

Is combined treatment more effective than switching to monotherapy in patients with resistant depression? A retrospective study

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Abstract

OBJECTIVE: The aim of this retrospective study was to compare the efficacy of combination therapy (combinations of antidepressants and various augmentations) and antidepressant monotherapy in the treatment of patients, who failed to respond at least to one previous antidepressant trial in the routine clinical practice.

METHODS: We reviewed chart documents of patients hospitalized at Prague Psychiatric Center for depressive disorder from June 2005 to June 2007 and finished at least 4 weeks of new treatment. Depressive symptoms and overall clinical status were assessed using Montgomery and Åsberg Depression Rating Scale, Clinical Global Impression and Beck Depression Inventory – Short Form at the baseline and in the end of treatment.

RESULTS: We identified 49 inpatients (24-combined treatment, 25-monootherapy), who were suitable for analyses. Both groups were equal in baseline characteristics and in the duration of index episode treatment. The combined treatment was superior to the monootherapy switch in the MADRS median score reduction (16 vs. 9 points, $p=0.01$). The combined group achieved higher response rate compared to monootherapy group (67% vs. 36%, $p=0.05$). Number need to treat for response was 3.3 (95% CI, 1.85–37.3).

CONCLUSION: The findings of this study suggest that combined treatment is more efficacious than switch to monootherapy in the treatment of resistant depression.

Abbreviations :

AD	- antidepressant	MDD	- major depressive disorder
BDI-SF	- Beck Depression Inventory – Short Form	MONO	- antidepressant monotherapy
CI	- confidence interval	NNT	- number needed to treat
COMB	- combined therapy	STAR*D	- The Sequenced Treatment Alternatives to Relieve Depression
CTRD	- Center for Treatment of Resistant Depression	TRD	- treatment resistant depression
ES	- effect size	TR-S	- Thase and Rush staging system of resistant depression
IQR	- interquartile range		
MADRS	- Montgomery and Åsberg Depression Rating Scale		

INTRODUCTION

The lifetime prevalence of major depressive disorder (MDD) is approximately 20%, with about twice as many women affected as men (Kessler *et al.* 2005). Despite the progress in the development of new antidepressive compounds, outcomes studies have consistently reported that at least one third of patients do not respond satisfactorily to the first antidepressant (AD) trial (Fava, 2000; Trivedi *et al.* 2006). The nonresponse is associated with disability and higher medical costs. The partial response and response without remission increase risk of relapses and recurrences (Nierenberg *et al.* 2007).

Episodes can be classified as treatment resistant when adequately administered treatments fail to bring depressed patients to response or remission (Fava, 2003). Several models how to classify stage of resistance to treatment were introduced to clinical and research practice (Fava, 2003; Souery *et al.* 1999; Thase&Rush, 1997). A commonly used staging model for differentiating the levels of resistance in TRD patients was proposed by Thase and Rush (TR-S, Thase&Rush, 1995; Thase&Rush, 1997). Using this model, treatment resistance in patients can be defined by 5 stages ranging from a lack of response to at least one adequate trial of an antidepressant to failure to respond to multiple classes of antidepressants and to electroconvulsive therapy.

Pharmacologic options to manage treatment resistant depression (TRD) include augmentation of AD (atypical antipsychotics, triiodothyronine, lithium, pindolol, buspirone etc.), combination of two distinctly different ADs, and switching within the same antidepressant class or across antidepressant classes. The level of evidence on the efficacy of these approaches is various (Anderson *et al.* 2008; Nemeroff, 2007; Zajecka&Goldstein, 2005). Currently, no clear consensus exists on the strategy which should be preferred for the non-responding patient (Bauer *et al.* 2007; Blier, 2006).

Based on results of previous studies some authors suggest that combined treatment (e.g. combination of antidepressants or augmentation of AD, COMB) is more effective in the treatment of resistant depression than antidepressant monotherapy (MONO) (Pridmore&Turnier-Shea, 2004; Rojo *et al.* 2005; Rosenzweig-Lipson *et al.* 2007; Shelton, 2007). Furthermore, according to STAR*D (The Sequenced Treatment Alternatives to Relieve Depression, Fava *et al.* 2003) study, which was to identify optimal treatment after failure of initial MONO, only 1 of 3 patients remitted with citalopram and rates of remission for each consecutive monotherapy were gradually lower (Rush *et al.* 2006; Rush, 2007; Trivedi *et al.* 2006). The aim of this retrospective study was to compare the efficacy of COMB (combination of 2 ADs and various augmentations) and MONO in the treatment of patients, who failed to respond to at least one previous antidepressant

trial in the routine clinical practice. We hypothesized that COMB would produce a greater treatment effect than MONO.

MATERIAL AND METHODS

Subjects and treatment

We performed retrospective chart analysis. All subjects were hospitalized at Prague Psychiatric Center from June 2005 to June 2007. They were admitted by referral from a number of outpatient clinics and psychiatric hospitals in the Czech Republic and treated at the Center for Treatment of Resistant Depression (CTRD), which is a part of Prague Psychiatric Center. Charts were retrospectively reviewed for all individuals with a DSM IV (American Psychiatric Association, 1994) major depression recurrent or single episode (total number of charts screened=85), confirmed using The Mini – International Neuropsychiatric Interview – M.I.N.I., Czech version 5.0.0 (Sheehan *et al.* 1998). Forty-nine patients, who had fulfilled at least Stage I criteria for resistant depression (≥ 1 adequate antidepressant treatment in current episode) according to Thase and Rush (TR-S, Thase and Rush, 1997) and finished at least 4 weeks of new treatment were included to analysis. We excluded subjects with drug or alcohol abuse and those who suffered from organic mental disorder, personality disorders and other comorbidities on Axis I of DSM IV. The standard psychiatric examination and M.I.N.I were performed to exclude psychiatric comorbidities. Both types of treatment were prescribed according to clinical judgment of the psychiatrist in charge and with regard to the history of previous treatments. COMB was defined as AD combination or augmentation of AD with atypical antipsychotics, triiodothyronine, lithium etc. (Table 1). Concomitant treatment e.g. hypnotics and anxiolytics were not restricted. For purposes of analysis, patients were divided into two groups: MONO group (n=25) and COMB group (n=24). In the CTRD, rating scales assessing clinical status and depressive symptoms are routinely performed by attending physicians. The project of CTRD, which includes systematic mapping and observation of various demographic and clinical parameters during the treatment of depressive patients, was approved by the Prague Psychiatric Center Institutional Review Board and written informed consent to participate in the research program of CTRD was obtained from all subjects.

Clinical assessment

The primary outcome measure for the study was the score change in the Montgomery and Åsberg Depression Rating Scale (MADRS, Montgomery & Åsberg, 1979). The secondary outcome measures were the changes in the Clinical Global Impression (CGI, Guy, 1976) and Beck Depression Inventory – Short Form (BDI-SF, Beck *et al.* 1974). The patients were assessed at baseline and at the end of treatment. Ratings were

made by experienced clinical psychiatrists who were trained to the criterion of intraclass correlation >0.80 for each clinician (Kobak *et al.* 1996). Clinical response was defined a >50% reduction of MADRS total score.

Statistical methods and data analyses

Mann Whitney U test, Fisher Exact test and X² – test were used to investigate differences between the groups on baseline demographic and clinical variables. These characteristics are presented as the median and interquartile range (IQR). The number of responders in both groups was compared with Fisher Exact test. Furthermore, clinical measures (MADRS and BDI-SF) and above mentioned demographic and clinical variables of responders and nonresponders in both treatment groups were tested using non-parametric analyses of variance (Kruskal-Wallis test). Number needed to treat (NNT) for response and posthoc effect size (ES) were also calculated. All tests were 2–sided and an exact significance level of 0.05 was adopted. Analyses were performed using STATISTICA version 7.

RESULTS

Baseline patients characteristics

A total of forty-nine patients with unipolar depression in both treatment groups (MONO: n=25, COMB: n=24) were analyzed. Baseline demographic and clinical characteristics did not differ between the groups (Table 1). We did not find any differences between responders and nonresponders in these parameters nor in scores of baseline rating scales in both groups (Table 2).

Efficacy measures

We detected significant differences in MADRS (16 vs.9 points, U=171.5, p=0.01) and BDI-SF (7 vs. 3 points, U=25.5, p=0.001) median score reductions between COMB and MONO groups. We did not find this difference in CGI scores (Table 3).

The clinical response rate of COMB group was different (higher) from response rate to monotherapy (67% vs. 36%, Fisher Exact test, p=0.05). The post-hoc ES of COMB compared to MONO was moderate (w=0.32). NNT for response was 3.3 (95% CI, 1.85–37.3). The number of responders, who took benzodiazepines in both groups during the study, did not differ (Table 2).

DISCUSSION

The results of this study indicate that the COMB is more effective than MONO. The response rate and MADRS score reduction found for the COMB were significantly higher than those that have been identified for MONO. NNT for response which was estimated in our sample is clinically meaningful (Citrome, 2008).

Our results are in accord with authors, who suggest that early use of COMB (augmentation or combination of ADs) may help more patients to reach response or remission than repeated monotherapy treatments (for instance Rush, 2007). We did not find difference between groups in the reduction of CGI score. We suppose that CGI could be less appropriate tool for measure of changes in the clinical status than MADRS or BDI-SF and according to some authors CGI may induce inconsistent rating behavior (Beneke & Rasmus,

Tab. 1. Clinical characteristics of treatment groups.

	MONO group (n=25)	COMB group (n=24)	Statistical significance level*
Median (IQR)	Median (IQR)		
Age	49 (38 – 54)	48 (42–55)	NS ^a
Sex (F:M)	18:7	15:9	NS ^b
Age of onset of depressive disorder	35 (27.5–42)	39.5 (28.5–43.5)	NS ^a
Number of previous depressive episodes	2(1–3)	2 (0.5 – 6)	NS ^a
Duration of current episode before start of index treatment (wks)	24(12–46)	22 (12–38)	NS ^a
Number of previous treatments of current episode	1.5 (1–2.5)	1(1–2)	NS ^a
Duration of index treatment (wks)	4(4–5)	5 (4.5–6)	NS ^a
Treatment	17 SNRI, 5 SRI, 3NDRI	15 - combination of 2 AD 6-AD+AP2 3 - others	NA
Number of subjects taking benzodiazepines during the study	19	17	NS ^b

Abbreviations: * - p<0.05, - Mann-Whitney U test, b- Fischer Exact test, AD - antidepressant, AP 2-2nd generation antipsychotics, COMB - combined therapy, IQR - interquartile ratio, MONO - antidepressant monotherapy, NA-not applicable, NDRI - norepinephrine and dopamine reuptake inhibitors, NS - nonsignificant, SNRI - serotonin and norepinephrine reuptake inhibitors, SRI - serotonin reuptake inhibitors, wks - weeks

Tab. 2. Clinical characteristics of responders and nonresponders in both treatment groups.

	Nonresponders MONO group (n=16) Median (IQR)	Responders MONO group (n=9) Median (IQR)	Nonresponders COMB group (n=8) Median (IQR)	Responders COMB group (n=16) Median (IQR)	Statistical significance level *
Age	45.5 (34.5–54.5)	50 (41–53)	49 (31.5–55)	48 (44–52)	NS ^a
Sex (F:M)	11:5	7:2	9:7	6:2	NS ^b
Age of onset of depressive disorder	29(24–10)	36 (35–13)	34 (23–12)	42 (30.5–14.5)	NS ^a
Number of previous depressive episodes	1 (1–3)	2 (1–3)	5.5 (2–9)	1(0–3)	NS ^a
Duration of current episode before start of index treatment (wks)	30 (17–70,5)	22(8–44)	30 (20–66)	19(9.5–29)	NS ^a
Number of previous treatments of current episode	2 (1–3)	1(1–2)	1 (1–3.5)	1.5(1–2)	NS ^a
Duration of index treatment (wks)	4(4–5)	5 (4–6)	5 (4.5–5.5)	5 (4.5–6)	NS ^a
Number of subjects taking benzodiazepines during the study	11	8	6	11	NS ^b
MADRS baseline score	28.5 (23.5–34.5)	25(24–30)	28 (25–36.5)	29 (27–33.5)	NS ^a
BDI-SF baseline score	22 (17–26)	15(13–17)	21.5 (18–27)	20.5 (17.5–24)	NS ^a
CGI baseline score	5 (4–5.5)	5 (4–5)	5 (5–5.5)	5 (4.5–5.5)	NS ^a

Abbreviations: * - $p < 0.05$, ^a - non-parametric analyses of variance (Kruskal-Wallis test), ^b - χ^2 test, BDI-SF - Beck Depression Inventory – Short Form, CGI - Clinical Global Impression, COMB - combined therapy, F - female, IQR - interquartile ratio, M - male, MONO - antidepressant monotherapy, MADRS - Montgomery and Asberg Depression Rating Scale NS - nonsignificant, wks - weeks

Tab. 3. Results of the clinical rating scales.

	MONO group (n=25) Median (IQR)	COMB group (n=24) Median (IQR)	Statistical significance level *,^a
MADRS baseline score	26 (24–33)	29 (26.5–33.5)	NS
MADRS final score	16(11–27)	12(7–20)	NS
reduction of MADRS score	9(5–15)	16(11–21)	0.01
BDI-SF baseline score	18.5 (14.5–26)	21 (17–25)	NS
BDI-SF final score	14 (9–24)	11 (6–19)	NS
reduction of BDI-SF score	3(1–6)	7 (3–12)	0.01
CGI baseline score	5(4–5)	5 (5–5.5)	NS
CGI final score	3 (2–4)	2 (2–4)	NS
reduction of CGI score	2(1–2)	2(1–4)	NS

Abbreviations: * - $p < 0.5$, ^a - Mann-Whitney U test, BDI-SF - Beck Depression Inventory – Short Form,- CGI -Clinical Global Impression, COMB - combined therapy, IQR - interquartile ratio, MADRS - Montgomery and Asberg Depression Rating Scale, MONO - antidepressant monotherapy

1992). In addition, there are mixed results in the studies which compared level of correlation between CGI and MADRS or Hamilton Depression Rating Scale (Jiang & Ahmed, 2009; Ruhe *et al.* 2005).

The results of this study must be interpreted with caution as there were several study limitations. First, we used retrospective design as in our previous study

(Kopecek *et al.* 2007). This type of study does not allow the use of clearly defined inclusion criteria and the assignment to treatment groups is not random. However, the clinical data at the CTRD are carefully monitored and standard and validated instruments for evaluation of depressive symptoms are applied (MADRS, CGI, BDI-SF). Diagnosis of depression was

confirmed using M.I.N.I (Sheehan *et al.* 2008) and stage of resistance was evaluated according to worldwide used classification system (Thase & Rush, 1995). These factors have been highlighted as important in the research of treatment resistant depression (Fava, 2003; Whyte *et al.* 2004).

Second, we did not compare two specific antidepressive treatments, but only two types of treatment (combined therapy, monotherapy). Based on the results of previous studies we expected better efficacy of combined treatments (combinations of ADs and augmentation), which can provide multiple therapeutic mechanism of action or boosted effect to specific neurotransmitter or receptor system (Nelson *et al.* 2004; Stahl, 2008).

Third, the mean duration of treatment in our sample was 4.9 ± 0.9 weeks. We can not exclude the possibility of further clinical response emerging during longer treatment. However, in our opinion and in agreement with other authors, a period of 4 weeks of treatment without signs of response is sufficient to justify a change in treatment in clinical practice (Posternak & Zimmerman, 2005; Pridmore & Turnier-Shea, 2004; Sackeim *et al.* 2005; Souery *et al.* 2007).

We demonstrated better efficacy of COMB in patients with resistant depression in this study. A retrospective study, such as this, offers the advantage of collecting real-world clinical data outside of the framework of randomized clinical trials. Although randomized, double-blind studies are essential to establish efficacy and tolerability, they do not represent everyday clinical practice (Marchiaro *et al.* 2005). Retrospective studies should be considered as complementary to randomized controlled trials.

CONCLUSION

The findings of this retrospective study suggest that COMB is more efficient than MONO in the treatment of resistant depression.

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