Disease Burden of Bipolar and Schizoaffective Disorder in an Australian Cohort: Results after 12 months

M. Berk[1,6,7], P.B. Fitzgerald[2], A.R. de Castella[2], S. Filia[2], K. Filia[2], S. Dodd[1], L. Berk[1], F. Biffin[2], K. Kelin[3], M. Smith[4], A. Brnabic[5], R.E. Granger[5], W. Montgomery[3] and J. Kulkarni[2]

1 Department of Clinical and Biomedical Sciences: Barwon Health, The University of Melbourne, P.O. Box 281, Geelong VIC 3220
2 Alfred Psychiatry Research Centre, The Alfred and Monash University, School of Psychology, Psychiatry & Psychological Medicine, Commercial Road, Melbourne VIC 3004, Australia
3 Eli Lilly Australia Pty Ltd, 112 Wharf Road, West Ryde NSW 2114, Australia
4 School of Social Sciences, University of Western Sydney, Locked Bag 1797 Penrith South DC 1797 NSW, Australia
5 Intercontinental Information Sciences, Eli Lilly Australia Pty Ltd, 1/16 Giffnock Ave, Macquarie Park NSW 2113, Australia
6 Orygen Research Centre, Parkville VIC 3052, Australia
7 Mental Health Research Institute, Parkville VIC 3052, Australia

A CASE STORY

- Ms J – aged 48
- 25 years of BPAD
- Recent episode of mania, sexual disinhibition
- Mostly depression in the past
- 2 children, 2 ex-husbands

BACKGROUND

- Bipolar I and schizoaffective disorders are debilitating, long-term, recurrent conditions with significant personal, social, and societal costs.[1]
- These patients are often excluded from randomised clinical trials and many previous observational studies of these patients have been of limited size, duration, and scope.[2]
- The **B**ipolar **C**omprehensive **O**utcomes **S**tudy **(BCOS)** is the first Australian prospective observational study evaluating the actual care of participants with bipolar I and schizoaffective disorders, and is also the first study to measure health care costs in this population.
- BCOS aims to:
  - Examine the effectiveness of mood stabilisers in the treatment of participants with bipolar I disorder (manic, mixed, or depressed episode) or schizoaffective disorder.
  - Assess economic, clinical, and functional outcomes associated with treatment in a "real-life" context.

METHODOLOGY

STUDY DESIGN

- Two-year, prospective, observational, open-label study
- Two study centres in Melbourne and Geelong, Australia
- Participants treated with:

- Olanzapine
- Lithium carbonate
- Sodium valproate
- Carbamazepine

- Usual standard-of-care at the discretion of the treating team
- No concomitant medication was excluded
- Study assessments at baseline and every 3 months

ENROLMENT

- Males or females ≥18 years
- Diagnosis of bipolar or schizoaffective disorder [DSM-IV TR criteria, confirmed by Mini-International Neuropsychiatric Review, Version 5 (MINI)[3]
- Written informed consent

MEASURES

- **Demographics**
  - Age
  - Gender
  - Diagnosis (DSM-IV TR)
  - Employment status
- **Clinical Status**
  - Severity of illness (CGI-BP overall)
  - Symptoms of mania (YMRS total; CGI-BP Mania)
  - Symptoms of depression ($HAMD_{21}$ total; CGI-BP Depression)
  - Hospital admission (3 months prior; no. of visits)
- **Quality of Life & Social Functioning**
  - EQ-5D & VAS: self-rated; overall health status
  - SF-36: self-rated; functioning and well-being
  - SLICE/LIFE: self-rated; impairment in activities and relationships
  - DIP: structured interview; socioeconomic and disability measures

DATA ANALYSIS

- Participants were compared based on illness severity at baseline:
  - Mania: YMRS <15 = mild/moderate, YRMS >15 = severe.
  - Depression: $HAMD_{21} \leq 13$ = mild, $13 < HAMD_{21} > 19$ = moderate, $HAMD_{21} \geq 19$ = severe.
- Study Entry comparisons were assessed using Fisher's Exact Test for categorical measures and ANOVA or the medians test for continuous measures.
- All longitudinal profiles were assessed using Mixed Model Repeated Measures (MMRM) adjusted for the following:
  - Study entry factors: Age, gender, diagnosis, length of stay in previous 3 months, hospitalised, overall CGI-BP-S, alcohol dependence past 12 months (from MINI), smoking status, partner status, employment status, visit and site.
  - Medications taken during 12 months observation: amount of time on Mood Stabilisers and/or Antidepressants and/or Antipsychotic and/or Benzodiazepines/Hypnotics.
- MMRM using random effect for time & intercept. Model statement includes visit & $visit^2$. Covariance Structure used was Spatial Power.
- Interaction effects were assessed at the 0.1 level.

DATA ANALYSIS CONT…

- Predictors of baseline illness severity were assessed using logistic regression with the same factors as the longitudinal analysis, with the following changes:
  - The factors SF-36 PCS & MCS, EQ-5D, partner status, current suicidality (past month), and income status were added. Visit and site were removed.
  - Medications taken in the past 3 months since study entry was used instead of during 12 months of study.
- A backwards elimination approach was adopted to reduce the models.
- Clinically significant predictors were kept in the models despite statistical significance.

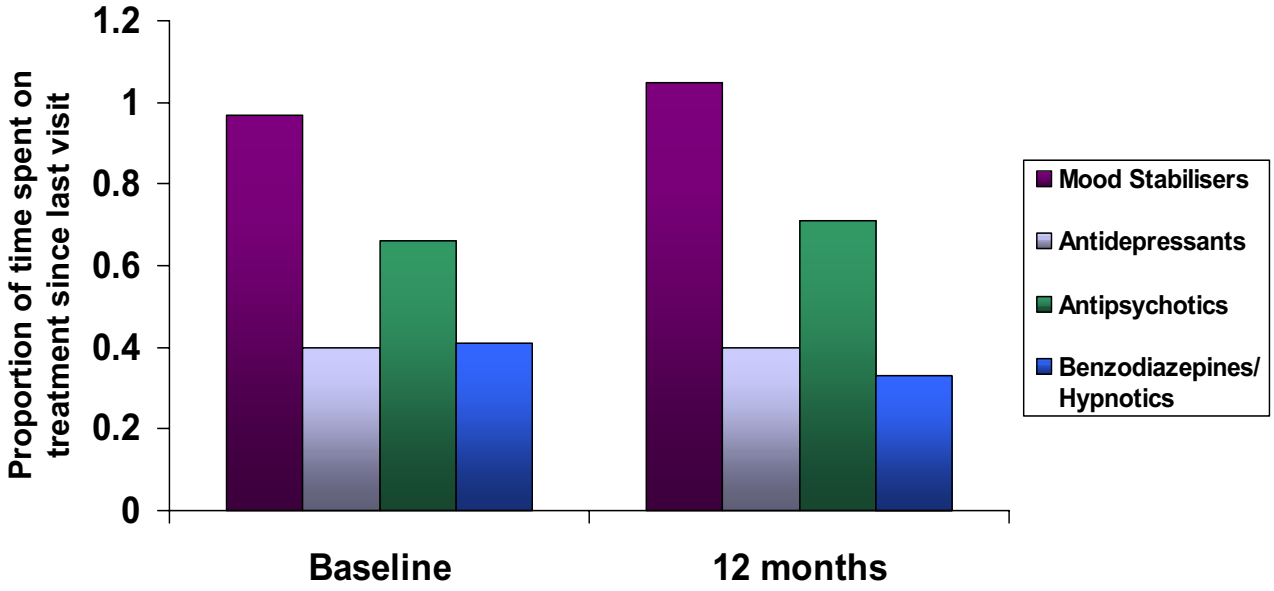
Enrolment has been completed.
We now present data after 12 months follow-up

DEMOGRAPHICS

Characteristics		Overall
Age (years), (range)		41.8 (18 to 79)
Women		58%
Bipolar I disorder		73%
Smoke Daily		51%
Consumed alcohol 3+ days/week (3 months pre-enrolment):		20%
Unemployed		30%
Prevented from working by mental illness		18%
Currently in a romantic relationship		42%
At least 1 day in hospital (3 months pre-enrolment)		33%
Mania:	YMRS <15 (mild/moderate)	81%
	YMRS >15 (severe)	19%
Depression:	$HAMD_{21} \leq 13$ (asymptomatic/mild)	51%
	$13 < HAMD_{21} < 19$ (moderate)	23%
	$HAMD_{21} \geq 19$ (severe)	25%

Treatment patterns over 12 months

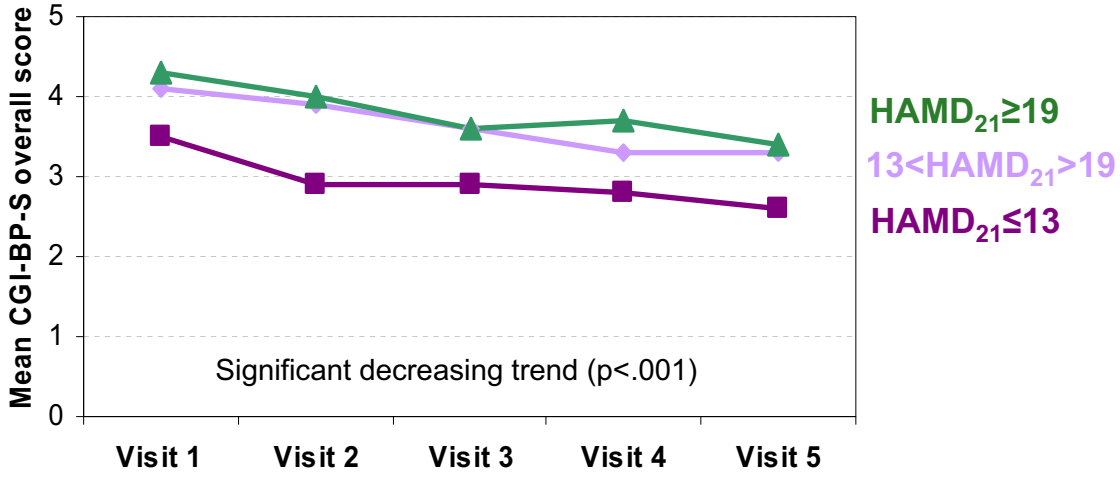
- The most commonly prescribed treatment was atypical antipsychotics combined with mood stabilisers (12.6%).
- Few changes in the number of medications taken over 12 months:
  -Overall mean (range): 3.1 (1-8) vs. 3.2 (0-10) at baseline
- Few changes over 12 months in amount of time spent on treatment by drug class:*



* Values may exceed '1' as some participants may be receiving more than one treatment from the same drug class.

CLINICAL STATUS

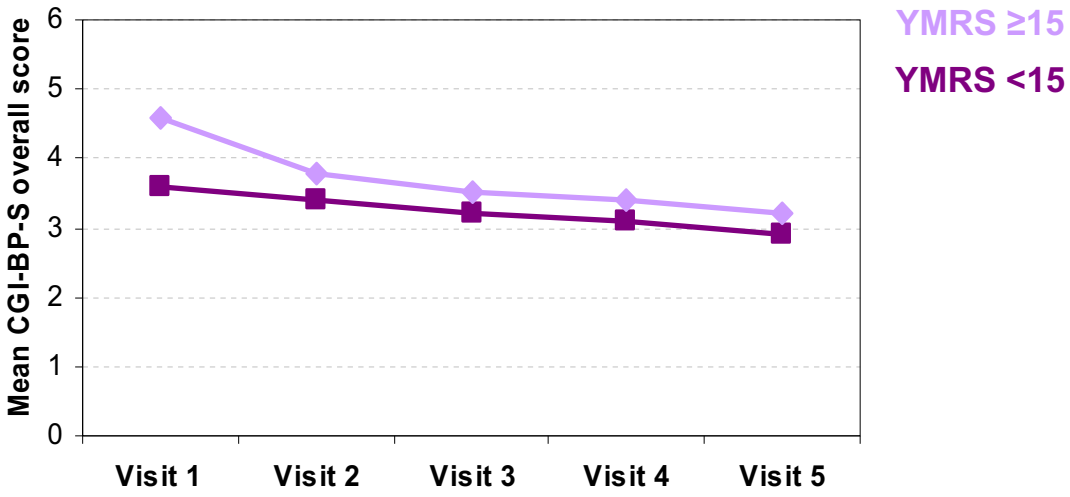
- Overall improvement in clinical outcomes after 12 months (mean±SE):
  - CGI-BP-S: 3.0±0.08 vs. 3.8±0.09 baseline (p=.044)
  - $HAMD_{21}$ Total: 11.5±0.56 vs. 13.4±0.55 (p<.001)
  - CGI-BP Depression: 2.8±0.08 vs. 3.2±0.09 (p=.018)
  - CGI-BP Mania: 2.2±0.08 vs. 3.0 ±0.10 (p=.003)
- CGI-BP-S total scores split by level of depression:



Overall Comparison:
mild vs. moderate p<.001; mild vs. severe p<.001; moderate vs. severe p=.755

CGI-BP-S total scores split by level of mania:

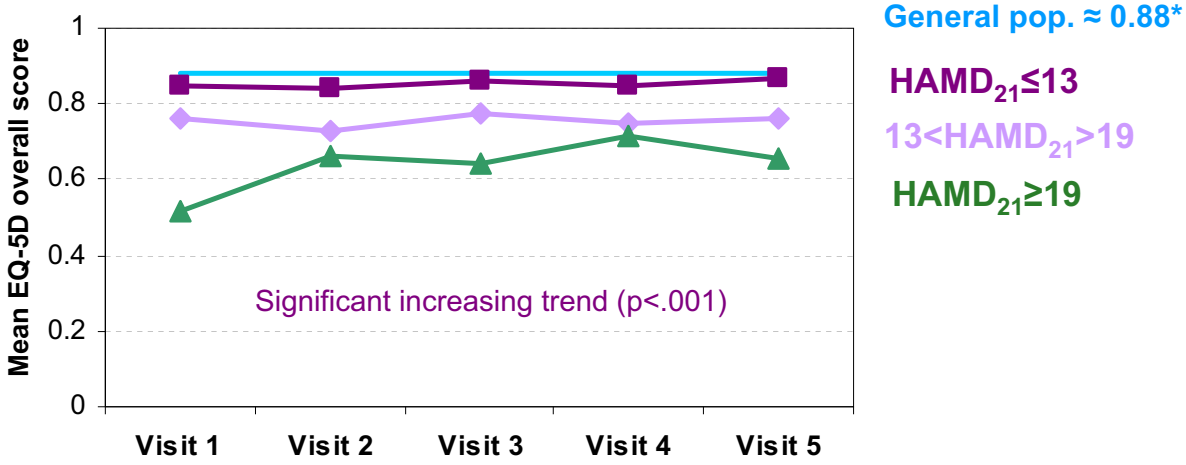
Significant decreasing trend (p<.001)



Overall Comparison: p=.0467

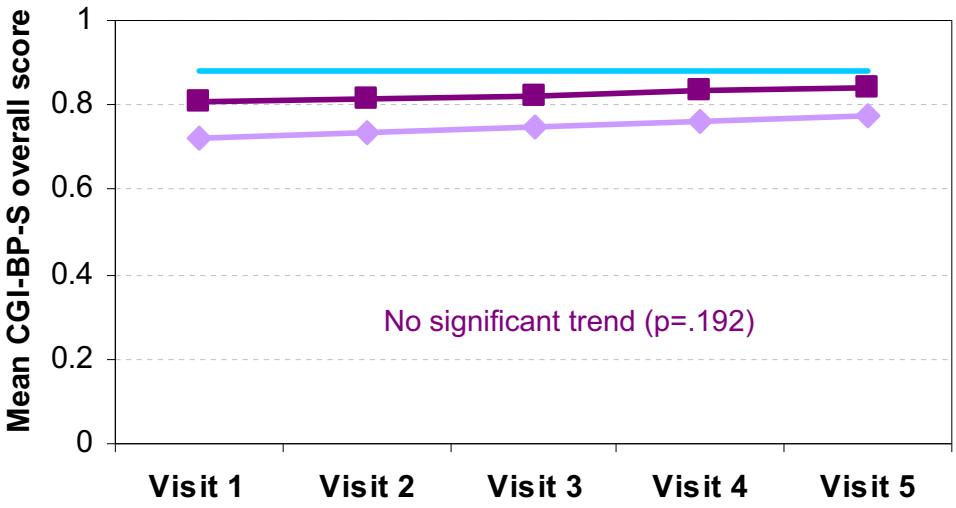
FUNCTIONAL STATUS

- 67% of patients 'Low' on EuroQoL - Normal Indicator (age/sex adjusted)
- EQ-5D utility scores split by level of depression:



Overall Comparison:
Mild vs. moderate p=.006; mild vs. severe p<.001; moderate vs. severe p<.001

EQ-5D total scores split by level of mania:



General pop. ≈ 0.88*

YMRS <15

YMRS ≥15

Overall Comparison: p=.039

**** Australians aged 36-50 years.[4]***

Summary of 12 Month Outcomes: split by $HAMD_{21}$ scores

	$HAMD_{21}$ ≤13 (n=122)	$HAMD_{21}$ >13 & <19 (n=56)	$HAMD_{21}$ ≥19 (n=60)	LS Mean Difference[a] (95% CI)	P-Value[a]
EQ-5D VAS	79.06	72.15	64.82	14.24 (9.90 to 18.58)	**<.001**
EQ-5D Utility	0.84	0.77	0.64	0.20 (0.15 to 0.25)	**<.001**
SF-36 MCS	45.03	39.18	36.68	8.35 (5.52 to 11.17)	**<.001**
SF-36 PCS	49.49	45.85	42.89	6.60 (3.99 to 9.21)	**<.001**
HAMD Total	8.16	12.86	17.44	-9.29 (-10.77 to -7.80)	**<.001**
YMRS Total	7.86	10.64	11.31	-3.45 (-5.25 to -1.65)	**<.001**
CGI-BP-S	2.96	3.61	3.65	-0.70 (-0.95 to -0.44)	**<.001**
CGI-BP-Mania	2.37	2.89	2.76	-0.38 (-0.66 to -0.11)	**.006**
CGI-BP-Depression	2.54	3.21	3.47	-0.93 (-1.18 to -0.68)	**<.001**
Slice/Life Total	2.05	2.33	2.43	-0.39 (-0.53 to -0.24)	**<.001**

[a] **Comparing mild (HAMD21≤13) vs. severe (HAMD21 ≥19) depression.**

Summary of 12 Month Outcomes: Split by YMRS Scores

	YMRS <15 (n=194)	YMRS ≥15 (n=45)	LS Mean Difference (95% CI)	P-Value
EQ-5D VAS	77.75	71.79	5.97 (0.31 to 11.62)	**.039**
EQ-5D Utility	0.82	0.74	0.08 (0.00 to 0.15)	**.039**
SF-36 MCS	42.89	41.53	1.37 (-2.30 to 5.03)	.464
SF-36 PCS	48.36	46.58	1.78 (-1.52 to 5.09)	.289
HAMD Total	9.39	12.26	-2.87 (-5.21 to -0.53)	**.016**
YMRS Total	4.69	12.60	-7.91 (-9.77 to -6.05)	**<.001**
CGI-BP-S	3.13	3.48	-0.34 (-0.68 to -0.01)	**.048**
CGI-BP-Mania	2.27	2.97	-0.70 (-1.03 to -0.37)	**<.001**
CGI-BP-Depression	2.85	3.03	-0.18 (-0.52 to 0.16)	.292
SLICE/LIFE Total	2.12	2.23	-0.11 (-0.29 to -0.07)	.216

Predictors of Baseline Illness Severity

	Mania		Depression	
Parameter	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Age at Visit 1	1.00 (0.97 to 1.04)	0.864	1.00 (0.96 to 1.03)	0.878
Female	0.63 (0.26 to 1.52)	0.304	0.95 (0.43 to 2.13)	0.906
Length of Stay	1.05 (1.01 to 1.09)	**0.018**	N/A	N/A
In hospital on Visit date	16.67 (2.44 to 100.00)	**0.004**	N/A	N/A
Overall CGI-BP-S score	1.37 (0.87 to 2.17)	0.172	1.28 (0.87 to 1.82)	0.229
Euroqol: EQ-5D Utility Score	N/A	N/A	0.04 (0.01 to 0.18)	**<.001**
SF-36 MCS	1.02 (0.98 to 1.06)	0.320	0.95 (0.92 to 0.99)	**0.010**
Time on Mood Stabilisers	0.50 (0.21 to 1.19)	0.117	1.11 (0.51 to 2.44)	0.784
Time on Antipsychotics	0.90 (0.39 to 2.08)	0.813	1.64 (0.83 to 3.23)	0.152
Time on Antidepressants	0.98 (0.32 to 3.03)	0.974	1.20 (1.02 to 2.86)	0.680
Time on Benzos/Hypnotics	0.77 (0.30 to 1.92)	0.577	1.49 (0.80 to 2.86)	0.208
Smoking Daily	N/A	N/A	0.47 (0.20 to 1.12)	0.091
Alcohol Dependence (12 months)	3.13 (1.11 to 9.09)	**0.030**	N/A	N/A
Current Suicidality (past month)	2.33 (0.81 to 6.67)	0.117	1.89 (0.74 to 4.76)	0.187
No Partner	2.10 (0.84 to 5.23)	0.113	1.76 (0.79 to 3.92)	0.168
Income - $500+/Week	0.28 (0.08 to 1.01)	0.051	0.38 (0.12 to 1.16)	0.092

KEY FINDINGS

- Overall improvement in clinical and functional outcomes over 12 months
- Participants with clinical depression had poorer clinical and functional outcomes than asymptomatic participants. Severity of mania predicted fewer outcome differences.
- Participants with poor self-assessed mental health and quality of life were more likely to be clinically depressed at baseline.
- Participants with alcohol dependence and longer hospitalisation periods were more likely to be clinically manic at baseline.
- Few changes were observed in distribution of treatment by class or number of medications over 12 months.

CONCLUSION

Clinical outcomes improved overall after 12 months observation in the BCOS study, with depression severity associated with poorer outcomes. Emerging trends can be further explored at the 24 month study endpoint.

References

[1] Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL. 1993. The enduring psychosocial consequences of mania and depression. Am J Psychiatry 150: 720-727.

[2] Gomez JC, Sacristan JA, Hernandez J, Breier A, Ruiz CP, Anton SC, Fontova CE. 2000. The safety of olanzapine compared with other antipsychotic drugs: results of an observational prospective study in patients with schizophrenia (EFESO Study). J Clin Psychiatry 61: 335-43.

[3] Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC.1998. The Mini International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview. J Clin Psychiatry 59(20 Suppl): 22-33.

[4] Koltowska-Häggström M, Hennessy S, Mattson AF, Monson JP, Kind P. 2005. Quality of Life Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA): Comparison of Normative Reference Data for the General Population of England and Wales with Results for Adult Hypopituitary Patients with Growth Hormone Deficiency. Horm Res 64: 46-54.

Acknowledgements

THE BCOS STUDY TEAM

THIS STUDY WAS FINANCIALLY SUPPORTED BY ELI LILLY AND COMPANY