

Research paper

Early improvement and response to antidepressant medications in adults with major depressive disorder. Meta-analysis and study of a sample with treatment-resistant depression



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ABSTRACT

Background: Initial improvement in the first weeks of antidepressant (AD) treatment is a useful early predictor of complete AD response. We performed a meta-analysis of AD studies to investigate whether a partial decrease in depressive symptoms by week 4 was associated with response and remission by weeks 6–14 in major depressive disorder (MDD). Finally, we focused on treatment-resistant depression (TRD: lack of response to prior AD) to test the impact of early improvement on a second AD treatment outcome and to compare different switching strategies.

Methods: Meta-analysis was conducted on AD naturalistic studies published between 01.01.2000 and 06.30.2017. TRD was an exclusion criterion. TRD was analyzed in 407 MDD patients treated with venlafaxine for 6 weeks. The MADRS was used to define very early improvement (VEI: > 20% decrease at week 2), early improvement (EI: > 30% decrease at week 4) and remission (week 6 MADRS < 10). A theoretical model was used to simulate AD switch in TRD patients who failed to achieve remission (**Algorithm A**), VEI (**Algorithm B**) or EI (**Algorithm C**).

Results: Our meta-analysis (9 studies; N = 6185) showed significant associations between early improvement, response (OR: 3.28 95% C.I.: 2.06–5.20) and remission (OR: 2.10 95% C.I.: 1.53–2.87). 24.6% of TRD sample remitted. VEI was a poor outcome predictor: sensitivity = 0.52 (0.40–0.63); specificity = 0.82 (0.76–0.86); AUC = 0.67 (0.62–0.71). EI had a moderate predictive power: sensitivity = 0.87 (0.77–0.93); specificity = 0.71 (0.66–0.77); AUC = 0.76 (0.71–0.80). The best treatment scenario was **Algorithm C** (switch after 4 weeks) in which remission rate was marginally increased (35.1% vs 33.7% of **Algorithm A**). **Algorithm B** (switch after 2 weeks) led to a 4.3% decrease in remission compared to **Algorithm A**.

Limitations: Inclusion of a naturalistic sample without a control arm; simulation of treatments.

Conclusion: Although literature data suggest a correlation between an initial improvement of depressive symptoms and later response and remission during AD treatment, our analysis shows that such an early improvement is not a reliable outcome predictor in TRD. The nature of TRD is complex and different biological mechanisms and treatments might be necessary for TRD patients.

1. Introduction

Major depressive disorder (MDD) is a common mental disorder, which is estimated to affect 1 in 6 people in their lifetime, and it is a leading cause of disability worldwide (Ferrari et al., 2013).

Antidepressant (AD) medications are used to treat major depressive episodes in 2–3 months, with remission rates of 40–60% in randomized trials (Cipriani et al., 2007) or lower (20–40%) in naturalistic studies (Cuffel et al., 2003; Rush et al., 2006). Individuals who fail to respond to first AD treatment are treated with a second or third AD (Rush et al.,

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2006; Montgomery et al., 2014). However, the long-time persistence of depressive symptoms has a negative impact on patients' lives, leading to more individual suffering and a serious risk for suicidal behavior, and it is associated with higher economic costs for society (Greenberg et al., 2015; Paykel, 2006). Therefore, knowing as early as possible whether a patient will or will not ultimately respond to an AD medication can encourage ultimate responders to continue taking the medication, while minimizing the time that ultimate non-responders are kept on an ineffective treatment. These considerations led researchers to investigate early predictors of AD treatment outcome. Several trials have reported an association between a partial improvement of depressive symptoms in the first weeks of AD treatment and endpoint response and remission (Lam, 2012). Recently a systematic review identified 17 randomized controlled trials investigating early improvement in more than 14,000 patients with MDD (Wagner et al., 2017). In this meta-analysis early improvement was found to predict response and remission after 5–12 weeks of treatment with high sensitivity and low to moderate specificity. However, to opt for switching to a new AD, clinicians are interested in the results of naturalistic studies, in which patients and treatment conditions are more similar to everyday practice. Our main objective was to perform a systematic search and meta-analysis of naturalistic studies including patients with MDD treated with an AD for 6–14 weeks in order to investigate the association between a > 20% and < 50% improvement of depressive symptoms during the first four weeks and endpoint remission. The predictive power of an early partial improvement for complete response to an AD medication could be different in patients with treatment-resistant depression (TRD). Several definitions and staging models for TRD have been proposed, based on criteria such as number of failures to treatment, chronicity of illness, modalities of treatments used and duration of the trials (McIntyre et al., 2014). In this paper TRD describes a condition in which a patient has failed to achieve response in a previous and adequate AD trial. TRD subjects could be affected by more severe forms of depression that need longer periods of treatment. We highlight our prior study in which a group of patients who had not responded to an AD were treated with citalopram or desipramine for eight weeks (Souery et al., 2011). Response rate was assessed after four weeks and those who were identified as non-responders, randomized to either not initially prescribed AD, reported lower remission rates and higher depression scores than those who continued initial AD for further four weeks. In the second part of the current study we analyzed the impact of early improvement on TRD. We used a sample of major depressed patients classified as non-responders to a prior AD, treated with venlafaxine for 6 weeks (Souery et al., 2015). A post hoc analysis was carried out to test the predictive power of different definitions of early improvement at weeks 2 and 4 for week-6 remission. In addition, we performed a simulation of switching to escitalopram before the end of venlafaxine trial in individuals showing no improvement during the first weeks of venlafaxine use, who were likely to be non-responders to the medication.

2. Methods

2.1. Systematic review and meta-analysis

We performed a systematic search of AD studies that fulfilled the following inclusion criteria: I) Participants: adults (18–65 years) with MDD diagnosed according to DSM IV, IV-TR and V criteria or ICD-10 criteria were included. Exclusion was due to administration of a prior AD for at least 6 weeks without achieving a complete response or remission of depressive symptoms, bipolar depression, dementia/cognitive impairment or other brain organic disorders. TRD was an exclusion criterion in our meta-analysis because we aimed to test the association between early improvement and final response in an easier to treat depression and, then, to confirm this finding in difficult patients such as those affected by TRD, not reported in the meta-analysis. II) Intervention: an oral AD was given in monotherapy or with co-

medications (AD + benzodiazepine; AD + AD; AD + antipsychotic; AD + mood stabilizer) as it is common in clinical practice. The AD was administered for 6–14 weeks. Switching to a different AD was not allowed for 6 weeks as well as varying AD dose. Actually any change at such an early stage of treatment could modify final response and the association between the early course of depressive symptoms and outcome. We speculate that the lack of an early improvement, being a reliable predictor of the lack of final response to AD treatment, could be used to switch AD medication or dose, however the objective of this review was to investigate the association between early improvement and later complete AD response, not the benefits of early switches. Control groups were treated with placebo or active medications; III) Comparator: in each study patients were divided into two comparison groups: a) patients with a partial improvement of depressive symptoms (> 20% and < 50% decrease in depression scale scores such as Hamilton Depression Rating Scale (HDRS), Montgomery Asberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptomatology (QIDS)) within 4 weeks of AD administration; b) patients without improvement. IV) Outcome: response ($\geq$ 50% decrease in depression scale scores) and remission (HDRS < 7 or MADRS < 10 or QIDS < 6) rates assessed within week 6–14 range. V) Design: randomized controlled trials (RCTs) with double-blind design were not eligible for our meta-analysis. In fact RCTs were included in previous meta-analyses (Szegedi et al., 2009; Wagner et al., 2017). We decided to exclude RCTs because their treatment conditions were not considered to be representative of everyday clinical practice. The systematic review of studies was conducted according to PRISMA guidelines: 1. Six electronic databases (PubMed; Google Scholar; SCOPUS EMBASE; ClinicalTrials.gov; ISI Web of Science) were used to identify relevant papers by entering the following sets of key-words: 'antidepressant' + 'early improvement' + 'remission'; 'SSRI' + 'early improvement' + 'remission'; 'antidepressant' + 'early improvement' + 'response'. To refine search detailed definitions of early improvement were added ('week 2 improvement'; 'week 2 decrease'; 'week 4 improvement'; 'week 4 decrease') as well as specific AD agents ('fluoxetine'; 'fluvoxamine'; 'citalopram'; 'sertraline' etc.). Additional papers were collected by reviewing the reference lists of original papers. Publication year range was from 01.01.2000 to 06.30.2017. 2. Duplicate records were removed; 3. Abstracts not reporting original studies such as reviews, meta-analyses or comment papers were removed as well as papers written in a different language from English, which could not be read and understood by all researchers involved in review process. 4. The full-text papers of AD studies were screened for the fulfilling of inclusion criteria I-V: studies with negative screenings were ruled out. Two authors (PO and AS) independently searched online databases. Each investigator reviewed titles and abstracts to identify eligible papers. Both investigators analyzed and discussed full-text papers in a joint session at the University of Bologna (Italy). Finally, studies on which they agreed were included in meta-analysis. A Delphi method could be pursued to solve disagreements between PO and AS: five authors (DS; MD; SK; JZ; JM) who had not participated in previous phases of review process were included in a panel responsible for final decisions on contended papers under the supervision of SM. However no study was included by applying Delphi procedure. A meta-analysis was carried out on selected studies to estimate the strength of the association between a partial improvement (> 20% and < 50%) of depressive symptoms reported in the first four weeks of AD treatment and response and remission after 6–14 weeks. The number of individuals with early improvement, if not originally available, was estimated from sensitivity and specificity values. To perform meta-analysis we estimated odds ratios for the association between early improvement and outcome measures in single studies, then the weighed pool OR at meta-analytic level. Heterogeneity statistic was incorporated to calculate summary OR under random-effects model (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) (Table 1).

Table 1
Studies included in meta-analysis.

Authors (year)	Antidepressants	Sample size	Scales	Outcome	Weeks
Stamm et al. (2014)	venlafaxine	88	HAMD-17	response and remission	6
Jakubovski, Bloch (2014)	citalopram	1857	QIDS and HAMD-17	remission ^a and response ^b	14
Mikoteit et al. (2014)	duloxetine	25	HAMD-17	response and remission	6
Gilaberte et al. (2013)	escitalopram	251	HAMD-17	response and remission	8
Gorwood et al. (2013)	agomelatine	2351	QIDS	response	6
Kim et al. (2011)	various ADs	568	HAMD-17	response and remission	12
Tadic et al. (2010)	various ADs	84	HAMD-21	response and remission	6
Henkel et al. (2009)	various ADs	795	HAMD-21	response and remission	6–14
Vergouwen et al. (2007)	SSRIs	166	HAMD-17	remission	10

Total number of patients: 6185.

^a Remission assessed in all 1857 cases.

^b Response assessed in 1641 cases.

2.2. AD non-responder sample

We performed a new analysis of a sample reported in the Patterns of Treatment Resistance and Switching Strategies in Unipolar Affective Disorder (PTRSSUAD) study (Souery et al., 2015). The PTRSSUAD study included adults (18–65 years) with MDD (DSM IV-TR) who failed to respond to a previous and adequate, retrospectively assessed, AD treatment, recruited during a six-year period (from January 2005 to December 2011) in tertiary psychiatric centers. The study was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study. The protocol of the study was approved by Ethical Committees of all participating centers. The sample was assessed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to diagnose MDD and a current moderate or severe major depressive episode. Other assessment tools included: 1. Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979); 2. Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987); 3. a structured examination tool consisting of modules developed to collect: 1) socio-demographic data; 2) somatic illnesses; 3) current and previous medications; 4) psychiatric familial antecedents. These assessments were made at baseline and on day 14, 28 and 42 of AD treatment. The sample was treated with venlafaxine (VEN) for 6 weeks. Initial daily dose was 75 mg which could be increased to 150 mg after one week, based on a judgment of unsatisfactory response by the clinical investigator. If necessary, the dose could be increased up to a maximum of 225 mg, since this is the highest recommended dose for moderately depressed outpatients (80% of our sample) in most countries (Souery et al., 2015). The original design of the PTRSSUAD study (Souery et al., 2015) is illustrated by Fig. 3. There were two treatment phases: A. the whole sample was given VEN for 6 weeks. Response (> 50% decrease in the total MADRS from baseline score) was assessed at the end of this period; B. patients who did not meet response criterion were eligible for inclusion in a 6-week treatment with escitalopram (ESC). Instead VEN treatment was continued in patients who were classified as responders. In the current study we focused on phase A and assessed remission (MADRS total score < 10) at week 6 and two outcome categories not analyzed before (Souery et al., 2015): 1) Very early improvement (VEI): a > 20% decrease in MADRS after 2 weeks of VEN treatment; 2) Early improvement (EI): a > 30% decrease in MADRS score after 4 weeks of VEN treatment. A threshold of 20% was used in various studies to define a significant improvement of depressive symptoms within 2 weeks of treatment (Lam, 2012). 30% is a more conservative threshold, suggested as an optimal cut-off value for the assessment of depression improvement after 4 weeks of treatment (Gilaberte et al., 2013). The characteristics of individuals who remitted at the end of 6-week VEN trial and of those not remitting are reported in Table 2. We analyzed such differences by multiple logistic regression (OR 95% CI). We estimated the prevalence of EI/VEI and analyzed their association with the

likelihood of remission ($\text{Chi}^2 p < 0.01$). We tested EI and VEI as predictors of remission status by estimating the following parameters: true positive number (TP); false positive number (FP); true negative number (TN); false negative number (FN); positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity (95% CI) (MedCalc Statistical Software version 17 – MedCalc Software bvba, Ostend, Belgium. www.medcalc.org). We obtained receiver operating characteristic (ROC) curves for each test (VEI/EI) and estimated areas under curve (AUC) (MedCalc Statistical Software) (Figs. 1 and 2).

2.3. Simulation of switching approaches

We built a theoretical decision-analytic model to simulate switch from VEN to ESC at different time points and by symptom thresholds not considered in the PTRSSUAD study (Souery et al., 2015). The model comprised a pre-switch and a post-switch phase and it consisted of three treatment algorithms:

2.3.1. Algorithm A

VEN was administered to the whole sample until week 6. At this point, patients who achieved remission continued VEN until study endpoint (week 12). Instead individuals who failed to remit at clinical assessment point were switched to ESC and treated for further 6 weeks. This algorithm reflected the design of the PTRSSUAD study (Souery et al., 2015) (Fig. 3) except for decision of switching, here based on the lack of remission instead of simply response.

2.3.2. Algorithm B

We hypothesized that VEN was administered to the whole sample for 2 weeks, then patients who failed to achieve a significant improvement of at least 20% of MADRS in this early stage of treatment were switched to ESC. Instead, if there was a very early improvement (VEI; see above), VEN was continued until week 6. Then, if there was no remission, VEN was replaced by ESC.

2.3.3. Algorithm C

In this modified version of Algorithm B, VEN was replaced by ESC in patients without a > 30% improvement of MADRS after 4 weeks of VEN administration (no EI group) and in those who did not remit after 6 weeks. Titration and mean doses of VEN and ESC were based on the PTRSSUAD study (Souery et al., 2015). The study analyzed the results of a simulation, to alternatively apply each of the three algorithms to research sample (see Section 2.2), by estimating the number of treated remitters (TR), who completed venlafaxine or escitalopram trial having a MADRS score < 10 at endpoint, and of those who were still depressed (MADRS > 10) despite treatment (treated non-remitters, TNR). These categories were associated with utility scores of 0.90 and 0.40 respectively (Revicki and Wood, 1998), which reflected the amount of quality of life attached to them. Treatment related side effects were associated with a negative score of 0.04 (Revicki and Wood, 1998), so adjusted

Table 2
Characteristics of TRD sample. Remitter vs non-remitter groups.

	Remitters (N = 100)	Non-remitters (N = 307)	p [*]	O.R (95%CI) ^{**}
Age	48.8 ± 12.6	46.6 ± 12.5	0.130	1.02 (0.98–1.05)
Gender			0.313	1.31 (0.66–2.62)
– Men	0.30	0.36		
– Women	0.70	0.64		
Number of episodes	3.67 ± 3.15	3.64 ± 2.92	0.943	1.02 (0.90–1.15)
Duration of current episode (days)	135.5 ± 145.7	178.3 ± 204.2	0.030	0.99 (0.98–1.00)
Age at first episode	33.4 ± 14.6	31.4 ± 13.1	0.219	0.99 (0.96–1.03)
Baseline MADRS	29.1 ± 4.95	32.3 ± 6.42	< 0.001	0.92 (0.86–0.98)
Very early improvement (VEI)	0.56	0.22	< 0.001	1.01 (0.50–2.05)
Early improvement (EI)	0.88	0.38	< 0.001	21.72 (8.65–54.50)
Venlafaxine dose (mg)	156.3 ± 40.4	170.1 ± 42.1	0.006	0.99 (0.98–1.00)

All patients were of Caucasian origin. Venlafaxine dose was measured after 4 weeks.

* Univariate analysis: significant p < 0.01.

** Multiple logistic regression: overall model fit p < 0.00001.

utility scores were 0.86 and 0.36. Drop out patients (D) were no more experiencing side effects due to antidepressant medications. We assumed that 25% of these patients dropped out from treatment after achieving remission and 75% were not remitting as reported in previous publications (Olgiati et al., 2013; Serretti et al., 2011). Finally, the utility score of drop out cases was estimated to be 0.53. A Markov model was used to estimate TR, TNR and D at two time points (weeks 6

and 12), and quality-adjusted life years (QALYs). Sensitivity analysis was performed to test the robustness of our predictions against the variation of key parameters: probability of remission with VEN; probability of remission with ESC; probability of remission without treatment; drop out probabilities (weeks 6 and 12). These parameters were assumed to have beta-distribution (Andronis et al., 2009). Baseline values, which were drawn from the PTRSSUAD sample (by combining

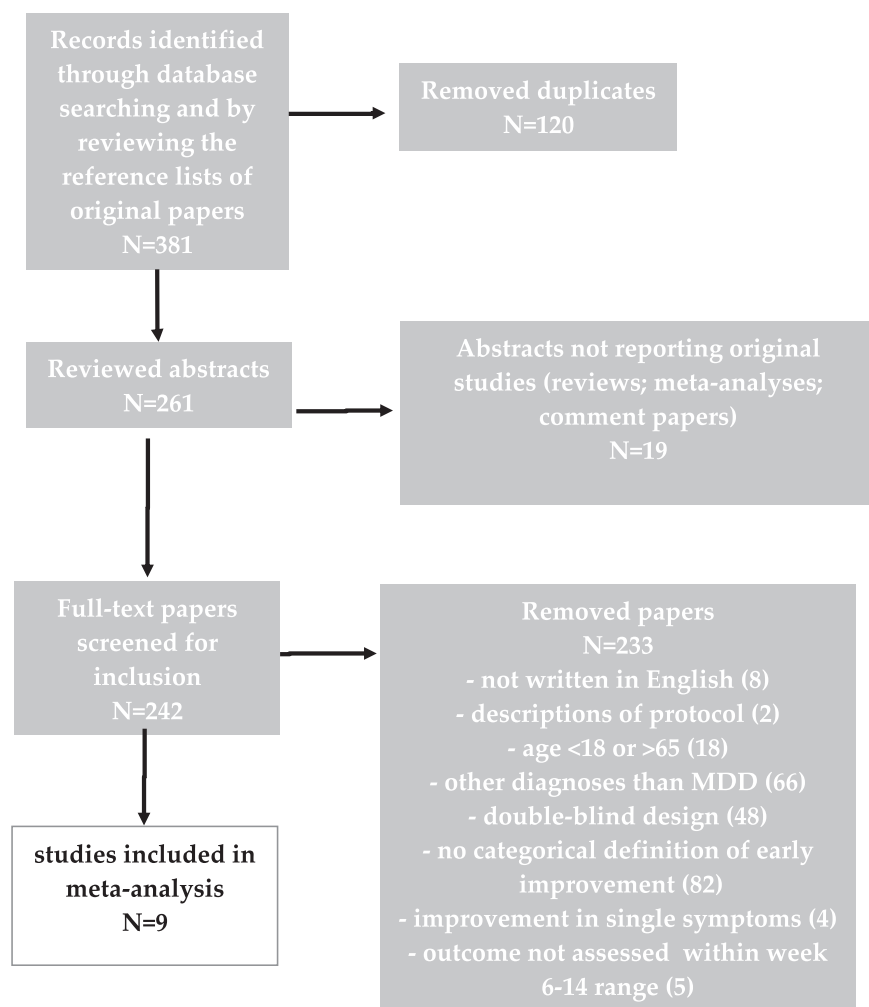
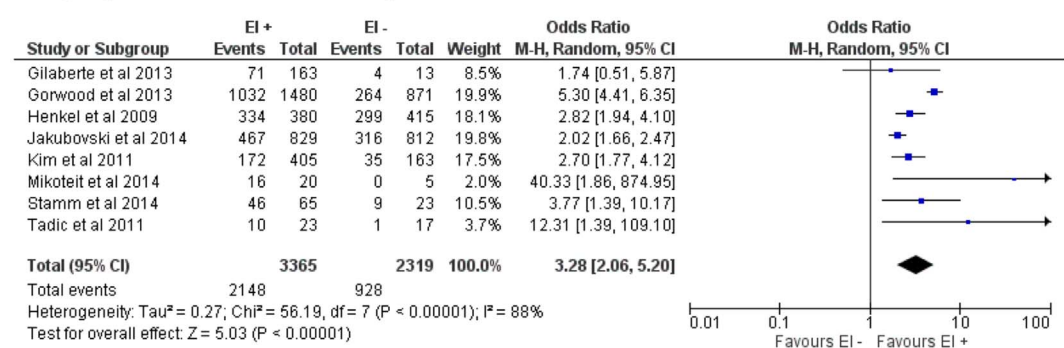


Fig. 1. Selection of papers included in meta-analysis (flow diagram).

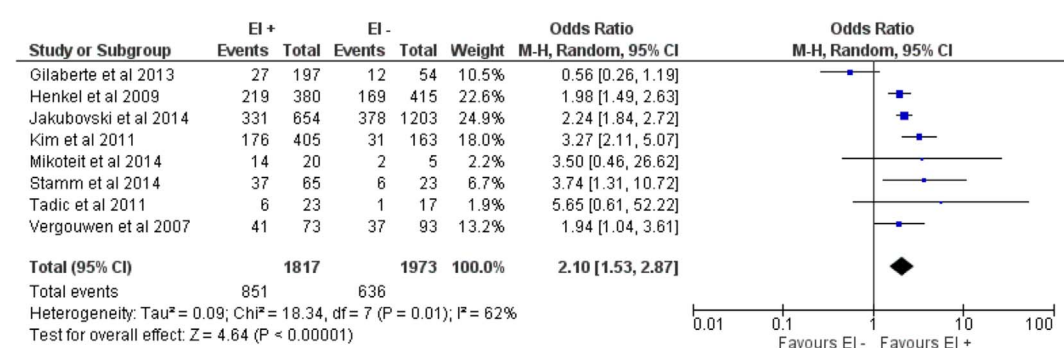
All studies were published from January 1st 2000 to June 30th 2017

a. Early improvement (1 – 4 weeks) vs response (6 – 12 weeks)



EI +: subjects with early improvement; EI-: subjects without early improvement. Early improvement (EI): >20% and <50% decrease in HAMD-17 and QIDS. Events: cases of response (≥50% decrease in HAMD or QIDS)

b. Early improvement (weeks 1 - 4) vs remission (weeks 6 – 14).



EI +: subjects with early improvement; EI-: subjects without early improvement. Early improvement (EI): >20% and <50% decrease in HAMD-17 and QIDS. Events: cases of remission (HAMD<7; QIDS<6)

Fig. 2. Results of meta-analysis.

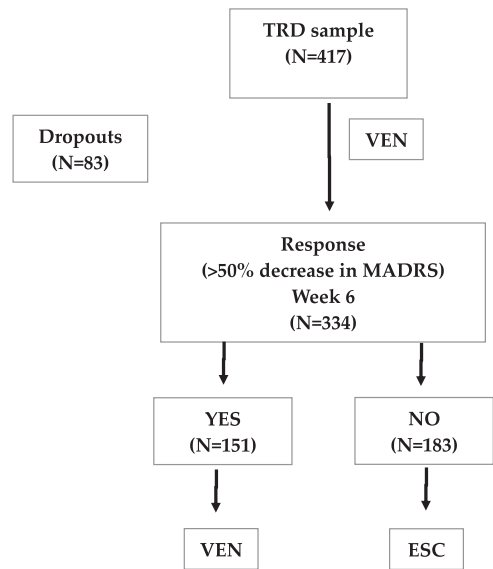


Fig. 3. PTRSSUAD study design.

the results of the predicting power of EI/VEI estimated in this study and the effect of continuing VEN or switching to ESC as reported in previous publications (Souery et al., 2015)) and literature sources (spontaneous remission rate: Posternak et al., 2003; utility scores: Revicki and Wood, 1998) as reported above, were assumed to be the means of distribution. The lower limit was set equal to 0.75 times the baseline value (Serretti

et al., 2011). The difference between the baseline value and the lower limit was estimated to be 1/3 the difference between the upper and lower limit (Golenko-Ginzburg, 1998).

3. Results

3.1. Meta-analysis

Three hundred and eighty-one records were identified through database searching and by reviewing the reference lists of original papers (see Fig. 1). After removing duplicates (N = 120), two hundred and sixty-one abstracts were reviewed. Nineteen abstracts were excluded because they did not report original studies but reviews, meta-analyses or comment papers. Eight papers were not analyzed because written in a different language from English and two only reported objectives and methods of study whereas results were not yet available. Two hundred and thirty-two studies were screened for the fulfilling of inclusion criteria and eventually ruled out due to the following reasons: in eighty-four studies samples were not eligible because of age < 18 or > 65 years (N = 18) or different diagnoses from MDD (N = 66); forty-eight studies were characterized by a double-blind design; in eighty-two studies there was no categorical definition of early improvement whereas four analyzed the improvement of single symptoms without providing an assessment of overall depressive symptomatology; in five studies response or remission rates were not assessed within week 6–14 range. Finally, nine studies (N = 6185) meeting eligibility criteria were included in meta-analysis (Table 1). Response was assessed in 5684 cases included in eight studies. In this sample, 3365 patients (59.2%) reported improvements (> 20% decrease in depression scores) in

weeks 1–4. As there was great heterogeneity across studies ($\text{Chi}^2 = 56.19$ $\text{df} = 7$ $p < 0.0001$; $I^2 = 88\%$), we used random-effects model to estimate the OR of the association between early improvement and response: 3.28 (95% C.I: 2.06–5.20) (Fig. 2a).

Remission was assessed in 3890 patients from eight studies, of whom 1917 (49.3%) met improvement definition. Heterogeneity across studies was moderate ($\text{Chi}^2 = 18.34$ $\text{df} = 7$ $p < 0.01$; $I^2 = 62\%$). Early improvement was associated with remission status: OR = 2.10 (1.53–2.87)(Fig. 2b).

3.2. Analysis of AD non-responder sample

AD non-responder sample comprised 417 patients with MDD aged 47.2 ± 12.6 years. Depression (MADRS) score at baseline was 31.4 ± 6.2 . 83 patients (19.9%) did not complete 6 week venlafaxine trial. In LOCF sample (inclusion of all patients with at least one post-baseline evaluation, $N = 407$) 100 patients (24.6%) achieved remission. 122 patients (29.9%) were found to have a very early improvement (VEI) after 2 weeks of treatment. An early improvement (EI) was reported in 205 patients (50.3%) after 4 weeks. Differences between remitter and non-remitter groups (LOCF) are reported in Table 2. Remitters were characterized by lower MADRS score at baseline ($p < 0.001$), higher venlafaxine dose on day 28 ($p = 0.006$), larger numbers of individuals with VEI ($\text{Chi}^2 = 40.5$; $p < 0.0001$) and EI ($\text{Chi}^2 = 113$; $p < 0.0001$). By performing multiple logistic regression analysis only baseline MADRS score (O.R = 0.86–0.98) and EI (O.R: 8.65–54.50) were associated with remission status. VEI was investigated as a predictor of remission. The predictive power of VEI was defined by the following parameters: TP = 43 (10.5%); FP = 44 (10.8%); TN = 197 (48.4%); FN = 40 (9.8%); sensitivity = 0.52 (0.40–0.63); specificity = 0.82 (0.76–0.86); PPV = 0.49 (0.41–0.58); NPV = 0.83 (0.79–0.86). EI was significantly associated with remission status. The number of positive and negative subjects were as follows: TP = 72 (17.6%); FP = 70 (17.2%); TN = 181 (42.3%); FN = 11 (2.3%). The predictive power of EI for remission was estimated as follows: sensitivity = 0.87 (0.77–0.93); specificity = 0.71 (0.66–0.77); PPV = 0.50 (0.45–0.56); NPV = 0.94 (0.90–0.97). We analyzed ROC curves for each definition of improvement (VEI/EI) and estimated their areas under curve. VEI: AUC = 0.67 (0.62–0.71) EI: AUC = 0.76 (0.71–0.80) (Table 3).

Table 3
Probabilities and utility scores.

	Baseline (SA range)	QALY gain (C–A)
<i>Probabilities (6 weeks)</i>		
remission on venlafaxine ^a	0.20 (0.15–0.30)	from 0.0022 to 0.0010
remission on escitalopram ^a	0.23 (0.17–0.34)	from 0.0010 to 0.0030
drop out (phase 1) ^a	0.18 (0.13–0.26)	from 0.0018 to 0.0020
drop out (phase 2) ^a	0.08 (0.06–0.12)	from 0.0019 to 0.0018
remission without treatment ^b	0.12 (0.09–0.18)	from 0.0014 to 0.0028
<i>Utility scores</i>		
Remission ^c	0.90 (0.67–1.00)	from 0.0010 to 0.0022
Lack of remission ^c	0.40 (0.30–0.60)	from 0.0022 to 0.0011
Side-effects ^c	0.04 (0.03–0.06)	from 0.0019 to 0.0020

Baseline values.

Sensitivity analysis (SA). Probabilities and utilities have beta distribution. Baseline value correspond to the mean of distribution. The lower (LL) and upper (UL) limits are estimated as follows: the LL is set equal to 0.75 times the baseline value. The difference between the baseline value and the LL is assumed to be 1/3 the difference between the UL and LL (Golenko-Ginzburg, 1998).

TRD: treatment-resistant depression.

^a Based on the PTRSSUAD study (Souery et al., 2015).

^b Based on literature (Posternak et al., 2006).

^c Based on literature (Revicki, and Wood, 1998).

3.3. Effects of switching simulations

Algorithm A. Remission and drop out probabilities were estimated from the PTRSSUAD study (Souery et al., 2015) Phase 1: all patients were treated with VEN for 6 weeks. Remission and drop out were 20.3% and 20.1% respectively. Phase 2: ESC administration to patients who had not remitted during VEN treatment (59.6%) was associated with 22.9% of remitters and 8% of drop out cases. Pooling the results of all treatment phases, cumulative remission and drop out rates were 33.7% and 24.8% respectively.

Algorithm B. It was hypothesized that early switch from VEN to ESC could increase the probability of achieving remission during the first treatment weeks. Thus, to estimate the remission rate within 6 weeks (phase 1), we pooled the number of true positives continuing VEN and of true negatives switched to ESC and then remitting. The therapeutic effect of any antidepressant reached its peak within four weeks of treatment. Therefore, the incremental effect of switching from VEN to ESC was entirely ascribed to phase 1 in Algorithm B. Phase 1: VEN was replaced by ESC in 197 true negative patients (48.4%), of whom 22.9% were estimated to remit. These patients were added to 43 true positive subjects (10.5%) who continued VEN. Based on these findings, overall remission rate was estimated to be 21.5% during phase 1. Phase 2: once the therapeutic effect of antidepressant change was no more expected, patients could continue to remit due to their spontaneous tendency to recover from depressive episode. This probability was estimated from literature sources (Posternak et al., 2006) and incorporated into the longitudinal model of illness time course. The probability of remitting of patients treated with ESC and drop out rates were estimated from the PTRSSUAD study (Souery et al., 2015). Remission rate was calculated as follows: A (FP $\times$ prob. of remitting by ESC treatment: $0.108 \times 0.229 = 0.024$) + B (FN $\times$ prob. of spontaneous remission during 6 weeks: $0.098 \times 0.12 = 0.011$) + C (TN $\times$ prob. of spontaneous remission during 6 weeks: $0.372 \times 0.12 = 0.044$): 7.9%. The cumulative rate of remission (phases 1 and 2) was estimated to be 29.4%.

Algorithm C. Since VEN was substituted by ESC after 4 weeks, the pharmacological effect of this substitution was expected to be detectable for 2 weeks within phase 1 and for subsequent weeks during phase 2. Therefore response to switch was ascribed 50% to phase 1% and 50% to phase 2. Phase 1: out of 172 true negative patients without EI (42.3%), in which VEN was replaced by ESC, 22.9% achieved remission as estimated from the PTRSSUAD study (Souery et al., 2015), half within week 6, the endpoint of phase 1. These subjects were added to 72 true positives (17.7%) who continued VEN treatment and remitted by week 6, thus leading to 22.7% of remitters by the end of phase 1. Phase 2: remission rate was calculated by the sum of A (FP $\times$ prob. of remission by ESC treatment: $0.172 \times 0.229 = 0.039$) + B (FN $\times$ prob. of spontaneous remission during 6 weeks: $0.023 \times 0.12 = 0.003$) + C (in TN subjects, who had already been on ESC for 2 weeks, the probability of achieving remission was 50% of overall remission rate by ESC treatment for 2 weeks (11.4%), then it decreased to 2% weekly due to spontaneous recovery for 4 subsequent weeks: $0.423 \times 0.194 = 0.082$). Based on these probabilities, phase 2 remission rate was 12.4%. The cumulative rate of remission (phases 1 and 2) was equal to 35.1%.

We compared early switch simulations (Algorithms B and C) with control scenario (Algorithm A).

1. Algorithm B (switch after 2 weeks of AD treatment), the worst outcome of our simulation, was associated with a decrease of 4.3% in the probability of achieving remission compared to Algorithm A. Algorithm B produced 0.162 QALYs, 0.002 less than Algorithm A (0.164 QALYs).
2. Algorithm C (switch after 4 weeks) led to an increase of 1.4% in remission rate compared to Algorithm A, corresponding to 0.002

QALYs (0.166 vs 0.164 by applying [Algorithm A](#)). In sensitivity analysis QALY gain was estimated to range from 0.001 to 0.003.

4. Discussion

4.1. Early improvement and remission. Meta-analysis

Our review focused on the association between a partial improvement of depressive symptoms in the first four weeks of AD treatment and outcome at 6–14 weeks. We included naturalistic studies in which patients and treatment conditions were considered to be more similar to clinical practice whereas double-blind randomized controlled trials were excluded. The O.R. values of meta-analytic sample were estimated to be 3.3 for response and 2.1 for remission. In another large study on inpatients treated with various AD medications, not included in this review because of their heterogeneous diagnostic profile, the most striking result, in line with ours, was that patients displaying an earlier onset of improvement within the first 2 weeks of AD treatment were at least 3 times more likely to become responders than late improvers ([Stassen et al., 2011](#)). Based on these findings early improvement should be positioned at the same level as other socio-demographic and clinical variables that have been pointed to as predictors of AD treatment outcome with O.R. values of 1.5–3.0 ([Souery et al., 2007](#); [Weinberger et al., 2008](#)). Similarly, the role of genetic predictors (e.g. 5-HTTLPR serotonin transporter gene promoter polymorphism) was supported by O.R. values of 1.5–2.5 ([Kato and Serretti, 2010](#); [Porcelli et al., 2012](#)). Previous studies reported a more straightforward association between early improvement and later complete response to AD treatment. In a meta-analysis of forty-one randomized controlled trials including 6500 patients, a 20% score reduction on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) within 2 weeks of antidepressant administration was found to predict later response and remission with high sensitivity (81–87%) and negative predictive values (82–100%) ([Szegedi et al., 2009](#)). In meta-analytic work conducted by [Wagner et al. \(2017\)](#), early improvers had a 8 fold higher likelihood to become responder and a 6 fold higher likelihood to be remitter compared to non-improvers. A possible explanation for these differences is due to the naturalistic context of studies included in our meta-analysis, in which environmental factors could delay the onset of AD effect. In the STAR*D study, for example, one third of responders did so only after 6 weeks of treatment ([Rush et al., 2006](#)). Another reason is the use of AD medications with a faster onset of therapeutic action such as mirtazapine ([Schatzberg et al., 2002](#); [Thompson, 2002](#)), that was taken by a large group of patients in [Szegedi et al. \(2009\)](#).

4.2. Early improvement as an outcome predictor in patients with prior lack of response to an AD

Although several models have been proposed to describe TRD, consensus is still needed on the criteria (i.e., dose, duration, compliance, number of trials required) used to define treatment response and resistance ([McIntyre et al., 2014](#)). A series of factors such as number of medications used, severity of depression and duration of presenting episode can be used to stage TRD and to predict treatment outcome ([Fekadu et al., 2009](#)). In the STAR*D study remission rate was 28–33% for level one and about 25% for level 2 ([Rush et al., 2006](#)). We analyzed patients with lack of response to one previous AD treatment, therefore comparable to those reported in STAR*D level 2, and similarly, one quarter achieved remission. In our sample the improvement of depressive symptoms could occur later than in depressed patients without TRD. This hypothesis was not corroborated by our results. In fact we found that more than 50% of patients showed an improvement of symptoms in the first four weeks of treatment and 29.9% by week 2. On the contrary there are suggestions that the prognostic significance of early improvement for later remission might be different in patients who failed to respond to previous AD treatments. In our sample,

a > 20% decrease in MADRS score within the first two weeks of treatment, defined as very early improvement (VEI), showed a poor performance as a predictor of remission (ROC curve analysis: AUC < 70), inferior to other studies not specific to TRD ([Henkel et al., 2009](#); [Gorwood et al., 2013](#)). Clinically, the usefulness of assessing the improvement of depressive symptoms in the first weeks of AD treatment is related to the generation of negative results. Indeed, subjects without early improvement are not likely to respond to ongoing AD treatment, therefore they may have a benefit from switching to another AD. Instead false negative patients could not become responder if the initial AD agent was changed earlier. In our sample false negative rate was 10% using VEI definition, although the most critical aspects were related low sensitivity and PPV, suggesting that other indicators are needed to classify a patient as a true responder to second-line treatment. Recently, reductions in depression score as early as weeks 1 and 2 were investigated as predictors of AD response in patients with TRD ([Bares et al., 2015](#)). In line with our findings, these definitions alone were not characterized by good prediction performances. In fact, it was necessary to combine a clinical definition of early improvement and neurophysiological reduction of theta wave concordance in prefrontal areas to achieve an adequate prediction power. We found that a more marked improvement of depressive symptoms (at least 30% of MADRS score) occurring after 4 weeks of treatment, usually referred as early improvement (EI), was a slightly better outcome predictor, with good properties as a screening test for ruling out the likelihood of response in a negative patient (sensitivity: 77–93%; NPV: 90–97%). The analysis of ROC curves showed that AUC was better when testing the week 4 improvement. This suggests that much longer waiting, for example 12 weeks as in the STAR*D study ([Rush et al., 2006](#)), may not be the best option.

4.3. Simulation of treatment switch

Our simulation took a further step by analyzing the results of a hypothetical change of AD treatment if there was no improvement at week 2 and 4 time thresholds. These scenarios were compared to control one in which AD switch was scheduled at week 6 in individuals without remission. Although there was a statistically significant correlation between symptom changes during the first two weeks of treatment and outcome at the end of the trial in our major depressive sample, a very early strategy of switching based on week 2 lack of improvement was inferior to control scenario. This approach was associated with a minimal increase in the probability of remitting during the first weeks of treatment: simulated remission rate was 21.5% at the end of phase 1, which was only slightly better than 20.3% of control scenario in which the same AD was maintained for 6 weeks. Conversely a lot of patients, with a slower onset of antidepressant effect, changed their treatment too early, before they could reach the time of responding. This caused a decrease in remission rate, about 4.3% in the whole study period. These findings are in line with our previous observation that a longer treatment is more effective in treatment resistant depression compared to early switch ([Souery et al., 2011](#)). In the current study switching to a new antidepressant after four weeks of no adequate response was associated with a modest clinical benefit: remission rate was increased by 2.4% after 6 weeks of treatment whereas incremental rate was 1.4% at study endpoint. This led to a modest increase of 0.002 QALYs in cumulative period. Sensitivity analysis confirmed these results once controlling for expected variations of remission and drop out probabilities. Other studies also suggest that the strategy of early switch might have a limited clinical impact. In a sample of major depressed patients who had no or minimal improvement after four weeks on escitalopram, this SSRI was replaced by duloxetine or it was administered for four weeks more, then patients without response were switched to duloxetine. Early switch solution was associated with a greater remission rate, but the difference from normal switch approach was only marginally significant ([Romera et al.,](#)

2012). In another study, patients with severe major depression who failed to respond to 2 weeks of escitalopram 10 mg/day were randomized to 8 weeks of double-blind treatment with a higher dose of escitalopram (20 mg/day) or duloxetine. Significantly more patients continuing escitalopram achieved remission by week 8 than those switched to duloxetine (Bose et al., 2012). This study is therefore confirming the poor effectiveness of switching antidepressant therapy after few weeks of treatment. In the EMC-trial, early medication change after 14 days of treatment was not more effective than control intervention in which initial antidepressant was continued for 28 days (Tadic et al., 2016). The only significant finding favoring an approach of early switch is derived from a small study (Nakajima et al., 2011). A slow response to treatment is critical in patients who have already had failures, because it could increase suffering, morbidity and the risk for discontinuation. A 4-week lag phase to ascertain the lack of early improvement and to switch to a different AD might be too long. At present, a convincing body of evidence exists for the augmentation of antidepressants with second-generation antipsychotic drugs and lithium (Dold and Kasper, 2017). Recent findings suggest also a promising use of ketamine (Papadimitropoulou et al., 2017), although they are only preliminary and need to be replicated in larger samples.

The nature of TRD is complex. Based on current knowledge of this phenomenon, it cannot be excluded that TRD and treatment-responsive depression are characterized by different biological backgrounds, thus the two conditions could not be treatable using the same drug classes. TRD might not be a homogeneous entity but a broadly defined category pooling pathophysiologically heterogeneous disorders. This suggests that some patients might respond late and maintain longer their response whereas others might not respond at all but they need a different treatment approach.

4.4. Strength and limitations of the study

In our meta-analysis sample size varied considerably across studies as well as the length of treatments. There was also a great heterogeneity in medications used, AD monotherapy or combined treatments with two or more ADs, antipsychotics and mood stabilizers. These characteristics emphasize similarities with clinical practice but there are also confounding effects due to different treatments. Therefore larger samples are needed to stratify by homogeneous treatment groups on which to perform separated analyses. An important feature of our model of TRD, more adherent to real life but seldom considered in AD trials, was to include the spontaneous tendency of depressive episode towards remission. Kraepelin speculated that, left untreated, major depressive episodes would tend to last about 6–8 months in most cases (Kraepelin, 1886). This would indicate a probability of remitting of approximately 2.5% per week. Subsequent reports have generally supported this assertion though these studies were largely based on clinical observation and retrospective analyses (Posternak and Miller, 2001). Only few studies used more rigorous methodologies. Posternak et al. (2006) analyzed 130 patients who were not receiving any somatic treatment for at least four weeks following the onset of a recurrence of major depressive disorder (Posternak et al., 2006). This sample was similar to our one because we included most patients with recurrent depression. Forty-six subjects ultimately obtained an antidepressant after a median time of 62 weeks. In untreated depression, the cumulative recovery rates were 37% after three months, 52% after six months and 70% after one year. Based on these findings in our sample, with a mean length of intake episode of about 5 months, the weekly spontaneous hypothetical remission rate was about 2%. Sensitivity analysis was performed on a relatively smooth slope of probability distribution, with a minimum value of 1.5% per week and a maximum of 3.0%. This variation range included most findings reported in the literature (Posternak and Miller, 2001). Our research sample was collected to ascertain the clinical effectiveness of switching to a third antidepressant in those patients who failed to respond to a second one,

and some characteristics of the original study, naturalistic, non-randomized, open-label and without a control arm, may limit the generalization of results to other samples. We highlight other important limitations. The study was not originally designed to investigate the feasibility of changing antidepressant treatment earlier in individuals who had not at least a partial improvement. To perform this analysis, we implemented a decision-analytic model and made a simulation. Nevertheless a large number of hypothetical data and assumptions were used to build the model whereas only real data are useful to corroborate or reject a treatment strategy. The study involved a sample with resistant depression to a prior AD treated in tertiary specialized centers. This disorder might thus require a longer treatment before achieving an initial improvement (Fekadu et al., 2009). We used an algorithm for switching from venlafaxine to escitalopram. In clinical practice individuals with resistant depression and at least two prior treatment failures are often treated by tricyclic antidepressants as mirrored by the STAR*D study (Fava et al., 2006). Finally, a range of different strategies other than switching or continuing are possible (Kato and Chang, 2013; Kato et al., 2017; Montgomery et al., 2014), but the choice of the best strategy should be performed on the basis of all features of the subject according to the recent direction of individualized treatment (Sankar and Parker, 2016).

4.5. Conclusion

A growing body of evidence suggests that a substantial improvement in depressive symptoms might occur as early as 2 weeks after intake into AD treatment or with a small delay within four treatment weeks. Although this improvement has been related to sustained remission in randomized controlled trials and naturalistic samples, as confirmed by our meta-analysis, the benefit to perform AD treatment change early in TRD subjects it is not consistently supported by available literature (Dold and Kasper, 2017). TRD is a complex condition in which the number of medications used is important for staging (Fekadu et al., 2009) and it is associated with a lower probability of achieving remission (Rush et al., 2006). In resistant patients, with only one previous unsuccessful AD treatment, an improvement in depressive symptoms as early as 2 weeks after the introduction of a second AD is not a good outcome predictor. A small but consistent increase in the probability of achieving remission and quality of life is only estimated if switch to the new AD is implemented after 4 weeks of no adequate response to the previous one. Resistant depression treatment should therefore be continued for 4–6 weeks regardless of the initial course of symptoms and early signs of no response. These findings, derived from a theoretical model, should be replicated in empirical studies. Due to the complexity of TRD, which is most likely associated with multiple biological mechanisms, a variety of treatment options should be available for patients who had not responded to a first AD medication.

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