

Appendix 6 Summary of Peto odds ratios, risk differences and 95% confidence intervals for neuropsychiatric events (all doses of varenicline combined vs placebo) [posted as supplied by author]

Neuropsychiatric adverse event	Varenicline group number of events/ number treated	Placebo group number of events/ number treated	Peto odds ratio and 95% confidence interval	p value	Risk difference and 95% confidence interval	p value
Primary outcomes						
Depression	175/5875	139/4487	0.97(0.76 to 1.23)	0.78	-0.001 (-0.008 to 0.006)	0.79
Suicidal ideation	15/2799	18/2191	0.58 (0.28 to 1.20)	0.14	-0.003 (-0.009 to 0.002)	0.24
Suicide attempt	2/2437	2/1842	0.63 (0.08 to 5.12)	0.67	-0.0004 (-0.005 to 0.004)	0.87
Suicide and suicide attempt	4/6173	2/4478	1.56 (0.29 to 8.28)	0.6	0.0003 (-0.002 to 0.003)	0.85
Secondary outcomes						
Abnormal dreams	660/6157	235/4773	2.22 (1.91 to 2.58)	<0.0001	0.05 (0.04 to 0.06)	<0.0001
Aggression	39/4290	24/3524	0.90 (0.52 to 1.57)	0.72	-0.001 (-0.005 to 0.004)	0.76
Anxiety	246/6016	232/4650	0.76 (0.63 to 0.93)	0.009	-0.01 (-0.02 to -0.002)	0.01
Death	13/6595	11/4887	1.01 (0.45 to 2.29)	0.98	0.00002 (-0.003 to 0.003)	0.99
Fatigue	327/6361	212/4733	1.28 (1.06 to 1.54)	0.01	0.01 (0.003 to 0.02)	0.01
Insomnia	787/6466	390/4794	1.52 (1.33 to 1.73)	<0.0001	0.04 (0.02 to 0.05)	<0.0001
Irritability	340/6233	266/4615	0.97 (0.81 to 1.16)	0.72	-0.002 (-0.01 to 0.007)	0.72
Sleep disorders	225/5894	123/4284	1.58 (1.25 to 2.01)	<0.0001	0.01 (0.01 to 0.02)	<0.0001
Somnolence	184/6227	101/4574	1.24 (0.96 to 1.61)	0.09	0.005 (-0.001 to 0.011)	0.09

Notes for Appendix 6

This secondary analysis was done in response to reviewers' comments on the original submitted manuscript. It is not part of the original PROSPERO protocol.

For the analysis of varenicline (all doses) vs placebo, the studies by Hong et al. (2011) and Mocking et al. (2013) cited in the discussion but originally excluded from the systematic review as they included 0.5 mg varenicline would now meet the inclusion criteria. The Mocking et al. (2013) study could not be included in the meta-analyses as the numbers of adverse events or deaths were not reported.

Original analysis after exclusion of 5 trials (39 trials) discussed in the main manuscript- n= 5817 varenicline, n=4944 placebo

Secondary analysis (40 trials-i.e. 39 trials as above plus the Hong et al. (2011) trial (0.5 mg varenicline) with all doses of varenicline included in the following trials- Burstein et al. (2006), Faessel et al. (2009)- since this study included adolescents and varenicline is only recommended for use in adults only, the doses in the high body weight adolescents were used, Nakamura et al. (2007), Nides et al. (2006) and Oncken et al. (2006)- n=6684 varenicline, n=4976 placebo.