EFFECTS OF N-ACETYL CYSTEINE ON TOBACCO CONSUMPTION IN BIPOLAR DISORDER AND SCHIZOPHRENIA

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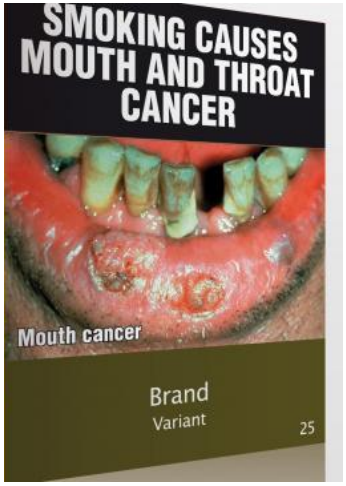
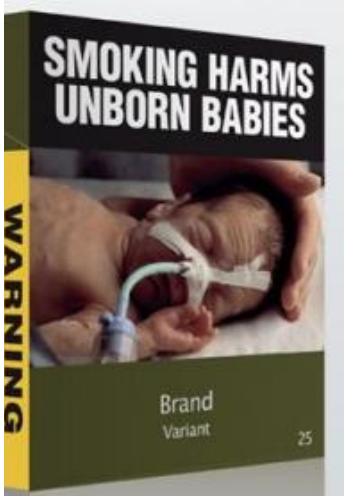
- **The schizophrenia RCT:** Stanley Medical Research Institute.
  - Trial registration: Australian Clinical Trials Registry, Protocol 12605000363684, www.actr.org.au.

Australian anti-tobacco marketing





Prevalence

- WHO: tobacco kill **six million people/year**.
- Approx. **290 people** die from smoking **every week** in Australia*
- About **32%** of people with a **mental illness** smoke cigarettes*
  - 66.6% current (81% lifetime) for people with psychotic conditions**.

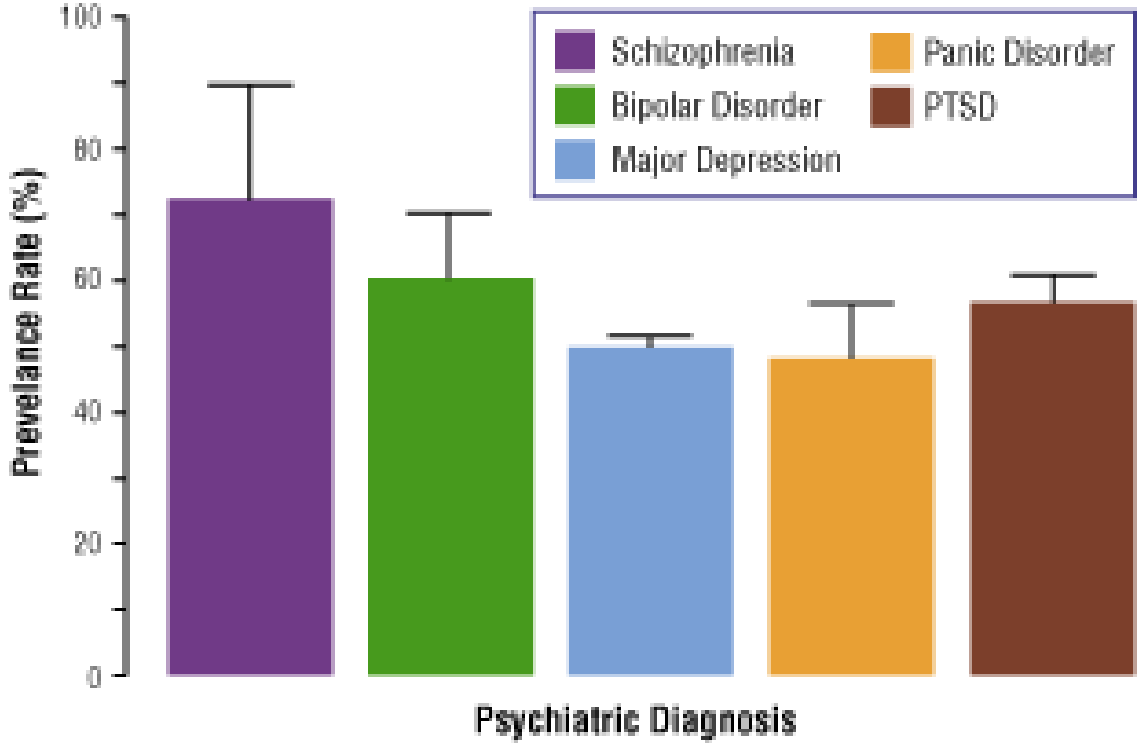
*ABS National Health Surveys, 1989–90, 1995, 2001, 2004–05, and 2007–08.

**Cooper et. al., 2012 Aust N Z J Psychiatry.

Prevalence

Figure

Prevalence Rates* of Tobacco Use in Psychiatric Disorders



*Average prevalence rates (±SD) from published studies of tobacco use in patients with schizophrenia (n=13), bipolar disorder (n=2), major depression (n=3), panic disorder (n=2) and posttraumatic stress disorder (PTSD) (n=2).

Source: George TP (2000)

- **SZ:** 50-90%
- **BP:** 60-70%

VS

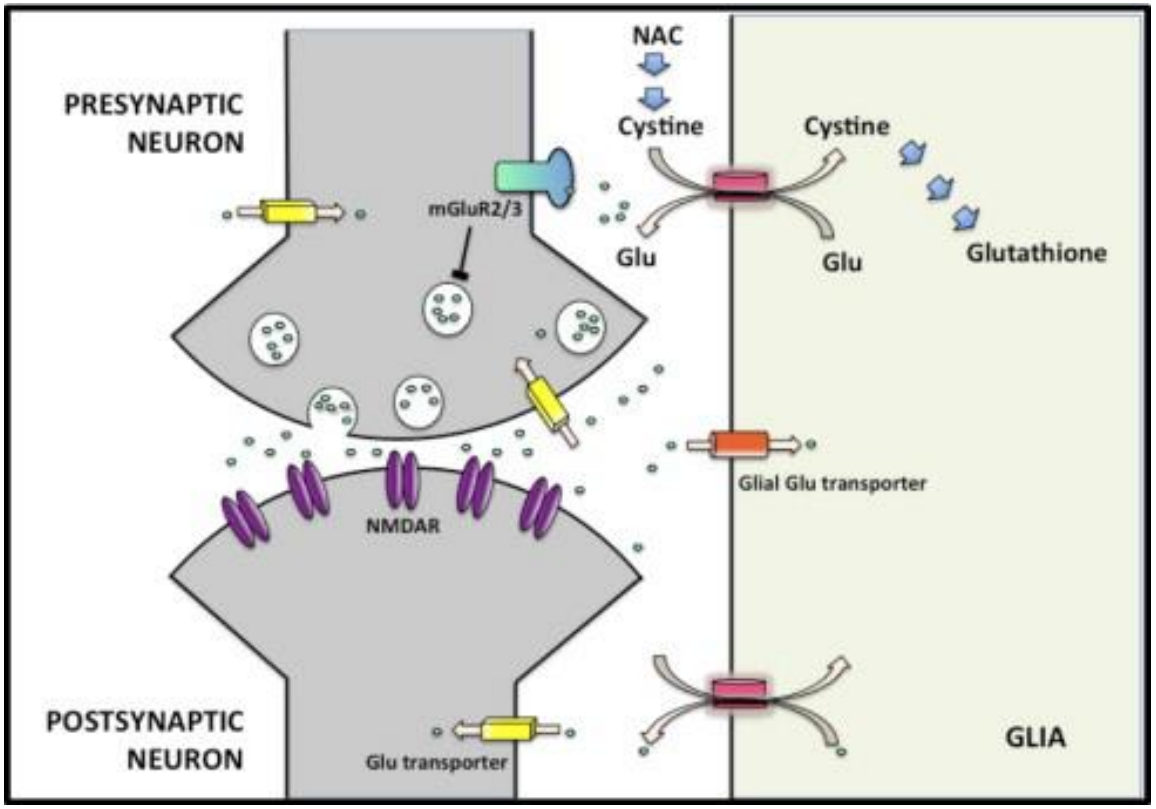
- 25-30% general population

Smoking and mental illness

- Heavy users
- Increased nicotine dependence
- Reduced success in smoking cessation
- Associated with poorer outcomes of these disorders
  - Cardiovascular risk and respiratory disease
  - Increased rate of relapse and number of hospitalizations

Myles et. al., 2012 J Clin Psychiatry.

N-acetyl cysteine

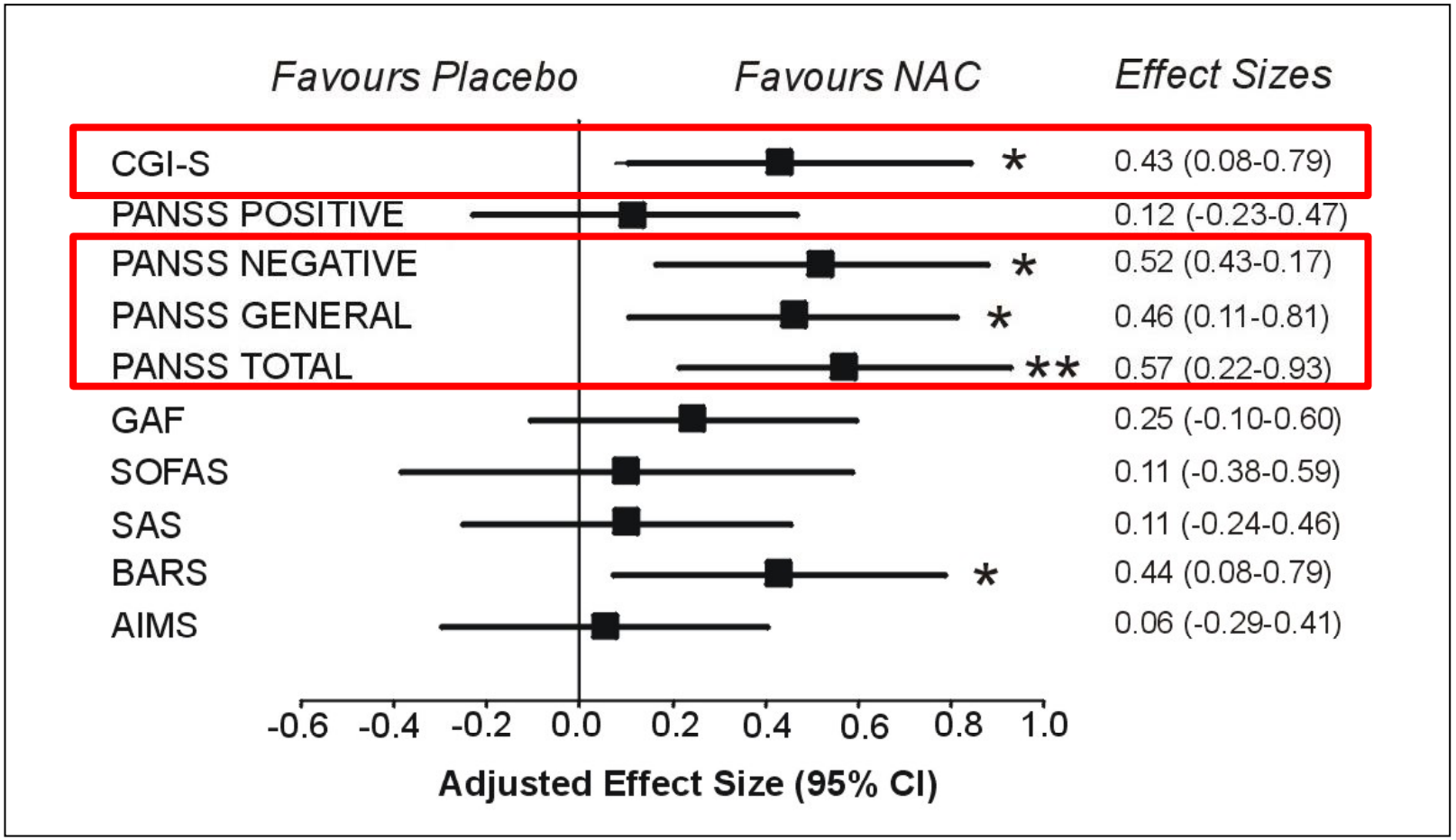


- **NAC stimulates the cysteine-glutamate exchange** mechanism which
  - decreases nicotine self-administration
  - reinstatement of nicotine-seeking behaviour.

Gunduz-Bruce et al., 2012

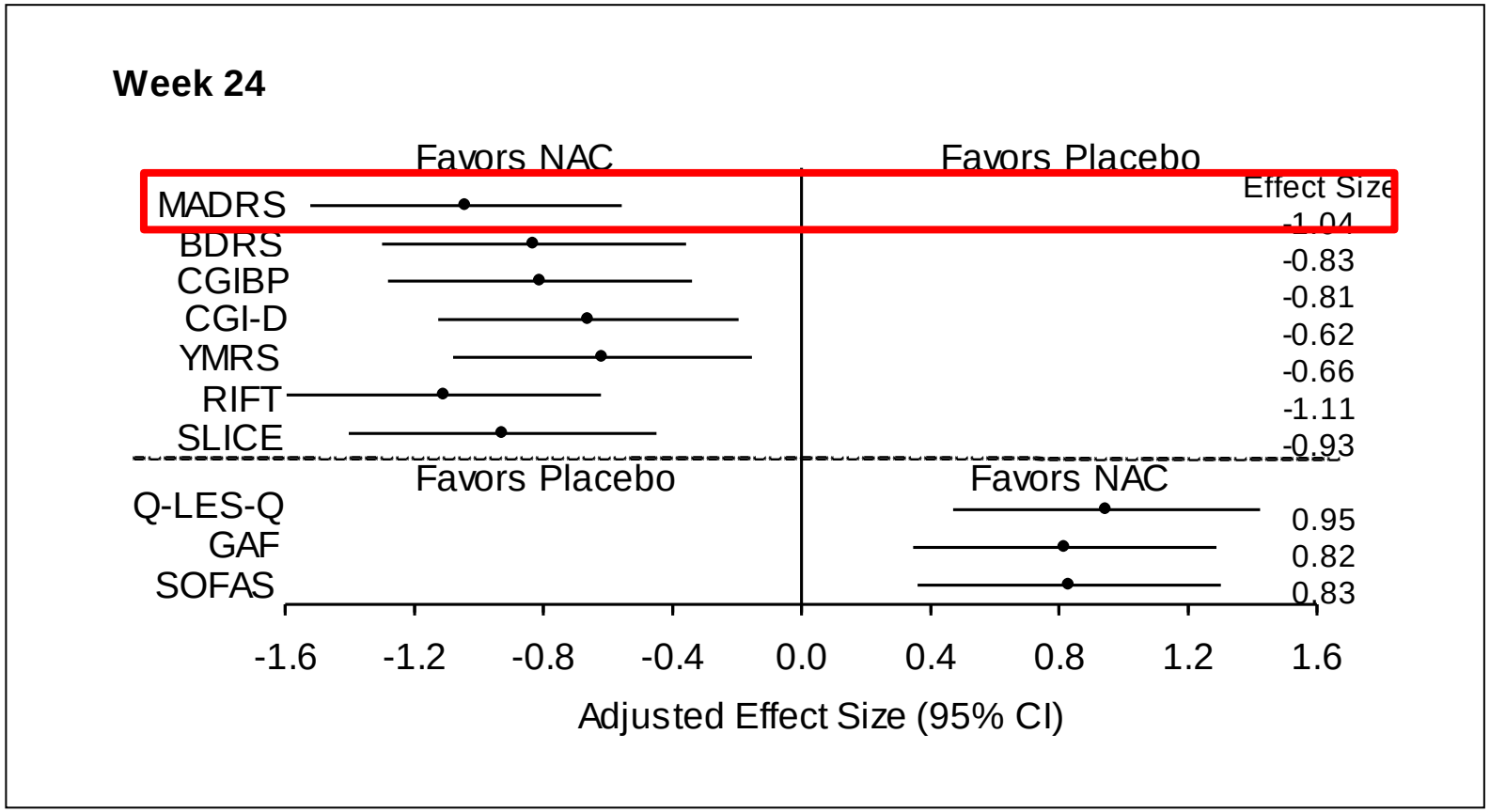
Knackstedt et al., 2009; Kalivas et al., 2009;

NAC in Schizophrenia (N=140) Effect sizes



Berk et al., Biological Psychiatry 2008

NAC in Bipolar Disorder
Effect sizes (MMRM, N=75)



Berk et al., Biological Psychiatry 2008

HYPOTHESIS

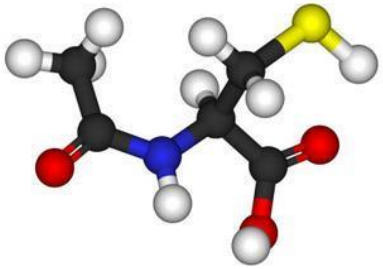
- NAC may exert **beneficial effects on tobacco consumption** in BP and SZ by **restoring glutamate levels** through the activation of the cysteine-glutamate exchange system.

OBJECTIVE

- To examine the **potential of NAC as a novel pharmacotherapeutic approach** for **tobacco consumption** in schizophrenia and bipolar disorder.

METHODS

- A **subgroup analysis** of two RCT on smokers at baseline (SZ n=34; BD n=29)
  - **NAC (2g/day)**: SZ=16; BD=12
  - **Placebo:** SZ=18; BD=17.
- The **CGI-SU** was used to measure **change on smoking** from baseline at week 8 and week 24 (end-up point).
- **GLM** were used to determine changes
  - **NAC vs. Placebo** (adjusted for treatment and site)
  - **SZ vs. BP** (adjusted for site).

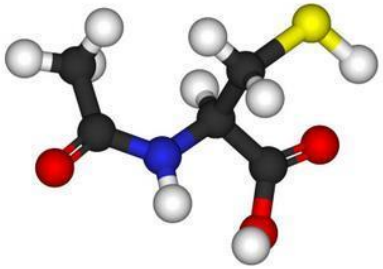


RESULTS

Table 1. Comparison between NAC and Placebo treatment groups on clinical and sociodemographical variables at baseline (mean observed cases scores)

	NAC			*Placebo*			*NAC vs. Placebo*	
	SZ	***BP***		***SZ***	***BP***			
	N=24	**N=15**	*Test*[1]	**N=*20***	**N=*19***	*Test*[1]	***SZ***	***BP***
	Mean (SD)*	*Mean* (SD)*		*Mean* (SD)*	*Mean* (SD)*		*Test*[1]	
Age	37,5 (10.4)	39.9 (8.8)	t=-0.74 *p*=0.31	37.4 (12.4)	42.6 (13.8)	t=-1.24 *p*=0.81	t=-0.03 *p*=0.57	t=0.67 *p*=0.43
Sex (F/M)	5/19	10/5	χ^2=8.19 **p=0.004**	4/16	14/5	χ^2=11.29 **p=0.001**	χ^2=0.01 p=0.95	χ^2=0.10 p=0.66
Years of Illness	10.9 (8.7)	6.6 (5.1)	t=1.72 *p*=0.09	12.4 (9.8)	9.3 (10.1)	t=0.92 *p*=0.79	t=0.53 *p*=0.66	t=0.95 ***p*=0.03**
CGI_S	3.6 (0.7)	3.3 (1.4)	t=0.96 *p*=0.12	3.9 (0.8)	3.0 (1.1)	t=3.03 *p*=0.59	t=1.46 *p*=0.67	t=-0.64 *p*=0.53
GAF	51.9 (10.5)	61.1 (11.3)	t=-1.91 *p*=0.12	46.9 (11.0)	67.0 (12.6)	t=-5.31 *p*=0.69	t=-1.15 *p*=0.13	t=1.40 *p*=0.48
SOFAS	59.5 (13.6)	63.5 (13.9)	t=-0.88 *p*=0.977	51.1 (10.5)	66.6 (13.7)	t=-3.98 *p*=0.15	t=-2.24 *p*=0.11	t=0.65 *p*=0.82

[1] Paired t-test or Pearson's chi-square test (p<.05).

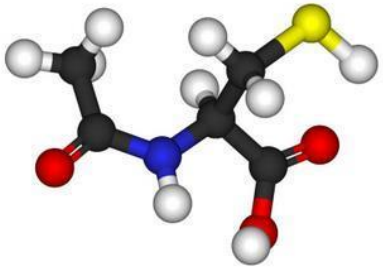


RESULTS

Table 2. Changes on symptom scores (mean observed cases scores)

	SZ NAC		*SZ Placebo*		*NAC vs. Placebo*
	Bs	***Wk24***	***Bs***	***Wk24***	
	Mean (SD)*	*Mean* (SD)*	*Mean* (SD)*	*Mean* (SD)*	*Test*
PANSS_P	15.3 (5.1)	12.1 (4.4)	14.4 (4.8)	13.7 (5.0)	F=2.26 *p*=0.12
PANSS_N	13.8 (4.5)	12.8 (3.6)	14.4 (4.8)	14.8 (5.4)	F=0.21 *p*=0.65
PANSS_G	32.8 (9.3)	27.3 (7.7)	31.9 (8.8)	30.6 (8.3)	F=6.80 ***p*=0.01**
PANSS_T	61.8 (14.7)	52.2 (13.0)	62.4 (15.4)	59.1 (15.8)	F=4.88 ***p*=0.04**
CGI-S	3.6 (0.7)	3.2 (1.0)	3.9 (0.8)	3.9 (1.1)	F=0.42 ***p*=0.04**
GAF	51.9 (16.5)	53.7 (14.7)	46.9 (11.0)	49.2 (12.3)	F=0.36 *p*=0.55
SOFAS	59.5 (13.6)	57.0 (12.7)	51.1 (10.5)	53.6 (13.0)	F=0.19 *p*=0.67

[2]One-way ANCOVA model with site as covariate (Change scores: end-up point minus baseline).



RESULTS

Table 3. Changes on symptom scores (mean observed cases scores)

	BP NAC		*BP Placebo*		*NAC vs. Placebo*
	Bs	***Wk24***	***Bs***	***Wk24***	
	Mean (SD)*	*Mean* (SD)*	*Mean* (SD)*	*Mean* (SD)*	*Test*
MADRS	17.6 (12.2)	8.6 (7.8)	11.5 (8.8)	13.3 (13.4)	F=5.17 ***p=0.04***
YMRS	4.3 (5.1)	2.9 (4.4)	3.1 (3.1)	2.9 (3.1)	F=0.07 *p*=0.80
CGI-S	3.3 (1.4)	2.5 (0.9)	3.0 (1.1)	3.1 (2.0)	F=1.21 *p*=0.29
GAF	61.1 (11.3)	68.6 (17.1)	66.9 (12.6)	64.2 (17.0)	F=1.50 *p*=0.24
SOFAS	63.5 (13.9)	71.6 (16.2)	66.6 (13.7)	66.2 (17.3)	F=1.87 *p*=0.19

[2]One-way ANCOVA model with site as covariate (Change scores: end-up point minus baseline).

RESULTS

Table 4. Comparison between NAC and Placebo treatment groups on tobacco use (mean observed cases scores)

	NAC			*Placebo*			*NAC vs. Placebo*	
	SZ	***BP***	*Test*[1]	***SZ***	***BP***	*Test*[1]	***SZ***	***BP***
	Mean (SD)*	*Mean* (SD)*		*Mean* (SD)*	*Mean* (SD)*		*Test*[2]	
Week 8	2.25 (1.92)	3.92 (1.08)	F=6.03 ***p=0.02***	3.00 (1.72)	3.12 (1.58)	F=0.42 *p*=0.52	F=0.69 p=0.42	F=0.87 p=0.36
Week 24	2.38 (1.86)	4.00 (1.41)	F=4.56 ***p=0.04***	3.68 (1.00)	3.55 (1.92)	F=1.13 *p*=0.30	**F=5.79 p=0.02**	F=1.15 p=0.30

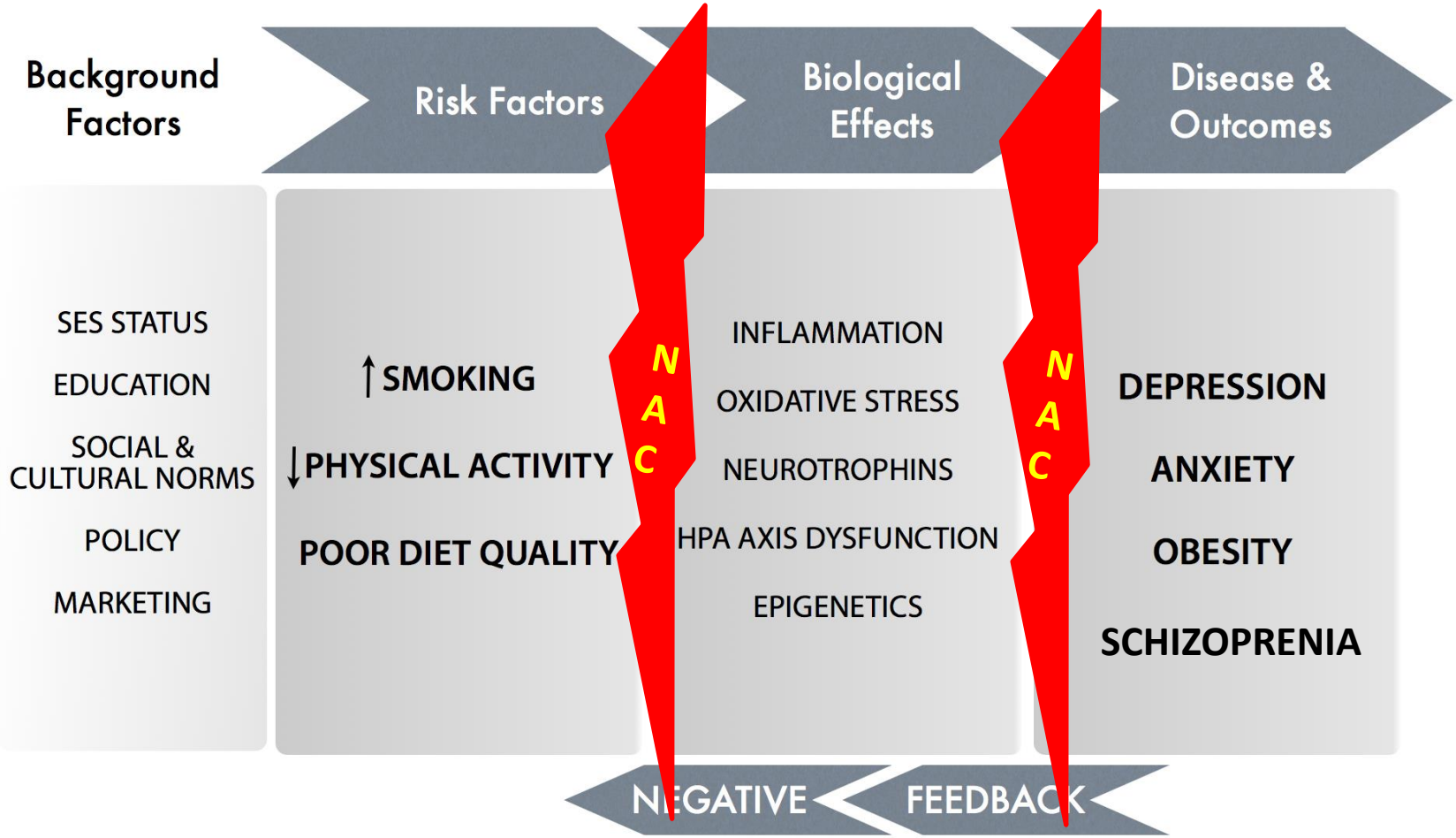
[1] GLM ANCOVA model with site and sex as covariate. [2] GLM ANCOVA model with site, years of illness and treatment as covariate.

*The CGI-SU rates change from baseline in tobacco use on a 7-point Likert scale where 1 = do not use at all now, 2 = using much less, 3 = using slightly less, 4 = unchanged, 5 = using slightly more, 6 = using much more and 7 = using very much more.

CONCLUSIONS

- **NAC may impact on tobacco consumption** in schizophrenia.
- The **potential of glutamatergic compounds** such as NAC may constitute an important step forward on the **development of novel therapies for nicotine addiction**
  - with specific implication on major disorders such as schizophrenia.

Implications for therapy



FUTURE

Measuring nicotine levels

Number of cigarettes per day

RCT NAC on smokers

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Dr. Olivia Dean

Zhi Xiang On

Barwon Psychiatric Research Unit and Deakin University

NAC?

What about…

Hmm…

th!nk differently

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THE UNIVERSITY OF MELBOURNE

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