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Editorial

Treatment-resistant depression: a challenge for future research

The term treatment-resistant depression (TRD) was introduced in 1974 and since then it has been a topic for different publications and research strategies (1,2). Unfortunately, different definitions of TRD are used. On the basis of the literature available, it is evident that the following four categories need to be distinguished (Table 1).

These definitions have practical as well as research implications, because quite often inadequate response, non-response treatment, treatment refractory and chronic depression are mixed up; moreover, needless to say, different results can be expected when these patients are summarised as a group. The Sequenced Treatment Alternatives to Relieve Depression Study might be one of these examples, as the patients included in this trial have had a mean of over 100 weeks of depression and therefore can be regarded as chronically depressive. This explains the low response rate in this trial that cannot be projected to the whole population of depression.

Interestingly, there is as yet no treatment indication for non-response to treatment; however, health regulatory authorities in Europe (EMA) and in the United States (FDA) granted indication for inadequate response to quetiapine in Europe, and quetiapine, olanzapine and aripiprazole in the United States. The difference between the two health regulatory authorities is that the EMA also requires long-term studies, which were not available for apiprazole and olanzapine and only for quetiapine. Nevertheless, clinicians use atypical antipsychotics for non-response to treatment, treatment refractory and chronic depression as recently depicted in the publication by Konstantinidis et al. (2013) (3) in Austria, Germany and Switzerland.

Table 1. Definitions of treatment response

Inadequate response: Insufficient response to one adequate therapy
Treatment non-response: Insufficient response to two adequate therapies
Treatment refractory: Insufficient response to 'more' treatment options
Chronic depression: Depression over 2 years

The European Group of the Study of Treatment-Resistant Depression (GSRD) has initiated and coordinated collaborative research programmes on TRD, in which several European centres have been involved at different stages from the following countries (2,4): Austria, Belgium, France, Greece, Israel and Italy.

In a recent review, the GSRD Group published the clinical and genetic findings (2). It was evident that the clinical characteristics outweighed, so far, the genetic variables in the sense that treatment resistance (defined as insufficient response to two adequate therapies) was significantly apparent in more patients and who were comorbid with anxiety disorders (4). The statistically significant differences can be depicted from Table 2.

Furthermore, this group obtained evidence in retrospective and prospective evaluation that switching the mechanism of action does not benefit the patient (6), a finding that is supported by a meta-analysis by

Table 2. Prediction of treatment resistance in unipolar and bipolar depression calculated by logistic regression analysis on data published by Souery et al. and Mendlewicz et al. (4,5)

Clinical factors	TRD ($N = 702$)	TRBD ($N = 261$)
Non-response to the first antidepressants received lifetime	$p = 0.019$	
Comorbid anxiety disorder	$p < 0.01$	
Comorbid panic disorder	$p < 0.01$	
Social phobia	$p = 0.008$	$p = 0.02$
Current suicidal risk	$p = 0.001$	$p = 0.02$
Melancholic features	$p = 0.018$	$p = 0.01$
Severity of current episode	$p = 0.001$	$p = 0.01$
Number of hospitalisations >1	$p = 0.003$	
Recurrent episodes vs. single episode	$p = 0.009$	
Early age at onset (<18 years)	$p = 0.049$	
Personality disorder (DSM-IV criteria)	$p = 0.049$	

TRD, treatment-resistant depression; TRBD, treatment-resistant bipolar depression.

Table 3. Treatment options for therapy-resistant depression

Optimising treatment
Duration
Dosing
Add-on
Atypical antipsychotics
Antidepressants
Lithium
T3
Non-pharmacological Rx
Switch classes
If side effects
If no effects at all

Papakostas et al. (7) For clinical practice, it is apparent that augmentation with another agent, for instance, atypical antipsychotics, lithium or T3, or the combination with another antidepressant (e.g. mirtazapine or trazodone) might provide a better option (8) (Table 3).

With regard to the candidate gene studies, it was evident that the metabolism status, according to the cytrochrome P450 gene polymorphism, may not be helpful to predict response and remission rates to antidepressants (9). However, a significant association with major depression and antidepressant treatment response was found in this cohort for COMT single nucleotide polymorphisms (10,11). Specifically, the impact of COMT on suicidal behaviour was interesting as it depicted a significant association with suicide risk in major depressive disorder patients not responding to antidepressant treatment (12). Other significant associations with treatment response phenotypes were found for BDNF, 5HTR2A and CREP1.

As depicted in Table 2, a stepwise approach for treatment of depression can be recommended (8) that encompasses, first, optimising treatment, second, add-on treatment, and third, switching classes, specifically if side effects are evident or if there is no effect at all. The question as to which add-on medication should be used is dependent on a stratified approach, and it is apparent that these data are available for the addition of atypical antipsychotics within the group of antidepressants as add-on treatment of mirtazapine to selective serotonin reuptake inhibitors (followed by lithium and then T3). The question of non-pharmacological treatment such as psychotherapy or biologically founded non-psychiatric treatment (e.g. sleep deprivation, light therapy or electroconvulsive treatment) can be added at any stage based on the specific needs of the patient.

Although the genetic characterisation of the phenotype of TRD until now explains only 2–5% of the variance (13), and is therefore not helpful for clinical practice and outweighed by the clinical evidence of comorbidity of depression and anxiety disorders in unipolar as well as bipolar disorder, it is necessary to study the characterisation of the genetic subphenotype of TRD to provide further insights into the disease process. A more refined methodology such as the new generation exome and full genome-sequencing and genome-wide pathway analysis promises to be helpful for prediction and prevention of depression together with other psychiatric diseases and to identify molecular targets for new generations of psychotropic medication (14).

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