

EDITORIAL

Editorial for Treatment-Resistant Depression (TRD)

Siegfried Kasper, Alan Frazer

Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria (Dr Kasper);
Department of Pharmacology, UT Health San Antonio, Texas (Dr Frazer).

Correspondence: Siegfried Kasper, MD, Professor and Chair, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria (sci-genpsy@meduniwien.ac.at).

Major depressive disorder (MDD) is one of the most frequent diseases worldwide and ranks fourth in the leading courses of the global disease burden (WHO, 2001). Antidepressants have been studied thoroughly over the past 3 decades and represent now a well-established and very effective treatment in the pharmacotherapy of MDD (Cipriani et al., 2018). Despite this, up to 60% of MDD patients do not respond sufficiently to the initial antidepressant treatment (Dold and Kasper, 2017; Souery et al., 2006). To tackle this topic, a specific, thematic meeting of the International College of Neuropsychopharmacology in Prague in 2017 focused on the diagnosis, epidemiology, and underlying biological mechanisms as well as new treatment modalities for treatment-resistant depression. The main papers of this conference are summarized in this special issue.

The impact and concept of treatment-resistant depression is summarized by Demyttenaere and Van Duppen (Demyttenaere and Van Duppen, 2018) in this issue outlining that there is a categorical as well as a dimensional approach and additionally also divergence between diagnostic criteria and the items in the assessment scales of depression. The colleagues indicate that there might be a substantial influence of patients' characteristics dramatically impacting the outcome based on the so-called pseudo-resistance. Furthermore, the authors conclude that the impact and burden of MDD on treatment-resistant depression (TRD) are out of scale and influence strongly the economic situation; they also indicate that TRD is often associated with suicidality and with nonsuicidal mortality and even may result in a request for assisted dying in some countries, where this is unfortunately possible.

The underlying genetics of TRD are reviewed and an outline for future perspectives is given from the European Group for the Study of Resistant Depression (GSRD), which is working not only on psychopathological and disease characteristics but also on genetic and therapeutic areas in this issue (Fabbri et al., 2018). In the review, the genetic studies of TRD including data from candidate genes studies as well as genome-wide association studies are summarized, limitations of these approaches are discussed,

and suggestions to improve the design of future studies are provided. The review indicates that improvement is possible if aggregated tests (e.g., pathway analysis, polygenic risk scores), possibly using variant/gene prioritization criteria, increase in the covering of genetic variants and clinical-demographic predictors of TRD are incorporated in future pharmacogenomic studies. From this overview, it is evident that there are no recommended genetic biomarkers as yet to predict the risk of TRD or to guide treatment choice in TRD patients. However, clinical guidelines such as the [Clinical Pharmacogenetics Implementation Consortium \(2014\)](#) recommend that cytochrome functional genotypes are considered for some antidepressant treatments. It is evident based on this knowledge that genetic testing of polymorphisms in 2 genes (CYP2D6 und CYP2C19) may be helpful in some patients with TRD treated with drugs metabolized by these cytochromes in order to exclude a major metabolic alteration.

The Vienna group headed by Lanzenberger and Kasper, (Höflich et al., 2018) embarks on the mechanism of reward, anhedonia, and depression in the framework of TRD and summarizes both animal and human data to depict the function of networks encoding for reward and substrates of anhedonia on a network level. Based on the data provided, it is evident that the refinement of methodological approaches needs to include measurements of anhedonia in psychiatric disorders to improve the relevance of targeting this phenotype for a successful psychiatric treatment.

The NIH-group led by Zarate (Kadriu et al., 2019) in this issue summarize the relevance of the glutamatergic system to develop rapid-acting antidepressant treatments and outline that traditional monoaminergic hypotheses have largely fallen short in their ability to provide a complete picture of MDD. However, based on the summary provided, the conclusion of a dysfunctional glutamatergic neurotransmission may give a clue for better understanding the underlying patterns of pathophysiology in MDD. Glutamatergic modulators have been demonstrated to elicit fast-acting, robust, and relatively sustained antidepressant as well as antisuicidal and antianhedonic

effects in patients with TRD. It is evident that clinical studies have prompted tremendous interest in treatment but also understanding the mechanism of action of this glutamatergic approach. The authors summarize that not only ketamine, but also other potentially novel glutamate-based treatments including NMDAR-antagonists, glycine binding site ligands, metabotropic glutamate receptor modulators, and other glutamatergic modulators are being studied in basic science, and some of them are already in clinical trials and promise therefore a better management of our TRD patients in the future.

Although all of these papers use the abbreviation “TRD” for treatment-resistant depression, we should be aware that this definition is very likely not welcomed by the patients and the nonpsychiatric community. We should be aware of other misleading and possibly discriminating wordings used in psychiatry like “atypical antipsychotic” for treatment augmentation of depression as well as “atypical antipsychotic” for treatment of schizophrenia. A staging model for different disease stages, a system that is also performed in internal medicine, would be more applicable in the sense that patients nonresponding to the first treatment could be termed as stage 1 (e.g., insufficient response), not responding to 2 trials could be called stage 2 (e.g., treatment resistant), and thereafter stage 3 and stage 4 would be the further clinical applicable connotations. Quite often the term treatment refractory is also used, which could mean that patients are not responding to at least 3 psychopharmacological trials (stage 3) probably also including electroconvulsive therapy, which could be called stage 4. Based on these stages, future treatments could be applied and the neutral wording of stages will not discriminate our psychiatric patients and represents psychiatric diseases within medical disciplines.

References

- Bartova L, Dold M, Kautzky A, Serretti A, Souery D, Mendlewicz J, Zohar J, Montgomery S, Schosser A, Kasper S (2019) Results of the European Group for the study of resistant depression (GSRD)—basis for further research and clinical practice. *World J Biol Psychiatry* (submitted)
- Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 391:1357–1366.
- Clinical Pharmacogenetics Implementation Consortium (2014) CPIC Guidelines. Available at: <https://cpicpgx.org/guidelines/>. Accessed November 27, 2017.
- Demyttenaere K, Van Duppen Z (2018) The impact of (the Concept of) treatment-resistant depression: an opinion review. *Int J Neuropsychopharmacol* doi: 10.1093/ijnp/pyy052.
- Dold M, Kasper S (2017) Evidence-based pharmacotherapy of treatment-resistant unipolar depression. *Int J Psychiatry Clin Pract* 21:13–23.
- Fabbri C, Corponi F, Souery D, Kasper S, Montgomery S, Zohar J, Rujescu D, Mendlewicz J, Serretti A (2018) The genetics of treatment-resistant depression: a critical review and future perspectives. *Int J Neuropsychopharmacol* doi: 10.1093/ijnp/pyy024.
- Höflich A, Michenthaler P, Kasper S, Lanzenberger R (2018) Circuit mechanisms of reward, anhedonia and depression. *Int J Neuropsychopharmacol* doi: 10.1093/ijnp/pyy081.
- Kadriu B, Musazzi L, Henter ID, Graves M, Popoli M, Zarate CA (2019) Targeting the glutamatergic system to develop novel rapid-acting antidepressant treatments. *Int J Neuropsychopharmacol* (submitted)
- Souery D, Papakostas GI, Trivedi MH (2006) Treatment-resistant depression. *J Clin Psychiatry* 67(Suppl 6):16–22.
- WHO (2001) World Health Report 2001. Mental health - new understanding, new hopeGenf.