAPAP3 gene. These mice exhibited anxious and excessive grooming behaviour which improved after several weeks on SSRI

Welch JM et al., 2007
Genes, Glutamate and OCD

• Case reports have suggested that some patients with OCD spectrum disorders also lack SAPAP3
• Certain dog breeds (notably Dobermans; Bulldogs and German Shepherds have a high rate of Canine-OCD and there have been linkages with lack of SAPAP3
CLOZAPINE

- CLOZAPINE and maybe some other atypical antipsychotic agents have been reported to precipitate OCD symptoms in some patients with schizophrenia.

- Clozapine alters Glutamatergic Systems and so it may lead to OCD in those patients with a specific genetic polymorphism.
Common Agents which effect Glutamate and may have positive effects in OCD

- Agents which are being explored include:
  - Ketamine
  - Topiramate
  - N-Acetyl-Cysteine
  - Riluzole
  - Memantine
  - Glycine
  - Sarcosine (N-methyl glycine)
Common Agents which effect Glutamate and may have positive effects in OCD

• Agents which are being explored include:-
  – Gabapentin
  – Amantadine
  – D-Cycloserine
  – Acamprosate - NO CURRENT PUBLISHED STUDIES
  – PREGABALIN
KETAMINE

POOPULAR STREET NAMES

- Ketamine is called a "club drug" and also a "date rape" drug
- Special K, Ket, Cat Tranquilizer
- Vitamin K, Kit Kat, Keller
Ketamine and OCD - Bloch et al., 2012

- Open-label study of ketamine in 10 refractory OCD patients
- Some improvement in depressive symptoms in first 3 days after infusion
- No real improvement in OCD symptoms in first 3 days post infusion (<12% symptom reduction)
Topiramate – Afshar et al., 2014

- Randomised Controlled Trial of 13 OCD patients failed to show benefit
N-Acetyl-Cysteine – Review by Oliver et al. 2015

- Identified 4 randomised controlled trials of N-Acetyl Cysteine (several open label studies and case reports).
- Variable responses in these. At least 3 ongoing trials
- OVERALL LOOKS PROMISING IN OCARDs
Riluzole – Pittenger et al, 2015

- Placebo-controlled study
- Patients on riluzole seemed to respond more but NOT STATISTICALLY SIGNIFICANT
Memantine

- Several small placebo controlled trials as well as open-label studies have shown positive results eg Haghighi et al, 2013

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\begin{align*}
\text{NH}_2 \\
\text{Me} & \quad \text{Me} \\
\text{OH} & \\
\end{align*}
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Other drugs so far examined with open-label studies WHICH LOOK PROMISING

- Glycine (high-dose) eg Cleveland et al 2010.
- Sarcosine eg Wu et al, 2011
- Gabapentin - Onder, Tural and Gokbakan, 2008. VERY FEW REPORTS
- Amantidin - Stryjer et al, 2014
D-Cycloserine – Review by Xia et al, 2015

• Thought to enhance ERP treatment of OCD
• Trials have shown mixed results
• Small placebo controlled trials have failed to demonstrate efficacy
PREGABALIN
Pregabalin Characteristics

• First used for DIABETIC NEUROPATHY, POST-HERPETIC NEURALGIA, and CENTRAL NEUROPATHIC PAIN and subsequently EPILEPSY and FIBROMYALGIA

• Recommended for treatment of GAD by NICE 2011

• Actions reported to be as fast as Benzodiazepines but does not appear to have as great a tendency for tolerance and dependence
Pregabalin and OCD

- Oulis et al. 2011 used pregabalin as an adjunctive to SRI medication in OCD and found it was well tolerated and patient’s improved.
- We decided to examine the possible role of pregabalin in patients with profound OCD and high anxiety.
Application in a National Service for Profound, Refractory OCD

Treatment in an Inpatient Unit for Level 6 patients who also present a danger to self or others (needing 24 hour nursing care)

ASUKA LESLIE: ALEX CAIN
LYNNE M DRUMMOND
Basic criteria for treatment in National Service for OCD/BDD

- **YBOCS>30** = Profoundly severe OCD
- **2 trials of different SRIs** at BNF approved doses for >3 months
- **Augmentation** of above with dopamine antagonists or supra-normal SRI dosage or mood stabilisers
- **2 trials of CBT** which should include Exposure and Self-Imposed Response Prevention – one of these trials should normally be carried out in a situation where symptoms are maximal e.g. intensive community and home-based treatments.
Criteria for admission to Inpatient Unit

- **Danger to self** either due to chronic suicidality (acute suicidal episodes should be managed by local services) or due to extreme self-neglect (e.g. failure to drink sufficiently with incipient renal failure without nursing input)
- **Danger to others** due to OCD (e.g. impulsive acts)
- **Compulsions** so severe that cannot manage without **24 hour care** (e.g. regular incontinence due to OCD; Compulsions: taking >3 hours to get up in morning)
In other words….

- All patients had received 2 or more trials of SRI
- All were on augmentation
- All had had previous trials of CBT
- All remained profoundly unwell
Sample

- Patients were offered Pregabalin if they appeared highly aroused and anxious.
- During the study period 16 patients were prescribed Pregabalin.
- Mostly it was well tolerated.
- 2 patients stopped the medication but both had been taking for many months prior to admission and found it unhelpful.
- 14 patients were prescribed Pregabalin during the study and were examined at the end of treatment stay.
14 patients were given Pregabalin in conjunction with other treatments (SRI; Dopamine Blocker; CBT)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Average Age</th>
<th>Marital Status</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 women (36%) and 9 men (64%)</td>
<td>38 years (23-56; sd10.4)</td>
<td>11 were single (79%)</td>
<td>12 (86%) white</td>
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<tr>
<td></td>
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<td>3 In relationship (21%)</td>
<td>1 Asian and 1 Iranian</td>
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Response to Pregabalin and other treatment using YBOCS

This represents an average reduction of 11.5 on the YBOCS (range = -2 to 19; sd = 7.1)

This is significant p<0.0009

This is an average 31% drop in YBOCS (-6.3-54.3; 19.2)
Individual Responses to Pregabalin in Combination with other Treatments

- RESPONSE: >35% reduction = 7 patients
- PARTIAL: 25-35% reduction = 3
- NO RESPONSE: <25% reduction = 4
YBOCS SCORING – increase in bands of 8
Comparison of Severity Measured by YBOCS Before and After Treatment

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>PreYBOCS</th>
<th>Post YBOCS</th>
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<tbody>
<tr>
<td>Moderate</td>
<td>1 patient</td>
<td>6</td>
</tr>
<tr>
<td>Severe</td>
<td>13 patients</td>
<td>4</td>
</tr>
<tr>
<td>Profound</td>
<td>4</td>
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Pregabalin in this Study

- Well tolerated
- Clinically believed to assist in reduction of symptoms
- No evidence yet but overall patients did improve
Thank-you for Listening!!