



Clinical trial results: Effects of Varenicline and Cognitive Bias Modification on Neural Response to Smoking Cues Summary

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|--------------------------|----------------|
| EudraCT number | 2011-004169-34 |
| Trial protocol | GB |
| Global end of trial date | 01 July 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 28 July 2018 |
| First version publication date | 28 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | UoB1407 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------------------|
| ISRCTN number | ISRCTN65690030 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Funder-Pfizer: WS676950 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Bristol |
| Sponsor organisation address | Senate House, Tyndall Avenue, Bristol, United Kingdom, BS8 1TH |
| Public contact | Dr Birgit Whitman, University of Bristol, Research Enterprise and Development, +44 01173317130, Birgit.Whitman@bristol.ac.uk |
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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 | 11 January 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 July 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 July 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

1) Does cognitive bias modification alter neural response to smoking-related cues? H1a: We hypothesise that experimental procedures designed to induce attentional bias towards smoking-related cues will lead to an increase in neural response to smoking-related cues, in brain regions previously implicated in cue reactivity in cigarette smokers. H1b: We hypothesise that experimental procedures designed to induce attentional bias away from smoking-related cues will lead to a decrease in neural response to smoking-related cues, in brain regions previously implicated in cue reactivity in cigarette smokers.

Protection of trial subjects:

The study medication was a licensed medication to aid smoking cessation, and no serious adverse events were expected. The drug (varenicline) is associated with some side effects which were explained to the participant who was told they were able to stop the study medication at any time. The more common side effects may be unpleasant but are not considered serious or long lasting (e.g., fatigue, vivid dreams, nausea).

There is some weak scientific evidence to suggest a small increase in cardiovascular events for participants taking varenicline compared to placebo. The research has been criticised methodologically but to mitigate any risk we included an upper age limit of 40 years (the mean ages of participants in studies in the meta analysis in question was 39 - 57). There is also association of the drug with depressive symptoms. To mitigate risk participants were screened by a psychiatrist prior to enrolment.

Background therapy:

None

Evidence for comparator:

N/a

| | |
|---|------------------|
| Actual start date of recruitment | 01 November 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 89 |
| Worldwide total number of subjects | 89 |
| EEA total number of subjects | 89 |

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) | 89 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from the Bristol area (south west United Kingdom). All participants were current smokers (i.e., at least 10 manufactured or 15 roll-up cigarettes per day).

The first participant was enrolled on 5th November 2011 and the last participant was enrolled on 24th June 2014.

Pre-assignment

Screening details:

Inclusion: aged 18-40

Exclusion: pregnancy/breastfeeding, drug misuse disorder, psychiatric illness, clinically significant abnormality (including CV risk), ongoing medication, uncorrected visual/auditory impairment, hypersensitivity to varenicline, cannot have MRI scan.

Exclusion breakdown information no longer available.

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 312 ^[1] |
| Number of subjects completed | 89 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-----------------------------------|
| Reason: Number of subjects | Not eligible or lost contact: 223 |
|----------------------------|-----------------------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The pre-assignment phase is a screening phase in which potential participants were screened for eligibility. This occurred before enrollment and therefore the number is higher than those enrolled.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Baseline |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Baseline measurements taken on all participants prior to randomisation to drug and CBM experimental conditions

Arms

| | |
|-----------|----------|
| Arm title | Baseline |
|-----------|----------|

Arm description:

Baseline testing (pre-randomization)

| | |
|--|-------------|
| Arm type | Baseline |
| Investigational medicinal product name | None |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Wound stick |
| Routes of administration | Other use |

Dosage and administration details:

No product given in this stage. Above (pharmaceutical forms) added as was mandatory, but not relevant here.

| Number of subjects in period 1 | Baseline |
|--------------------------------|----------|
| Started | 89 |
| Completed | 89 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Drug regime (7 days) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Varenicline or matched placebo was prescribed for one week, to be taken as 0.5 mg once daily for days 1 - 3, and 0.5 mg twice daily for days 4 - 6, and 0.5 mg once daily for day 7. Drugs were dispatched from Bristol Royal Infirmary Pharmacy, who randomised drug to participant numbers. Pharmacy provided drug bottles pre-labelled with blinded condition allocation, and a unblinding sheet for study file

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Varenicline |

Arm description:

Active drug condition

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Varenicline |
| Investigational medicinal product code | CP526-555 |
| Other name | Champix, Chantix |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Varenicline was administered for one week, to be taken as 0.5 mg once daily for days 1 - 3, and 0.5 mg twice daily for days 4 - 6, and 0.5 mg once daily for day 7, consistent with early standard dosing regimen for smoking cessation. Smoking cessation usage usually extends beyond a single week however (depending on need of patient).

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Control drug (matched placebo to varenicline)

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

Dosage and administration details:

Matched to active drug

| Number of subjects in period 2 | Varenicline | Placebo |
|---------------------------------------|-------------|---------|
| Started | 46 | 43 |
| Completed | 44 | 41 |
| Not completed | 2 | 2 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | 1 | 1 |

Period 3

| | |
|------------------------------|-----------------------------|
| Period 3 title | Cognitive bias modification |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Participants were randomly assigned to CBM groups, but equal numbers of participants per group were maintained, and groups were balanced for sex and drug condition.

In advance of the study, an experimental collaborator prepared a numeric code using random number assignment software.

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | CBM Avoid |

Arm description:

Cognitive bias modification that trained participants to avoid smoking related cues

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | CBM Avoidance training (computer-based task) |
| Investigational medicinal product code | n/a |
| Other name | |
| Pharmaceutical forms | Wound stick |
| Routes of administration | Other use |

Dosage and administration details:

Pharmaceutical form (wound stick) is wrong. Entry was mandatory but not relevant. This product is an active version of a computer based cognitive bias training programme. This version trains smokers to attend away (i.e., avoid) smoking-related cues.

| | |
|------------------|-------------|
| Arm title | CBM Neutral |
|------------------|-------------|

Arm description:

Control task with no active training

| | |
|--|-----------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | CBM Neutral (computer based task) |
| Investigational medicinal product code | n/a |
| Other name | |
| Pharmaceutical forms | Wound stick |
| Routes of administration | Other use |

Dosage and administration details:

Pharmaceutical form (wound stick) is wrong. Entry was mandatory but not relevant. This product is a the control version of a computer based cognitive bias training programme.

| | |
|---|----------------------------------|
| Arm title | CBM Attend |
| Arm description: | |
| Cognitive bias training that trained participants to attend to smoking related cues | |
| Arm type | Active comparator |
| Investigational medicinal product name | CBM Attend (computer-based task) |
| Investigational medicinal product code | n/a |
| Other name | |
| Pharmaceutical forms | Wound stick |
| Routes of administration | Other use |

Dosage and administration details:

Pharmaceutical form (wound stick) is wrong. Entry was mandatory but not relevant. This product is an active version of a computer based cognitive bias training programme. This version trains smokers to attend towards (i.e., attend) smoking-related cues.

| Number of subjects in period 3 | CBM Avoid | CBM Neutral | CBM Attend |
|---------------------------------------|-----------|-------------|------------|
| Started | 38 | 23 | 24 |
| Completed | 22 | 22 | 24 |
| Not completed | 16 | 1 | 0 |
| Computer task failed to record | - | 1 | - |
| Computer error | 16 | - | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Baseline |
|-----------------------|----------|

Reporting group description:

Baseline characteristics for all subjects in final analysis (n = 68), excluding withdrawals (n = 4) and participants who had to be replaced due to computer error (n=17).

| Reporting group values | Baseline | Total | |
|--|----------|-------|--|
| Number of subjects | 89 | 89 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 23 | | |
| standard deviation | ± 5 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 41 | 41 | |
| Male | 48 | 48 | |
| Smoking heaviness | | | |
| Units: Cigarettes per day | | | |
| arithmetic mean | 15 | | |
| standard deviation | ± 3 | - | |

End points

End points reporting groups

| | |
|---|---------------------------|
| Reporting group title | Baseline |
| Reporting group description: Baseline testing (pre-randomization) | |
| Reporting group title | Varenicline |
| Reporting group description: Active drug condition | |
| Reporting group title | Placebo |
| Reporting group description: Control drug (matched placebo to varenicline) | |
| Reporting group title | CBM Avoid |
| Reporting group description: Cognitive bias modification that trained participants to avoid smoking related cues | |
| Reporting group title | CBM Neutral |
| Reporting group description: Control task with no active training | |
| Reporting group title | CBM Attend |
| Reporting group description: Cognitive bias training that trained participants to attend to smoking related cues | |
| Subject analysis set title | Varenicline / CBM Avoid |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Participants who received varenicline and completed CBM training to avoid to smoking cues | |
| Subject analysis set title | Varenicline / CBM Attend |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Participants who received varenicline and completed CBM training to attend to smoking cues | |
| Subject analysis set title | Varenicline / CBM control |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Participants who received varenicline and completed CBM control task (no training) | |
| Subject analysis set title | Placebo / CBM attend |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Participants who received placebo and completed CBM training to attend to smoking cues | |
| Subject analysis set title | Placebo / CBM avoid |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Participants who received placebo and completed CBM training to avoid to smoking cues | |
| Subject analysis set title | Placebo / CBM control |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Participants who received placebo and completed CBM control task (i.e., no training) | |

Primary: Neural response to smoking cues

| | |
|---|---------------------------------|
| End point title | Neural response to smoking cues |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| One measure after 7-day drug regime and immediately after CBM | |

| End point values | Varenicline / CBM Avoid | Varenicline / CBM Attend | Varenicline / CBM control | Placebo / CBM attend |
|-----------------------------|-------------------------|--------------------------|---------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 10 ^[1] | 10 | 12 |
| Units: % BOLD signal | | | | |
| number (not applicable) | -0.003 | 0.092 | 0.057 | 0.139 |

Notes:

[1] - Two participants were removed from the analysis due to poor quality images

| End point values | Placebo / CBM avoid | Placebo / CBM control | | |
|-----------------------------|----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 10 | 11 ^[2] | | |
| Units: % BOLD signal | | | | |
| number (not applicable) | 0.038 | 0.222 | | |

Notes:

[2] - One participant were removed from the analysis due to poor quality images

Statistical analyses

| | |
|--|---|
| Statistical analysis title | ANOVA |
| Statistical analysis description: | |
| A 2 (varenicline, placebo) × 3 (attend, avoid, control) mixed-model whole-brain ANOVA was used to examine smoking cue reactivity (smoking greater than control) between each group | |
| Comparison groups | Varenicline / CBM Avoid v Varenicline / CBM Attend v Varenicline / CBM control v Placebo / CBM attend v Placebo / CBM avoid v Placebo / CBM control |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANOVA |

Primary: Stroop Time 2 (Generalised Attentional Bias post drug, pre CBM)

| | |
|-----------------|---|
| End point title | Stroop Time 2 (Generalised Attentional Bias post drug, pre CBM) |
|-----------------|---|

End point description:

A pictorial version of the modified Stroop task was used to investigate the effect of dot-probe CBM on a different measure of cognitive bias. The task began with 16 practice trials followed by two experimental

blocks, each comprising 8 buffer and 96 experimental trials (i.e., 208 trials in total). For each trial a picture was presented (smoking-related or neutral) centrally on screen. The picture was surrounded by a coloured border and the participant was required to identify the colour of the border (red, blue, yellow or green) using colour-marked keys on the keyboard. Error scores are bias scores calculated by subtracting the number of errors made to neutral images from the number of errors made to smoking images) - thus positive scores are indicative of smoking attentional bias.

Note on outliers: For error data, three participants were identified as outliers in the pre-CBM condition and one in the post-CBM condition. These data were removed from analyses.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

This measure of attentional bias was taken on day 7 (i.e., after varenicline treatment), but before CBM training.

| End point values | Varenicline | Placebo | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 ^[3] | 31 ^[4] | | |
| Units: Errors (bias) | | | | |
| arithmetic mean (standard deviation) | 0.13 (± 1.91) | -0.45 (± 1.87) | | |

Notes:

[3] - One outlier removed

[4] - Three outliers removed

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Stroop by drug group |
|----------------------------|----------------------|

Statistical analysis description:

Test of attentional bias following 7 day drug regime. This Univariate ANOVA comprised one between-subjects factor of drug: varenicline/placebo.

| | |
|---|--------------------------------|
| Comparison groups | Varenicline v Placebo |
| Number of subjects included in analysis | 64 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.22 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.55 |
| upper limit | 0.81 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.34 |

Secondary: Stroop Time 3 (Generalised attentional bias post drug and training)

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|-----------------|---|
| End point title | Stroop Time 3 (Generalised attentional bias post drug and training) |
|-----------------|---|

End point description:

A pictorial version of the modified Stroop task was used to investigate the effect of dot-probe CBM on a different measure of cognitive bias. The task began with 16 practice trials followed by two experimental blocks, each comprising 8 buffer and 96 experimental trials (i.e., 208 trials in total). For each trial a picture was presented (smoking-related or neutral) centrally on screen. The picture was surrounded by a coloured border and the participant was required to identify the colour of the border (red, blue, yellow or green) using colour-marked keys on the keyboard. Error scores are bias scores calculated by subtracting the number of errors made to neutral images from the number of errors made to smoking images) - thus positive scores are indicative of smoking attentional bias.

Note on outliers: For error data, three participants were identified as outliers in the pre-CBM condition and one in the post-CBM condition. These data were removed from analyses.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| This measure of attentional bias was taken on day 7 (i.e., after varenicline treatment and CBM training) | |

| End point values | CBM Avoid | CBM Neutral | CBM Attend | Varenicline / CBM Avoid |
|--------------------------------------|-------------------|-------------------|-------------------|-------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 19 ^[5] | 22 ^[6] | 22 ^[7] | 10 |
| Units: Errors (Bias) | | | | |
| arithmetic mean (standard deviation) | -1.16 (± 2.29) | -0.95 (± 1.91) | -0.09 (± 1.82) | -1.2 (± 2.97) |

Notes:

[5] - Outliers removed

[6] - Outliers removed

[7] - Outliers removed

| End point values | Varenicline / CBM Attend | Varenicline / CBM control | Placebo / CBM attend | Placebo / CBM avoid |
|--------------------------------------|--------------------------|---------------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 10 | 10 | 11 | 9 |
| Units: Errors (Bias) | | | | |
| arithmetic mean (standard deviation) | -1.18 (± 1.47) | -1.0 (± 2.30) | 1.0 (± 1.48) | -1.11 (± 1.36) |

| End point values | Placebo / CBM control | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 12 | | | |
| Units: Errors (Bias) | | | | |
| arithmetic mean (standard deviation) | -0.92 (± 1.62) | | | |

Statistical analyses

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|----------------------------|--------------------------------------|
| Statistical analysis title | Stroop by CBM group (post training) |
| Comparison groups | CBM Avoid v CBM Neutral v CBM Attend |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 63 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.194 |
| Method | ANOVA |
| Parameter estimate | Slope |
| Point estimate | -0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.18 |
| upper limit | -0.099 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.428 |

| | |
|---|---|
| Statistical analysis title | Stroop: Drug by CBM |
| Comparison groups | Varenicline / CBM Avoid v Varenicline / CBM Attend v Varenicline / CBM control v Placebo / CBM attend v Placebo / CBM avoid v Placebo / CBM control |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.134 |
| Method | ANOVA |
| Parameter estimate | Slope |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.23 |
| upper limit | 0.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.614 |

Secondary: Visual dot probe 2 (Attentional bias)

| | |
|-----------------|---------------------------------------|
| End point title | Visual dot probe 2 (Attentional bias) |
|-----------------|---------------------------------------|

End point description:

Each trial began with a fixation cross (500 ms), before a picture pair (smoking image, neutral image) was presented on a computer screen. The picture pair stayed on screen for 500 ms and then was replaced by a probe (small square or circle) in a location previously occupied by one of the pictures. Participants were required to identify whether the probe was a square or circle by pressing designated keyboard keys. There were 128 test with the probe appearing with equal frequency in the location of the smoking-related or neutral picture. The inter-trial interval jittered between 750 ms and 1,250 ms.

To create a reaction time bias score, RTs to smoking images were subtracted from RT to neutral images. Thus positive RT scores are indicative of a smoking attentional bias.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

This measure of attentional bias was taken on day 7 (i.e., after varenicline treatment), but before CBM

| End point values | Varenicline | Placebo | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 34 | | |
| Units: Reaction Time Bias (ms) | | | | |
| arithmetic mean (standard deviation) | 11.97 (\pm 37.76) | -1.76 (\pm 29.38) | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | VDP after varenicline treatment |
| Comparison groups | Varenicline v Placebo |
| Number of subjects included in analysis | 68 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.099 |
| Method | ANOVA |
| Parameter estimate | Slope |
| Point estimate | 11.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.387 |
| upper limit | 23.552 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.801 |

Secondary: Visual Dot Probe 3 - Attentional bias

| | |
|-----------------|---------------------------------------|
| End point title | Visual Dot Probe 3 - Attentional bias |
|-----------------|---------------------------------------|

End point description:

Each trial began with a fixation cross (500 ms), before a picture pair (smoking image, neutral image) was presented on a computer screen. The picture pair stayed on screen for 500 ms and then was replaced by a probe (small square or circle) in a location previously occupied by one of the pictures. Participants were required to identify whether the probe was a square or circle by pressing designated keyboard keys. There were 128 test with the probe appearing with equal frequency in the location of the smoking-related or neutral picture. The inter-trial interval jittered between 750 ms and 1,250 ms.

To calculate a reaction time bias score, reaction time to smoking images was subtracted from reaction time to neutral images. Thus positive reaction time scores are indicative of smoking attentional bias. Due to computer malfunction, post-training CBM data were not recorded for one participant, therefore post-training sample comprises 67 participants.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

This measure of attentional bias was taken on day 7 (i.e., after varenicline treatment and CBM training).

| End point values | CBM Avoid | CBM Neutral | CBM Attend | Varenicline / CBM Avoid |
|--------------------------------------|-----------------|-----------------|-----------------|-------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 23 | 12 |
| Units: Reaction time bias (ms) | | | | |
| arithmetic mean (standard deviation) | -1.63 (± 18.34) | -9.32 (± 29.14) | 11.75 (± 45.07) | -1.79 (± 15.16) |

| End point values | Varenicline / CBM Attend | Varenicline / CBM control | Placebo / CBM attend | Placebo / CBM avoid |
|--------------------------------------|--------------------------|---------------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 10 | 10 | 12 | 10 |
| Units: Reaction time bias (ms) | | | | |
| arithmetic mean (standard deviation) | 15.42 (± 48.29) | -8.36 (± 40.22) | 8.39 (± 43.78) | -1.45 (± 22.45) |

| End point values | Placebo / CBM control | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 12 | | | |
| Units: Reaction time bias (ms) | | | | |
| arithmetic mean (standard deviation) | -10.12 (± 17.22) | | | |

Statistical analyses

| Statistical analysis title | VDP after CBM treatment |
|---|--------------------------------------|
| Comparison groups | CBM Avoid v CBM Neutral v CBM Attend |
| Number of subjects included in analysis | 67 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.103 |
| Method | ANOVA |
| Parameter estimate | Slope |
| Point estimate | -9.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.36 |
| upper limit | 4.73 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.03 |

| | |
|---|---|
| Statistical analysis title | VDP by CBM and varenicline treatment |
| Comparison groups | Varenicline / CBM Avoid v Varenicline / CBM Attend v Varenicline / CBM control v Placebo / CBM attend v Placebo / CBM avoid v Placebo / CBM control |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.931 |
| Method | ANOVA |
| Parameter estimate | Slope |
| Point estimate | -8.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.67 |
| upper limit | 12.95 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 10.66 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data collection period from November 2011 to July 2014

Adverse event reporting additional description:

Participants were given reporting cards to log any AEs. These were collected by the researcher on day 7 (final day) of drug regime. Participants were advised to contact the researcher during the drug regime if they were concerned about side effects, or were experiencing unexpected or severe side effects.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|-------------|
| Dictionary name | Champix CDS |
|-----------------|-------------|

| | |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Varenicline group |
|-----------------------|-------------------|

Reporting group description:

Participants allocated to varenicline medication for 7 days.

| | |
|-----------------------|---------------|
| Reporting group title | Placebo group |
|-----------------------|---------------|

Reporting group description:

Individuals in control arm who were administered 7 days placebo treatment

| Serious adverse events | Varenicline group | Placebo group | |
|---|-------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 43 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

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

| Non-serious adverse events | Varenicline group | Placebo group | |
|---|-------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 46 (43.48%) | 18 / 43 (41.86%) | |
| General disorders and administration site conditions | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 4 / 43 (9.30%) | |
| occurrences (all) | 3 | 4 | |
| Tiredness/drowsiness | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 7 / 43 (16.28%) | |
| occurrences (all) | 2 | 7 | |

| | | | |
|--|----------------------|---------------------|--|
| Vivid dreams / disrupted sleep subjects affected / exposed occurrences (all) | 7 / 46 (15.22%) 7 | 1 / 43 (2.33%) 1 | |
| Thirst/dry mouth subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 1 / 43 (2.33%) 1 | |
| Cigarettes tasted bad subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 43 (0.00%) 0 | |
| Fainting subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 43 (2.33%) 1 | |
| Eye disorders Eye twitch subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 43 (2.33%) 1 | |
| Gastrointestinal disorders Nausea, vomiting, stomach cramps subjects affected / exposed occurrences (all) | 8 / 46 (17.39%) 8 | 4 / 43 (9.30%) 4 | |
| General subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | 1 / 43 (2.33%) 1 | |
| Appetite loss subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 43 (2.33%) 1 | |
| Psychiatric disorders Anxiety/agitation subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 1 / 43 (2.33%) 1 | |
| Mood changes subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 1 / 43 (2.33%) 1 | |
| Infections and infestations Cold symptoms subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | 3 / 43 (6.98%) 3 | |

Additional description: Includes diarrhea, constipation, heartburn

Additional description: Low mood / mood swings

Additional description: Includes runny nose, sore throat, cough

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 09 July 2012 | Correction of description of drug vehicle in study documentation from capsule to tablet. Inclusion criteria regarding cannabis use was relaxed to aid recruitment. |
| 24 June 2013 | A structural scan was originally scheduled for baseline session (week one). This was moved to the test session (week two) when there was a function scan. This negated the need to book the scanner twice. |
| 05 February 2014 | 17 participants had to be replaced (new participants recruited) due to computer error |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--|---------------|
| 12 December 2011 | After original target was met and data were extracted, we found that computer data had failed to record for one condition. We therefore had to replace 17 participants who did not complete their allocated training appropriately. There was an interruption to testing in order for us to obtain ethics approval (amendment) to continue and to receive more drug. | 18 March 2014 |

Notes:

Limitations and caveats

None reported