



Clinical trial results:

Mirtazapine added to SSRIs for treatment resistant depression in primary care: a placebo controlled randomised controlled trial

Summary

EudraCT number	2012-000090-23
Trial protocol	GB
Global end of trial date	19 December 2017

Results information

Result version number	v1 (current)
This version publication date	14 March 2019
First version publication date	14 March 2019

Trial information

Trial identification

Sponsor protocol code	UoB1651
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Additional study identifiers

ISRCTN number	ISRCTN06653773
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Bristol
Sponsor organisation address	One Cathedral Square, Bristol, United Kingdom, BS1 5DD
Public contact	Rachel Davies, University of Bristol, +44 1174284021 , rachel.davies@bristol.ac.uk
Scientific contact	Rachel Davies, University of Bristol, +44 1174284021 , rachel.davies@bristol.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 December 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effectiveness of the addition of the antidepressant mirtazapine to an SSRI or SNRI in reducing depressive symptoms and improving quality of life at 12 weeks, 24 weeks and 12 months (compared to the addition of a placebo).

Protection of trial subjects:

usual standard operating procedures in the event of disclosure of ideas of suicide or self harm.

Background therapy:

not applicable

Evidence for comparator:

not applicable

Actual start date of recruitment	26 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 480
Worldwide total number of subjects	480
EEA total number of subjects	480

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	406
From 65 to 84 years	74
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place from August 2013 to October 2015 in four centres, all in the United Kingdom

Pre-assignment

Screening details:

751 patients assessed for eligibility

481 eligible, 270 ineligible (Not depressed)

480 randomised

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The treatment allocation schedule was computer generated by a statistician independent of the trial team in a 1:1 ratio, stratified by centre and minimised by baseline depression score, sex and whether the participant was receiving a psychological intervention. Packs contained encapsulated mirtazapine 15mg or identical placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Mirtazapine

Arm description:

participants treated with the active medication

Arm type	Active comparator
Investigational medicinal product name	Mirtazapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were asked to take one capsule daily for 2 weeks and then increase to 2 capsules daily thereafter

Arm title	Placebo
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Arm description:

Patients treated with placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were asked to take one capsule daily for 2 weeks and then increase to 2 capsules daily thereafter

Number of subjects in period 1	Mirtazapine	Placebo
Started	241	239
Completed	214	217
Not completed	27	22
Lost to follow-up	27	22

Baseline characteristics

Reporting groups

Reporting group title	Mirtazapine
Reporting group description: participants treated with the active medication	
Reporting group title	Placebo
Reporting group description: Patients treated with placebo	

Reporting group values	Mirtazapine	Placebo	Total
Number of subjects	241	239	480
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	197	209	406
From 65-84 years	44	30	74
85 years and over	0	0	0
Age continuous Units: years			
geometric mean	50.4	49.9	
standard deviation	± 13.8	± 12.5	-
Gender categorical Units: Subjects			
Female	168	164	332
Male	73	75	148
Baseline Beck Depression Inventory Score Units: Subjects			
14-25	77	79	156
26-34	78	78	156
>34	86	82	168
ICD-10 Diagnosis of Depression Units: Subjects			
mild	38	44	82
moderate	138	144	282
severe	65	51	116
Mean BDI score Units: scale 0-63			
geometric mean	31.5	30.6	
standard deviation	± 10.2	± 9.6	-
General Anxiety Disorder (GAD7) Units: scale 0-21			

geometric mean	11.3	10.7	
standard deviation	± 4.8	± 4.8	-

End points

End points reporting groups

Reporting group title	Mirtazapine
Reporting group description: participants treated with the active medication	
Reporting group title	Placebo
Reporting group description: Patients treated with placebo	

Primary: mean BDI score

End point title	mean BDI score
End point description:	
End point type	Primary
End point timeframe: 12 weeks	

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	217		
Units: scale 0-63				
geometric mean (standard deviation)	18 (\pm 12.3)	19.7 (\pm 12.4)		

Statistical analyses

Statistical analysis title	Change in mean BDI score analysed as a continuous
Comparison groups	Mirtazapine v Placebo
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.09
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.92
upper limit	0.27

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were reported from the time a signed and dated informed consent form was obtained until completion of the last trial related procedure (collection of follow-up data 12 months after randomisation)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	SMPC and BNF
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Dictionary version	latest
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Reporting groups

Reporting group title	Mirtazapine group
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Reporting group description:

Participants randomised to Mirtazapine

Reporting group title	Placebo group
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Reporting group description:

Participants randomised to placebo

Serious adverse events	Mirtazapine group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 241 (3.32%)	3 / 239 (1.26%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Ischaemia			
subjects affected / exposed	1 / 241 (0.41%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 241 (0.41%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Dental care			
subjects affected / exposed	1 / 241 (0.41%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Hysterectomy			
subjects affected / exposed	1 / 241 (0.41%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 241 (0.41%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
chest infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 241 (0.83%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
trauma			
subjects affected / exposed	0 / 241 (0.00%)	2 / 239 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
infected ulcer			
subjects affected / exposed	0 / 241 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Mirtazapine group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	180 / 241 (74.69%)	89 / 239 (37.24%)	
Nervous system disorders			
psychiatric	Additional description: This includes drowsiness, headache, TIA, unpleasant dreams, sleep disturbance		
subjects affected / exposed	70 / 241 (29.05%)	27 / 239 (11.30%)	
occurrences (all)	70	27	
General disorders and administration site conditions			
see below	Additional description: includes anticholinergic effects, allergic reactions, minor endocrine, ENT, Dental, dermatological, ophthalmological, haematological and infective disorders		
subjects affected / exposed	27 / 241 (11.20%)	26 / 239 (10.88%)	
occurrences (all)	27	26	
Gastrointestinal disorders			
Appetite disorder	Additional description: this includes appetite changes, nausea and weight gain		
subjects affected / exposed	34 / 241 (14.11%)	18 / 239 (7.53%)	
occurrences (all)	34	18	
Reproductive system and breast disorders			
minor disorders			
subjects affected / exposed	2 / 241 (0.83%)	1 / 239 (0.42%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
minor respiratory disorders			
subjects affected / exposed	6 / 241 (2.49%)	3 / 239 (1.26%)	
occurrences (all)	6	3	
Musculoskeletal and connective tissue disorders			
minor injury			
subjects affected / exposed	15 / 241 (6.22%)	17 / 239 (7.11%)	
occurrences (all)	15	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30442772>