

Data supplement

Table DS1 Baseline sample characteristics				
	Randomised		Non-randomised	
	Escitalopram (n=233)	Nortriptyline (n=235)	Escitalopram (n=225)	Nortriptyline (n=118)
Female, n (%)	146 (63)	161 (69)	137 (61)	70 (59)
Age, years: mean (s.d.)	41.9 (11.6)	42.5 (11.6)	43.5 (11.7)	41.9 (12.6)
Education, years: mean (s.d.)	12.2 (3.2)	12.1 (3.1)	12 (3)	12.1 (3.1)
Marital status, n (%)				
Married/cohabiting	123 (53)	125 (53)	103 (46)	57 (48)
Separated/divorced	40 (17)	43 (18)	61 (27)	30 (25)
Widowed	8 (3)	14 (6)	5 (2)	3 (3)
Single	62 (27)	53 (23)	56 (25)	28 (24)
Children, n (%)				
0	75 (32)	62 (26)	64 (28)	33 (28)
1	68 (29)	73 (31)	78 (35)	36 (31)
2	68 (29)	79 (34)	73 (32)	39 (33)
3+	22 (9)	21 (9)	10 (4)	10 (8)
Occupation, n (%)				
Full-time work	88 (38)	84 (36)	85 (38)	32 (27)
Part-time work	28 (12)	29 (12)	23 (10)	15 (13)
Student	15 (6)	9 (4)	15 (7)	12 (10)
Home-maker	8 (3)	13 (6)	6 (3)	7 (6)
Retired	28 (12)	41 (17)	17 (8)	12 (10)
Unemployed	66 (28)	59 (25)	79 (35)	40 (34)
Age at onset, years: mean (s.d.)	32.2 (10.6)	31.4 (9.9)	34.4 (8.7)	33.3 (10.1)
Episodes, n (%)				
1	47 (20)	59 (25)	115 (51)	43 (36)
2	149 (64)	138 (59)	99 (44)	66 (56)
3+	37 (16)	38 (16)	11 (5)	9 (8)
Current episode duration, weeks: mean (s.d.)	19.5 (14.3)	17.8 (13.1)	18.9 (8.5)	20.7 (13)
History of taking drug, n (%)				
Antidepressants	103 (44)	118 (50)	90 (40)	56 (48)
SSRI antidepressants	67 (29)	74 (31)	56 (25)	46 (39)
Tricyclic antidepressants	39 (17)	44 (19)	30 (13)	18 (15)
Currently taking drug, n (%)				
Antidepressants	48 (21)	62 (26)	38 (17)	22 (19)
Benzodiazepines	90 (39)	80 (34)	84 (37)	36 (31)
Psychotropic medication	113 (49)	117 (50)	103 (46)	47 (40)
Baseline severity, mean (s.d.)				
Montgomery-Åsberg Depression Rating Scale	29.1 (6.6)	29.4 (6.7)	27.6 (6.7)	28.6 (6.9)
Hamilton Rating Scale for Depression-17	22.2 (5.1)	22.3 (5.4)	20.8 (5.4)	21.6 (5.2)
Beck Depression Inventory	28.6 (9.4)	28.6 (9.9)	26.9 (9.8)	28.0 (9.6)
Observed mood	49.8 (9.4)	50.2 (10.6)	48.3 (10.6)	48.6 (10.2)
Cognitive symptoms	49.9 (9.8)	50.1 (10.2)	47.9 (10.7)	49.2 (10.5)
Neurovegetative symptoms	50.8 (9.9)	50.1 (10.1)	48.6 (9.9)	49.8 (8.6)

SSRI, selective serotonin reuptake inhibitor.

Table DS2 Antidepressant dosage in milligrams by study week				
Week	Randomised, mean (s.d.)		Non-randomised, mean (s.d.)	
	Escitalopram	Nortriptyline	Escitalopram	Nortriptyline
1	10.31 (3.74)	66.86 (24.47)	9.73 (4.28)	57.60 (22.56)
2	11.47 (3.83)	81.54 (25.59)	11.08 (4.32)	71.40 (26.38)
3	14.18 (4.64)	91.56 (28.63)	12.31 (5.02)	75.07 (25.50)
4	15.38 (5.05)	100.25 (31.18)	12.86 (5.36)	85.28 (34.58)
5	16.46 (5.88)	101.14 (32.76)	13.70 (6.34)	88.48 (35.08)
6	17.20 (6.78)	102.70 (35.97)	14.59 (7.05)	89.92 (38.68)
7	17.59 (6.80)	102.97 (38.74)	15.02 (7.06)	91.82 (41.40)
8	17.70 (6.83)	102.39 (41.15)	15.21 (7.22)	92.94 (41.66)
9	17.95 (6.39)	111.00 (31.04)	15.86 (7.41)	98.37 (32.34)
10	18.16 (6.91)	110.90 (35.27)	15.88 (7.53)	98.94 (31.92)
11	18.12 (7.19)	112.36 (34.92)	15.93 (7.47)	98.90 (32.17)
12	18.45 (7.58)	112.20 (38.90)	16.19 (7.74)	98.44 (32.55)

Response and remission with last observation carried forward

Analysis of clinical trials with missing data has traditionally been performed with the last observation carried forward (LOCF) procedure. It has been demonstrated that this approach introduces a systematic bias and underestimates the level of uncertainty.^{1,2} Therefore, LOCF is not considered a valid analysis by many experts in the field.³ However, some researchers still prefer LOCF analysis for the purposes of simplicity and comparability with previous reports. Therefore, we report Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression-17 (HRSD) and Beck Depression Inventory (BDI) at week 8 and week 12 with the LOCF in cases of drop out, switching or missing data. We report the rates of response (50% symptom reduction) and remission (HRSD=7; MDRS=10; BDI=10) according to standard definitions.⁴

Results for response and remission: last observation carried forward

Depression severity levels at weeks 8 and 12 with missing values inputted following the LOCF rule are presented in online Table DS3. There were no significant between-drug differences in response (defined as 50% score reduction on MADRS, HRSD-17 or BDI). More participants allocated to escitalopram reached criteria for remission at week 8 on MADRS ($\chi^2(1)=4.02$, $P=0.045$), HDRS ($\chi^2(1)=5.69$, $P=0.017$) and BDI ($\chi^2(1)=5.69$, $P=0.017$). More participants allocated to escitalopram reached criteria for remission at week 12 on MADRS remission week 12 ($\chi^2(1)=11.05$, $P=0.001$) and on BDI ($\chi^2(1)=3.84$, $P=0.050$). Analysis of the randomised sample confirmed differences in rates of remission at week 8 on BDI ($\chi^2(1)=5.57$, $P=0.018$) and at week

12 for MADRS ($\chi^2(1)=5.87$, $P=0.015$) and BDI ($\chi^2(1)=7.14$, $P=0.008$).

Discussion

We caution against the interpretation of the significant differences in LOCF analysis for several reasons. First, unlike the mixed-effect models, the LOCF analysis does not take into account variations between study centres. Second, LOCF introduces systematic bias in the context of drop out.¹⁻³ Indeed, the results of LOCF analysis replicate a previous report by Joyce *et al*⁵ and illustrate the effect of differential attrition on the LOCF analysis. The meaning of differences in 'remission' in the absence of any significant differences in 'response' or in the rate of change is questionable. This discrepancy between analyses is explained by inequality in baseline severity among non-randomly allocated participants and differential attrition among randomly allocated participants.

References

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Table DS3 Descriptive statistics, response and remission with last observation carried forward (LOCF) procedure

	Randomised		Non-randomised	
	Escitalopram (n=233)	Nortriptyline (n=235)	Escitalopram (n=225)	Nortriptyline (n=118)
Baseline, mean (s.d.)				
MADRS	29.1 (6.6)	29.4 (6.7)	27.6 (6.7)	28.6 (6.9)
HRSD-17	22.2 (5.1)	22.3 (5.4)	20.8 (5.4)	21.6 (5.2)
BDI	28.6 (9.4)	28.6 (9.9)	26.9 (9.8)	28.0 (9.6)
Week 8 (LOCF)				
MADRS, mean (s.d.)	15.9 (9.4)	16.8 (8.9)	16.2 (10.2)	17.4 (9.1)
HRSD-17, mean (s.d.)	12.1 (7.2)	12.8 (6.9)	11.8 (7.5)	12.3 (6.9)
BDI, mean (s.d.)	16.4 (11.7)	17.5 (10.1)	16.8 (11.5)	17.6 (10.8)
MADRS 50% reduction, n (%)	102 (44)	96 (41)	97 (43)	46 (39)
MADRS ≤ 10, n (%)	70 (30)	58 (25)	77 (34)	32 (27)
HRSD-17 50% reduction, n (%)	110 (47)	99 (42)	108 (48)	55 (47)
HRSD-17 ≤ 7, n (%)	70 (30)	54 (23)	73 (32)	29 (25)
BDI 50% reduction, n (%)	106 (45)	88 (37)	88 (39)	45 (38)
BDI ≤ 10, n (%)	84 (36)	61 (26)	77 (34)	35 (30)
Week 12 (LOCF)				
MADRS, mean (s.d.)	13.5 (10.1)	14.9 (9.8)	13.7 (10.8)	15.9 (10.3)
HRSD-17, mean (s.d.)	10.3 (7.5)	11.3 (7.5)	10.1 (7.9)	11.3 (7.7)
BDI, mean (s.d.)	14.1 (11.3)	15.7 (10.8)	15.0 (12.0)	16.3 (11.2)
MADRS 50% reduction, n (%)	133 (57)	128 (54)	131 (58)	55 (47)
MADRS ≤ 10, n (%)	110 (47)	85 (36)	105 (47)	39 (33)
HRSD-17 50% reduction, n (%)	140 (60)	127 (54)	134 (60)	61 (52)
HRSD-17 ≤ 7, n (%)	97 (42)	88 (37)	105 (47)	46 (39)
BDI 50% reduction, n (%)	135 (58)	115 (49)	112 (50)	54 (46)
BDI ≤ 10, n (%)	105 (45)	85 (36)	98 (44)	38 (32)

MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS-17, Hamilton Rating Scale for Depression (17 items); BDI, Beck Depression Inventory.