

## Autoantibodies against voltage-gated potassium channel and glutamic acid decarboxylase in psychosis: A systematic review, meta-analysis, and case series.

### AUTHOR(S)

Rosemary Grain, John Lally, Brendon Stubbs, Steffi Malik, Anne LeMince, Timothy R. Nicholson, Robin M. Murray, Fiona Gaughran

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Title: Autoantibodies against voltage-gated potassium channel (VGKC) and glutamic acid decarboxylase (GAD) in psychosis: A systematic review, meta-analysis and case series

Running head: VGKC and GAD antibodies in psychosis

Authors: Rosemary Grain<sup>+1</sup>, John Lally<sup>+\*2,3,4</sup>, Brendon Stubbs<sup>5,6</sup>, Steffi Malik<sup>7</sup>, Anne LeMince<sup>3</sup>, Timothy R Nicholson<sup>2</sup>, Robin M Murray<sup>2,3</sup>, Fiona Gaughran<sup>2,3</sup>

<sup>+</sup>Both are first named authors and should be acknowledged as such

\*Corresponding author

Affiliations:

<sup>1</sup>King's College London, UK

<sup>2</sup>Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

<sup>3</sup>National Psychosis Service, South London and Maudsley NHS Foundation Trust, London, UK

<sup>4</sup>Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Ireland

<sup>5</sup>Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, UK

<sup>6</sup>Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.

<sup>7</sup>Medical School, University of Bristol, Senate House, Tyndall Avenue, Bristol BS8 1TH, UK

Authors:

Dr Rosemary Grain MBBS, LLB,

King's College London, United Kingdom

Dr John Lally, MB MSc MRCPsych,

Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London; National Psychosis Service, South London and Maudsley NHS Foundation Trust, London, UK and Senior Clinical Lecturer, Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Ireland

Dr Brendon Stubbs, MSc, MCSP, BSc (Hons), PhD, Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, UK and Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, Box SE5 8AF, UK.

Steffi Malik, MSc,

Medical student, Medical School, University of Bristol, Senate House, Tyndall Avenue, Bristol BS8 1TH, UK

Anne Lemince, BSc (Hons) Psychology and Criminology, National Psychosis Unit, South London and Maudsley NHS Foundation Trust, UK

Dr Tim R Nicholson, MBBS, MSc, PhD, MRCPsych, MRCP

NIHR Clinician Scientist, Section of Cognitive Neuropsychiatry, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Prof Sir Robin M Murray, MD DSc FRCP FRCPsych FMedSCI FRS, Professor of Psychiatric Research, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London

and Honorary Consultant, National Psychosis Service, South London and Maudsley NHS  
Foundation Trust, London, UK

Dr Fiona Gaughran MB, BCh, BAO, FRCPI, FRCP, FRCPsych, MD,

Lead Consultant Psychiatrist, National Psychosis Service, South London and Maudsley NHS  
Foundation Trust, London, Senior Lecturer, Institute of Psychiatry, Psychology and Neuroscience,  
King's College London, UK and The Collaboration for Leadership in Applied Health Research and  
Care (CLAHRC), South London Psychosis Research Team, UK

Corresponding author:

Dr John Lally

PO63, Department of Psychosis Studies

Institute of Psychiatry, Psychology and Neuroscience King's College London and

National Psychosis Service,

South London and Maudsley NHS Foundation Trust,

King's Health Partners

De Crespigny Park

London SE5 8AF

Email: [john.lally@kcl.ac.uk](mailto:john.lally@kcl.ac.uk)

Tel: (0044) (0)203 2286000

Fax:(0044) (0)203 2284312

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Title: Autoantibodies against voltage-gated potassium channel (VGKC) and glutamic acid decarboxylase (GAD) in psychosis: A systematic review, meta-analysis and case series

Abstract

Antibodies to the voltage-gated potassium channel (VGKC) complex and glutamic acid decarboxylase (GAD) have been reported in some cases of psychosis. We conducted the first systematic review and meta-analysis to investigate their prevalence in people with psychosis and report a case series of VGKC-complex antibodies in refractory psychosis. Only five studies presenting prevalence rates of VGKC seropositivity in psychosis were identified, in addition to our case series, with an overall prevalence of 1.5% (25/1720) compared to 0.7% in healthy controls (12/1753).

Meta-analysis established the pooled prevalence of GAD65 autoantibodies was 5.8%(95%CI:2.0-15.6%;I<sup>2</sup>=91%;9 studies) in psychotic disorders,with a prevalence of 4.6%(95%CI:1.2-15.9%;9 studies;I<sup>2</sup>=89%%) and 6.2% (95%CI:1.2-27.0%;2 studies;I<sup>2</sup>=69%) in schizophrenia and bipolar disorder respectively. People with psychosis were more likely to have GAD65 antibodies than controls (OR 2.24;95%CI:1.28- 3.92%;p=0.005;8 studies;I<sup>2</sup>=0%).Among 21 participants with treatment-resistant psychosis, none had VGKC antibodies.

The prevalence of VGKC antibodies is low in psychosis. Our preliminary meta-analysis suggests GAD autoantibodies are more common in people with psychosis than in controls, although few studies accounted for the possibility of co-existing type 1 diabetes mellitus and the clinical significance of reported GAD titres remains unclear. The paucity of studies reporting thresholds for

defining GAD abnormality, and rates of comorbid type 1 DM,preclude interpretations regarding the influence of GAD antibodies on the development of psychotic disorders;and may have led to an overestimate of the prevalence of GAD. Our case series fails to support the hypothesis that VGKC antibodies are linked to treatment resistance in psychosis, but the literature to date is remarkably sparse.

Keywords: Antibodies; Encephalitis; Glutamic acid decarboxylase; Schizophrenia; Voltage-gated potassium channel complex

Title: VGKC and GAD antibodies in psychosis; A systematic review, meta-analysis and case series.

## 1. Introduction

Over recent years interest in a possible autoimmune aetiology of psychosis has grown. (1, 2) It has long been known that people with schizophrenia and their families have a higher risk of autoimmune disease than the general population. (3-6) Latterly there has been interest in the sub-group of people with psychosis who have serum antibodies to neuronal antigens. (1, 7, 8) Most current interest focuses on antibodies to the N-Methyl-D-Aspartate receptor (NMDA-R); Voltage Gated Potassium Channel (VGKC) complexes and Glutamic Acid decarboxylase (GAD).(9-12) A previous meta-analysis identified NMDA-R positivity in 7.98% ( $n=115/1441$ ) of schizophrenia spectrum psychosis.(8) Given this previous review of NMDA-R antibodies, we will not discuss these further in our study. Psychosis is a common feature of the encephalitis syndromes that are classically associated with these antibodies – often as an early feature before the development of other features of encephalitis, such as seizures, movement disorders, autonomic instability and impaired consciousness.(13, 14) The importance of these antibodies is clear when psychosis presents in the context of encephalitis, but the challenge in psychiatry is to determine their relevance in clinically uncomplicated psychosis.

### ***VGKC-complex antibodies***

VGKC antibody-mediated limbic encephalitis was first described in 2001.(15) Most VGKC-complex antibodies are directed against neuronal cell surface antigens, where they bind to leucine-rich glioma inactivated-1 (LGI-1) or contactin-associated protein-2 (CASPR-2) which are cell

surface proteins that form part of the VGKC-complex.(16) The targets of other VGKC-complex antibodies are unclear. By 2004, Vincent et al. reported a retrospective case series of 10 patients with VGKC antibody-mediated limbic encephalitis, several of whom had experienced psychiatric symptoms such as hallucinations ( $n=3$ ), depression ( $n=1$ ), anxiety and delusions ( $n=1$ ). (17) A later retrospective case series of 152 US patients who tested positive for serum VGKC antibodies, reported neuropsychiatric symptoms in 44%, in particular anxiety and depression, with two patients initially given psychiatric diagnoses.(18)

### ***GAD antibodies***

Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme for the generation of gamma amino-butyric acid (GABA), the main inhibitory central nervous system neurotransmitter.(19)

There are two subtypes of GAD. GAD65 is present in both pancreatic islet cells and neuronal tissue, while GAD67 is present mainly in neuronal tissue.(20)

GAD autoantibodies are directed against intracellular synaptic antigens, and are found in several neurological conditions such as Stiff person syndrome (SPS), limbic encephalitis and epilepsy. (21) It is unclear whether the presence of GAD65 in these disorders is pathogenic or an epiphenomenon of another immune dysfunction.

GAD65 antibodies are also a marker for Type 1 diabetes and latent autoimmune diabetes of adulthood (LADA). (22, 23) Patients with schizophrenia have an increased risk of type 1 diabetes.(3)

### ***Aims of the current paper***

There is no previous systematic review investigating the prevalence of VGKC seropositivity in psychosis. A systematic review of the prevalence of a variety of other antibodies in schizophrenia identified four studies assessing for GAD antibodies. (11)

Given the aforementioned, we conducted a systematic review and meta-analysis to determine the prevalence of VGKC-complex and GAD antibodies in psychosis. The coprimary outcomes were the prevalence of study-defined VGKC and GAD positivity in psychosis. Secondary outcomes included the comparison of the coprimary outcomes in diagnostic subgroups (e.g. schizophrenia; bipolar disorder) with healthy controls. In addition we aimed to describe the clinical characteristics of patients with VGKC-complex and GAD65 antibody-positive psychotic illness. Within the second stage of this paper, we conducted a retrospective case series to investigate VGKC-complex antibodies in patients with refractory psychosis.

## 2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standard. (24)

### *2.1 Inclusion and exclusion criteria*

Included in this systematic review were studies which included subjects 1) with a diagnosis of, or who were being treated for, a psychotic illness, 2) where serum or cerebrospinal fluid (CSF) was analysed for the presence of VGKC or GAD antibodies, 3) comparative (contained a healthy control group) or non-comparative (without a control group) studies and prevalence or observational studies 4) studies in peer reviewed journals, 5) written in English and 6) published before June 2016.

The exclusion criteria were 1) studies in which subjects were screened for antibodies as part of a medical work-up without an actual or suspected psychiatric diagnosis; 2) studies where individuals were diagnosed with an organic psychosis from the outset; 3) studies which were not reported in English.

### *2.2 Information sources and searches*

Two independent reviewers (RG, JL) performed an electronic search using Medline, PsychInfo, Pubmed, Scopus and Google Scholar from database inception to June 2016. The following basic search terms were used, both alone and in combinations: 'psychosis' 'psychotic'(and truncated terms psychos\*, psychot\*), 'schizophrenia' 'schizoaffective' and 'bipolar' were combined with 'gad' 'glutamic acid decarboxylase' 'glutamate decarboxylase' 'diabetes', 'VGKC' 'voltage-gated potassium channels' 'CASPR', and 'LGI1' and 'antibodies', 'antibody' and 'antibod\*'.

'VGKC' alone was also searched to identify all records in Pubmed. The abstracts of the 2012, 2014, and 2016 SIRS (Schizophrenia International Research Society) and the 2009, 2011, 2013 and 2015 ICOSR (International Congress on Schizophrenia Research) conferences were searched for abstracts containing 'antibod\*' to identify any unpublished works. The bibliographies of included studies and literature reviews were also hand searched. The titles of all articles retrieved were screened, and the abstracts of those considered potentially relevant were read. All articles considered relevant at this initial screening were retrieved and taken to full reading. A hand search of the references of retrieved articles was conducted to identify additional studies. When required, we contacted the primary/corresponding authors of potential studies to (a) confirm eligibility, and (b) acquire the variables of interest if they were not available in the publication.

### ***2.3 Study selection and exclusion***

All applicable abstracts were obtained, and examined by two reviewers (RG & JL). The two authors applied the eligibility criteria and a list of full text articles was developed through consensus.

### ***2.4 Data extraction***

Articles were critically reviewed by two authors (RG and JL) and the following information extracted where available: clinical characteristics and outcomes; size of the cohort; diagnoses and any control groups; antibodies tested; threshold for antibody positivity; numbers and proportions of patients with antibody positivity.

### ***2.5 Meta-analysis***

If data were sufficient, we anticipated conducting a random effects -analysis with Comprehensive Meta-Analysis software (CMA, Version 3). First, we calculated the prevalence of GAD65 antibody positivity in each diagnostic subgroup (all psychotic disorders, schizophrenia, bipolar disorder and controls) together with 95% confidence intervals (CI). We then compared the prevalence of GAD65 antibodies in each SMI cohort separately with the controls to determine the odds ratio (OR)

and 95% *CI*. Heterogeneity was assessed with the Cochran Q and *I*<sup>2</sup> statistics for each analysis.

(25) Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau (26) and Egger bias test. (27)

## **2.6 Case series**

A retrospective case series was obtained from a cohort of inpatients to a specialist service with treatment resistant psychotic disorders (International Classification of Diseases (ICD)-10 (F20-F29 and F30-F33)).

The clinical notes of 203 consecutive admissions with treatment resistant psychosis between 2009 and 2015 were reviewed. Routine socio-demographic and clinical data (gender, age, diagnosis, and duration of illness) were collected along with VGKC-complex antibody status where available. Serological analyses were performed by Professor Angela Vincent at the Department of Clinical Neurology, John Radcliffe Hospital, University of Oxford. Serum VGKC-complex antibodies were tested using a radio-immunoprecipitation assay.(28)

## **2.7 Ethics**

Study approval was granted by the Psychosis Clinical Academic Group Audit committee at South London and Maudsley NHS Foundation Trust, London UK. All clinical information was anonymised. .

# **3. Results**

## **3.1 Systematic review**

The results of the selection process are summarised in a flow diagram (Figure 1 ).

*Insert figure 1 here*

## **3.2 VGKC Studies**

The results of the VGKC studies are summarised in Table 1.

*Insert table 1 here*

The literature search revealed five studies reporting on VGKC positivity in psychotic disorders. (10, 29-32) Two of the studies measured VGKC antibodies using a radioprecipitation assay, (10, 30) while three used an immunofluorescence assay. (29, 31, 32) One of the studies assessed serum and cerebrospinal fluid (CSF) for VGKC positivity.(32) Only one of the studies defined a cut off for VGKC positivity with a VGKC level of > 100 pM established as consistent with positivity.(30)

### **3.2 Case series results**

#### ***VGKC in treatment refractory psychosis***

Between August 2009 and February 2015, 203 patients with diagnoses of treatment resistant psychosis were referred to our specialist inpatient service. Twenty-one patients (12 males) based on clinical suspicion, were tested for VGKC-complex antibodies. The mean age was 38 years (SD=17) (range 19 –78 years). Diagnoses were: schizophrenia (n= 14), schizoaffective disorder (n=5), psychotic depression (n=2). The mean duration of illness was 12 years (SD=10) (range=3-33 years). All patients tested negative for VGKC-complex antibodies.

The remaining five studies, (10, 29-32) and our case series, described 1720 patients (1574 schizophrenia patients, 46 first episode psychosis (FEP), 50 bipolar affective disorder, and 50 patients with unstated chronic psychotic disorders) and 1753 controls.

### **3.3 VGKC prevalence studies**

The overall prevalence of VGKC-complex antibodies in cases was 1.5% (25/1720), with 0.7% (12/1753) in controls. (30, 31) One of the VGKC-complex antibody-positive patients had a diagnosis of FEP, but presented with no distinguishing clinical features from other patients within the service.

### **3.4 GAD65 antibody studies**

Table 2 presents the results of the GAD65 studies. The literature search revealed nine studies satisfying eligibility criteria. Eight of these were case control studies (20, 30, 31, 33-37) and one was an observational study (with general population rates of GAD65 positivity used for comparison in Cohen et al 2005).(38) All of the included studies assessed serum for GAD antibody positivity.

*Insert table 2 here*

### **3.5 GAD65 seropositivity in case control and observational studies**

The included studies involved 2019 psychosis patients and 2116 healthy controls. 57 patients were positive for GAD65 antibodies, giving a prevalence of 2.8% (57/2019). Eleven controls (20/2116; 0.95%) were positive for GAD65 antibodies. Rates of co-morbidity with type 1 diabetes mellitus were not given in any of the studies. A definition of GAD positivity defined in units of GAD antibodies was used in only three of the case control studies (GAD positivity defined as GAD65 antibodies >1.05 (20, 33) and positive with GAD levels > 10 U/mL). Two other studies established cut off values for GAD positivity at specified percentile of the control groups (97<sup>th</sup> percentile (35) and 98<sup>th</sup> percentile of the healthy control group GAD level (20)). Of note, only serum titres higher than 1000 U/ml are generally considered related to neurological pathologies; none of the patients reported in these studies reached that threshold.

### **3.6 Diagnostic subgroupings**

The only study in FEP patients reported a GAD65 antibody prevalence rate of 18.75%. These patients had no distinguishing features from other FEP patients within the service.

### **3.7 Case-control studies**

One study found statistically significant differences in prevalence rates of GAD65 between cases and controls. Padmos, Bekris et al. 2004 found that 11.3% of the bipolar disorder group had

positivity for serum antibodies to GAD65 compared with only 2.6% of the healthy control group ( $p=0.002$ ).<sup>(35)</sup> Patients with GAD65 positivity had more active forms of the illness (either mania/hypomania or depression) compared with the GAD65 negative patients. GAD65 levels were not found to significantly correlate with duration of illness or treatment, symptom severity or rapid cycling. Seven case-control studies did not find statistically significant differences in GAD65 positivity between cases and controls. (20, 30, 31, 33, 34, 36, 37)

Yarlagadda, Helvink et al. 2008 found that patients with chronic psychosis and Tardive dyskinesia(TD) had significantly higher GAD65 antibody levels compared to chronic psychosis patients without TD ( $p=0.044$ ), with 38.5% of the TD group (5/13) being positive for GAD 65 antibodies, and no antibodies found in patients without TD (0/7).<sup>(34)</sup>

Seven of the case-control studies assessed antibody levels in patient and control groups and two found statistically significant differences. Padmos, Bekris et al. 2004 identified a mean GAD65A index that was significantly higher in bipolar patients compared with control subjects ( $p=0.038$ ). In the same study there was no significant difference in the mean GAD65 index between schizophrenia patients and controls. (35) Yarlagadda, Helvink et al. 2008 found that patients with chronic psychosis and Tardive dyskinesia (TD) had significantly higher antibody levels compared to chronic psychosis patients without TD ( $p=0.044$ ), with 38.5% of the TD group (5/13) being positive for GAD 65 antibodies, and no antibodies found in patients without TD (0/7).<sup>(34)</sup>

### **3.8 GAD 65 and GAD 67**

Three studies tested for both GAD65 and 67 antibody positivity in patient and control groups, (20, 31, 35) with significantly increased rates of GAD65, but not GAD67 found in bipolar disorder cases in two of the studies. (20, 35)

## **4. Meta-analysis results**

There was insufficient data to pool the prevalence of VGKC-complex antibodies.

#### **4.1 GAD65 antibodies**

It was possible to pool data from 9 studies to establish that the pooled prevalence of GAD65 antibodies among people with psychosis was 5.8% (95% CI 2.0 to 15.6%,  $I^2=91\%$ , 9 studies) with no evidence of publication bias (Begg=-0.14,  $p=0.6$ ; Egger=-0.43,  $p=0.84$ ) (Figure 2); the prevalence of GAD65 antibodies was 4.6% (95% CI 1.2 to 15.9%, 9 studies,  $I^2=89\%$ ; Begg =0.00,  $p=1.0$ ; Egger=1.50,  $p=0.54$ ) and 6.2% (95% CI 1.2 to 27.0%, 2 studies,  $I^2=69\%$ , ) in schizophrenia and bipolar disorder participants respectively. The prevalence of GAD65 antibodies was 2.7% (95% CI 1.0 to 7.0%, Studies=8,  $I^2=73\%$ ) among healthy controls.

*Insert figure 2 here*

#### **4.2 Risk of GAD65 antibodies in SMI versus controls**

A comparative meta-analysis established that people with psychosis were more than two times more likely to have GAD65 antibodies (OR 2.24 95% CI 1.28 to 2.92%,  $p= 0.005$ , 8 studies,  $I^2=0\%$ ) than controls (Figure 3). No significant difference was observed in schizophrenia participants versus controls (OR 1.49, 95% CI 0.76 to 2.92%,  $p=0.24$ , 6 studies,  $I^2=0\%$ ). An increased odds was observed in bipolar disorder participants versus controls but caution should be noted as only two studies were pooled in the analysis (OR 4.41, 95% CI 1.85 to 10.5,  $p<0.001$ ,  $I^2=0\%$ ).

*Insert figure 3 here*

### **5. Discussion**

To our knowledge, this is the first systematic, quantitative review of studies on VGKC and GAD antibodies in schizophrenia and psychotic spectrum disorders. There are several findings of note. We have carried out the largest review of GAD antibodies in psychosis. Our meta-analysis establishes that the prevalence of GAD antibodies among people with psychosis was 5.8% (95% CI 2.0 to 15.6%), whilst 4.6% (95% CI 1.2 to 15.9%), and 6.2% (95% CI 1.2 to 27.0%) of people with schizophrenia and bipolar disorder participants respectively tested positive. Moreover, our

comparative meta-analysis suggests that people with psychosis are at a more than two fold risk of having GAD auto antibodies compared to the general population (OR 2.24 95% CI 1.28 to 2.92%,  $p= 0.005$ ). Whilst we generally found low or moderate levels of heterogeneity and no publication bias, the sample sizes are relatively small and some methodological differences exist.

We identified a pooled prevalence rate of 5.8% for GAD65 in psychotic disorders, with a rate of 2.7% in controls. The case-control studies of GAD65 in psychotic disorders were marked by methodological heterogeneity which makes the interpretation of results difficult. Except for Dahm et al 2014 and Padmos et al.,2004, studies had small sample sizes, with contrasting methodologies used to measure and detect GAD antibodies. Three studies (30, 33, 34) used the ELISA (Enzyme-linked immunosorbent assay) method, with GAD levels calculated using absorbance values, rather than by antibody titers as in the other of the Yarlagadda group studies.(20) The other studies used radioimmunoassays to measure GAD antibodies.

It is possible that GAD65 antibodies may directly affect the brain. Abnormalities in GABA have been implicated in schizophrenia(39, 40) and GAD is the major rate-limiting enzyme in GABA production. (41)

One significant limitation in the available data is the lack of information on co-morbid type 1 diabetes mellitus, which may have explained some of the findings. Nevertheless, the excess of type 1 diabetes mellitus in schizophrenia is of a smaller magnitude (3.1%) (4) than the excess of GAD65 antibodies reported here, and type 1 diabetes mellitus is unlikely to account for all of these findings. Further, the paucity of studies defining the threshold for abnormal GAD levels limits interpretation of the influence of GAD antibodies on the development of psychotic disorders, particularly since GAD antibodies levels of  $> 1000\text{IU/L}$  are considered to be indicative of a need for immunotherapy in neurological disorders. (42)

We found a low prevalence of VGKC positivity in psychotic disorders, in the context of a paucity of prevalence studies. The available data (5 studies) identified 25 patients with VGKC

antibodies.(31, 32, 43) This low prevalence is consistent with the findings in our case series in treatment-resistant psychosis where no VGKC antibody-positive patients were identified.

Contrary to expectations, there was a low prevalence of VGKC positivity, which may be reflective of the currently attainable sample size due to a low number of studies. Only two studies have assessed VGKC positivity in cases and controls,(30, 31) thus limiting our ability to draw firm conclusions, though the majority of cases sampled were drawn from these two studies. In extracting data in relation to VGKC-complex antibodies, we compiled an overall prevalence rate, including studies assessing for antibodies against any component of the VGKC complex, including LGI1 and CASPR antibodies. This method of data extraction may have led to an underestimation of those antibodies which are more closely related to encephalitis, namely LGI1 and CASPR. Further, given that VGKC-complex antibody positivity tends to occur in the acute encephalitic stage, the lack of data on the stage of illness at which cases were tested for VGKC-complex antibodies is a limitation. Thus, we cannot exclude the possibility that the prevalence of VGKC complex antibody positivity would be higher in more acute stages of illness, and that negative results in later stages, or more chronic stages dose not outrule an autoimmune aetiology.

### ***5.1 Clinical characteristics of VGKC positive cases***

There were no prototypical clinical characteristics reported for these VGCK positive patients identified in our review. In Endres et al., 2015, two of the cases presented with neurological features, one with fluctuating levels of consciousness , and another with seizures, aphasia and stupor.(32) One patient was unfortunately lost to follow-up, although the lack of distinguishing factors makes that case clinically important.(43)

When VGKC antibodies are found in patients with limbic encephalitis with an initial presentation of psychotic illness, these cases do not indicate a characteristic phenotypic presentation of VGKC antibody-related limbic encephalitis, although neurological signs and seizures should raise

suspicion of this. Data from case reports of VGKC-complex limbic encephalitis with an initial presentation of psychosis ( $n=5$ ), indicates a broad clinical heterogeneity, including seizure-like episodes ( $n=4$ ), disordered speech ( $n=3$ ), delusions ( $n=3$ ), behaviour change ( $n=2$ ), aggression ( $n=2$ ), depressive symptoms ( $n=2$ ), auditory and visual hallucinations ( $n=2$ ) self-harm ( $n=1$ ) and mutism ( $n=1$ ), and hyponatraemia in three cases.(44-48)

More studies with larger cohorts are needed in order to give a more robust estimate of the prevalence of VGKC antibody positivity in psychosis. This may identify sub groups of patients with higher rates of VGKC antibodies, and determine when VGKC antibody testing is indicated.

### ***5.2 Clinical implications of GAD positivity***

This review identified one case report of limbic encephalitis presenting with psychosis in the presence of GAD autoantibodies.(49) A female patient was diagnosed with treatment resistant schizophrenia aged 17. Subtle abnormal features, such as intermittent semirhythmic diffuse theta slowing on EEG monitoring, without epileptiform abnormalities, and episodes of impaired responsiveness were not associated with EEG changes, prompted a frontal lobe biopsy that showed immunological activity. Serum GAD65 antibody levels were 112 IU/ml (normal range 0-5). Treatment with immunosuppressive therapies resulted in some improvement, but not the excellent recovery seen in many of the VGKC-complex antibody cases. It is possible that the pathogenesis in this case was not GAD autoantibody-mediated and reflected a co-morbid condition. Furthermore, the symptom profile in this case was more characteristic of schizophrenia, with no seizure activity, neurological signs or hyponatraemia identified.

### ***5.3 Implications for future research***

Further studies are needed to determine whether GAD65 antibodies are related to the pathogenesis of psychotic disorders, and if so with which particular clinical features. Future studies should also

control for potential confounding factors such as age, ethnicity, BMI, antipsychotic medication use, stage of illness, and importantly a diagnosis of type 1 diabetes mellitus.

It is possible that autoimmune-mediated brain changes may occur early in life, with antibody levels becoming reduced or undetectable following a long duration of psychosis.

#### ***5.4 Case series of VGKC-complex antibody positivity in TRS***

Our case series found a zero prevalence rate for VGKC antibodies in patients with refractory psychosis. The case series was small, with a low frequency of testing. However, the clinicians who selected those tested had an interest in autoimmune causes of psychosis, which is likely to have introduced an over-estimate rather than an underestimate. It is possible that antibody titres could be affected by treatment, as antipsychotic medication can have immunomodulatory effects,(50) and we are unable to exclude the possibility that patients are more likely to test positive for auto-antibodies early in the course of their illness or when drug-naive. Based on this case series, routine testing for VGKC antibodies cannot be recommended in refractory psychosis.

## **6. Conclusions**

The potential for VGKC and GAD antibodies to cause psychosis is a fairly novel proposal, and relatively few studies exist. This review has identified 5 studies on VGKC antibodies in psychosis and, including our case series, the prevalence stands at 1.5% ((25/1720). There remain unsolved issues and more studies are needed on larger patient cohorts to give a more accurate picture of prevalence and the role(s) of these antibodies.

This review identified an overall pooled prevalence rate of 5.8% for GAD65 antibody-positivity in psychosis. More studies are needed to gain a more accurate picture of GAD65 antibody prevalence in psychosis and to determine whether these antibodies are clinically relevant to the disease process.

## **7. Key learning points**

- The first meta-analysis on the relationship of VGKC and GAD antibodies and psychotic disorders.
- There are few studies on VGKC antibody positivity in psychosis, but the available evidence indicates a low prevalence (1.5%).
- Our results do not support the hypothesis that a significant subpopulation of those with psychotic disorders are patients with misdiagnosed VGKC-antibody positive autoimmune limbic encephalitis.
- The raw, unadjusted prevalence rates of GAD positivity were 2.8% in psychosis and 0.95% in controls. Meta-analysis identified a pooled prevalence for GAD antibodies of 5.8% in psychosis compared to 2.7% in healthy controls.
- More patients were identified as having GAD antibodies, but there are still few studies overall and the clinical significance of the titres reported is unclear. A paucity of studies reporting on concurrent type 1 diabetes mellitus, indicates that the identified prevalence rate of GAD antibodies may be somewhat accounted for by concurrent type 1 DM.
- Our review demonstrates that patients with psychosis have an increased likelihood of GAD antibody positivity- the extent to which this finding contributes to the aetiology of psychotic disorders remains uncertain.

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#### Authors' contributions

We affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

All authors made substantial contributions to the conception and design of the work. RG, JL, BS, SM, AL and FG were involved in the acquisition and analysis of the data, and RG, JL, BS, SM, TN, RMM and FG in the interpretation of data for the work;

RG and JL created the first draft of the work and RG, JL, BS, SM, TN, RMM and FG were involved in the revision and completion of the work.

All authors gave final approval of the version to be submitted and published and in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The corresponding author had full access to all the data and had the final decision to submit for publication.



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## Figure legends

Figure 1. Flow diagram of selected article

Figure 2: Proportion meta-analysis plot (random effects) of GAD65 antibodies in psychotic disorders

Figure 3. Comparison of GAD65 antibodies across 8 studies among people with psychotic disorder and controls