### Autoimmune Psychosis – The SINAPPS2 Trial

www.sinapps.org.uk



## Neuronal cell surface antibodies – treatable causes of encephalitis

- Voltage Gated Potassium Channel complex (LGI1, CASPR2, contactin-2) 2001, 2010
- N-Methyl-D-aspartate receptor (NMDA) 2008
- GABA-A receptor 2015



#### Neuronal cell surface antibodies = pathogenic



Antibody immunolabelling on hippocampal slices, hippocampal neuronal cultures, HEK cell based assays (from Dalmau et al 2011)



#### NMDAR encephalitis symptoms and signs





Irani et al Brain (2010)

## NMDAR encephalitis responsive to early immunotherapy





Could NMDAR (and other) antibodies be responsible for some cases of psychosis?



# Neuronal cell surface antibodies in psychosis

Live cell-based assay	Titres	FEP Patients (n=228)	Controls (n=105)	Odds ratio (95% CI)
NMDAR antibodies	1:30 - 1:150	7 (3·1%)	0	5.4 (p=0.02)*
LGI1 antibodies	1:20 - 1:100	3 (1·3%)	0	2.3 (p=0.13)*
CASPR2 antibodies	1:100 - 1:250	2 (0·9%)	3 (2·9%)	0·3 (0·1 - 1·8)
GABA-AR antibodies	1:50 - 1:100	8 (3·5%)	1 (1%)	3.8 (0.5 - 30.7)
AMPAR antibodies	-	0	0	
Prevalence any neuronal cell surface antibody		20 (8·8%)	4 (3·8%)	2·4 (0·8 - 7·3)

\* Likelihood ratio Lennox et al The Lancet Psychiatry 2016



#### Increased NMDAR antibodies in psychosis?

Author	Diagnosis	Assay	NOS score	Psychosis n/N	Controis n/N									OR (95% CI)	% Weight
Jézéquel et al (2017)	Schizophrenia	Live	4	9/48	3/104						-	•	-	7.77 (2.00, 30.21)	17.07
Lennox et al (2017)	FE Psychosis	Live	5	7/228	0/105				1					7.14 (0.40, 126.27)	5.27
Pathmanandavel et al (2015)	FE Psychosis	Live	2	5/43	0/17			80) 197			•			5.00 (0.26, 95.50)	5.03
Lennox et al (2009c1)	FE Psychosis	Live	2	1/16	0/23						•			4.55 (0.17, 118.99)	4.18
Arboleya et al (2016)	FE Psychosis	Fixed	6	2/61	0/47									3.99 (0.19, 85.15)	4.70
Bergink et al (2015)	PP Psychosis	Fixed	4	2/96	0/65									3.47 (0.16, 73.37)	4.73
Lennox et al (2009c2)	Schizophrenia	Live	2	0/22	0/23	-				÷				1.04 (0.02, 54.92)	2.92
Gaughran et al (2018)	FE Psychosis	Live	8	1/96	1/98					<u>₩</u>				1.02 (0.06, 16.56)	5.56
Masopust et al (2015)	FE Sz/SzPF	Fixed	5	0/50	0/50					÷				1.00 (0.02, 51.38)	2.95
Timucin et al (2016)	Schizophrenia	Live	3	0/49	0/48				2	÷i-				0.98 (0.02, 50.37)	2.95
Steiner et al (2014)	Schizophrenia	Fixed	8	1/184	2/357		_			÷÷		_		0.97 (0.09, 10.77)	7.17
Masdeu et al (2012)	FE Psychosis	Fixed	3	0/80	0/40									0.50 (0.01, 25.82)	2.96
Dahm et al (2014)	Sz/SzAff	Fixed	8	8/1378	20/1703				•	+ !				0.49 (0.22, 1.12)	28.83
Mantere et al (2018)	FE Psychosis	Fixed	6	0/70	0/34									0.49 (0.01, 25.19)	2.95
Rhoads et al (2011)	Schizophrenia	Fixed	2	0/7	0/3 ←								-	0.47 (0.01, 28.73)	2.71
Overall (I-squared = 15.1%, p =	= 0.285)										>			1.58 (0.78, 3.17)	100.00
NOTE: Weights are from randor	m effects analysis												_		
					.01	.025	.05 .1	.2	.5	1 2	4	8 16	32		
						IgG r	more common	in controls			IgG more	common in psycl	nosis		



Cullen et al Lancet Psychiatry 2021

Only with the live Cell Based Assay Only available through PPiP2



Cullen et al Lancet Psychiatry 2021



- So what?
- Do patients with psychosis and antibodies get better with immunotherapy in the same way as those with encephalitis?



## SINAPPS1 feasibility study

Participant Number	Antibody type	Duration of illness (months)	Treatment given
1	NMDAR	2	PLEX
2	NMDAR	10	PLEX + steroids
3	NMDAR	1	PLEX + steroids
4	NMDAR	2	PLEX
5	NMDAR	5	PLEX+steroids
6	VGKC	60	IVIG
7	VGKC	7	IVIG
8	VGKC	10	PLEX+steroids
9	VGKC	24	IVIG
10	GABAA	11	IVIG

Lennox et al JNNP 2018



#### Yes – for psychosis + NMDAR antibodies PANSS before and after immunotherapy





Lennox et al JNNP 2018

## SINAPPS 2

A randomised, phase II, double-blinded, placebo controlled trial of intravenous immunoglobulins and rituximab in patients with antibody-associated psychosis.

2017-2024

Objectives

To test the **efficacy and safety** of immunotherapy (IVIG and rituximab) in patients with acute psychosis associated with anti-neuronal membrane antibodies.





## Methods Participants

#### **Inclusion Criteria:**

- 1. Age 16-60
- Acute psychosis symptoms: lasting for at least the past two weeks but no longer than two years (relapse or first episode of psychosis)
- 3. Presence of anti-neuronal membrane antibody in serum or CSF

#### **Exclusion criteria:**

- Co-existing severe neurological disease
- Hepatitis B, C, HIV, previous malignancy, pregnancy, severe infection, severe heart failure and other health safety reasons.



### SINAPPS 2 Treatment

#### All patients:

Antipsychotic treatment as recommended by treating psychiatrist.

#### Immunotherapy:

- 1. Intravenous immunoglobulin given over 2-4 days
- 2. Intravenous rituximab: 1<sup>st</sup> infusion between days 28-35, 2<sup>nd</sup> 14 days later



#### SINAPPS2 Trial



