Trial Synopsis
(according to ICH E3)

International randomised double-blind placebo-controlled study on the initial treatment of acute mania with methylphenidate

MEMAP

Name of Finished Product/Name of Active Substance:

Medikinet/Methylphenidate

Indication/Diagnosis:

Hypomanic + manic episodes (ICD-10: F30.0, F30.1; F31.0; F31.1)

Phase of Development:

IIIb

EudraCT-Number:

2010-023992-24

Registration-Number:

NCT01541605

Date of report: 18.11.2016
Version: Final 1.0

Trial start: 14.08.2012

End of Trial: 08.02.2016

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Signatures

The signing authors approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable statutory provisions.

Legal representative of the sponsor and principal investigator	Prof. Dr. med. U. Hegerl	1.12.16 Date
Biometry	PD Dr. med. M. Kluge	30/11/2016 Date
Further authors	Roland Mergl Dr. R. Mergl	30/11/2016 Date

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1 Name of the Sponsor / Representative of the Sponsor

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2 used IMP(s)	3 used active ingredient(s)
Medikinet	Methylphenidate

4 Individual table of trials

Not applicable

5 Title of study

International randomised double-blind placebo-controlled study on the initial treatment of acute mania with methylphenidate.

6 Investigator	7 Trial site
PD Dr. med. M. Kluge	University hospital Leipzig AöR, Department of Psychiatry and Psychotherapy Address: Semmelweisstrasse 10, D-04103 Leipzig Germany
Univ.-Prof. Dr. med. Juckel	LWL-Klinik für Psychiatrie, Psychotherapie, Psychosomatik und Präventionsmedizin der Ruhr-Universität Bochum Address: Alexandrinenstrasse 1-3 D-44791 Bochum Germany
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PD Dr. Dr. Bergemann	Sächsisches Krankenhaus für Psychiatrie und

6 Investigator	7 Trial site
	Neurologie Rodewisch Address: Bahnhofstraße 1 08228 Rodewisch Germany
Prof. Dr. Sienaert	UPC K.U. Leuven campus Kortenberg Address: Leuvensesteenweg 517 3070 Kortenberg Belgium
Prof. Dr. Ayuso Mateos	Hospital Universitario la Princesa Address: Diego de León 28006 Madrid Spain
Prof. Dr. Vieta	Hospital Clinic Address: Villarroel 170 8036 Barcelona Spain
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Prof. Dr. Istvan Bitter	Semmelweis University Budapest, Department of Psychiatry and Psychotherapy Address: Balassa u. 6 Budapest H-1083, Hungary

The trial was performed as an international multi-centre trial.

8 Publications

Kluge, Michael; Hegerl, Ulrich; Sander, Christian; Dietzel, Jens; Mergl, Roland; Bitter, Istvan et al. (2013): Methylphenidate in mania project (MEMAP): study protocol of an international randomised double-blind placebo-controlled study on the initial treatment of acute mania with methylphenidate. In: *BMC psychiatry* 13, S. 71. DOI: 10.1186/1471-244X-13-71.

9 Study period (in years)

First patient in: 14.08.2012

Last patient out: 05.11.2015

According to the trial protocol, **adaptive interim analysis** was performed **after inclusion of 20 patients** per study arm should decide on trial continuation, or – in case of futility – trial termination. In agreement with the rules lined out in the trial protocol (chapter 9.2.2, page 49), the trial was terminated on **February 8th, 2016**.

10 Development Phase

The MEMAP-trial was a two-arm, randomised, placebo-controlled, double-blind, parallel, multi-centre phase IIIb exploratory study to evaluate the efficacy and safety of methylphenidate in the initial treatment of acute mania in patients with bipolar affective disorders.

11 Objectives

Primary objective:

To test the hypothesis that methylphenidate immediate release given twice daily (BID) is significantly superior to placebo in the treatment of manic symptoms in patients with bipolar disorder after 2.5 days of treatment as assessed by the Young Mania Rating Scale (YMRS).

Secondary objectives:

- Methylphenidate immediate release given BID is significantly superior to placebo in the treatment of manic symptoms in patients with bipolar disorder after 2 hours of treatment as assessed by the YMRS and PANSS
- Change from baseline to endpoint (after 2.5 days of treatment) on the CGI-BP and PANSS-EC
- 2.5 days of treatment with methylphenidate but not with placebo stabilise vigilance regulation as assessed by the 'Vigilance Algorithm Leipzig' (VIGALL)
- Instability of vigilance regulation as assessed by the VIGALL predicts response to methylphenidate
- Methylphenidate immediate release given BID is associated with significantly less movements over the study period than placebo as assessed by actigraphy
- Methylphenidate is significantly superior to placebo in improving cognitive performance as assessed by the "Screen for Cognitive Impairment in Psychiatry" (SCIP)

12 Methods

The MEMAP was a two-arm, randomised, placebo-controlled, double-blind, parallel, multi-centre phase IIIb exploratory study to evaluate the efficacy and safety of methylphenidate in the initial treatment of acute mania in patients with bipolar affective disorders.

After being screened for eligibility and signing the informed consent (day -5 to day -1), patients were randomised to either 2.5 day treatment with methylphenidate BID or placebo BID at a 1:1 ratio (day -1/day 0).

A block randomisation was used. The block size varied from 2 (alternating verum and placebo) to 6 (up to 3 times placebo/verum in a row). The number of blocks and the block size was unknown to the sites. Randomisation was not stratified.

Medication was administered at 10.00 and 15.00 h on day 0 (15 mg methylphenidate or placebo BID), at 09.00 and 15.00 h on day 1 (20 mg methylphenidate or placebo BID), and at 09.00 h on day 2 (20 mg methylphenidate or placebo). EEG should be conducted prior to first medication and 2 h after the morning dose on day 2. Manic symptoms were assessed using the Young Mania Rating Scale Sum Score (YMRS). YMRS was scored at baseline and 2 h after the morning dose on every day. In addition, the CGI-BP and PANSS-EC were scored. Furthermore, movements were tracked using actigraphy and a cognitive test (SCIP) was performed.

Pre-existing medication for treatment of bipolar disorder including benzodiazepines, lithium, anticonvulsants or antipsychotics will be continued in the same dose. Only patients receiving

up to 2 such drugs are eligible for study participation. The treatment period is 2.5 days. There will be two post treatment visits at day 3 and 9.

13 Overall number of trial participants

Planned number: 88 patients (44 patients per treatment group)

Registered/screened subjects: 157

Recruited subjects 42

Analyzed patients: 42

Drop-outs: 4

For details see the CONSORT-flow diagram in appendix**Fehler! Verweisquelle konnte nicht gefunden werden.**.

According to the planned adaptive interim analysis after the inclusion of 20 patients per arm, the trial was stopped due to futility.

14 Indication and main criteria for inclusion

The study population was planned to comprise 88 adults of either sex with the diagnosis of a manic episode according to ICD-10.

All patients had to meet all of the following **inclusion criteria**:

1. Inpatients
2. Written informed consent by patients who are competent to consent to study participation.
3. Diagnosis: Current manic episode according to ICD-10 classification: F30.0, F30.1, F31.0 or F31.1. A previous diagnosis of schizoaffective disorder is NOT an exclusion criterion.
4. Male or female ≥18 years of age
5. YMRS total score ≥ 15 and ≤ 45 points
6. BMI > 17
7. Patients must be able to swallow tablets (study drug).

Patients were excluded for ANY ONE of the following **exclusion criteria**:

1. Any other current major psychiatric ICD-10 disorder is an exclusion criterion **except for the following**:
    a) ADHD or other hyperkinetic disorders (F90)
    b) Harmful use of tobacco (F17.1) or dependence syndrome of tobacco (F17.2)

c) F40-48 Neurotic, stress-related and somatoform disorders

d) F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors

e) F60-F69 Disorders of adult personality and behaviour

2. Contraindications for treatment with methylphenidate except as noted otherwise (see point 3 to 14):

   a) Hypersensitivity to methylphenidate or components of the drug

   b) Patients with extreme anxiety and agitation

   c) Women with child bearing potency without effective contraception (i. e. implants, injectables, combined oral contraceptives, some IUDs or vasectomised partner) during the conduct of the trial. Patients using hormonal methods of contraception must be informed about possible influences of the study drug on contraception.

3. Serious non-psychiatric disease (e.g. infectious, autoimmune or metabolic), that may interfere with the objectives of the study or with the safety or compliance of the subject, as judged by the investigator

4. Oral administration of MAO-inhibitors within two weeks, fluoxetine within 6 weeks and of any other antidepressant or primarily psychotropic substance except for those specified below within one week before study entry.

5. Stable treatment with mood stabilisers including lithium, anticonvulsants (e.g. valproate, carbamazepine) or antipsychotics (e.g. haloperidol, melperone, risperidone, olanzapine) or benzodiazepines is NOT an exclusion criterion and will be continued; however, patients receiving more than 2 of these substances are NOT eligible for inclusion

6. Medical history of other disorders of CNS including tics or dyskinesia

7. Medical history of cardiovascular diseases, severe hypertension, glaucoma, hyperfunction of the thyroid

8. Patients with congenital or acquired long QT syndrome, or with a family history of QT prolongation, sudden cardiac death or other significant inherited cardiac disorders (e.g. family history of hypertrophic cardiomyopathy).

9. History of electroconvulsive therapy within the last 3 months

10. Known alcohol and drug addiction or abuse, except for patients with abstinence > 3 months. Patients with sporadic abuse of cannabis (products) will not be excluded from the study. That is even true with a positive THC screen in urine.

11. Pregnant or nursing woman

12. Concomitant participation in other clinical trials or participation during the 30 days prior to screening

13. Prior participation in this study

14. Suicidality

15 Information on the trial product

Dose: 30 mg/day (day 0), 40 mg/day (day 1), 20 mg/day (day 2)

Route of application: per os

Charge-numbers:

MEM080312a	MEM210612a	MEM130314a
MEM090312b	MEM150612a	MEM130314b
MEM080312b	MEM140612b	MEM170215a
MEM090312a	MEM140612a	MEM170215b
MEM190412a	MEM150612b	MEM160715a
MEM190412b	MEM220812a	MEM160715b
MEM230412b	MEM210812a	MEM191015b
MEM230412a	MEM220812b	MEM191015a
MEM180612a	MEM210812b	
MEM210612b	MEM030713a	
MEM180612b	MEM240713a	

16 Duration of application

Two and a half days.

17 Information on comparators

The trial product was compared to placebo, which was manufactured by the Pharamacy of the University Hospital Leipzig, Stephanstrasse 11, D-04103 Leipzig, Germany.

18 Evaluation criteria

18.1 Efficacy

The primary efficacy measure in this study was the severity of manic symptoms as measured by a clinician-administered mania rating scale, the Young Mania Rating Scale (YMRS) (Young et al., 1978). A YMRS sum score of at least 12 points reflects mania (for further details see Kluge et al., 2013). The primary endpoint was determined after 2.5 days of treatment with methylphenidate or placebo.

The secondary efficacy measures were as follows (see Kluge et al., 2013):

- Severity of agitation as measured by the Positive and Negative Syndrome Scale – excited component (PANSS-EC) (Montoya et al., 2011) (administered at baseline, day 1 and day 2);
- Clinical impressions as measured by using the Clinical Global Impressions Scale Bipolar version (CGI-BP) (Spearing et al., 1997) rated twice (before the first and after the last treatment with methylphenidate or placebo);
- Cognitive performance as measured by the “Screen for Cognitive Impairment in Psychiatry” (SCIP) (Purdon, 2005) (administered at baseline, day 1 and day 2);
- EEG-vigilance during a 15-minutes resting EEG recorded twice, before the first and after the last treatment with methylphenidate or placebo;

- Total amount of movements over the study period as measured by actigraphy.

18.2 Safety

Evaluation of safety comprised the measurement of vital signs (systolic and diastolic blood pressure, heart rate), monitoring of the cardiac function by a 12-lead electrocardiogram (ECG), clinical laboratory tests (for details see Kluge et al., 2013) as well as monitoring of adverse events.

Adverse events were registered in the afternoon of each visit by asking the patient to answer non-leading questions like: “Have you had any health problems today/since you were last asked?”

All reported SAEs receive a thorough review and a secondary evaluation regarding a potential relatedness to the trial product.

During the course of study safety analyses were performed at the ZKS Leipzig to prepare the Annual Safety Reports (ASR).

Safety assessments via SAEs/AEs:

Center-ID	Center adress	Adverse Events				% Patients who dropped out
		AEs		SAEs[1]		
		Number of patients with an AE	Number of AEs / affected patient	Number of patients with an SAE	Number of SAEs / affected patient	
D-001	Klinik für Psychiatrie und Psychotherapie Universität Leipzig Semmelweisstrasse 10, D-04103 Leipzig	5	1,2	0	0	3
D-002	LWL-Klinik für Psychiatrie, Psychotherapie, Psychosomatik und Präventionsmedizin der Ruhr-Universität Bochum Alexandrinenstrasse 1-3, D-44791 Bochum	0	0	0	0	0
D-003	Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden Klinik und Poliklinik für Psychiatrie und Psychotherapie Fetscherstr. 74, D-01307 Dresden	2	1	0	0	0
D-004	Martin-Luther-Universität Halle-Wittenberg Klinikum der Medizinischen Fakultät Universitätsklinik und Poliklinik für Psychiatrie, Psychotherapie und Psychosomatik Julius-Kühn-Str.7, D-06112 Halle/Saale	0	0	0	0	0
B-001	UPC K.U. Leuven campus Kortenberg Leuvensesteenweg 517, BE – 3070 Kortenberg	0	0	0	0	0
S-001	HOSPITAL UNIVERSITARIO LA PRINCESA PI Diego de León 62, ES - 28006 Madrid	1	1	0	0	0
S-002	HOSPITAL CLINIC Villarroel 170, ES-8036 Barcelona	0	0	0	0	0
S-003	HOSPITAL SANT PAU Sant Antoni Maria Claret 167, ES - 8025 Barcelona	0	0	0	0	0
S-004	HOSPITAL SANTIAGO APÓSTOL Olaguibel 29, 8ª planta. Pabellón B, ES - 01004 Vitoria	3	1,7	0	0	0
Overall		**11**	**1,4**	**0**	**0**	**3**

[1] *related to the number of reported SAEs*

19 Statistical Methods/analysis procedures

Prior to statistical analyses, two populations had been defined (see Kluge et al., 2013):

- Full analysis set: This population consists of all randomized patients, who get at least one dosage of treatment regardless of protocol violations. Unless otherwise noted, all analyses were conducted on this population corresponding to an Intent-to-Treat (ITT) population, with the last observations carried forward (LOCF).
- Per protocol (PP) population: This population consists of all patients from the Full analysis set who completed the RCT and did not show any major protocol violations. Secondary analyses on the PP analysis set were restricted to the primary outcome.

Analysis of covariance (ANCOVA) was computed in order to analyze differences between methylphenidate and placebo regarding the primary outcome (the mean change from baseline in the sum score of the YMRS at day 2), with gender, age and the severity of mania (as reflected by the YMRS total score at baseline) being the covariates. Regarding secondary efficacy outcomes, analogous ANCOVA models were applied. Regarding actigraphic parameters, Mann-Whitney U tests were chosen in view of the rather low sample sizes and/or non-normal distribution of the dependent variables as assessed by the Kolmogorov-Smirnov test ($p < 0.05$).

Using Spearman-Brown correlation coefficients, the association of the lability index at baseline and changes of the severity of mania (as reflected by differences between YMRS sum scores (baseline – day 2)) was analyzed for patients in the methylphenidate group and patients in the placebo group separately. For effect size calculations, Cohen's d and the corresponding 95% confidence intervals (CI) were computed.

For safety analyses, descriptive statistics were applied.

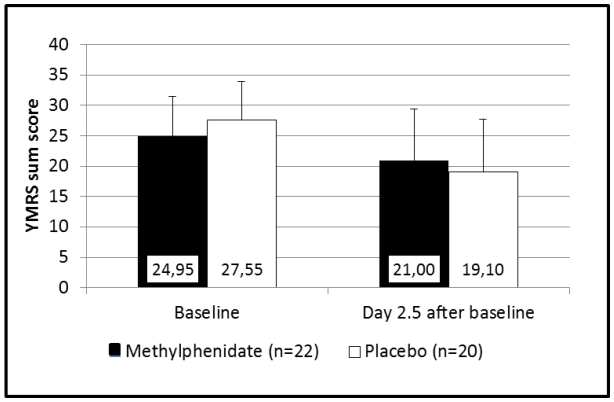
The SPSS® version PASW 20.0 was utilized for the afore-mentioned statistical tests and the significance level was set at $\alpha = 0.05$. All statistical tests were two-sided.

20 Summary/Conclusion

20.1 Efficacy results

The results for the primary efficacy outcome (YMRS, analysis of covariance (ANCOVA) with YMRS baseline sum scores, age and gender as covariates are as follows (see Figure 2).

The change from baseline in the YMRS total score at day 2.5 after baseline was not significantly different between both groups ($F(1,37) = 0.23$; $p = 0.64$; difference from placebo: -4.50 points; effect size (Cohen's d): -0.48; 95% confidence interval (CI): -1.08 to 0.14). Given this result and the fact that the two-sided p value (0.64) clearly surpassed the p value boundary ($p1 = 0.30$) for rejection of the alternative hypothesis (methylphenidate is significantly superior to placebo), futility was declared for methylphenidate and the RCT was stopped:



Analysis on the Per Protocol analysis set which consisted of all patients who completed the study and did not have any major violations of the study protocol, was conducted for the primary efficacy outcome, too. It supported the finding that the methylphenidate group and the placebo group did not significantly differ regarding the change from baseline in the YMRS total score at day 2.5 after baseline ($F(1,27) = 0.01$; $p = 0.92$). The same was true for short-term changes of manic symptoms within four hours (measured by the YMRS) (mean baseline score at 08.00 h (S.D.): 24.95 (6.51) in the methylphenidate group versus 27.55 (6.34) in the placebo group; mean change in YMRS total score from baseline (08.00 h) (S.D.): 1.82 (4.94) in the methylphenidate group versus 3.05 (4.68) in the placebo group; difference from placebo: -1.23 points; effect size (Cohen's d): -0.26; 95% CI: -0.86 to 0.36; $F(1,39) = 0.07$; $p = 0.80$).

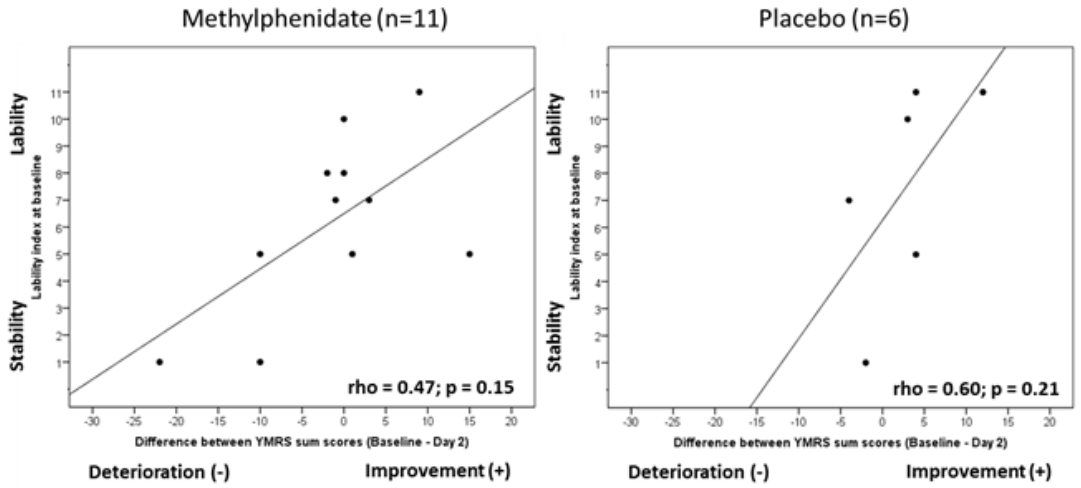
Secondary analyses of scores on the PANSS-EC, CGI-BP and SCIP demonstrated lack of efficacy for methylphenidate on these endpoints (see Table 2), too.

Variables (mean (S.D.))	**Methylphenidate (N=22)**	**Placebo (N=20)**	**Effect size (Cohen's d) (95% CI)**	**p value (two-sided)**
PANSS-EC				
Baseline PANSS-EC total score (08.00 h)	14.27 (4.04)	16.40 (4.98)	---	---
Total PANSS-EC score at baseline (12.00 h)	12.41 (3.80)	13.20 (5.45)	---	---
Change in PANSS-EC total score from 08.00 h to 12.00 h	1.86 (3.85)	3.20 (5.05)	-0.30 (-0.90 to 0.31)	0.77
Total PANSS-EC score at baseline	14.27 (4.04)	16.40 (4.98)	---	---
Total PANSS-EC score at day 2.5 after baseline	11.81 (4.88) [n=21]	10.85 (4.75)	---	---
Change in PANSS-EC total score from baseline	2.33 (5.88) [n=21]	5.55 (5.31)	-0.57 (-1.19 to 0.06)	0.28
CGI-BP				
Total CGI-BP score at baseline	4.77 (0.87)	4.95 (1.05)	---	---
Total CGI-BP score at day 2.5 after baseline	4.43 (0.75) [n=21]	3.95 (1.43)	---	---
Change in CGI-BP total score from baseline	0.33 (1.02) [n=21]	1.00 (1.34)	-0.56 (-1.18 to 0.07)	0.10
SCIP				
List learning test				
Total score at baseline	19.91 (5.77)	18.05 (5.17)	---	---
Total score at day 2.5 after baseline	18.67 (4.41) [n=21]	17.95 (4.66)	---	---
Change in score from baseline	1.71 (3.69) [n=21]	0.10 (3.49)	0.45 (-0.18 to 1.06)	0.44
Consonant repetition test				
Total score at baseline	17.91 (4.62)	16.00 (4.01)	---	---
Total score at day 2.5 after baseline	19.52 (4.25) [n=21]	17.55 (4.61)	---	---
Change in score from baseline	-1.57 (2.42) [n=21]	-1.55 (3.07)	-0.01 (-0.62 to 0.61)	0.65

Variables (mean (S.D.))	Methylphenidate (N=22)	Placebo (N=20)	Effect size (Cohen's d) (95% CI)	p value (two-sided)
Verbal fluency test				
Total score at baseline	15.68 (7.69)	17.35 (8.07)	---	---
Total score at day 2.5 after baseline	18.62 (8.10) [n=21]	18.45 (7.88)	---	---
Change in score from baseline	-2.48 (5.48) [n=21]	-1.10 (5.12)	-0.26 (-0.87 to 0.36)	0.49
Delayed list learning test				
Total score at baseline	5.36 (2.82)	4.65 (3.27)	---	---
Total score at day 2.5 after baseline	4.14 (2.24) [n=21]	3.40 (2.66)	---	---
Change in score from baseline	1.33 (1.96) [n=21]	1.25 (2.10)	0.04 (-0.57 to 0.65)	0.64
Visuomotor tracking test				
Total score at baseline	8.95 (3.84)	8.05 (4.22)	---	---
Total score at day 2.5 after baseline	10.14 (4.21) [n=21]	8.85 (4.39)	---	---
Change in score from baseline	-1.00 (1.82) [n=21]	-0.80 (2.88)	-0.08 (-0.69 to 0.53)	0.68

Secondary efficacy outcomes: Changes of the Positive and Negative Syndrome scale – excited component (PANSS-EC), the Clinical Global Impression-Bipolar scale (CGI-BP) and cognitive performance as measured by using the "Screen for Cognitive Impairment in Psychiatry" (SCIP) (N=42)

The association between the vigilance lability index at baseline and improvement of the YMRS total scores at day 2.5 was positive and moderately high in the methylphenidate group (rho = 0.47; p = 0.15; n = 11); however, a positive association between these variables was also found in the placebo group (rho = 0.60; p = 0.21; n = 6):



Changes in motor activity over the study period did not differ between methylphenidate and placebo:

Variables (mean (S.D.))	Methylphenidate (N=11)	Placebo (N=11)	p value (two-sided)
Mean activity score at baseline	56.46 (12.50)	56.44 (27.11)	0.31
Changes in the mean activity score (baseline – day 1)	0.75 (7.83)	2.58 (10.44)	0.58

Actigraphic parameters (N=22)

20.2 Safety results

Vital parameters (blood pressure and heart rate) did not differ significantly between the methylphenidate group and the placebo group regarding changes from baseline (see Table 4).

Variables (mean (S.D.))	Methylphenidate (N=22)	Placebo (N=20)	p value (two-sided)
	Diastolic blood pressure		
Score at baseline (mm Hg)	81.18 (14.46)	83.80 (10.15)	---
Change from baseline (mm Hg)	0.86 (18.67) [n=21]	9.79 (10.79) [n=19]	0.11
	Systolic blood pressure		
Score at baseline (mm Hg)	128.50 (17.03)	131.70 (24.03)	---
Change from baseline (mm Hg)	4.62 (12.70) [n=21]	11.42 (15.87) [n=19]	0.17
	Heart rate		
Score at baseline (/minute)	81.36 (15.07)	86.35 (12.32)	---
Change from baseline (/minute)	-6.24 (14.66) [n=21]	-0.26 (9.64) [n=19]	0.26

Changes of vital parameters (N=42)

Adverse events reported in more than one patient in the methylphenidate group included worsening of mania (n=2) and headache (n=2). Further adverse events in the methylphenidate group were: worsening of arterial hypertension (n=1), discrete paraesthesia on the scalp (n=1), increase of an already existing tardive dyskinesia (n=1), facial edema and stiffness (n=1), rough skin of both hands (n=1) and general pain (n=1).

In the placebo group, the following adverse events were present: worsening of instable mood and lability of the affect (n=1), diarrhea and vomiting (n=1) and worsening of mania (n=1).

There were no serious adverse events during the trial.

One participant in the methylphenidate group retracted his consent because of a potentially treatment-related adverse event (worsening of mania). Three other patients were excluded from the study ex post because of loss to follow-up (one patient from the methylphenidate group), or because of wished discharge of the hospital (one patient from the methylphenidate group, one patient from the placebo group).

20.3 Conclusions

The hypothesis that acute short-term treatment with methylphenidate has acute antimanic effects in patients with bipolar affective disorder was not confirmed. Also concerning secondary outcomes such as cognitive performance (SCIP (Purdon, 2005)), global functioning (CGI-BP (Spearing et al., 1997)) and severity of agitation (PANSS-EC (Montoya et al., 2011) no group differences were found.

It was hypothesized that there might be a causal relationship between the instability of vigilance regulation and response to methylphenidate. However, although it seemed as if

there was a trend toward this relationship in the methylphenidate group, this could not be confirmed since a similar association was observed in the placebo group.

Methylphenidate treatment was not associated with a reduction of motor activity as assessed by actigraphy; however, this finding is based only on a small subsample of patients.

Overall, methylphenidate was a safe drug and well tolerated in patients with acute mania.

Some methodological limitations should be discussed: first, the inclusion and exclusion criteria of the MEMAP trial were rather strict; therefore, the generalizability of the study findings is clearly limited. Second, the selected dosages of methylphenidate (day 1: 30 mg/day, day 2: 40 mg/day; day 3: 20 mg/day) might have been too low, the group differences regarding co-medication too pronounced and treatment duration too short in order to make clinically relevant anti-manic effects possible. A dosage of 40 mg/day was reached only at the penultimate day. In adult patients with ADHD, which shows several similarities to mania at the symptomatic level (see Hegerl and Hensch, 2014), often higher dosages are needed in order to see a clear clinical effect (Huss et al., 2014). Thus, it would be worthwhile to design a RCT with higher doses of methylphenidate for the initial treatment of acute mania. The reasons for choosing a relatively low dose of methylphenidate and the short duration of the trial were basically ethical, given the theoretical risk of worsening mania by giving a dopamine agonist to manic patients. In view of the results of this proof-of-concept trial, the safety of methylphenidate would now justify a trial with higher doses and longer duration. However, our study does not support a rapid-onset effect of any anti-manic action of methylphenidate as postulated previously (Bschor et al., 2001; Hegerl and Hensch, 2014).

In summary, the MEMAP trial revealed that methylphenidate (20-40 mg/day per os) despite being well tolerated and safe failed to show efficacy in the initial treatment of acute mania. However, in view of the low dosage and short duration of this RCT it would be premature to exclude anti-manic efficacy of methylphenidate in mania.

21 Appendices

21.1 CONSORT Flow Diagramm