



## Clinical trial results:

### Effects of oxycodon and venlafaxine on human pain processing. A randomized, double-blinded, placebo-controlled, cross-over study

#### Summary

EudraCT number	2013-000170-30
Trial protocol	DK
Global end of trial date	12 December 2014

#### Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

#### Trial information

##### Trial identification

Sponsor protocol code	MULTIPAIN-2-3-2013
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Hobrovej 18-22, Aalborg, Denmark,
Public contact	Department of Gastroenterology, Mech-Sense, Aalborg University Hospital, +45 97663562, amd@rn.dk
Scientific contact	Department of Gastroenterology, Mech-Sense, Aalborg University Hospital, +45 97663562, amd@rn.dk

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	27 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2014
Global end of trial reached?	Yes
Global end of trial date	12 December 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to establish a model that is capable of evaluating the effects of analgesics on the pain matrix on both peripheral, spinal, supraspinal, and modulatory level.

Protection of trial subjects:

Subjects were informed verbally and in written about the study before participating and were free to terminate and withdraw from the experiment at any time. Subjects with a history of substance abuse or psychiatric illness were not included in the study. Adverse effects were monitored during the stay at the hospital and after each treatment arm.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 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	Denmark: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Inclusion for the study required medical examinations to be normal, blood pressure below 140/90, no use of medication and Caucasian origin.

### 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	Investigator, Data analyst, Subject

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Placebo

Arm description:

Placebo arm

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:

All drugs followed the same administration: on day 1 and day 5 once, and on day 2-4 b.i.d. in total 8 doses. The tablets were produced by the pharmacy at Aarhus University Hospital.

<b>Arm title</b>	Oxycodone
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Arm description:

Oxycodone arm

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

Dosage and administration details:

10 mg extended release. All drugs followed the same administration: on day 1 and day 5 once, and on day 2-4 b.i.d. in total 8 doses. The tablets were produced by the pharmacy at Aarhus University Hospital.

<b>Arm title</b>	Venlafaxine
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Arm description:

Venlafaxine arm

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

Dosage and administration details:

Venlafaxine dosages were 37.5mg extended release. All drugs followed the same administration: on day 1 and day 5 once, and on day 2-4 b.i.d. in total 8 doses. The tablets were produced by the pharmacy at Aarhus University Hospital.

<b>Number of subjects in period 1</b>	Placebo	Oxycodone	Venlafaxine
Started	20	20	20
Completed	20	20	20

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
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Reporting group description:

20 subjects participated in all treatment arms

Reporting group values	Overall trial	Total	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	24.6		
standard deviation	± 2.5	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	20	20	

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo arm	
Reporting group title	Oxycodone
Reporting group description:	
Oxycodone arm	
Reporting group title	Venlafaxine
Reporting group description:	
Venlafaxine arm	

### Primary: Quantitative sensory testing

End point title	Quantitative sensory testing
End point description:	
The overall sensory responses were investigated using ice water (the cold pressor test) and electrical stimulations (together with reflex determinations). The mean scores on the visual analogue scale (VAS) for the cold pressor test is presented as end point values for each treatment arm. More details are published by Lelic et al. (Neuropharmacology. 2017. DOI:10.1016/j.neuropharm.2017.06.022) and Lelic et al. (Eur J Neurosci. 2016. DOI: 10.1111/ejn.13443).	
End point type	Primary
End point timeframe:	
At baseline and after 5 days of treatment	

End point values	Placebo	Oxycodone	Venlafaxine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: VAS (no unit)				
number (not applicable)	7.3	6.8	7.0	

### Statistical analyses

Statistical analysis title	Reflex pain (VAS)
Statistical analysis description:	
Reflex: mixed model with treatment and reflex intensity, mixed model with reflex sensory threshold, reflex threshold and treatment	
Comparison groups	Placebo v Oxycodone

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.552
Method	Mixed models analysis

<b>Statistical analysis title</b>	Reflex pain (VAS)
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Statistical analysis description:

Reflex: mixed model with treatment and reflex intensity, mixed model with reflex sensory threshold, reflex threshold and treatment

Comparison groups	Placebo v Venlafaxine
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.288
Method	Mixed models analysis

<b>Statistical analysis title</b>	Ice pain (VAS)
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Statistical analysis description:

Ice pain: mixed model with treatment and time

Comparison groups	Placebo v Oxycodone
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.036
Method	Mixed models analysis

## Primary: Electroencephalography

End point title	Electroencephalography
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End point description:

Electroencephalography (EEG) was recorded during tonic pain stimulation. Spectral analysis and sLORETA source localization were performed in five frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta1 (12-18 Hz) and beta2 (18-32 Hz). The number of frequency bands that were significantly changed after treatment are presented in end point values. Details about the analyses and results are published by Lelic et al. (Neuropharmacology. 2017. doi: 10.1016/j.neuropharm.2017.06.022).

End point type	Primary
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End point timeframe:

From baseline and a 5-days treatment

End point values	Placebo	Oxycodone	Venlafaxine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: number of frequency bands, no unit	0	2	1	

## Statistical analyses

<b>Statistical analysis title</b>	EEG during tonic pain, placebo
Comparison groups	Placebo v Oxycodone v Venlafaxine
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	> 0.05
Method	t-test, 2-sided

Notes:

[1] - Data from baseline and after five days of treatment were compared for the placebo arm and no changes were observed.

<b>Statistical analysis title</b>	EEG during tonic pain, oxycodone
Comparison groups	Oxycodone v Venlafaxine v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
P-value	< 0.05 <sup>[3]</sup>
Method	t-test, 2-sided

Notes:

[2] - Data from baseline and after five days of treatment were compared for the oxycodone arm.

[3] - Oxycodone decreased the spectral indices and brain source activity in delta and theta frequency bands.

<b>Statistical analysis title</b>	EEG during tonic pain, venlafaxine
Comparison groups	Venlafaxine v Oxycodone v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
P-value	< 0.05 <sup>[5]</sup>
Method	t-test, 2-sided

Notes:

[4] - Data from baseline and after five days of treatment were compared for the venlafaxine arm.

[5] - Venlafaxine decreased spectral indices in one frequency band (alpha) of the EEG during tonic pain.

## Primary: Nociceptive withdrawal reflex

End point title	Nociceptive withdrawal reflex
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End point description:

Nociceptive withdrawal reflex (NWR) was elicited under the sole of the foot. Both sensory threshold and reflex threshold were found. The following intensities were used for pain ratings:

- 1.0 x reflex threshold
- 1.3 x reflex threshold
- 1.6 x reflex threshold

5 runs with 18 reflex stimulations in randomized intensity were applied for electromyography (EMG) recordings to assess the spinal (lumbar) response to pain and brain analysis with EEG evoked potentials



was done to the same stimulations.

The mean NWR thresholds after treatments are presented together with the statistical analysis of NWR area under the curve (AUCs).

Details about the analyses and results are published by Lelic et al. (Eur J Neurosci. 2016. doi: 10.1111/ejn.13443.)

End point type	Primary
End point timeframe:	
From baseline and a 5-days treatment	

End point values	Placebo	Oxycodone	Venlafaxine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: mA				
number (not applicable)	14.5	12.7	14.2	

### Statistical analyses

Statistical analysis title	NWR AUC
Statistical analysis description:	
Details are published by Lelic et al. (Eur J Neurosci. 2016. doi: 10.1111/ejn.13443)	
Comparison groups	Placebo v Oxycodone v Venlafaxine
Number of subjects included in analysis	60
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.05 [6]
Method	ANOVA

Notes:

[6] - Venlafaxine decreased the NWR AUC, and no differences were observed in the placebo or oxycodone arms

### Primary: Median nerve stimulation

End point title	Median nerve stimulation
End point description:	
Median nerve stimulation was elicited on the right wrist, and both spinal (cervical) evoked potential (just above C7) to assess the upstream activity, and brain (EEG) evoked potentials were recorded. The sensory and twitch of the thumb thresholds were taken. Then two runs of 1000 stimulations (two per second) were done for spinal and evoked EEG recordings.	
Sensory thresholds to median nerve stimulation after treatments are provided and more details about analyses and results are published by Lelic et al. (Br J Clin Pharmacol. 2017. doi: 10.1111/bcp.13177).	
End point type	Primary
End point timeframe:	
From baseline and a 5-days treatment	

End point values	Placebo	Oxycodone	Venlafaxine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: mA				
number (confidence interval 95%)	2.7 (2.4 to 3.0)	2.5 (2.2 to 2.8)	2.6 (2.4 to 2.8)	

## Statistical analyses

Statistical analysis title	Median nerve stimulation sensory data
Statistical analysis description:	
Two-way repeated measures analysis of variance with time point and treatment as the two factors were performed and no differences in sensory thresholds were identified.	
Comparison groups	Placebo v Oxycodone v Venlafaxine
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	ANOVA

## Primary: MR spectroscopy

End point title	MR spectroscopy
End point description:	
MR spectroscopy was performed during rest at baseline and during treatments in the anterior cingulate cortex, insula and prefrontal cortex. Mean glutamate/creatine ratios from the anterior cingulate cortex are presented as end point values and statistics are provided including all three brain areas. More details about the analyses and results are published by Hansen et al. (J Neuroimaging. 2016. doi: 10.1111/jon.12345.)	
End point type	Primary
End point timeframe:	
From baseline and after a 5-day treatment	

End point values	Placebo	Oxycodone	Venlafaxine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	19	20	
Units: no units (ratio)				
number (not applicable)	1.35	1.29	1.32	

## Statistical analyses

Statistical analysis title	Glutamate/creatine changes oxycodone vs placebo
Statistical analysis description:	
The change in glutamate/creatine following oxycodone was calculated as compared to the measurement	

before treatment and compared to placebo.

Comparison groups	Oxycodone v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other <sup>[7]</sup>
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	percentage
Point estimate	-8.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	-1.7
Variability estimate	Standard deviation
Dispersion value	0.3

Notes:

[7] - A mixed effect model with treatment type and area as fixed effects (full factorial) and subject as a random effect was used.

<b>Statistical analysis title</b>	Glutamate/creatine changes venlafaxine vs placebo
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Statistical analysis description:

The level of glutamate/creatine following venlafaxine was calculated as compared to the measurement before treatment and compared to placebo.

Comparison groups	Venlafaxine v Placebo
Number of subjects included in analysis	39
Analysis specification	Post-hoc
Analysis type	other <sup>[8]</sup>
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	percentage
Point estimate	-6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	0.2
Variability estimate	Standard deviation
Dispersion value	0.4

Notes:

[8] - A mixed effect model with treatment type and area as fixed effects (full factorial) and subject as a random effect was used.

## Secondary: Offset analgesia

End point title	Offset analgesia
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End point description:

Offset analgesia (OA) was induced with a thermode on the arm. To determine the pain tolerance threshold, the temperature was slowly increased from 35°C at 1.5°C per second rate and the volunteers pressed a button when they reached their individual pain tolerance threshold. Offset analgesia magnitude (in percentage) was calculated as  $\Delta\_VAS$  normalized with respect to peak value  $((\Delta\_VAS/peak)*100)$  and presented.

End point type	Secondary
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End point timeframe:

From baseline and after 5-days treatment

End point values	Placebo	Oxycodone	Venlafaxine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: percent				
number (not applicable)	60.3	69.3	61.2	

## Statistical analyses

Statistical analysis title	Offset analgesia magnitude
Statistical analysis description:	
Offset analgesia magnitude (in percentage) was calculated as $\Delta\_VAS$ normalized with respect to peakvalue ( $(\Delta\_VAS/peak)*100$ ). The average baseline values were calculated as a mean of the three baseline measurements for each participant. A repeated measures regression with treatment as random effect was used.	
Detailed analysis description and results are published elsewhere (Olesen et al. Basic Clin Pharmacol Toxicol. 2018. doi: 10.1111/bcpt.13078).	
Comparison groups	Placebo v Oxycodone v Venlafaxine
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

## Secondary: Resting state MRI

End point title	Resting state MRI
End point description:	
Resting state magnetic resonance imaging was performed and functional connectivity analyses were explored between four predefined seeds (dorsal anterior cingulate cortex, rostral anterior cingulate cortex, posterior insula, and prefrontal cortex), and the whole brain. The number of seeds that revealed changed connectivity is presented. Details about the analyses and results are published by Hansen et al. (CNS Neurosci Ther. 2018. doi: 10.1111/cns.12827.)	
End point type	Secondary
End point timeframe:	
From baseline and after a 5-day treatment	

End point values	Placebo	Oxycodone	Venlafaxine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	18	19	
Units: Number of seeds affected	4	4	4	

## Statistical analyses

Statistical analysis title	Functional connectivity oxycodone vs placebo
Statistical analysis description:	
Treatment effects were investigated in four predefined seeds to the whole brain.	
Comparison groups	Oxycodone v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 <sup>[9]</sup>
Method	t-test, 2-sided

Notes:

[9] - The main results were that oxycodone decreased functional connectivity between limbic structures and to supra limbic areas.

Statistical analysis title	Functional connectivity venlafaxine vs placebo
Statistical analysis description:	
Treatment effects were investigated in four predefined seeds to the whole brain.	
Comparison groups	Placebo v Venlafaxine
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 <sup>[10]</sup>
Method	t-test, 2-sided

Notes:

[10] - The main results were that venlafaxine decreased functional connectivity between limbic structures and to supralimbic areas, and increased functional connectivity to structures in the midbrain and brain stem.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

November 2013 - December 2014

Adverse event reporting additional description:

All the non-serious adverse events were known side-effects to the treatments.

More details about side-effects are published in

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo was administered once on day 1 and day 5, and twice a day on day 2-4, in total eight doses with 12 hours in between.

Reporting group title	Oxycodone
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Reporting group description:

Oxycodone (10 mg extended release) was administered orally as tablets once on day 1 and day 5 and twice on day 2-4 in total eight doses with 12 hours in between.

Reporting group title	Venlafaxine
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Reporting group description:

Venlafaxine (37.5 mg extended release) was administered orally once on day 1 and day 5, and twice a day on day 2-4, in total eight doses with 12 hours in between.

Serious adverse events	Placebo	Oxycodone	Venlafaxine
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Placebo	Oxycodone	Venlafaxine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)	17 / 20 (85.00%)	18 / 20 (90.00%)
Cardiac disorders			
Heart rate increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	2 / 20 (10.00%) 2	4 / 20 (20.00%) 4
General disorders and administration site conditions			
Dizziness subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	4 / 20 (20.00%) 4	6 / 20 (30.00%) 6
Sedation subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	8 / 20 (40.00%) 8	5 / 20 (25.00%) 5
Discomfort subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	5 / 20 (25.00%) 5	8 / 20 (40.00%) 8
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	3 / 20 (15.00%) 3	10 / 20 (50.00%) 10
Mouth dryness subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	8 / 20 (40.00%) 8
Constipation subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0
Low appetite alternative dictionary used: n/a 0 subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	2 / 20 (10.00%) 2
Skin and subcutaneous tissue disorders			
Itching subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	6 / 20 (30.00%) 6	0 / 20 (0.00%) 0
Sweating subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28648913>

<http://www.ncbi.nlm.nih.gov/pubmed/29938898>

<http://www.ncbi.nlm.nih.gov/pubmed/27748551>

<http://www.ncbi.nlm.nih.gov/pubmed/27028269>

<http://www.ncbi.nlm.nih.gov/pubmed/27808426>

<http://www.ncbi.nlm.nih.gov/pubmed/29468854>