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ORIGINAL ARTICLE

Antidepressant monotherapy compared with combinations of antidepressants in the treatment of resistant depressive patients: A randomized, open-label study

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Abstract

Objective. This randomized, 6-week, open-label study compared efficacy of CAD and antidepressant monotherapies (ADM) that had been chosen according to clinical judgment of the attending psychiatrist. *Methods.* A total of 60 inpatients (intent-to-treat analysis) with depressive disorder (≥ 1 unsuccessful antidepressant treatment) were randomly assigned to the interventions. The responders who completed the acute phase of study, were evaluated for relapse within 2 months of follow-up treatment. The primary outcome measure was change in the Montgomery–Åsberg Depression Rating Scale (MADRS) and response was defined as a ≥ 50% reduction of MADRS score. *Results.* Mean changes in total MADRS score from baseline to week 6 for patients in both treatment modalities were not different (ADM = 13.2 ± 8.6 points; CAD = 14.5 ± 9.5 points; $P = 0.58$). The analysis of covariance performed for significantly higher value of imipramine equivalent dose in CAD group showed only a non-significant between-group difference for total MADRS change ($P = 0.17$). There were also no differences between groups in response rate (ADM = 48%; CAD = 58%) and number of drop-outs in acute treatment as well as proportion of responders' relapses in the follow-up. *Conclusions.* Both treatment modalities produced clinically relevant reduction of depressive symptomatology in acute treatment of patients with resistant depression and their effect was comparable.

Key Words: *Resistant depression, treatment, antidepressant monotherapy, combination of antidepressants*

Introduction

Major depressive disorder (MDD) is a chronic, recurrent illness associated with significant morbidity and mortality. Despite recent progress in psychopharmacology and treatment possibilities many (about 30%) patients do not respond to standard antidepressant monotherapy (ADM) [1,2]. The most frequent pharmacological methods to manage resistant depression are switching antidepressants (ADs), augmentation of ADs with various compounds (second-generation antipsychotics, triiodothyronine, lithium, pindolol, buspirone, etc.), and combinations of two distinctly different ADs. However, there is no clear consensus in current guidelines of treatment which strategy should be preferred [3–5]. Antidepressant combination (CAD) is an often used strategy to overcome resistance to treatment in current clinical practice [6,7]. A combination of ADs might increase the number of patients who could benefit from treatment [8,9]. Synergy between various mechanisms of action might affect a wider range of neurotransmitter or neuromodulator systems that might lead to faster onset of action and potential avoidance of side effects [10,11]. There are plenty of possible combinations but the evidence supporting their efficacy ranges from nothing or case reports to randomized clinical trials [12–14]. CAD can be applied in two different approaches: (1) Continuing the first AD and adding the second one, (2) combining two new ADs from the initiation of treatment. Several double-blind studies demonstrated higher efficacy

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of CAD in the latter approach compared to new ADM [8,9,15–18]. In contrast, the results of the Level IV of the STAR*D project as well as a recent single-blind, randomized study did not support superiority of CAD over ADM [19,20].

Our previous retrospective study demonstrated higher response rate in patients treated with CAD compared with ADM [21]. Therefore we conducted a prospective, 6-week, randomized, open-label study comparing the efficacy and tolerability of ADM and CAD applied from the initiation of treatment in resistant patients. We also compared the ability of the treatment modalities to maintain response to treatment during 8 weeks follow-up.

Materials and methods

Study design

This single-centre study involved a two-arm open-label, randomized trial. Following a short initial wash out period (1–2 days), eligible subjects received 6-week treatment. Patients were randomly allocated according to permuted block design with a fixed block size 4, in a 1:1 ratio (no stratification) to either CAD or ADM groups. The responders from both groups who completed the acute phase of the study entered the follow-up phase lasting 8 weeks.

The design adhered to the latest version of the Declaration of Helsinki and ICH/Good Clinical Practice guidelines (Tokio 2004). The Prague Psychiatric Centre Institutional Review Board reviewed and approved this study protocol and a written informed consent to participate in the research was obtained from all subjects. This clinical study was registered at Current Controlled Trials, Ltd. – ISRCTN65259480 (www.controlled-trials.com).

Subjects

The participants in the study were hospitalized at the Open Department of Prague Psychiatric Center from January 2009 to March 2011 with major depressive disorder (recurrent or single episode) without psychotic symptoms according to DSM IV criteria [22], confirmed using The Mini International Neuropsychiatric Interview (M.I.N.I.), Czech version 5.0.0 [23]. They were admitted due to unsatisfactory response to previous treatments by referral from a number of outpatient clinics and psychiatric hospitals in the Czech Republic. Patients fulfilled at least Stage I criteria for resistant depression (≥ 1 adequate antidepressant treatment in current episode) according to Thase and Rush [24]. Evaluation of adequacy of previous medication in the index episode was based on the Antidepressant Treatment History Form (ATHF) [25] with a score of at least 3 (more than 4 weeks of treatment in adequate dose). The last treatments before enrollment are displayed in the Table I. Only subjects (18–65 years old) who reached Montgomery–Åsberg Depression Rating Scale (MADRS) [26] score ≥ 25 and Clinical Global Impression (CGI) [27] score ≥ 4 were included. We excluded subjects with current psychiatric comorbidities on Axis I and II according to DSM-IV in the last 6 months before enrollment to the study, severe or uncontrolled medical illness that might cause depressive symptoms and high risk of suicide (clinical judgment and item 10 of MADRS ≥ 3), who were not suitable for hospitalization at the open department. The patients' selection was based on a psychiatric examination by one of investigators (MB, JC, MK, TN, PS). The standard physical examination, medical history evaluation, blood and urine biochemistry screening and electroencephalography were performed to exclude depression due to general medical condition. There was no financial compensation for patients.

Study treatment

After the signing of informed consent, patients were randomly allocated to either ADM or CAD treatment groups. The new treatment was chosen according to clinical judgment of the attending psychiatrists and with respect to the history of previous treatments, clinical status (anxiety, insomnia, psychomotor retardation etc.) and current guidelines for treatment [3–5]. We applied ADs or their combinations from classes whose efficacy in the treatment of depressive disorder is generally accepted (see Table I) and in flexible doses within the range cited in the Summary of Product (SPC) by the Czech State Institute for Drug Control (www.sukl.cz). The ADs that had been ineffective in the treatment of the current episode were excluded and within-class change of antidepressants was not allowed with the exception of selective serotonin reuptake inhibitors (SSRIs) since the demonstrated efficacy of within-class change of SSRIs was comparable to across-class changes of ADs [28,29]. New anxiolytics (benzodiazepines) and hypnotics were only permitted in cases of severe anxiety or insomnia. We did not taper stable anxiolytic treatment regime already introduced before the start of the study. The use of other psychotropic drugs (mood stabilizers, second generation antipsychotics, etc.) as well as formal psychotherapy was not allowed. The responders were treated for an additional 8 weeks with established successful ADM or CAD.

Clinical assessment

The primary outcome measure for the study was the score change in the MADRS. The patients were assessed with the MADRS, the Beck Depression Inventory – Short Form (BDI-SF) [30], CGI and Frequency, Intensity, and Burden of Side Effects (FIBSER) [31] bi-weekly up to week 6 and responders were rated 2 months after the end of acute phase of study. The FIBSER is self-rated scale which does not provide information on specific side effects but mapped how the antidepressant treatment and its side effects interfere with patients' functioning. The raters (MB, JC, MK, TN, PS) were trained to the criterion of intraclass correlation >0.80 for each clinician prior to conducting ratings [32]. The response to treatment was defined as a reduction of the MADRS $\geq 50\%$ and remission as MADRS score ≤ 12 points, as previously used in antidepressant studies [33–36]. Since there is no generally accepted criterion of relapse we used as a definition the score ≥ 20 points in the MADRS together with increase of MADRS $\geq 50\%$ at the time of follow-up visit comparing to the score at the final visit of acute phase, or change of antidepressant treatment due to substantial worsening of clinical status [37–39].

Statistical methods and data analyses

t-Test and Fisher exact test were used to investigate differences between the groups on demographic and clinical variables. Mann–Whitney *U*-test (MWU) was applied to compare nonparametric data. Data are presented as the mean and standard deviation. The primary efficacy analyses were based on the intent-to-treat (ITT) data set that was defined as the subset of patients who completed baseline and at least one post-baseline

Table I. Baseline demographic, clinical and treatment characteristics of patients (intent-to-treat sample).

	ADM ($n=29$)	CAD ($n=31$)	Statistical significance
Age (years)	46.7 ± 12.3	45.6 ± 10.2	NS[a]
Sex (F:M)	22:7	22:9	NS[b]
Illness duration (month)	80.3 ± 92.1	94.7 ± 104.5	NS[a]
Number of previous episodes	2.3 ± 2.9	2.3 ± 2.3	NS[a]
Duration of index episode before enrollment (weeks)	31.8 ± 2.9	27.0 ± 2.3	NS[a]
Number of previous adequate treatment trials of index episode	1.5 ± 0.8	1.5 ± 0.7	NS[a]
Last treatment before enrollment	NaSSA + NDRI-1 NaSSA (SARI) + SSRI-4 NaSSA(SARI) + SNRI-3 NDRI + SSRI-1 SNRI (SSRI) + SGA-4 SNRI-4 SSRI-11 TCA-1	NaSSA-1 NaSSA (SARI) + SSRI-6 NaSSA (SARI) + SNRI-3 NDRI + SSRI-1 SNRI-3 NDRI + NaSSA-1 SNRI (SSRI) + SGA-5 SSRI-9 RIMA-1 TCA-1	NS[c,*]
TR-S before enrollment	1.5 ± 0.7	1.4 ± 0.6	NS[d]
MGH-S before enrollment	2.0 ± 1.4	1.9 ± 0.9	NS[d]
Treatment in the study	NaSSA-5 NDRI-4 SNRI-11 SSRI-7 TCA-2	NaSSA (SARI) + NDRI-2 NaSSA (SARI) + SNRI-8 NaSSA (SARI) + SSRI-9 NDRI + SSRI-7 TCA +TCA-5	NA
Imipramine equivalent dose (mg/day) – final visit of the acute phase	233.1 ± 74.9	407.8 ± 117.1	$P<0.001$

ADM, antidepressant monotherapy; BDI-SF, Beck Depression Inventory – Short Form; CAD, combination of antidepressants; CGI, Clinical Global Impression; MADRS, Montgomery–Åsberg Depression Rating Scale; MGH-S, Massachusetts General Hospital Staging Method to Classify Treatment-Resistant Depression; NA, not applicable; NaSSA, noradrenergic and specific serotoninergic antidepressants; NDRI, norepinephrine and dopamine reuptake inhibitors; NS, nonsignificant; RIMA, reversible inhibitor of monoaminoxidase; SARI, serotonin antagonist/reuptake inhibitors; SGA, second-generation antipsychotics; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; TR-S, Thase and Rush Treatment-Resistant Depression Staging Method.

*Non-significant difference in the number of subjects with combined treatment, i.e. combinations and augmentations.

[a]Unpaired *t*-test, [b]Fischer exact test, [c]McNemar's chi-square test, [d]Mann–Whitney *U*-test.

visit with the last observation analysis (LOAN) method. The primary efficacy measure (MADRS) as well as BDI-SF, CGI and FIBSER in both groups were tested using a repeated measure of analyses of variance with the Greenhouse-Geisser adjustment (RM ANOVA G-G). Within group differences in the scores of rating scales between baseline and final visits were examined using paired *t*-tests. The proportions of responders, remitters and patients who had dropped-out from the study, taken benzodiazepines and relapsed within the follow-up phase of study in both groups were compared using Fisher exact test. We also analyzed observed cases (completers) to evaluate differences in response and remission rates between treatment groups. Finally, imipramine equivalent doses (IMID) estimated from daily doses cited in SPC (www.sukl.cz) were calculated for both groups using daily doses applying at the time of the final visit in the acute phase of study as well as the baseline scores in the Thase and Rush Treatment-Resistant Depression Staging Method (TR-S) [24] and the Massachusetts General Hospital Staging Method to Classify Treatment-Resistant Depression (MGH-S) [40]. To evaluate the potential confounding influence of different doses of ADs (IMID) as well as various types of intervention (TR-S, MHG-S) in the treatment history of index episode we used analysis of covariance (ANCOVA) with total MADRS change at the end of study as a dependent variable, response as grouping factor and values of IMID, TR-S and MGH-S as the covariates. We also assessed the relationship between values of IMID in the whole sample and reduction of MADRS score at the end of the study using Spearman's Rank correlation and compared values of IMID in responders and nonresponders in both treatment groups. Finally, we compared (McNemar's chi-square test) the number of patients treated in the last trial before enrollment with combined treatment (i.e. CAD and augmentations of ADs) in both groups. All tests were two-sided and an exact significance level of 0.05 was adopted. Analyses were performed using SPSS version 19. Sample size was based on the primary efficacy measure, the MADRS total score. A power analysis indicated that a total sample size of 52 patients would be sufficient to detect an effect size of 0.4 (RM-ANOVA) with 81% power at a 5% level of statistical significance.

Results

Patient characteristics

A total of sixty-one patients (44 females, 17 males, mean age 46.1 ± 11.2 years) were randomly assigned to the ADM ($n = 30$) and CAD ($n = 31$) treatments (Figure 1). One subject (ADM) refused to participate in the study before first post-baseline visit. Baseline demographic and clinical characteristics of ITT sample ($n = 60$) as well as treatment characteristics before enrollment (TR-S, MGH-S) did not differ between the groups (Table I). The overall discontinuation rate was not statistically different between the two groups of patients (ADM, 4/30, CAD, 6/31, $P = 0.30$).

There were no differences between treatment groups in proportions of patients who had taken

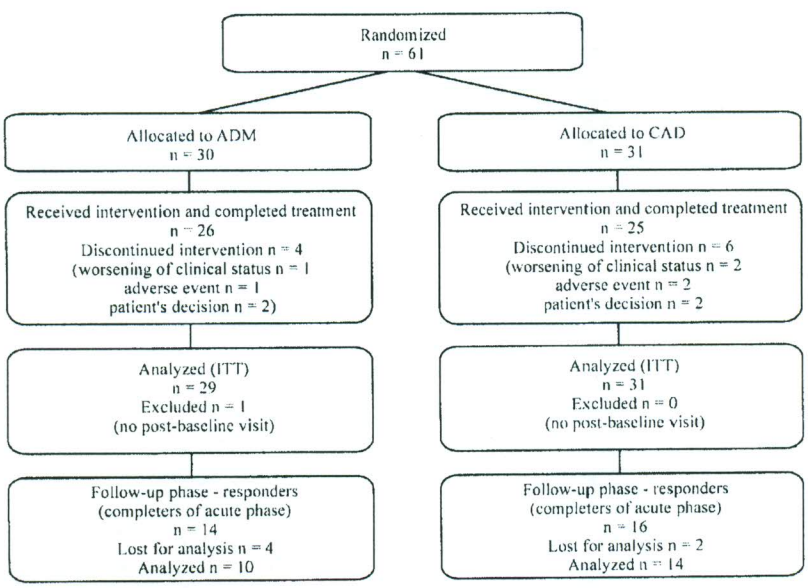

Figure 1. Study participants. ADM, antidepressant monotherapy; CAD, combination of antidepressants; ITT, intent-to-treat analysis.

benzodiazepines and doses of benzodiazepines in terms of diazepam equivalent [41] at the baseline (ADM 17/29; CAD = 20/31; $P = 0.79$; ADM = 10.7 mg/day; CAD = 10.8 mg/day; $t = 0.02$, df = 35, $P = 0.98$) nor at the end of the acute phase of the study (ADM 18/29; CAD 20/31; $P = 1.0$, ADM = 11.3 mg/day; CAD = 10.0 mg/day; $t = 0.63$, df = 36, $P = 0.53$). Thus, the use of hypnotics was similar in the groups.

Efficacy measures and side effects

Acute phase of study. Sixty patients completed baseline and at least one post-baseline visit and were included in the efficacy analyses (ITT). Mean change in MADRS score from baseline to week 6 for patients treated by ADM was 13.2 ± 8.6 points ($t = 8.25$, df = 28, $P < 0.001$) and 14.5 ± 9.5 points ($t = 8.48$, df = 30, $P < 0.001$) for patients from CAD group, thus the difference between groups was not significant ($t = 0.56$, df = 58, $P = 0.58$). The scores of rating scales used (MADRS, BDI-SF and CGI) at the baseline and at the end of the acute phase of treatment are displayed in the Table II.

On MADRS, RM-ANOVA-G-G confirmed a significant effect of time ($F = 89.16$, df = 3,174, $P < 0.001$) but no effect of group ($F = 0.43$, df = 1,58, $P = 0.52$) or group–time interaction ($F = 0.95$, df = 3,174, $P = 0.40$) (Figure 2). We also did not find any significant between-group differences in the other rating scales: BDI -SF (group–time interaction: $F = 0.57$, df = 3,174, $P = 0.57$) and CGI (group-time interaction: $F = 1.28$, df = 3,174, $P = 0.28$). The response rates of ADM and CAD groups were not different in either ITT (48 vs. 58%; $P = 0.61$) or "completers" analyses (54 vs. 64%; $P = 0.57$) or in remission rates (see Table III).

Table II. Clinical rating scales scores at baseline and final visit (week 6) in the ADM and CAD groups (intent-to-treat sample).

Scale	Treatment	Baseline visit week 0	Final visit week 6	*P* value[a]
MADRS	ADM	28.4 ± 3.2	15.2 ± 8.6	< 0.001
	CAD	28.6 ± 3.2	14.3 ± 9.6	< 0.001
BDI-SF	ADM	20.2 ± 6.6	13.1 ± 9.1	< 0.001
	CAD	18.9 ± 6.2	11.4 ± 6.7	< 0.001
CGI	ADM	4.6 ± 0.5	2.7 ± 1.2	< 0.001
	CAD	4.6 ± 0.6	2.7 ± 1.5	< 0.001

ADM, antidepressant monotherapy; BDI-SF, Beck Depression Inventory – Short Form; CAD, combinations of antidepressants; CGI, Clinical Global Impression; MADRS, Montgomery–Åsberg Depression Rating Scale.

No significant differences were observed between the both groups at baseline and week 6 in rating scales analyzed with repeated measure of analyses of variance with the Greenhouse–Geisser adjustment.

[a]Paired *t*-test.

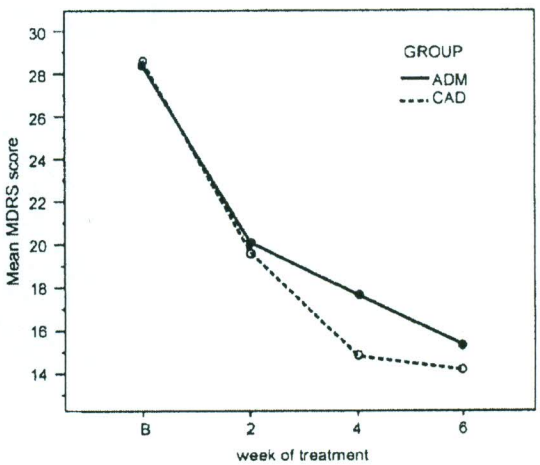

Figure 2. Change in mean MADRS[1] scores among depressive patients treated with ADM or CAD. ADM, antidepressant monotherapy; B, baseline visit; CAD, combination of antidepressants; MADRS, Montgomery–Åsberg Depression Rating Scale.

[1]Last observation analyses.

There was a significant difference between groups in the IMID at the end of study (Table I). To explore the influence of this finding, we re-analyzed our data by ANCOVA with the IMID as a covariate and we found only non-significant between-group difference for total MADRS change ($F = 1.97$, df = 1,57, $P = 0.17$). Separate analyses for ADM and CAD groups did not reveal higher IMIDs in responders comparing to nonresponders in ITT (ADM, responders = 209 mg/day; nonresponders = 255 mg/day; $U = 70.5$, $P = 0.13$; CAD, 379 vs. 448 mg/day, $U = 76.5$, $P = 0.11$) nor in completers (ADM, 209 vs. 247 mg/day, $U = 63$, $P = 0.3$; CAD, 381 vs. 460 mg/day, $U = 47$, $P = 0.17$) data sets. We also did not find a correlation (rho = –0.08, $P = 0.53$ between values of IMIDs and the reduction of MADRS score at the end of the study (ITT). As the next potential confounding factors were tested values of TR-S and MGH-S as covariates but analyses (ANCOVA), similarly to IMID, did not reveal significant difference between treatment modalities in term of MADRS change from baseline to final visit (TR-S, df = 1,56, $F = 0.21$, $P = 0.65$; MGH-S, df = 1,56, $F = 2,16$, $P = 0.15$). Additionally, the number of subjects treated in the last trial before start of the study with combined treatment was not different between ADM and CAD groups (McNemar's chi-square test, $P = 0.86$).

In addition, using RM-ANOVA-GG, we did not find any differences (group–time interaction) between groups in terms of frequency ($F = 0.09$ df = 2,116, $P = 0.91$), intensity ($F = 1.35$, df = 2,116, $P = 0.26$) and burden ($F = 0.40$, df = 2,116, $P = 0.67$) of side

Table III. Response rate in ADM and CAD groups (intent-to-treat and observed case analyses).

	Analysis	ADM	CAD	*P* value[a]
Response rate % (positive cases/subjects in group)	Intent-to-treat	48% (14/29)	58% (18/31)	0.61
	Completers	54% (14/26)	64% (16/25)	0.57
Remission rate % (positive cases/subjects in group)	Intent-to-treat	41% (12/29)	45% (14/31)	0.8
	Completers	46% (12/26)	52% (13/25)	0.78

ADM, antidepressant monotherapy; CAD, combination of antidepressants.
[a]Fisher exact test.

effects evaluated by FIBSER. No average values of FIBSER parameters (frequency, intensity and burden) in both groups at any study visit of acute phase did not exceed 2 points. There were three patients who dropped-out from the study due to adverse events (ADM $n = 1$, restless legs syndrome induced by escitalopram; CAD $n = 2$, switch to hypomania induced by combination mirtazapine + milnacipram, dermal allergic reaction to treatment with escitalopram + bupropion).

Follow-up phase. Thirty responders (ADM = 14; CAD = 16) who had completed acute phase of study entered the follow-up phase of study. Unfortunately, six (ADM = 4; CAD = 2) were lost for analysis since they refused to continue in the study and did not come to the research visit. There was no significant difference ($P = 1.0$) in relapse rate between ADM ($n = 2$) and CAD ($n = 3$) groups.

Discussion

The main finding of this open-label, randomized study comparing the efficacy of ADM and CAD in the acute treatment of patients with resistant depression is that the reduction of MADRS score, the response, remission as well as drop-out rates were not different between the treatment modalities at week 6. Despite the use of relatively high doses of ADs in term of IMID, especially in CAD group, both types of intervention were well tolerated and there were also no differences in the number of patients relapsing during the 2-month period of continuation treatment.

Our results on the efficacy of treatment with ADM and CAD are in accord with a recent, large, single-blind, randomized study [20] but in contrast to other studies that described higher efficacy of various CADs (e.g., mirtazapine + paroxetine, mirtazapine + fluoxetine, mirtazapine + venlafaxine, mirtazapine + bupropion, fluoxetine + desimipramine) used from treatment initiation, compared with ADMs [8,9,16,18]. Looking for possible explanations of different results in our study compared to previous ones, we have revealed higher level of resistance in our sample than in the above-mentioned studies demonstrating positive results for CAD. It is probable that this higher degree of resistance is connected with poorer response to treatment not only to ADM but also to CAD [42]. Moreover, a substantial proportion of subjects in both groups in our study were treated with combination of ADs or ADs augmented by second generation of antipsychotics before enrollment to the project (Table I) and the majority of administered ADMs in the study were ADs with multiple pharmacological mechanisms, e.g., tricyclics, serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, etc.

Perhaps also the differences between the results of the present study and those showing higher efficacy of CAD might be due to their use of specific ADs. Generally, the efficacy of ADs is considered to be similar to each other [3,5] but the results of some meta-analyses imply differences among them [43–45].

Our study was designed to be close to real clinical practice and did not evaluate the efficacy of specific ADs but compared efficacy and tolerability of two broadly defined treatment modalities. Therefore we are not able to estimate the efficacy of specific ADs in our trial. The choice of ADs, based on the clinical judgment of attending psychiatrists, took into account current guidelines of treatment [3,5] and reflected treatment history of the index episode as well as clinical symptoms such as anxiety, dyssomnia, etc. as is usual in clinical practice. We used CADs and ADMs whose efficacy in the treatment of resistant depression had been demonstrated in clinical studies [8,9,19,20, 29,46–52] or recommended in "guidelines" and reviews [3,5,10–13]. Hence, we believe that our data on overall efficacy can be interpreted within the framework of current studies in this field.

According to our results, the effect of ADs in our study was not dependent on their dosage since there

was no difference in the dose of ADs (IMID) between responders and nonresponders in both groups, and higher doses in CAD did not result in better treatment outcome (with no difference in side effects measured by FIBSER). Furthermore, there was neither association between values of IMID and the overall MADRS reduction in the acute phase of study nor influence of IMID on between-group difference. Current psychiatric literature provides ambiguous results on this topic [53,54]. We also did not find influence of number and type of previous treatments in terms of TR-S and MGH-S on our results. We analyzed not only TR-S but also MGH-S values since the latter ones consider into account also optimization of treatment (e.g., augmentation and combination of ADs) and do not suggest implicit hierarchy in the efficacy of ADs.

As we stated above both treatment modalities were well tolerated and there were no difference between groups in the number of dropped-out patients due to adverse events or side effects and this result is in accord with results of previous studies with various combinations [8,9,18,20,55–57] . Due to the heterogeneity of applied ADs we used the scale FIBSER that maps interference of side effects with patients' daily functioning and does not provide information on the occurrence of specific side effects. Hence, we are not able to compare their incidence in both treatment groups but the results of FIBSER did not reveal difference between groups. Furthermore, the impact of side effects in terms of FIBSER parameters was rated as a mild, not exceeding in average values of 2 out of 6 points.

The results of our study must be interpreted with caution as there are several study limitations. First, the duration of study may have been too brief to allow the full benefit of antidepressants to be expressed [2]. However, the same treatment period was used in two recent double-blind studies [8,9]and 6-week antidepressant intervention is the generally accepted time period to achieve response to treatment. Second, our sample size was limited. An a priori calculated sample size was sufficient to detect an effect size of 0.4, i.e. large effect, based on results of Nelson's study [18] and was similar to what had been used in our retrospective studies detecting better efficacy of CAD or combined treatment (CAD, augmentations of ADs with second generation of antipsychotics, etc.) [21,58]. Thus, we can not completely exclude false-negative results. However, an a posteriori effect size for MADRS score was 0.1, which is below the limit even for a small effect. Third, the raters were not blind to treatment. Fourth, the anxiolytic interventions were not strictly limited, but the number of subjects taking anxiolytics, as well as doses of benzodiazepines (diazepam equivalent), was not different in the groups. Finally, a significant proportion of acute responders (completers) was lost for the follow-up visit evaluating the stability of response.

Despite these limitations, our results show that the efficacy of ADM and CAD in terms of response, remission, tolerability and stability of response is comparable. In view of our results and status of the evidence in this topic, the use of CAD from treatment initiation as a first option intervention in patients with resistant depression still remains questionable [59,60].

Conclusions

Both treatment modalities (monotherapy and combination of antidepressants) produced clinically relevant reduction of depressive symptomatology in acute treatment of patients with resistant depression and their effect was comparable.

Key points

- This prospective, randomised, open-label, 6-week study compares efficacy and tolerability of antidepressant monotherapies and combinations of antidepressants applied from the initiation of treatment in resistant patients as well as the ability of the treatment modalities to maintain treatment response during eight weeks follow-up.
- The reduction of MADRS score, the response, remission as well as drop-out rates were not different between the treatment modalities at week 6. There were also no differences in the number of patients relapsing during the 8-week period of continuation treatment.
- Despite limitations of our study, we suppose that the use of CAD from treatment initiation as a first option intervention in patients with resistant depression still remains questionable.

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Statement of Interest

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Medicom, Nycomed, Krka. Other: faculty member, Lundbeck International Neuroscience Foundation.

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