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Consensus Statement

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STATE OF THE ART 2022

Treatment-resistant Depression: Diagnosis and Treatment

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Foreword of the Editors

Non-response to antidepressant therapy is a relevant clinical problem and a therapeutic challenge for every treating physician.

Currently, a distinction is made between different forms of response to antidepressant therapy. In addition to an insufficient response to therapy, a therapy-resistant depression and subsequently a therapy-refractory or chronic depression can be distinguished.

In the present consensus statement the different terminologies are presented and in this context the role of the biological basis is also discussed. Special attention is given to the therapeutic options in both drug and non-drug treatment of treatment-resistant depression. Therapy of this complex condition can be accomplished in a variety of ways, with algorithms providing guidance and non-pharmacologic therapeutic modalities also having a fixed place. The open discussion between doctor and patient is particularly important – not least in order to maintain adherence to therapy. Special attention is paid to the particularities of childhood, adolescence and the elderly in two further chapters.

We hope that the present consensus statement will enrich your daily work and that the thoughts and recommendations it raises will support your work. We look forward to receiving your feedback.

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Content

Treatment-resistant depression: Diagnosis and treatment

1 Introduction

The term "depression" does not actually represent a diagnosis, but refers to a syndrome that can occur within the context of many different psychiatric diagnoses - depressive adjustment disorder, organic depressive disorder, substance-induced depressive disorder, unipolar or bipolar affective disorder, and others.

Depressive episodes in the context of affective disorders in the majority of cases are well treatable pharmacologically as well as with non-pharmacological strategies. Therefore, in many cases the first antidepressant can at least largely achieve a remission of the symptoms.

Depressive episodes that do not or do not adequately respond to therapeutic interventions often cause a significant prolongation of suffering for patients and pose a number of challenges for treatment providers. If at least two attempts of medical treatment of sufficient duration and dosage fail, we speak of "treatment-resistant depression" (TRD). In the literature, the term "difficult to treat depression" has also been introduced in this context (McAllister et al. 2020). In addition, other terms exist such as "treatment-refractory depression" or "chronic" or "chronified depression", which should be distinguished from TRD (Table 1).

The efficacy of antidepressant therapy is determined by a variety of factors that may be based on the patient being treated, the pharmacon, and the physician mediating the relationship between the two, and may be of pharmacodynamic, pharmacokinetic, and psychological nature. Sometimes it is not the right substance, sometimes a dosing issue, sometimes an incomplete diagnosis (e. g. somatic and/or psychiatric comorbidities, neurotic factors), sometimes a conscious or even unconscious resistance of the patient.

With new treatment options now available, such as augmentation of existing antidepressant therapy with new-generation antipsychotics or add-on therapy with esketamine nasal spray, it is not surprising that the characteristic of TRD has recently received a great deal of interest in the international psychiatric societies. This is reflected, for example, in the current number of over 1200 entries in a PubMed search using the term "treatment-resistant depression [title]".

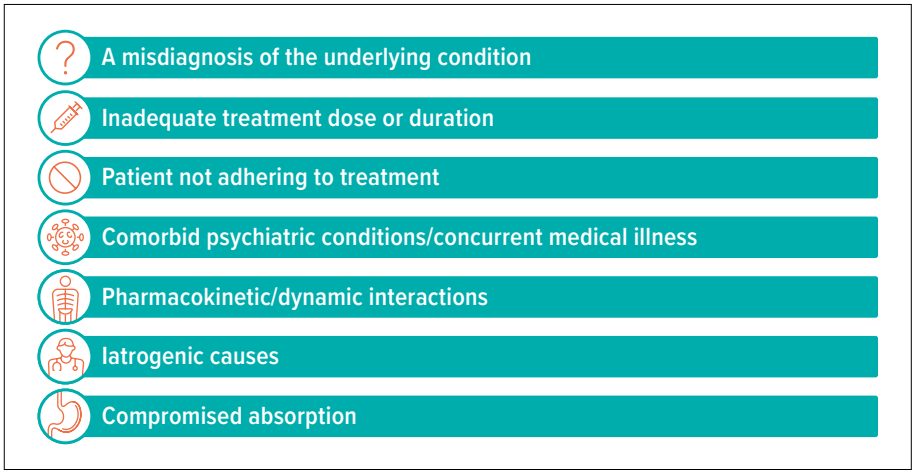

Figure 1: Potential causes of non-response or poor response to the treatment (pseudo-therapy-resistance) (according to Malhi and Bell 2020)

This consensus statement is intended to shed light on the understanding of TRD as well as its multiple therapeutic strategies in a condensed and practical manner.

2 Definitions

An inadequate response to initial antidepressant medication is common and affects around 60 % of all patients suffering from depression (Dold and Kasper 2017). However, this does not mean that TRD is actually present in the specific case, especially since a lack of treatment success can also be the result of so-called "pseudo-therapy-resistance" (Dold and Kasper 2017; Figure 1).

Pseudo-therapy-resistance is the term used when a lack of treatment success is caused by a (still) too short treatment duration or an insufficient dosage of the medication used. Furthermore, lack of treatment adherence, individual differences in metabolism (resulting in too low plasma levels of the active substances used), adverse drug reactions (ADRs), psychiatric and/or somatic comorbidities as well as psychosocial factors can be reasons for pseudo-therapy-resistance. Detailed psychiatric exploration and examination can reveal these factors and should therefore precede the beginning of any drug therapy.

The determination of drug levels in the blood (therapeutic drug monitoring, TDM) (Hiemke et al. 2018) allows statements to be made about the metabolism of the drugs used as well as conclusions to be drawn about enzyme variants (especially in the cytochrome P450 enzyme system of the liver), which can cause too high or too low plasma levels.

After exclusion of pseudo-therapy-resistance, the insufficient therapy response should be defined and quantified precisely. How this can be done in practice and which forms of insufficient therapy response can be distinguished was described

in 2013 (Kasper and Akimova 2013). Four terms were considered relevant (Table 1):

- Inadequate response

It occurs when a patient responds inadequately to the initial antidepressant therapy (partial remission). Adequate antidepressant therapy is given if the daily dose of the prescribed antidepressant is sufficient and the duration of treatment lasts at least four weeks.

- Treatment-resistant depression

It is defined by an inadequate response to two adequate antidepressant therapies with antidepressants of the same or different substance classes.

- Therapy-refractory depression

It exists when a patient responds inadequately to several different adequate antidepressant therapy options, including electroconvulsive therapy (ECT).

- Chronic depression

It exists when a patient has been suffering from a depressive episode for at least two years despite adequate therapeutic interventions. The symptoms of major depression must be present for at least half of all days.

A further diagnostic differentiation is possible and useful. Distinctions are: dysthymia (at least two years of mild to moderate depressive symptoms), double depression (dysthymia with additional depressive episodes), chronic major depressive disorder (criteria of a major depressive episode are consistently met over two years). Recurrent major depressive episodes without complete remission are also considered as chronic depression. The precise delineation of the aforementioned forms of depression is not only of academic but also of high practical relevance, since it is the prerequisite for the targeted use of currently available treatment options and thus for individualized therapy. In practice, however, the term "treatment-resistant depression" is often used as a synonym for all the above-mentioned clinical conditions.

Response can be defined using validated scores, as required by the criteria for treatment response established by international psychiatric societies such as the World Federation of Societies of Biological Psychiatry (WFSBP) (Bauer et al. 2017). The Montgomery-Åsberg Depression Scale (MADRS) (Montgomery and Åsberg 1979) and/or the Hamilton Depression Scale (HAMD) (Hamilton 1960) can be used: Remission is defined here by achieving a HAMD total score of ≤ 7. Response is defined as reduction in symptom severity of ≥ 50%, and partial response as reduction in depressive symptomatology of 26-49%. Symptom reduction of ≤ 25% is classified as non-response.

Generally, the term "treatment resistance" is now used after the failure of two adequate treatment attempts, regardless of the mode of action of the medication used (GSRD; Souery et al. 2011, Bartova et al. 2019).

Thus, older definitions of treatment resistance, which presupposed failed medication attempts with antidepressants from different substance classes (Thase and Rush 1997), implying an escalation of drug therapy based on the differing efficacy of different substance classes (Thase and Rush 1997) were abandoned. For example, according to Thase and Rush, monoamine oxidase inhibitors (MAO-I) should in principle be more effective than tricyclic antidepressants, which in turn should be more effective than selective serotonin-re-uptake inhibitors (SSRIs; Thase and Rush 1997).

This concept has been challenged by the work of the European Group for the Study of Resistant Depression (GSRD; Souery et al. 2011), amongst others. Based on the work of the GSRD group, a patient is considered resistant to treatment if he or she has not responded adequately to at least two consecutive adequate treatment trials with antidepressants regardless of their mode of action (Bartova et al. 2019).

Inadequate response	Inadequate response to an initial antidepressant therapy
Therapy-resistant depression	Inadequate response to two adequate antidepressant therapies
Therapy-refractory depression	Inadequate response to several adequate antidepressant therapies
Chronic depression	Depressive episode lasting longer than 2 years
according to Kasper and Akimova 2013; Kasper and Frazer 2019	

Table 1: Definitions for the classification of an inadequate response to an antidepressant therapy

3 Is TRD a distinct disease entity?

The complex disease process of TRD is rightly the target of special - also nosological - efforts. A depressive episode that later turns out to be resistant to therapy is initially at the onset of the symptoms a "normal" depressive episode. This episode then proves to be treatment-resistant due to poor response to adequate therapies and, with further inadequate treatment, becomes increasingly chronic. At the beginning of treatment, a depressive episode that later turns out to be treatment-resistant cannot be clearly distinguished from an episode that initially responds well and then remits. Therefore, TRD is not yet an independent disease entity (as, for example, Lewy body dementia is an independent disease entity compared to Parkinson's dementia), although it can be assumed with a high degree of probability that TRD represents a subgroup that can also be characterized biologically compared to the broad group of depressive disorders.

Various international classification systems do not describe TRD as a separate disorder, but interestingly, regulatory agencies such as the FDA (Food and Drug Administration) and the EMA (European Medicines Agency) grant approval of a medication for the indication of TRD if appropriate studies are available, as is the case with the now available therapeutic option of esketamine nasal spray (http://www.ema.europa.eu). Therefore, approval for major depressive disorder (MDD) does not simultaneously mean that data on efficacy in patients with TRD are also available.

It is worthwhile to shed special light on TRD not only with regard to its obviously more difficult treatment, but also with regard to its possible special characteristics. Here lies also the special importance of the search for predictors (e.g. neurobiological and psychopathological predictors): The earlier the risk for a possible

therapy resistance is recognized, the better one can prevent a chronification of the depression. As early as 1993, "neurotic personality traits," frequent episodes in the previous history, and depressive delusions were described as negative predictors of successful treatment with medication (Schmauß and Erfurth 1993). The definition of such risk factors allows early assignment to specific therapies (Erfurth and Möller 2000), including combination treatment (Schmauß and Erfurth 1996). Risk factors contributing to the development and maintenance of common comorbidities such as hypertension, diabetes, and myocardial infarction in depressed patients are lack of exercise and/or a detrimental dietary style in terms of a "western diet" (rich in saturated fat, sugar, and processed foods) (Teasdale et al. 2019, Jacka et al. 2017). In this context, it is worth highlighting that in addition to the aforementioned metabolic comorbidities, TRD patients had approximately twice the rate of hospitalization, approximately 36% longer average hospital stay, and a sevenfold increase in suicide rate (Figure 2).

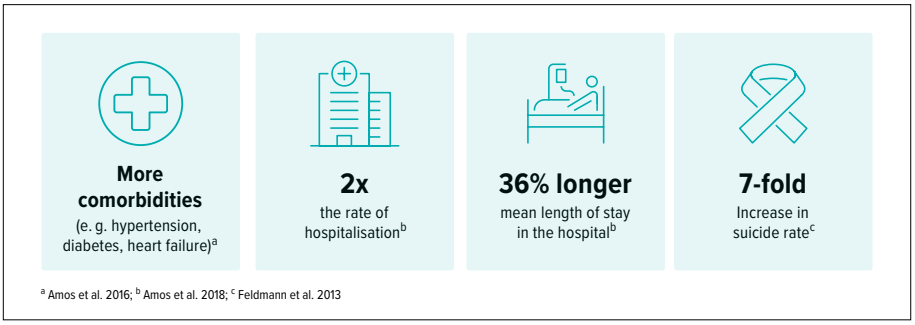

Figure 2: Consequences of failing two or more treatment lines

Large clinical studies like those by Souery et al. 2007 and by Perugi et al. 2019 (the latter elaborating on the particular importance of bipolar diathesis for the development of treatment resistance), as well as the use of machine learning (Kautzky et al. 2018 and 2019), have been able to significantly refine the prediction of treatment resistance, as can be seen in Figure 3 and presented in chapter 4 for the largest dataset of TRD patients in the GSRD group worldwide.

4 Clinical characteristics of TRD: Results of the European Group for the Study of Resistant Depression (GSRD)

The clinical phenotype of treatment resistance has been investigated in numerous international studies. Of particular note are the results of the European Group for the Study of Resistant Depression (GSRD), an international research consortium that has been systematically investigating both clinical and biological correlates of TRD and its treatment options for more than two decades in a total of eight countries (Austria, Italy, Germany, Switzerland, Belgium, France, Greece, Israel) (for review: Bartova et al. 2019).

In the course of the intensive twenty years of research, the GSRD staging model for assessing response to antidepressant treatment was developed, which takes into account the current severity of depressive symptoms as well as the psychopharmacotherapeutic strategies used. This model ultimately led the European Medicines Agency (EMA) to adapt the definition of TRD according to the results of the GSRD (http://www.ema.europa.eu), which is currently internationally accepted and widely used, for example in clinical trials (e.g., Wajs et al. 2020). Thus, TRD is currently defined as a lack of response to at least two consecutive treatments with antidepressants of the same or different substance classes administered over a sufficient treatment period (> 4 weeks) and at a sufficient daily dose in treatment adherent patients.

In addition, the results of the approximately 80 GSRD studies published to date, which were conducted in 2762 depressed patients, have increasingly strengthened the understanding of the clinical manifestation of TRD (Bartova et al. 2019). Consistent with other international research findings (for review, see Kraus et al. 2019), TRD is very often characterized by higher severity of depressive symptomatology as shown in Figure 3 (Souery et al. 2007; Balestri et al. 2016; Kautzky et al. 2019) and chronic course, with the latter being determined by the number of previous depressive episodes (Souery et al. 2007; Kautzky et al. 2019), previous psychiatric inpatient treatments (Souery et al. 2007; Zaninotto et al. 2013), and the duration of the current depressive episode (Zaninotto et al. 2013; Balestri et al. 2016; Kautzky et al. 2019). In addition, the presence of suicidality (Souery et al. 2007; Zaninotto et al. 2013; Balestri et al. 2016; Dold et al. 2018a; Kautzky et al. 2019), additional melancholic (Souery et al. 2007; Zaninotto et al. 2013), and psychotic symptoms (Zaninotto et al. 2013; Kautzky et al. 2019; Dold et al. 2019) as well as comorbid anxiety disorders (Souery et al. 2007; Zaninotto et al. 2013; Dold et al. 2017b; Kautzky et al. 2019) and personality disorders (Souery et al. 2007) are associated with an insufficient response or TRD.

Very often, the need for complex psychopharmacotherapeutic interventions was associated with an inadequate outcome (Dold et al. 2016 and 2018c). Corresponding associations were observed for add-on therapy with new-generation antipsychotics or lithium (Dold et al. 2018b) and/or benzodiazepines (Dold et al. 2020a) and for the number of antidepressants taken (Kautzky et al. 2019). Furthermore, earlier age of onset (Souery et al. 2007), high occupational employment level (Mandelli et al. 2016; Mandelli et al. 2019), a positive family history for affective disorders, and also the occurrence of adverse drug reactions ADRs were associated with a lack of response or TRD (Balestri et al. 2016).

In a recent replication study conducted in 916 GSRD patients, higher severity of depressive symptomatology, suicidality, higher number of previous depressive episodes, and comorbid anxiety disorder emerged as particularly robust risk factors for the development of TRD (Kautzky et al. 2019; Figure 3).

It should be added that international evidence also links stressful life events and somatic comorbidities to inadequate treatment response and TRD, respectively (for review, see Kraus et al. 2019), although the latter was only partially observed or associated with higher use of psychopharmacotherapeutic interventions in the GSRD studies (Fugger et al. 2018, 2019a, 2019b, and 2020).

5 Genetics and epigenetics

Genetic factors are not only significantly involved in the development of depression, but also influence the response to psychotropic drugs. This is demonstrated by clinical trials, family and twin studies, work in animal models, and basic research (Schulze and McMahon 2018; Bousman et al. 2021). Genetics or pharmacogenetics (PGx), in addition to treatment response, also influence the occurrence of ADRs as well as the risk of drug-induced ADRs – regarding this, please refer to the discussion on "Pharmacokinetic Interactions" (chapter 6) as well as the comprehensive, recent expert consensus review paper "Review and Consensus on Pharmacogenomic Testing in Psychiatry" by the International Society of Psychiatric Genetics (Bousman et al. 2021). Genetic traits have also been repeatedly proposed as predictive biomarkers to facilitate diagnosis and progression prediction of depressive disorder (Fabbri et al. 2019a and 2020).

Currently, so-called "Polygenic Risk Scores" (PRS), which are sum scores of gene variants associated with depression, are among the subjects of psychiatric genetics research. Interestingly, a recent paper by the GSRD group showed that the PRS for schizophrenia appears to be related to TRD, which would explain, among other things, the augmentative effect of the so-called atypical antipsychotics (Fanelli et al. 2020). However, individual risk prediction is not currently recommended by the International Society of Psychiatric Genetics (Lazaro-Munoz et al. 2019). Nonetheless, PRS are excellent tools for modern, hypothesis-driven research into the genetic basis of affective disorders as well as treatment response (Bengesser and Reininghaus 2018). Similarly, early candidate gene-based association studies were already able to provide initial clues to the genetic blueprint of depression (see section 5.1). However, it was the era of genome-wide association studies (GWAS) that led to the current breakthrough results (see Chapter 5.2).

5.1 Candidate gene studies

Candidate genes for hypothesis-driven studies include genes related to neurotransmitter systems or to processes thought to be relevant to disease - such as neuroplasticity.

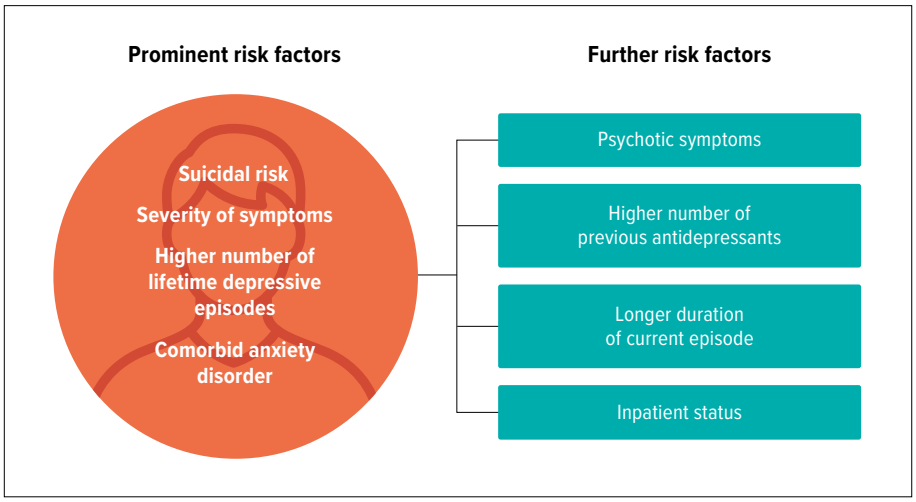

Figure 3: Clinical features of TRD patients, that can serve as predictors and for the determination of treatment response, and can easily be assessed in clinical routine (according to Kautzky et al. 2019)

Hypothesis-driven gene association studies and psychopharmacological association studies focused, among others, on genetic polymorphisms of the serotonergic system such as the length polymorphism of the serotonin transporter gene (5-HTTLPR in SLC6A4) or a functional polymorphism of the serotonin receptor 1A gene (rs6295 in 5HTR1A). Genes responsible for serotonin degradation, such as COMT, have also been intensively studied.

An association with depression in general was found among genes responsible for neuroplasticity and transcriptional regulation, particularly for BDNF, CREB1, and MAPK1 (Schosser et al. 2012).

5.2 Genome-wide association studies

Large international psychiatric genetics consortia, such as the Psychiatric Genomics Consortium (PGC), STAR*D, GENDEP, MARS, and GSRD, have further unraveled the genetics of depression and treatment response. Through modern genotyping-array technology, genome-wide association studies (GWAS), which compare millions of gene variants (SNP, "single nucleotide polymorphisms") between study participants with depression or TRD and healthy controls in a hypothesis-free manner, have deciphered genome-wide associated risk gene variants for depression. For example, a milestone in psychiatric genetics was the presentation of over one hundred gene variants associated with depression by David Howard at the World Congress of Psychiatric Genetics (WCPG) in Glasgow 2019. In a meta-analysis of GWAS data from 807 553 individuals (246 363 cases with depression and 561 190 controls), Howard et al. showed that 102 independent gene variants and 15 gene groups are associated with depression. These genes play a role in synaptic structure and neurotransmission, among others. The results were replicated in an independent replicate sample of 1 306 354 individuals (414 055 cases with depression and 892 299 controls), with 87 of the 102 associated variants remaining significant after strict correction for multiple testing (Howard et al. 2019). These findings expand our understanding of the complex, polygenic genetic architecture of depression and offer several future opportunities to understand etiology and develop novel treatment approaches. In comparison, few genome-wide significant gene variants were identified in TRD-GWAS (e. g., rs150245813) (Li et al. 2020; Fabbri et al. 2019b). Most gene variants nominally associated with TRD did not survive strict Bonferroni correction. However, enrichment analyses provide evidence for a role of cytoskeletal regulation, transcriptional modulation, and calcium signaling pathways in TRD (Fabbri et al. 2019b).

However, it should be noted that the TRDGWAS samples are currently relatively small and important results can be expected by expanding the data sets in the years to come. Nevertheless, the existing genomic data on TRD help to identify new potential pharmacological options for TRD using modern in silico methods, e. g., ketamine or lithium (Fabbri et al. 2021).

5.3 Epigenetics

Since, according to the vulnerability-stress model, the genetic blueprint is not the sole determinant of the development of a depressive episode, gene-environment interactions are important pieces of the puzzle in the molecular pathogenesis of depression and TRD. Epigenetic processes, such as methylation of cytosines in regulatory elements of the promoter of genes, can silence transcription, or gene reading. Results of hypothesis-driven methylation analyses repeatedly revealed epigenetic changes in candidate genes of serotonergic neurotransmission and neuroplasticity. Initial EWAS („epigenome wide association studies") revealed only a few methylation sites that continued to be associated with depression after Bonferroni correction. EWAS in the field of TRD are unfortunately currently still in an initial stage (Menke and Binder 2014).

5.4 Multifactorial gene studies

Ultimately, the interaction of a variety of genetic, epigenetic, clinical, and sociodemographic factors appears to be associated with TRD pathogenesis and treatment response. Consequently, in recent years, a focus of research has been on multifactorial models designed to integrate genetic and other predictors into a complementary system and to better account for interactions. Nowadays, attempts are being made to address the integrative interconnectedness of different molecular biological pathways in treatment response research in depression by applying machine learning (ML) (Maciukiewicz et al. 2018).

In summary, initial results of genome-wide and multifactorial studies suggest a potential of genetic markers for precision diagnostics and therapy prediction. The characterization of genetic markers of TRD represents a necessary focus of depression research.

6 Plasma levels and drug interactions

Therapeutic drug monitoring (TDM) and individualized psychopharmacotherapy are particularly advisable in TRD patients (Hiemke et al. 2018). Among other things, this means dose optimization based on the quantification of drug levels in blood serum or plasma.

Plasma level measurements are now routinely available for most psychotropic drugs. Falling below or exceeding the targeted levels may explain an inadequate response to medication or poor tolerance of medication. Causes may include patient non-adherence and the possible presence of a genetic polymorphism or a relevant pharmacokinetic interaction. Levels are usually evaluated using trough level measurements under steady-state conditions. In practice, this means that in most cases a plasma level measurement is only useful and meaningful one week after reaching a stable daily dosage and immediately before taking the morning dose. However, if ADRs occur, a plasma level determination may be useful at any time. In such cases, however, the dosing regimen must be included for the interpretation of the results (Hiemke et al. 2018).

Interactions between the individual substances must be considered for all combinations of drugs. The number of possible interactions increases exponentially with the number of drugs taken. This results in ten possible interactions for a combination therapy with five drugs, while 45 interactions are already possible with ten drugs. However, not all potential drug interactions are clinically relevant. A pharmacodynamic interaction is when the effect of a drug is directly influenced (synergistically or antagonistically) by another drug.

Pharmacodynamic interactions can lead to very relevant phenomena in clinical practice. In psychiatry, these include: hypertension/hypertensive crises, serotonin syndrome, sedation, extrapyramidal symptoms, arrhythmias, or QTc time prolongation (Gören and Tewksbury 2013).

Pharmacokinetic interactions occur when two drugs taken simultaneously affect each other's absorption, distribution, metabolism, or excretion in such a way that there is a change in the concentration of one of the two drugs (Cascorbi 2012). Consequences of the altered drug concentration may include loss of effect or a ADR. Isoenzymes of the cytochrome P450 (CYP450) system are responsible for the metabolism of most psychotropic drugs. Here, pharmacokinetic interactions may cause a change in the plasma level of the respective substance. Table 2 lists all six possible scenarios of pharmacokinetic interaction at the CYP450 enzyme system. The major CYP450 isozymes are: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 (Hiemke et al. 2018). Duloxetine, fluoxetine (and

Inhibitor is added to the substrate	Increase of substrate plasma levels (which can lead to toxicity).
Substrate is added to the inhibitor	Uptitration of the substrate according to the usual therapeutic scheme can lead to fast and significant increase of substrate plasma levels and eventually to undesireable drug effects.
Inductor is added to the substrate	Decrease of substrate plasma levels. Thereby the substrate possibly loses its effect.
Substrate is added to the inductor	Despite adherence to the usual up-dosing regimen, there is little or no therapeutic effect because the plasma level of the substrate is too low.
Void of an inhibitor	The affected isoenzyme regains normal function; this results in a reduction in the plasma level of a substrate for that isoenzyme and a concomitant increase in the metabolites of the substrate.
Void of an inductor	The isoenzyme concerned is reduced in its function. This results in an increase in the plasma level of the substrate and a reduction of the metabolite of the substrate.
Substrate: substance, which is metabolized through the respective isoenzyme *Inhibitor: substance, which hinders/blocks the respective isoenzyme in its function* *Inductor: substance, which promotes the respective isoenzyme in its funcion*	
according to Sandson et al. 2003	

Table 2: Possible scenarios for drug interactions in the CYP450-enzyme system

Substance	CYP450 metabolization	Therapeutic reference range
Agomelatine	**CYP1A2**, CYP2C19, CYP3A4	7–300 ng/ml (1–2 h after intake of 50 mg)
Aripiprazole	**CYP2D6**, **CYP3A4**	100–350 ng/ml
Bupropion (and hydroxybupropion)	CYP2C19, **CYP2B6**	850–1500 ng/ml
Citalopram/Escitalopram	**CYP2C19**, CYP2D6, CYP3A4	50–110 ng/ml/15–80 ng/ml
Esketamine	**CYP2D6**, **CYP3A4**, CYP2C19, CYP2C9	40–90 ng/ml*
Duloxetine	**CYP1A2**, CYP2D6	30–120 ng/ml
Fluoxetine (and Norfluoxetine)	CYP2B6, **CYP2C9**, **CYP2C19**, **CYP2D6**	120–500 ng/ml
Mirtazapine	CYP3A4, CYP1A2, CYP2D6	30–80 ng/ml
Olanzapine	**CYP1A2**, CYP2D6	20–80 ng/ml
Paroxetine	**CYP2D6**, CYP3A4	20–65 ng/ml
Quetiapine	**CYP3A4**, CYP2D6	100–500 ng/ml
Risperidone (and hydroxyrisperidon)	**CYP2D6**, CYP3A4	20–60 ng/ml
Sertraline	**CYP2B6**, **CYP2C19**, CYP2C9, CYP2D6, CYP3A4	10–150 ng/ml
Trazodone	**CYP3A4**, CYP2D6	700–1000 ng/ml
Venlafaxine (and O-Desmethylvenlafaxine)	**CYP2C19**, **CYP2D6**, CYP2C9, CYP3A4	100–400 ng/ml
Vortioxetine	**CYP2D6**, CYP3A4, CYP2A6, CYP2C9	10–40 ng/ml
Ziprasidone	CYP3A4	50–200 ng/ml

*If enzymes printed in bold are decreased or increased in activity by an inhibitor or inducer, there is a potentially clinically relevant increase or decrease in plasma concentration of the corresponding substance (according to Hiemke et al. 2018); * at T_{max}*

Table 3: CYP450 isoenzyme involvement and therapeutic range of some psychotropic drugs

norfluoxetine), and paroxetine are potent inhibitors of CYP2D6. In contrast, St. John's wort is an inducer of CYP2C19, CYP3A4; carbamazepine is an inducer of CYP1A2, CYP2B6, CYP2C9, as well as CYP3A4. Table 3 shows some psychotropic drugs and their metabolization.

In addition, genetically determined polymorphisms, which show significant ethnicity-specific differences in their frequency, can lead to a large variability in the equipment and performance of CYP enzymes among individuals (Müller et al. 2018). In this context, the terms "poor", "intermediate", "extensive" or "ultrarapid metabolizer" are used (Stingl et al. 2013). Pharmacogenetic testing can provide information about the presence of possible polymorphisms. "Poor metabolizers" for a particular isoenzyme have higher plasma levels for substrates of the affected isoenzyme, while "ultrarapid metabolizers" have low plasma levels for substrates of the affected isoenzyme.

Based on initial analyses by the University Department of Psychiatry and Psychotherapy in Vienna, it can be assumed that in the inpatient setting, about 8-10 % of depressed patients exhibit pharmacokinetic peculiarities, mostly "ultra rapid metabolizing," which requires for example to administer higher oral medication doses.

Changes in enzyme activity in the course of life are possible. Possible causes include a decline in enzyme activity with age or kidney or liver diseases. Smoking can also lead to relevant interactions. When tobacco is burned, numerous substances are formed that can influence the pharmacokinetic and pharmacodynamic properties of pharmaceuticals: The polycyclic aromatic hydrocarbons in tobacco smoke (benzpyrene, anthracene, phenantrene, etc.) are metabolic inducers of CYP1A1 and CYP1A2, while carbon monoxide induces CYP2D6. One to five, six to ten, and more than ten cigarettes per day increase isoenzyme activity by 1.2-, 1.5-, and 1.7-fold, respectively (Hiemke et al. 2018). Thus, for drugs that act as substrates for this isoenzyme (e. g., clozapine, duloxetine, or olanzapine), smoking leads to a reduction in its plasma levels (Tables 2 and 3). Clinically relevant is also the "deinduction", i. e. the increase of plasma levels during the reduction of tobacco smoking, for example during the switch to "electric cigarettes" or to nicotine patches.

The permeability of the blood-brain barrier is a major factor influencing the efficacy of antidepressants. The "guardian molecule" P-glycoprotein, which is located in the blood vessels and encoded by the ABCB1 gene, binds about 70 % of all common antidepressants and can thus impede the entry of the drugs into the brain tissue. The new ABCB1 test, which was developed at the Max Planck Institute in Munich, can be used to measure the DNA sequence variants in the ABCB1 gene that complicate the drug treatment of depression. This allows the identification of patients in whom antidepressants are less able to pass the blood-brain barrier due to polymorphisms and who therefore respond insufficiently to therapy. ABCB1 diagnostics are required only once in a lifetime and allow antidepressant therapy to be tailored to the individual ABCB1 genotype. The measurement provides an aid in the choice of treatment options for partial and nonresponse regarding confirmation of the choice of prescribed antidepressant, dose increase, augmentation strategies, or medication change, as noted in the Swiss treatment recommendations (Holsboer-Trachsler et al. 2016).

7 Psychopharmacotherapy of TRD

The treatment of TRD is often described as challenging. In order to achieve the best

possible outcomes, therapy should be based on the individual needs of the person affected and include non-pharmacological and social interventions in addition to psychopharmacotherapy (Dodd et al. 2020). These are outlined in more detail in the following chapters. Psychoeducation is of great importance in this context. A functioning doctor-patient relationship has a positive effect on the success of therapy and is therefore of eminent importance (Bartova et al. 2017).

Optimizing therapy response and the overall treatment process has been the subject of intensive research in recent years. Results have been therapy algorithms issued by international psychiatric societies such as the World Federation of Societies of Biological Psychiatry (WFSBP) (Bauer et al. 2017) and international research consortia such as GSRD (Bartova et al. 2019; Kasper et al. 2012; Dold and Kasper 2017; Kraus et al. 2019). The currently recommended treatment steps in drug therapy for unipolar depression are listed in Table 4 and Figure 5.

In terms of optimal therapy, drug treatment should serve as the baseline therapy in TRD, similar to many other medical conditions such as arterial hypertension (Kranz and Kasper 2019; Bartova et al. 2020). Baseline drug therapy should primarily include antidepressants, with evaluation of the effectiveness of initial antidepressant treatment usually two to four weeks after the target dose is reached (Kasper et al. 2012; DGPPN et al. 2015; Bauer et al. 2017). A lack of response to therapy as early as two weeks can be considered a predictor of further inadequate response. Adjustment of antidepressant therapy is therefore recommended after only two weeks if there is a lack of response (Bauer et al. 2017).

In case of an inadequate response to antidepressant therapy, a pseudo-therapy-resistance described in chapter 2 (see also Figure 1) must first be ruled out. After exclusion of pseudo-therapy-resistance, the following steps to optimize the therapy must be taken in hierarchical order:

1. an optimization of the existing antidepressant treatment

2. augmentation therapy (administration of an additional substance to ongoing pharmacotherapy with an antidepressant). New-generation antipsychotics or lithium have been shown to be very effective in this indication (DGPPN et al. 2015; Bauer et al. 2017; Dold and Kasper 2017; Dold et al. 2018b and 2018c; Taylor et al. 2020). Recently, esketamine nasal spray has also become available as an effective add-on therapy (for review, see Kasper et al. 2020).

3. combination therapy of antidepressants with different modes of action. For example SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) in combination with mirtazapine or trazodone may be considered (Dold et al. 2016; Bauer et al. 2017).

Other strategies commonly used in clinical practice, such as dose escalation (i. e., dose increase) with antidepressants from the reuptake inhibitor substance groups (Dold et al. 2017a) or switching (monotherapy with one antidepressant to monotherapy with another antidepressant) (Souery et al. 2011), do not represent a general evidence-based approach of the treatment of TRD and should therefore only be used in well-defined circumstances, which are described in subsections 7.4 and 7.5 below (Dold and Kasper 2017).

After the rapid onset and potent antidepressant efficacy of esketamine intranasally was confirmed in several international studies (Popova et al. 2019, Wajs et al. 2020; Ionescu et al. 2021, for review: Kasper et al. 2020) and a recent meta-analysis showed superiority to new-generation antipsychotics (Dold et al. 2020b; Carter et al. 2020), this innovative add-on therapy option, which is now officially approved in Austria, should be considered in TRD patients (for review: Kasper et al. 2020) (Table 4, Figure 4).

7.1 Psychopharmacotherapy with antidepressants

Antidepressants are the first-line therapeutic option in the treatment of unipolar depression (DGPPN et al. 2015; Holsboer-Trachsler et al. 2016; Bauer et al. 2017; Dold and Kasper 2017). Their efficacy has been demonstrated in numerous internationally conducted clinical trials and meta-analyses (Cipriani et al. 2018). Currently, the most commonly used substance group among antidepressants in Europe and the United States are SSRIs, followed by SNRIs. Other substance groups in use include noradrenergic and specific serotonergic antidepressants (NaSSAs), noradrenaline dopamine reuptake inhibitors (NDRIs), serotonin reuptake inhibitors and receptor antagonists (SARIs), norepinephrine reuptake inhibitors (NARIs), reversible and irreversible MAO-Is, tricyclic antidepressants (TCAs), and the serotonergic-melatonergic antidepressant agomelatine, the glutamate modulator tianeptine, and the multimodal serotonin modulator vortioxetine.

The patient's clinical symptoms, comorbidities, preferences, and previous therapy experience (response, tolerability) should be ascertained as part of a precise diagnosis and taken into account when selecting the antidepressant in terms of an individualized therapy (Bauer et al. 2017).

In addition, the side effect profiles of the respective substances and, in this context, the targeted response of subjective quality of life and the occurrence of ADRs (Bartova and Winkler 2019) should be considered in particular. This is important, for example, in the context of the frequently unaddressed sexual dysfunction or adverse metabolic effects, which can cause considerable suffering. Consequently, this can lead to insufficient therapy adherence and ultimately also to TRD, which can be avoided or well treated by appropriate psychopharmacotherapy supported by regular psychoeducation and by adequate therapy modification (Bartova and Winkler 2019).

SSRIs are effective, safe, and therapeutically widely applicable antidepressants. They are well tolerated compared to the older TCAs. Antidepressants with sedative properties, such as the NaSSA mirtazapine or the SARI trazodone, are well suited for patients with sleep disturbances. The latter may also reduce SSRI-induced sexual dysfunction via inhibition of serotonin-2 receptors. Despite the lack of clear results in comparative clinical trials, according to theoretical considerations and preclinical data, antidepressants with noradrenergic and dopaminergic modes of action represent a useful therapeutic option for patients with marked loss of energy and anhedonia. The SNRIs venlafaxine, milnacipran, and duloxetine, as well as the NDRI bupropion, for example, fall into this category. The dual-acting duloxetine is also effective for comorbid symptoms such as anxiety or depression-associated pain and is also well

suited for the treatment in elderly patients. Bupropion can be very effectively used in patients who suffer from sexual dysfunction and or obesity or metabolic syndrome. Agomelatine is an MT_1-, MT_2-receptor agonist and a 5-HT_{2C} receptor antagonist with good antidepressant efficacy and a positive effect on sleep quality. Tianeptine, which exerts its antidepressant efficacy via the glutamate system and is most likely to be used as part of combination therapy, has a favorable side effect profile but must be administered three to four times daily because of its short half-life. Positive effects on cognitive symptoms as well as the low risk of sexual dysfunction are highlighted for vortioxetine, whose spectrum of action includes serotonin transporter inhibition as well as interference with various serotonergic receptors (agonism at 5-HT_{1A}, partial agonism at 5-HT_{1B}, antagonism at 5-HT_{1D}, 5-HT_3, 5-HT_7) (Bartova and Winkler 2019).

The substances mentioned above mostly have a favorable side effect profile. In contrast, TCAs have significantly more adverse effects (Spindelegger et al. 2014), which are largely due to their influence on the cholinergic system. Consequently, TCAs are now only recommended as a second-line treatment option. In the context of antidepressant treatment for TRD, the irreversible MAO-I tranylcypromine can be effectively used, whereby attention must be paid to the patient's adherence to a low-tyramine diet. Furthermore, the risk of serotonin syndrome must be pointed out if tranylcypromine is combined with antidepressants that exert their efficacy via monoamine reuptake inhibition (Schmauß et al. 1990, Dold and Kasper 2017).

With regard to antidepressant efficacy in depressive disorders in general, meta-analyses found no significant differences between SSRIs and TCAs (Bauer et al. 2017). However, SSRIs as well as the other modern substance groups show far more favorable side effect profiles and thus better tolerability than TCAs. This is associated with better treatment adherence and fewer treatment discontinuations. Consequently, modern antidepressants should be given preference over TCAs.

Table 5 lists the recommended starting and target doses for the most commonly prescribed antidepressants. Dose adjustments may be necessary in older patients or in the presence of somatic comorbidities (particularly hepatic or renal insufficiency) (Bauer et al. 2017; Dold and Kasper 2017). TDM can be used for dose optimization and is indicated in case of an insufficient response to identify blood levels that might be too low due to insufficient tratment adherence or metabolic features (Hiemke et al. 2018).

7.2 Augmentation therapy with new-generation antipsychotics and lithium

For augmentation therapy with both new-generation antipsychotics and lithium, efficacy has been demonstrated in numerous clinical trials and meta-analyses (Dold et al. 2018b; Dold et al. 2018c). Thereby, the better evidence in terms of a larger number of conducted studies exists for the use of antipsychotics. According to available data, efficacy (effect size) and tolerability are comparable for antipsychotic and lithium augmentation. However, it should be taken into account in this context that the evidence of efficacy for the new generation antipsychotics is firstly based on a much larger patient population, secondly on studies with a higher methodological quality,

1. **Optimization** of current antidepressant treatment and **exclusion of pseudoresistance**	• Sufficient treatment duration • Sufficient dosage • Laboratory tests (incl. blood count, metabolic screenings, iron status, vitamin D, folic acid, vitamin B12, thyroid function, hs-CRP) • Determination of drug plasma levels in blood and subsequently metabolic status in case of abnormal drug plasma levels and assurred treatment adherence • Evaluation of therapy adherence • Exploration of possible adverse drug effects, comorbidities, adverse lifestyle factors and psychosocial stress factors
2. **Augmentation therapy** (administration of an additional substance to ongoing antidepressant therapy) or **add-on therapy with esketamine nasal spray**	• New generation antipsychotics • Lithium • Esketamine nasal spray (in combination with **an selective serotonin re-uptake inhibitor (SSRI) or serotonin-norepinephrine re-uptake inhibitor (SNRI) in the absence of a response to** at least **two adequate antidepressant therapies**)
3. **Antidepressant combination therapy** (simultaneous prescription of two or more antidepressants)	• Preferably 2 antidepressants with different modes of action (e. g., selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors in combination with mirtazapine or trazodone, respectively)
4. **Dose escalation** (high-dose therapy)	• In patients with proven polymorphisms in the cytochrome P450-enzyme system ("rapid" or "ultrarapid" metabolization) • Efficacy was reported for tricyclic antidepressants and monoamine oxidase inhibitors
5. **Switching** (exchanging one antidepressant for another as part of monotherapy)	• In case of relevant adverse drug reactions or absolute non-response
according to Bartova et al. 2017	

Table 4: Recommended treatment steps in drug therapy for unipolar depression (see also treatment algorithm in Figure 5)

and thirdly, the majority of more modern antidepressants (mainly SSRI/SNRI) have been augmented (Nelson and Papakostas 2009), whereas lithium has been studied predominantly in combination with TCA (Crossley and Bauer 2007).

The choice between new-generation antipsychotics and lithium should also be made based on the clinical picture in terms of an individualized treatment approach. Psychotic symptoms occurring during the depressive episode suggest the use of antipsychotics, whereas lithium is the obvious option for patients with bipolar depression (Bauer et al. 2017, Dold and Kasper 2017). Lithium also shows very good antisuicidal efficacy independent of the underlying disease. When choosing an

Class of antidepressive active substance	Active substance	Recommendend starting dose (in mg daily)	Recommended target dose (in mg daily)	Recommendation grade for therapeutic drug monitoring (TDM)
Selective serotonin re-uptake inhibitor (SSRI)	Citalopram	20	20–40	2
	Escitalopram	10	10–20	2
	Fluoxetine	20	20–60	2
	Fluvoxamine	50	100–200	2
	Paroxetine	20	20–60	3
	Sertraline	50	50–150	2
Serotonin-norepinephrine re-uptake inhibitor (SNRI)	Duloxetine	30–60	60–120	2
	Milnacipran	50–100	100–200	2
	Venlafaxine	37,5–75	75–375	2
Noradrenaline-dopamine re-uptake inhibitor (NDRI)	Bupropion	150	150–450	3
Noradrenergic and specific serotonergic antidepressants (NaSSA)	Mirtazapin	15	15–45	2
	Mianserine	30	60–120	3
Serotonin re-uptake inhibitor and receptor antagonist (SARI)	Trazodone	50–100	200–600	2
Noradrenaline re-uptake inhibitor (NARI)	Reboxetine	4–8	8–12	3
Monoamine-oxidase inhibitor (MAO-I)	Moclobemide	150	300–600	3
	Tranylcypromin	10	20–60	4
Tricyclic antidepressants (TCA)	Amitriptyline	25–50	100–300	1
	Clomipramine	25–50	100–250	1
	Desipramine	25–50	100–300	2
	Imipramine	25–50	100–300	1
	Nortriptyline	25–50	75–200	1
	Trimipramine	25–50	100–300	2
Other antidepressants	Esketamine i.n.*	under 65 YL: 56 ≥ 65 YL: 28	56–84	–
	Agomelatine	25	25–50	4
	Tianeptine	12,5	25–37,5	–
	Vortioxetine	5–10	10–20	–

*Legend: 1 strongly recommended; 2 redommended; 3 beneficial; 4 potentially beneficial; – not examined. * Esketamine i.n. is not applied daily (see subchapter 7.8); YL: years of life*
Sources: Bauer et al. 2017, Hiemke et al. 2011; after Bartova et al. 2017, Dold und Kasper 2017

Table 5: Dose and recommendation grade for antidepressants according to the World Federation of Societies of Biological Psychiatry (WFSBP) and the Arbeitsgemeinschaft für Neuropsychopharmakologie and Pharmakopsychiatrie (AGNP)

optimal augmentation therapy, comorbidities and previous therapy experience must be taken into account in addition to clinical symptoms. The side-effect profiles of the agents being considered may be crucial, as well as potential drug interactions. TDM has also been shown to be helpful (Hiemke et al. 2018).

In a meta-analysis (Dold et al. 2020b), the effect size (efficacy) of pharmacotherapy with esketamine nasal spray (see also section 7.8) was twice as large as that of medication with new-generation antipsychotics for the reduction of depressive symptoms at study endpoint. Network analysis of 21 studies also found a high level of evidence for the NMDA (N-methyl-D-aspartate) antagonists ketamine/esketamine (Carter et al. 2020). In this study, the NMDA antagonists had a 99.8% probability of being an optimal choice (Figure 4).

7.2.1 Augmentation therapy with new-generation antipsychotics

If antipsychotics are administered as an add-on in addition to antidepressants to enhance their effectiveness, this is referred to as augmentation therapy. The effectiveness in this context is best documented for quetiapine, aripiprazole, olanzapine, and risperidone (Bauer et al. 2017). Based on the available study data, the EMA has given a corresponding indication for quetiapine XR. In the U.S., the FDA has approved the indication for quetiapine XR, aripiprazole, brexpiprazole, and the fixed combination of olanzapine and fluoxetine. There is currently no approval for the non-retarded formulation of quetiapine for unipolar depression. The difference in approvals is explained by the different requirements of the two regulatory agencies. The EMA requires long-term studies regarding efficacy for approval for the treatment of depression, whereas shorter observation periods are sufficient for the FDA.

For augmentation therapy with antipsychotics usually lower dosages than in the treatment of psychotic disorders are used (e. g., quetiapine XR 50-300 mg daily, aripiprazole 2.5-10 mg daily, olanzapine 2.5-10 mg daily) (Kasper et al. 2011). A potentially higher vulnerability for the occurrence of possible ADRs (metabolic changes, extrapyramidal-motor symptomatology) must be taken into account (Bauer et al. 2017; Dold and Kasper 2017).

7.2.2 Augmentation therapy with lithium

Lithium offers the advantage of a proven antisuicidal effect, which occurs independently of the antidepressant effects and also comes into play in augmentation therapy (Bauer et al. 2017, Dold and Kasper 2017).

For augmentation therapy, most guidelines recommend a lithium level that should be in the target range of 0.6-0.8 mmol/L. A treatment effect can be expected after about two to four weeks at the desired target dose. If the patient responds well, continuation of this add-on therapy for at least twelve months is recommended (Bauer et al. 2017). The narrow therapeutic range of lithium must be considered in the context of augmentation therapy. Therefore, evaluations of plasma levels should be performed regularly during the course of therapy. If lithium is taken on a long-term basis, the possible risk of hypothyroidism as well as renal damage must be taken into account (McKnight et al. 2012).

7.3 Antidepressant combination treatment

Whether antidepressant efficacy can be enhanced by combining two or more antidepressants prescribed simultaneously is in discussion. According to international treatment guidelines, antidepressant combination therapy is only recommended if two antidepressant substances with different modes of action are combined (e. g., SSRI or SNRI in combination with mirtazapine or trazodone) (Dold et al. 2016). In the case of combination therapy, a higher risk for the occurrence of ADRs might appear (Bauer et al. 2017; Dold and Kasper 2017).

7.4 Dose escalation

Another controversial issue represents dose escalation, which does not count to evidence-based treatment strategies for TRD according to international treatment guidelines. How effective dose escalation can be is likely to depend on the class of antidepressants used (Bauer et al. 2017, Dold and Kasper 2017). Positive study results are available for TCA and MAO-I (Adli et al. 2005). In contrast, recent meta-analyses for monoamine reuptake inhibitors (Dold et al. 2017a), SSRIs, venlafaxine, and mirtazapine (Furukawa et al. 2019) found no evidence of efficacy for dose escalation. However, high-dose therapy may be indicated in patients with proven polymorphisms in the cytochrome P450 enzyme system ("rapid" or "ultrarapid"

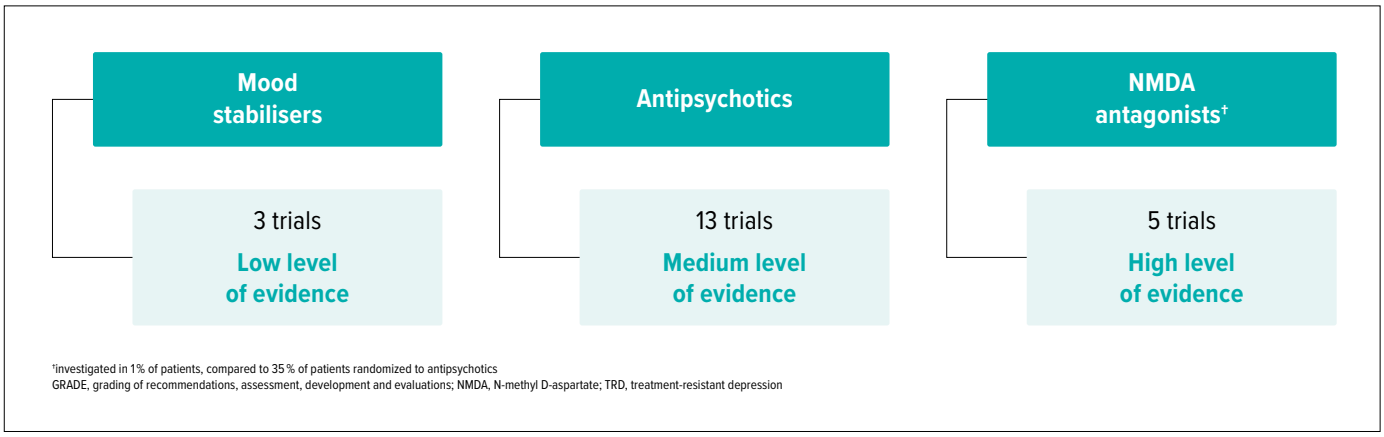

Figure 4: A systematic review and network meta-analysis of 27 trials involving augmentation interventions. Trials included mood stabilisers, antipsychotics, NMDA antagonists and treatments with other modes of action. Recommendations are based on the evidence of GRADE (according to Carter et al. 2020)

metabolization) (Bartova et al. 2017). If one decides to increase the dose beyond the recommended target level (Table 3), an increased rate of ADRs must be considered (Dold et al. 2017a).

7.5 Switching (change of the antidepressant monotherapy)

According to international therapy guidelines switching is only recommended in case of non-response or intolerable adverse effects (DGPPN 2015). In this case, switching to the irreversible MAO-I tranylcypromine, which has potent antidepressant efficacy, appears to be psychopharmacotherapeutically justifiable. Before starting treatment, however, attention should be drawn to the wash-out period and adherence to a low-tyramine diet and the exclusion of SSRI medication in order to avoid associated adverse effects such as hypertensive crises (Bartova et al. 2020).

7.6 Further psychopharmacotherapeutic add-on strategies

In addition to new-generation antipsychotics and lithium, several other agents have been studied as add-ons to ongoing antidepressant monotherapy, with largely inconclusive results. Study data are available for lamotrigine, thyroid hormones, buspirone, or pindolol, for example (Dold and Kasper 2017). According to WFSBP guidelines, augmentation therapy with thyroid hormones is an effective option when initial antidepressant monotherapy is ineffective. However, potential ADRs must be considered (Bauer et al. 2017). Furthermore, the administration of the progesterone metabolite allopregnanolone has proven effective in initial studies. The latter appears to be rapidly effective, particularly in peripartum depression (Dwyer et al. 2020). Substitution of sex hormones can currently be recommended only in cases of demonstrable deficits.

Over the past two decades, international studies have investigated other innovative compounds in the context of add-on therapy for TRD and considered them promising due to their rapid onset and robust antidepressant efficacy, largely attributed to modulation of glutamatergic NMDA receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and γ-aminobutyric acid (GABA)ergic neurotransmission (Kraus et al. 2019). Especially highlighted were ketamine and esketamine, which will be discussed in detail in the next subsections.

Positive study results regarding antidepressant efficacy have been partially reported for the drug combination of buprenorphine (partial μ-opioid receptor agonist and κ-opioid receptor antagonist) and samidorphan (κ-opioid receptor antagonist), which has been studied under the designation ALKS5461 and whose use is being considered in recently presented therapeutic algorithms as part of an experimental therapy in TRD patients with challenging disease courses (Kraus et al. 2019).

Moreover, in the context of an experimental treatment, psilocybin, known as a hallucinogen, showed superior antidepressant efficacy compared to placebo, which has been correlated with neurobiological findings and is most likely explained by prefrontal 5-HT_{2A} receptor agonism and interference with glutamatergic, serotonergic, and dopaminergic neurotransmission (Carhardt et al. 2016).

Another experimental therapy option is botulinum toxin A, known as a neurotoxin, which inhibits signal transmission between neurons and muscle cells, resulting in muscle paralysis. According to the so-called facial feedback theory, the mimic expression of emotion and its proprioception reinforce the original emotion. The paralytic effect of botulinum toxin on the frontal muscle groups involved in the expression of negative emotions might be associated with antidepressant efficacy (Bartova and Winkler 2019). In international studies, antidepressant effects of botulinum toxin applied to the glabella in the frontal facial area could be observed beyond the effective period of botulinum toxin (Qian et al. 2020).

For the treatment of comorbid anxiety disorders in depression, antidepressants acting predominantly via serotonergic mechanisms and pregabalin are preferably recommended. In terms of phytopharmaceuticals, the beneficial anxiolytic effect of silexan, a lavender oil preparation, in anxiety disorders and in subsyndromal anxiety disorders has been repeatedly reported in clinical trials (Kasper et al. 2018). Since no interaction potential is known, the combination of Silexan with an antidepressant can also be applied. Furthermore, this substance was shown to have no addiction potential and no impairment in the steering of a motor vehicle (Möller et al. 2021, Seifritz et al. 2021).

7.6.1 Augmentation of antidepressants with nutraceuticals/supplements

Supplements used for adjunctive treatment of depression include omega-3 fatty acids, vitamin D, folic acid (vitamin B9), vitamin B12, S-Adenosyl-L-methionine (SAMe), zinc, and probiotics (Schefft et al. 2017, Firth et al. 2019, Mörkl et al. 2021).

Some meta-analyses show that various inflammatory markers, especially proinflammatory cytokines (including TNF-α, IL-1 , IL-6, and IF-γ), are increased in depression. An increased inflammatory response influences several aspects of the pathogenesis of depression, including decreased production and availability of neurotransmitters and growth factors. Thus, therapeutics that regulate inflammation may be particularly useful in combination with existing strategies.

Omega-3 fatty acids are decreased in depressed patients and, as polyunsaturated fatty acids, influence inflammatory processes. They cannot be synthesized by the body itself. Omega-3 fatty acids relevant to the brain that have been shown to be effective in depression treatment are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). According to recent meta-analyses, EPA in particular, or a combination of EPA and DHA, has been shown to be effective in individuals with major depression on antidepressant therapy. Currently, dosages of 1-2 g EPA per day are recommended, either as a pure EPA supplement or in combination supplements, ideally with a ratio EPA/DHA > 2:1) (Guu et al. 2019), the EPA content should be at least 60% (Liao et al., 2019). Supplementation therapy in patients with severe depression and patients already taking antidepressants can be started with 1g/day, after 2-4 weeks a dose increase to 2 g should be aimed for. The duration of intake should be at least 8 weeks, probably a longer-term administration is useful. Omega-3 fatty acids can be used at the beginning of treatment (acceleration) or as an adjunct to already initiated antidepressant therapy (augmentation). Several studies have shown that the combination of omega-3 supplementation and antidepressants is superior to monotherapy. Because omega-3 fatty acids are involved in the regulation of inflammatory processes, they represent a well-tolerated

approach to adjunctive supplementation therapy for depression (Hallahan et al. 2016). In general, omega-3 fatty acids are well tolerated, rarely causing skin reactions (eczema, itching) and gastrointestinal ADR (Guu et al. 2019).

Some studies support the administration of magnesium to augment depression treatment (Serefko et al. 2016, Botturi et al. 2020). Magnesium regulates the HPA axis and - similar to ketamine - acts as an antagonist at the NMDA receptor, but also on other mechanisms of glutamatergic, serotonergic, dopaminergic, and noradrenergic neurotransmission (Botturi et al. 2020).

Similarly, recent meta-analyses showed small but significant antidepressant effects when augmenting antidepressant therapy with probiotics (live gut bacteria) (Chao et al. 2020). While nutrient deficiencies (such as the common vitamin D deficiency in depressed patients) should be adequately substituted, nutraceuticals are obviously not a substitute for a healthy diet. Changes in dietary style with abundant fruits and vegetables, such as the Mediterranean diet, modify the gut microbiome, significantly reduce inflammatory factors and depressive symptoms, and thus should be the basis of any antidepressant therapy (Firth et al. 2019).

7.7 Benzodiazepines in TRD

In the context of antidepressant treatment, benzodiazepines are often used with the intention of bridging the effect of antidepressants in the presence of anxiety, agitation, or insomnia, or in the presence of very severe symptom expression and suicidality. In the GSRD study program already characterized above, a prescription rate for benzodiazepines of 31 % in addition to antidepressant therapy was recorded in 1410 depressed patients. This add-on therapy with benzodiazepines was associated with the presence of severe depressive symptoms, suicidality, additional psychotic and melancholic symptoms, comorbid anxiety and obsessive-compulsive disorders, the need for inpatient treatment and further psychopharmacotherapeutic strategies, and older age and unemployment (Dold et al. 2020a). These data leave space for interpretation. While inadequate treatment of prominent depressive symptomatology as well as comorbidities is a significant predictor of chronicity and treatment resistance (Silberman and Weiss 2016; Dold et al. 2017b; Dold et al. 2020a), it is debated whether prolonged use of benzodiazepines may not itself contribute to the development of TRD (Parker and Graham 2015).

Benzodiazepines should never be prescribed as a permanent medication, but generally only for short periods. Their use must be assessed with regard to possible risks (e. g., sedation, cognitive impairment, dependence) (Bauer et al. 2017) and should only be administered in the context of regular psychiatric care. Non-indicated further prescriptions should be avoided (Dold et al. 2020a). Only clonazepam may be prescribed for longer periods in unipolar depression due to its long halflife and lower abuse potential (Winkler et al. 2003).

In the therapeutic process, attention should be paid to the mode of action of benzodiazepines, which is based on modulation of GABAergic neurotransmission, which is crucially involved in the underlying neurobiology of depression (Luscher et al. 2011). Since new compounds with GABA-modulating effects have been investigated in the treatment of depression and TRD in particular, and partially approved by the FDA given their rapid antidepressant effect in the absence of dependence potential (brexanolone, a progesterone metabolite, in post-partum depression) (Gunduz-Bruce et al. 2019), benzodiazepines could potentially be replaced by these promising compounds in future. Their implementation would represent a crucial advance in the psychopharmacotherapy of depression (Dold et al. 2020a).

7.8 Intranasal use of esketamine

Intranasal (i.n.) use of the levorotatory enantiomer of ketamine was approved in 2019 in both the United States and Europe for the treatment of TRD (Kasper et al. 2020; McIntyre et al. 2021). In accordance with the current European approval, esketamine nasal spray is recommended for use only in combination with an SSRI or SNRI in adult patients who have failed to respond to at least two adequate antidepressant therapies in the course of a moderate-to-severe depressive episode. This was preceded by clinical observations and studies in a small number of cases with the intravenous use of ketamine or esketamine (Kraus et al. 2017).

Initially, esketamine i.n. is administered at a dose of 56 mg/application; 65-year-old and older patients receive an initial dose of 28 mg. From the second application onwards, the application dose comprises 56 mg or 84 mg for those under 65 years of age, and 28 mg or 56 mg for patients ≥ 65 years of age, respectively, which is either maintained or increased to 84 mg in the course of further treatments, depending on individual therapy response and tolerability. During the so-called induction phase, scheduled for four weeks, esketamine i.n. is administered twice weekly. At the end of the induction phase at the latest, the therapeutic benefit is to be assessed in order to decide whether treatment should be continued. If there is adequate therapeutic response and good tolerability, the frequency of esketamine i.n. administration will be reduced to once weekly with the initiation of maintenance therapy beginning at the fifth week of treatment. From the ninth week, a further reduction to once every 2 weeks can be made. From improvement of symptomatology of depression, it is recommended to continue treatment for a period of at least 6 months.

To ensure optimal implementation of antidepressant therapy with esketamine i.n., both indication and regular treatment with esketamine nasal spray should be carried out exclusively by specialists in psychiatry who, compared to specialists in other medical disciplines, have extensive expertise in the field of psychiatric clinical pictures and their treatment options. The antidepressant treatment with esketamine i.n. itself as well as the follow-up, which is done by the medical staff after the application, can be implemented very well in both inpatient and extramural settings. Here, a pleasant and calm environment of the treatment premises, training of the staff and precise information of the patients in advance are key prerequisites for a successful treatment.

When determining the indication for antidepressant treatment with esketamine i.n., potential contraindications should be carefully considered. These include unsatisfactorily controlled blood pressure, condition after cardiovascular events in the last six weeks, condition after intracerebral hemorrhage in the history, vascular aneurysms including aneurysms of intracranial vessels, thoracic or abdominal aorta or peripheral arteries, known hypersensitivity

to the active substance or one of its other components, pregnancy and lactation. In addition, esketamine i.n. should not be used in patients in whom an increase in blood pressure or intracranial pressure has been shown to pose a serious risk. Furthermore, it is important to assess each patient's individual risk for abuse or dependence before prescribing esketamine.

Before starting treatment, a detailed medical history, a physical examination including blood pressure and heart rate measurement, an ECG (electrocardiogram) and laboratory tests should be carried out. Patients should be given a comprehensive explanation of the substance, its form of application, dosage, efficacy, tolerability, any adverse reactions, and how to deal with them properly. The treatment period and further treatment options should also be discussed in the event of a possible lack of response. In addition, patients should be informed in advance not to eat 2 h before esketamine administration, not to use decongestant nasal drops 1 h before, and not to consume beverages 30 min before.

In order to evaluate the severity and expression of current depressive symptoms as accurately as possible, documentation of treatment success using depression scales, which can be done by the treating physicians (HAMD, MADRS) or the patients themselves (Beck Depression Inventory, BDI [Beck AT et al. 1961]; Patient Health Questionnaire-9, PHQ-9 [Lowe B et al. 2004]), is additionally recommended.

The administration of esketamine nasal spray is to be carried out by the patients themselves under the supervision of the medical staff in ten steps, which are explained in practical terms as follows due to the still unfamiliar form of intranasal application in psychiatry:

1. Patients take a comfortable position in a recliner or on a couch and briefly blow their nose with a handkerchief.
2. After the blood pressure has been measured by the medical staff, the first applicator is given to the patients with normotensive RR values.
3. The applicator with 28 mg esketamine should be held by the patients with their right hand. The index finger and middle finger are placed on the finger rests, the plunger is slightly supported by the thumb.
4. The patients lean their head back about 45° and insert the tip of the first applicator straight into the right nostril. Care should be taken to ensure that the nasal pads make contact with the skin between the two nostrils.
5. While holding the left nostril closed with the fingers of their left hand, the patients inhale through the nose while pushing the applicator plunger up as far as it will go.
6. After the spray is now delivered, the air in the nose is pulled up slightly so that the drug remains in the nose.
7. The same first applicator is now taken in the patients' left hand to deliver the spray into the left nostril in the same way as described above.
8. After both spray cans of the first applicator have been dispensed, the operator checks that no green dot is visible in the display window (= confirmation that the application has been performed correctly).
9. Patients should now lean back comfortably for five minutes so that the drug can be absorbed sufficiently through the mucous membranes. If fluid drips from their nose, the nose should be dabbed with a cloth. Patients should not blow their nose under any circumstances. At a treatment dose of 56 mg, after five minutes, treatment is continued with the second 28 mg applicator in the same way as described above. At a treatment dose of 84 mg, the third applicator is used after the application of the second applicator and a subsequent five-minute break.
10. During the follow-up period, blood pressure should be monitored approximately 40 minutes after use and subsequently at clinical discretion, and patients should be monitored for well-being and potential adverse events. In the clinical trials, 93.2% of patients were discharged symptom-free after 90 minutes.

In the course of the antidepressant treatment with esketamine nasal spray, a rapid onset of action was observed with response rates up to 70% and remission rates up to 53% at 28 days (Popova et al. 2019). After 48 weeks, response rates ranged up to 77% and remission rates up to 58% (Wajs et al. 2020). From the patient perspective, rapid onset of relief is very commonly reported. This is often accompanied by regaining the ability to enjoy oneself or to engage in creative activities. Patients report that soon they no longer need to bring themselves to undertake everyday activities and subsequently have an increased drive to become socially and professionally active again. The self-administered intranasal application by the patients, accompanied by medical staff, is usually positively evaluated by the patients as an active contribution to the treatment. They have control over it and are relieved that immediately after application an observation phase is carried out by trained medical personnel.

Dissociative phenomena, which can occur in up to 28% of patients immediately after the use of esketamine nasal spray (Kasper et al. 2020), are among the most frequent adverse effects, which are predominantly mild and transient. These are experienced quite differently, but are very rarely the reason why patients do not want to continue this therapy. They are also not a marker for therapy response and should not be used as a reason for psychotherapeutic treatment, but should be explained to patients as adverse effects, just like dizziness and nausea.

Patients should be thoroughly informed that after the application of esketamine nasal spray on the day of treatment, they should not drive a car or operate machinery until the next day after a restful sleep. It is important to mention that the patients travel home by public transport or cab. In addition, nausea, vomiting, dysgeusia (altered taste sensation), dizziness, sedation, hypaesthesia (decreased sensation of pressure or touch), headache, or loss of balance were observed in ≥10% of the patients studied. A blood pressure increase ≥180 mmHg systolic occurred in approximately 4% of patients, while a diastolic blood pressure increase ≥110 mmHg occurred in approximately 3%. Craving or abuse behaviors have not been observed to date in the TRD patient population as a result of lege artis i.n. esketamine therapy (Wajs et al. 2020).

The esketamine nasal spray was also studied in depressed patients who were assessed as acutely suicidal (i.e., with suicidal intent) (Ionescu et al. 2021). Parallel to the decrease in depression scores, there was also a reduction in suicidality. In this context, however, it should be emphasized that all precautionary measures indicated

for suicidal patients should also be applied to suicidal patients under esketamine therapy (Kasper et al. 2005).

With the approval and availability of esketamine nasal spray, the previous off-label use of i.v. ketamine has been rendered unnecessary and is reserved for the intramural setting due to the associated devices.

8 Non-pharmacological, biologically-based therapy methods

Several nonpharmacological interventions are now used alongside pharmacological therapeutic strategies in the treatment of treatment-resistant depression. For example, although scientific data are very limited in TRD, chronotherapeutic procedures such as light therapy (using bright white visible light) or complete or partial sleep deprivation may be a valuable adjunct to antidepressant therapy in some patients with persistent chronobiological disturbances. However, four stimulation methods used in the treatment of TRD will be briefly described below with their modes of action and response rates:

- Electroconvulsive therapy
- Transcranial magnetic stimulation
- Vagus nerve stimulation
- Deep brain stimulation

8.1 Electroconvulsive therapy

Electroconvulsive therapy (ECT) is the most effective nonpharmacological therapy for the treatment of TRD (Conca et al. 2004). ECT is currently offered at the psychiatric departments of the following Austrian university hospitals and clinics: Medical University of Vienna, Medical University of Graz, Medical University of Innsbruck, Kepler University Hospital Neuromed Campus Linz, University Hospital Salzburg, Rankweil Regional Hospital, Pyhrn-Eisenwurzen Clinical Center Steyr, Villach Regional Hospital, Villach Private Clinic, Neunkirchen Regional Hospital, Salzkammergut Clinic Vocklabruck, and Wels-Grieskirchen Clinical Center. For about 150 patients with severe affective or schizophrenic disorders, a total of about 1500 to 2000 ECT treatments are performed per year in routine clinical practice at psychiatric departments in Austria.

Acute treatment of depression with ECT involves an average of ten individual treatments (ECT series) at a frequency of 2 to 3 times per week during an inpatient stay. An effect can only be expected after four to five treatments. Bilateral (BL) stimulation is more effective than right unilateral (UL). If treatment is to be/can only be given twice a week, the BL mode is preferable. Memory disturbances as an undesired side effect (see below) are more frequent and more pronounced with BL stimulation than with UL stimulation, but reversible in the long term (Hasse-Sander et al. 1998).

The main indications for ECT are severe unipolar and bipolar depression, depression with psychotic features, and TRD. However, ECT is also indicated in severe manic and mixed affective episodes, as well as in paranoid and catatonic schizophrenia. ECT has the highest evidence in TRD because TRD is frequent and prospective studies with consenting patients are well planned and abundantly published. In contrast, ECT is considered vitally indicated for life-threatening pernicious catatonia, although there are only impressive case series for this rare indication.

In ECT, patients under intravenous short-acting anesthesia (using methohexital or propofol or etomidate) and muscle relaxation (using succinylcholine, because it is short-acting, with mask ventilation, usually without intubation) by applying a current flow (short pulses in square wave) between two electrodes at the frontotemporal area of the skull (right unilateral or bilateral) a generalized epileptic seizure of 20 to 60 seconds duration is triggered (self-limiting). Response rates are high: patients with TRD show remission and response rates of about 40 % and 65 %, respectively. In patients with severe unipolar depression, who have not previously proven resistant to therapy, response rates are even significantly higher (75-95 %).

For ECT responders who have a history of relapse after completion of an ECT series, ECT maintenance therapy (one ECT per month for six months or longer) is indicated. For methodological reasons, there is not as much evidence on this as on the efficacy of the acute ECT series, but clinical experience has been very positive (Baldinger et al. 2014a). ECT is usually accompanied by a prescription of psychotropic drugs; on the one hand, ECT "off-drug" has not proved its worth, and on the other hand, there is no consensus recommendation in the literature for certain antidepressants or augmentation strategies. Lithium should be used in relatively low doses or paused during ECT (increased muscle relaxation during anesthesia; higher incidence of postictal disorientation), but lithium should be considered after the ECT series or concomitantly with maintenance ECT.

The complex mechanisms behind the antidepressant and antipsychotic effects of ECT are still not fully understood. In the scientific literature, there are several hypotheses that assume a change in various neurotransmitter systems (Lanzenberger et al. 2013; Baldinger et al. 2014b). Furthermore, an increase in neurotrophic factors under ECT has been observed in some studies (Vanicek et al. 2019) - a mechanism that is also discussed as a possible mode of action of certain antidepressants. In this context, it is interesting that an increase in volume in the hippocampus and amygdala has been described after ECT (Gryglewski et al. 2019).

A series of six to twelve individual treatments (2-3 x per week) is required to achieve an antidepressant and/or antipsychotic effect. During the treatment series, the seizure threshold increases, which usually necessitates a successive increase in the stimulus dose (max. 1000 millicoulombs, mC, are permitted). Thus, ECT also has an anticonvulsant effect. The risks of ECT performed lege artis are relatively low and essentially correspond to the risks of repeated brief anesthesia. The mortality risk of ECT under anesthesia is approximately 1:30 000.

During ECT, there is often a transient postictal increase in blood pressure (caution: insufficient blood pressure control and recent cardiovascular events are relative contraindications) and transient postictal confusion (< 10 %). Transient headache and nausea occur in less than 50 % of patients. During the course of the ECT series, anterograde amnestic disturbances occur in approximately 50 % of patients and remit within less than two months after the end of treatment (Semkovska and McLoughlin 2010). It should be emphasized that the risk-benefit ratio with regard to potential transient memory disturbances is clearly in favor of ECT.

8.2 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive stimulation proce-

dure in which a current flow is induced in the cortical areas by means of alternating magnetic fields. For this purpose, a magnetic coil is placed directly over the cortical areas to be stimulated in the awake patient and a magnetic field is induced with repetitive current pulses, which influences the neuronal activity of these cortical areas. Since 1993, TMS has been established in the treatment of depression of different severity levels as well as in TRD, starting from the working group of Kasper and Möller at the Psychiatric University Hospital in Bonn (Höflich et al. 1993; Kolbinger et al. 1995).

The underlying mode of action is still not fully understood. It is assumed that the altered activity of the stimulated areas, in particular the prefrontal cortex, influences deeper structures, such as the limbic system, and that this leads to an improvement in depressive symptoms.

Responder and remission rates have improved continuously over the years. While in older studies they ranged between 24 and 30 % and 14 and 20 %, respectively (e. g., O'Reardon et al. 2007), more recent studies show significantly better results of 38 to 50 % and 32 to 38 %, respectively (Levkovitz et al. 2015; Bakker et al. 2015). These successes are attributed to a number of optimizations in treatment protocols. Several international consensus statements and guidelines with treatment guidelines have been published (e. g., Rossini et al. 2015; Perera et al. 2016). They reflect the growing body of knowledge on TMS treatment. For example, it has become clear that higher stimulation intensities (e. g., 120 % of resting motor threshold) and longer treatments (over at least four weeks, with once-a-day treatment) tend to result in higher success rates. Notwithstanding a variety of promising new developments in coils, stimulation parameters, and treatment protocols, the standard protocol still recommended is high-frequency repetitive TMS (rTMS) over the left dorsolateral prefrontal cortex (localized using, for example, the 10-20 system of electrode application) over four to six weeks.

The recommendation for the use of TMS today is in adult patients with moderate to severe TRD in an acute depressive episode. Treatment should be provided in a clinical setting by a trained team and under the supervision of a psychiatrist. Accompanying psychopharmacotherapy is possible but not obligatory. If satisfactory treatment success is achieved during the acute treatment phase, subsequent maintenance TMS may also be recommended. Once treatment success has been achieved with TMS, repeat TMS treatment may be recommended if relapses occur. Care should also be taken to objectively document clinical effect with appropriate psychometric scales as part of routine treatment.

TMS is usually well tolerated and is considered safe and tolerable compared to other stimulation methods due to its non-invasive nature and treatment on awake patients. However, headaches occur in 30 % of cases and sleep disturbances in 8 % during TMS treatments. However, the disorders disappear completely shortly after the end of the therapy. Epileptic seizures after TMS are possible, but very rare with a frequency of less than 0.1 % of cases. Nevertheless, the TMS treatment team must be prepared for the unlikely event of a seizure. Guidelines for what to do if ADRs occur must be established and all personnel involved must be aware of them. Daily prefrontal rTMS shows an effect comparable to pharmacological treatment. According to current studies and clinical evidence, however, ECT is likely to be superior to TMS in terms of response rates.

A relatively new development of rTMS is theta burst stimulation (TBS) (Kreuzer et al. 2017). Due to a serial delivery of pulses in the 200 ms range, TBS gets by with shorter treatment durations of only a few minutes, which primarily brings advantages in clinical application. Similar to high-frequency TMS, TBS has excitatory effects on neurons below the stimulation area with very good tolerability. Transcranial direct current stimulation (tDCS) is currently still being investigated as a possible treatment modality for depression.

8.3 Vagus nerve stimulation (VNS)

Vagus nerve stimulation is a stimulation method originally developed for epilepsy therapy, which has also been approved for the treatment of TRD in some countries since 2005, for example by the FDA in the USA. Stimulation of the left vagus nerve is performed electrically by an implanted neurostimulator. This causes a reduction in sympathetic activity and subsequently a reduction in cortisol production.

The antidepressant effect is explained by different hypotheses. Besides the possible influence on cortisol secretion, it is assumed that vagus nerve stimulation leads to a change in the metabolism of limbic structures. Furthermore, a change in the "firing rate" of serotonergic neurons by the VNS could be shown. This leads to an increase in serotonin in the synaptic cleft, which could also explain the antidepressant effect. Studies have shown response rates - depending on the duration of treatment - of between 30 % (Sackeim H et al. 2020) and a maximum of 50 % (Bajbouj et al. 2010). Incidentally, stimulation of the vagus nerves also occurs during ECT.

Through longer observation periods in open studies it was discovered that the maximum effect of antidepressant VNS occurs only after six to twelve months of therapy. In trials response rates in these chronically depressed patients from 39 % to 67.6 % were reported compared to 40.9 % for treatment as usual ("TAU") - for treatment durations between one and five years. Remission rates were 43.3 % versus 25.7 % for TAU (Aaronson et al. 2017). Urgently needed sham treatment-controlled trials over a period longer than one year of treatment are currently being conducted worldwide.

Antidepressant VNS should be performed at a specialized center because it requires a neurosurgical procedure under general anesthesia of approximately 60-90 minutes. VNS therapy, which is easy to adjust, should be performed by a trained team over an extended period of months to years. The surgery is associated with few complications, mainly pain in and around the surgical site on the neck (19 %). During VNS stimulation, which is usually given for 30 s at intervals of 5 min, mild hoarseness occurs in up to 75 % of patients. If patients have a speaking job or have to sing, the stimulation can be switched off temporarily without any problems, which also relieves the hoarseness. Other ADRs include subjective dyspnea (32 %), sore throat (31 %), increased throat clearing and coughing (25 %), headache (18 %), and increased restlessness and anxiety (11 %). If ADRs interfere with daily living, stimulation parameters can be altered or VNS therapy can be briefly discontinued.

8.4 Deep brain stimulation

Deep brain stimulation (DBS) is currently successfully used in the treatment of

patients with Parkinson's disease. It has also been used experimentally in the treatment of patients with TRD for several years. For DBS, electrodes are implanted bilaterally in the target region of the brain - in the subgenual gyrus cinguli or in the nucleus accumbens/ventral striatum/internal capsula. It is therefore a highly invasive method that requires neurosurgical intervention and has only been used in about 500 patients worldwide in the indication TRD. Response rates of 40 to 70 % have been reported (Schlaepfer et al. 2010; Höflich et al. 2013). The observation periods in the positive studies are twelve months or more.

The implanted electrodes are connected via four stimulation contacts to a neurostimulator, which is placed subcutaneously below the collarbone and continuously stimulates the electrodes in the target region.

The antidepressant effect is probably due to a disturbance in the neuronal network that processes affective stimuli. Stimulation of individual brain regions in this network initiates a change in overall network activity. In studies, several regions in this network have been investigated as target regions. These are brain areas that play a vital role in the affective stimulus processing system: stimulation of the ventral striatum, where the nucleus accumbens is located between the caudate nucleus and the putamen, using DBS resulted in a 53 % response rate and a 40 % remission rate in patients with TRD (Malone et al. 2009). Stimulation of the nucleus accumbens resulted in a response rate of 50 % (Bewernick et al. 2010). Stimulation of the subgenual cingulate cortex resulted in a response rate of 64 % and a remission rate of 43 % (Kennedy et al. 2011). According to case reports, DBS has also been used in other brain regions and similarly produced a significant response in terms of a reduction in depressive symptoms. DBS is promising in the lateral habenula (Sartorius et al. 2010).

These significant response rates are offset by potentially significant adverse events. These include implantation-associated adverse events such as bleeding (0.2 to 5 %) and infections caused by the foreign material introduced into the brain (2 to 25 %). These complication rates are well known from neurology (Parkinson's disease) and, according to previous experience, also apply to psychiatric patients. In addition, however, continuous stimulation also potentially leads to ADRs such as paraesthesias, muscle contractions, dysarthria, diplopia, and autonomic dysfunction. Psychiatric ADRs such as agitation, anxiety, and hypomania may occur. In principle, continuous stimulation can be modulated or switched off. The experimental nature of this invasive procedure must be pointed out. In fact, despite promising study results, DBS has not yet become established in clinical routine.

There are also promising experimental results in two other psychiatric indications. In psychotropic drug-resistant obsessive-compulsive disorder, a target area in the ventral striatum is stimulated, resulting in response rates even higher than TRD. In severe motor tic disorders (Tourette syndrome), good results are reported with DBS of the thalamic nucleus areas (Höflich et al. 2013).

9 Psychotherapy in TRD

In the treatment of TRD, psychotherapy can be a possible add-on therapy. Up to now the following psychotherapies have been used as add-on procedures in efficacy studies: cognitive behavioral therapy (CBT), cognitive behavioral analysis system of psychotherapy (CBASP), mindfulness-based cognitive behavioral therapy (MBCT), and psychodynamic psychotherapy.

The DGPPN S3 care guidelines for unipolar depression (evidence-based psychotherapy of depression) recommend offering patients appropriate psychotherapy for TRD (S3 guideline/unipolar depression 2015, edited 2017). The UK NICE (National Institute for Health and Care Excellence) guideline suggests, too, that in the absence of a response to antidepressants, a change in antidepressant dosage or complementary therapy with another psychotropic drug should be undertaken or psychotherapy should be started.

However, studies of the effectiveness of psychotherapy for treatment-resistant depression often have methodological limitations. The definition of treatment-resistant is inconsistent, and small case numbers often do not differentiate between chronic depression and TRD, limiting the generalizability of these study results. There is definitional ambiguity, especially in the older studies, in distinguishing chronic depression lasting more than two years on the one hand from a treatment-resistant depressive episode on the other. The data to date indicate that CBT is most likely to be recommended as an adjunctive therapy to psychopharmacotherapy for TRD.

A systematic review by Trivedi et al. 2011 identified seven studies that examined psychotherapy (mainly cognitive behavioral therapy) as an add-on or alternative to medication for treatment-resistant depression. This showed that psychotherapy can provide additional benefit as an add-on to drug treatment in three high-quality studies, one moderate-quality studies, and two studies with methodological limitations.

Compared with routine treatment, Wiles et al. 2013 found that CBT (n = 469) significantly improved treatment outcome (46 vs. 22 %) and patient quality of life. Treatment success was still detectable at 12-month follow-up. Similarly, the study by Nakagawa et al. (2017) showed that a combination of psychopharmacotherapy with CBT reduced depressive symptomatology and relapse rate after 16 weeks, and the treatment effect was still present at 12-month follow-up.

Li et al. conducted a systematic meta-analysis in 2018 that included six randomized trials (n = 847). It confirmed that CBT can be an efficient therapy for reducing depressive symptoms and increases remission rates in TRD.

Strawbridge et al. (2019), in a meta-analysis of the efficacy of add-on psychotherapy for TRD, found that CBT was most effective with an effect size of 1.74; psychoanalytic therapy showed an effect size of 0.59. Furthermore, TRD uses procedures that are both disorder-specific and integrative.

These procedures include CBASP and MBCT. The Cognitive Behavioral Analysis System of Psychotherapy is a psychotherapy procedure specifically designed to treat chronic depressive episodes and includes cognitive-behavioral, interpersonal, and psychodynamic elements. The combination of CBASP with medication was superior to monotherapy with an antidepressant or psychotherapy alone. In the work of Wiersma et al. (2014), CBASP was shown to be more effective than treatment with CBT, interpersonal psychotherapy (IPT), and depth psychotherapy (TP), each

in combination with antidepressants, especially in the long-term course. Especially in TRD, the inpatient CBASP program may be an important treatment option (Brakemeier et al. 2015).

As another complement to pharmacotherapy in TRD, MBCT can be applied. This involves the cognitive regulation of emotion processing. Intensification of selective attention and executive functions through meditation can contribute to a decrease in the tendency to brood and thus to an improvement in depression. In TRD, this method was found to have a beneficial effect in relapse prevention (Eisendrath et al. 2016).

One study exists on long-term psychoanalytic treatment (Fonagy et al. 2015) in TRD. In long-term follow-up, there were improvements in remission rates, depressive symptomatology, and psychosocial adjustment. A meta-analysis (van Bronswijk et al. 2018) included 21 studies with 7 different psychotherapies. Superiority with moderate effect size was found for combination treatment of psychopharmacotherapy with psychotherapy for TRD. The network meta-analysis by Cuijpers et al. (2020) on the effect of psychopharmacotherapy, psychotherapy, or their combination on depression included 101 studies with 11 910 patients. For chronic and treatment-resistant depression, combination treatment was shown to be more effective than psychopharmacotherapy or psychotherapy alone in terms of a 50 % reduction in depressive symptomatology at six- and 12-month follow-up. Due to the small number of studies, no differentiation was made between chronic depression and treatment-resistant depression, and no definition was given for a specific outcome, so these results should be interpreted with caution. In the European Collaborative Study (GSRD) on TRD, it was retrospectively surveyed in the total group of 1279 patients that 32 % received psychotherapy (mostly CBT), which, however, did not prevent TRD (Bartova et al. 2021).

In summary, despite methodological limitations, it can be assumed that a combination of psychopharmacotherapy and psychotherapy may be an option in TRD. The efficacy data to date show the highest effect size for the efficacy of CBT. However, the choice of an add-on therapy also depends on the availability of the therapies and the motivation and acceptance of the patients.

10 Treatment algorithm for TRD

In the treatment of TRD, an approach according to a defined treatment algorithm has proven to be clearly superior to "treatment as usual" (TAU). Corresponding recommendations can therefore be found in both European and US treatment guidelines (Table 6).

Several studies show the superiority of systematic treatment of patients with TRD compared to TAU. For example, a study by Bauer et al. in 2009 achieved a remission rate of 39 % with TAU. A Japanese group (Yoshino et al. 2009) achieved remission rates of 50 % with TAU. However, treatment according to a defined therapy algorithm led to significantly higher remission rates in both studies of 54 % (Bauer et al. 2009) and 60 % (Yoshino et al. 2009), respectively.

The three factors listed below are reasons why the patient with depression does not respond to the first antidepressant prescribed:

1. Physician factors:
- Is there a TRD at all?
- Is the therapy adequate for the patient?
- Are there unrecognized depressive subtypes present (bipolar/atypical/psychotic)?
- Is there a delay in the onset of action of the prescribed antidepressant?
- Are there any problems in maintenance therapy?

2. Patient factors:
- Underestimation of the biological complexity of the disease
- Comorbidities (both psychiatric and somatic).
- Personality disorder

3. Social and interaction factors:
- Stressors for the patient
- Interaction with the patient
- Lack of adherence

A guideline-based approach means, among other things, that the above-mentioned factors are taken into account in the treatment of TRD, which can increase response and remission rates. Last but not least, an open and honest approach to patients is of great importance. Under no circumstances should unsustainable hopes be raised, as these can turn into disappointment if the hoped-for therapeutic success fails to materialize, thus increasing the risk of non-adherence. It should always be kept in mind that TRD is a challenge for both practitioners and patients.

An algorithm has recently been presented by European experts that incorporates the considerations for dose escalation, augmentation, combination, and also change of focus given in chapter 7 and in Table 4 (Kasper et al. 2020). Because intranasal use of esketamine has only been studied in patients with TRD, this administration appears in Figure 5 as a third possible treatment step. It is important to emphasize that psychotherapy or ECT can be considered at any treatment step and the patient should not be assigned to one of these treatments based on severity or duration of treatment if there is evidence from the history or current status for a favorable response to this form of therapy. In addition, reference should also be made to the S3 guideline "Psychosocial therapies in severe mental illness", which recommends the use of multimodal health-promoting interventions with a focus on healthy eating and physical activity (recommendation grade A; DGPPN 2019).

11 TRD in elderly patients

Especially in older patients, the principle "one must be patient with the patient" must be considered. Unfortunately, elderly patients in particular are often treated suboptimally. Experience shows that the randomly and inadequately dosed, uncontrolled succession of antidepressants is not uncommon and can be held responsible for the development of TRD. In particular, increasing drug doses should be viewed critically, especially since reviews (Adli et al. 2005) show that high-dose therapy may be a reasonable option only with certain antidepressants. Especially with the most frequently used SSRIs, however, no additional effect can be expected from high-dose therapy. Moreover, dosing up wastes valuable time (Bschor et al. 2014).

A 2011 systematic review by Cooper et al. provides guidance for the treatment of TRD in the elderly patient. Fourteen studies were identified for the paper after an electronic database search. However, these were almost exclusively open studies; double-blind randomized placebo-controlled

studies are lacking. The analysis showed an overall response rate to drug therapy of 52%. With regard to augmentation therapy, lithium proved to be the most effective option with a response rate of 42%. In individual randomized trials, venlafaxine XR was shown to be superior to paroxetine. A recent study on lithium augmentation was convincing with a response rate of 68% and at least a 50% improvement in depressive symptoms in TRD of elderly patients (Buspavanich et al. 2019).

Interestingly, older patients show twice the response rate compared to younger patients. A sequential treatment strategy for TRD is promising in older patients. In 2009 a trial (Kok et al. 2009) was conducted with 81 patients with TRD who had previously participated in a 12-week comparative study (venlafaxine vs. nortriptyline) and were subsequently invited to participate in a follow-up study that examined a sequential treatment protocol. 32 patients who had not achieved remission in the comparative study received the following therapies sequentially in an open-label protocol: augmentation with lithium, conversion to an MAO-I, or ECT. Over the three-year study period, 84% of patients achieved remission. Augmentation with lithium already resulted in a remission rate of almost 64% in previously treatment-resistant patients. Especially in the group of elderly patients, the choice of antidepressant medication should be guided not only by the efficacy proven in studies, but also by the side effect profile of the different substances (Table 7).

Therefore caution is also required in the use of atypical antipsychotics for the treatment of TRD in older age, especially since hardly any study data are available. They should therefore only be used under regular re-evaluation. Quetiapine XR should be titrated much more slowly in the initial phase of therapy in elderly depressed patients. An attempt of reduction or discontinuation after six weeks is recommended. The indication should be reviewed regularly, especially since cerebrovascular events have been reported with long-term use of atypical antipsychotics in elderly patients with dementia.

Of all atypical antipsychotics, augmentation therapy with aripiprazole has the best efficacy and safety data. One study reviewed aripiprazole augmentation in over-60s who did not show remission on a first-line antidepressant: 44% achieved remission with aripiprazole augmentation versus 29% on placebo (Lenze et al. 2015).

Recent trial data show that MAO-B inhibitors, such as selegiline at a dosage of 60 mg/d, were more effective than TCA in early-stage TRD in the elderly (Kim et al. 2019). Augmentation with methylphenidate, which was ineffective as monotherapy but showed greater efficacy than citalopram alone in a 16-week randomized double-blind study of 143 geriatric patients with depression at doses of 5-40 mg/d in addition to citalopram 20-60 mg/d, also appears to be interesting (Lavretsky et al. 2015). Intranasal esketamine with flexible doses was compared in a 4-week randomized double-blind trial together with an antidepressant versus an antidepressant and placebo. No significance was reached in the primary outcome parameter; however, a subgroup in the MADRS Total Score achieved significant improvement with intranasal esketamine (Bahr et al. 2019).

A systematic review further demonstrates that omega-3 fatty acids can provide improvement in mild to moderate depression (Bae and Kim 2018).

11.1 Depression in dementia

In general, depressive episodes in dementia are well treatable, but treatment resistance can also occur in this patient population (Nelson and Devanand 2011). Efficacy is higher in response to antidepressants in a previous episode or in major depressive episodes. A recent study documented that SSRIs could delay the conversion of MCI (mild cognitive impairment) to

Organization	URL	Publication	Target group	Disease
American Psychiatric Association (APA)	http://www.psychiatryonline.com/pracGuide/pracguideTopic_7.aspx	2000; partial update 2005; revision 2010	Psychiatrists	Depression Dysthymia Seasonal depression
British Association for Psychopharmacology (BAP)	http://www.bap.org.uk/docsby-category.php?docCatID=2	2008	Psychiatrists, general practitioners	Depression Subclinical depression
Canadian Network for Mood and Anxiety Treatments (CANMAT)	http://www.bap.org.uk/docsby-category.php?docCatID=2	2016	Psychiatrists	Depression
National Institute for Health and Clinical Excellence (NICE)	http://guidance.nice.org.uk/CG90	2009	Psychiatrists, general practitioners	Depression Dysthymia Mild depression
Texas Medication Algorithm Project (TMAP)	http://www.dshs.state.tx.us/mhprograms/TIMA.shtm	2008	Psychiatrists, general practitioners	Depression
World Federation of Societies of Biological Psychiatry (WFSBP)	http://www.wfsbp.org/treatment-guidelines/unipolar-depressive-disorder.html	2017	Psychiatrists, general practitioners	Depression Dysthymia

- *Clinical Practice Recommendations for Depression (2009) (according to Malhi et al. 2009)*
- *Institute for Clinical Systems Improvement (ICSI) Healthcare Guideline for Major Depression in Adults in Primary Care (Institute for Clinical Systems Improvement 2010)*
- *S3 Guidelines (Germany 2009)*

Table 6: Treatment according to algorithms in important guidelines in Europe and the USA

AD (Bartels et al. 2018). Lithium inhibits GSK3 (glycogen synthase kinase 3), a key enzyme in the metabolism of amyloid precursor protein and in the phosphorylation of tau protein, and therefore may provide additional benefits (Kessing et al. 2008).

11.2 Non-pharmacological strategies for TRD in the elderly

Non-pharmacological treatment options such as milieu therapy or support for family members should be used to treat depression in the elderly.

A recent study is available on rTMS in TRD in the elderly: bilateral TMS showed a response rate of 40% compared to unilateral and "sham" TMS with good tolerance and only low drop-outs (Trevizol et al. 2019). ECT is considered the most effective method for depression and TRD. This is supported by a recent study that 78% of elderly patients showed at least a 50% symptom reduction with ECT. Remission occurred in more than 60%. Particularly patients with psychotic symptoms benefited from ECT (Dols A et al. 2017).

12 TRD in childhood and adolescence

With the introduction of SSRIs, pharmacologic treatment of depressive episodes in adolescence increasingly occurred and declined after reports of a possible increase in suicidality. However, current data show no increase in suicidality (Näslund et al. 2018), so SSRIs remain psychopharmacologic agents of first choice. In terms of psychotherapeutic procedures, the main choices are CBT and interpersonal psychotherapy (IPT).

The therapeutic algorithm is less well established empirically for depressive disorders in childhood and adolescence than in adulthood. First-line drug therapy is fluoxetine, and escitalopram is now approved in the United States.

Only 40-60% of children and adolescents show sufficient response to treatment with an SSRI. In the largest pharmaceutical industry-independent study of treatment resistance (TORDIA study, n=334 patients; Brent et al. 2008), the following findings were obtained (treatment options were switch to another SSRI - fluoxetine, citalopram, or paroxetine - or venlafaxine with or without CBT):

It could be shown that the additional use of CBT produced a better outcome than switching medication alone. There was no evidence of superiority of switching to venlafaxine compared with switching to an alternative SSRI, but more ADRs were seen with venlafaxine (Brent et al. 2008). A reanalysis of efficacy and tolerability showed slight superiority of fluoxetine and citalopram compared with paroxetine (Strawn et al. 2019). Thus, it should be noted that in patients without CBT, SSRIs lead to faster and more significant improvement in depressive symptoms than venlafaxine; in patients with CBT, the effects of SSRIs and venlafaxine are comparable (Suresh et al. 2020).

Accordingly, the S3 guideline on depression in childhood and adolescence recommends the use of a previously unused form of psychotherapy or the use of a previously unused SSRI (fluoxetine, escitalopram, citalopram, or sertraline) or the use of a combination of CBT and one of the aforementioned medications in the absence of a response to an initial treatment attempt (DGKJP, 2015).

There is still little data for children and adolescents on augmentation strategies used in adults and on combining antidepressants from two classes. Concerning the therapy with ketamine, an open-label study with 13 adolescents (14.5-18.8 years) is available (Cullen et al. 2018). This showed an average decrease in Children's Depression-Rating Scale-Revised (CDRS-R) scores of 42.5% (p=0.0004) with i.v. use (six infusions over two weeks), with generally good tolerability.

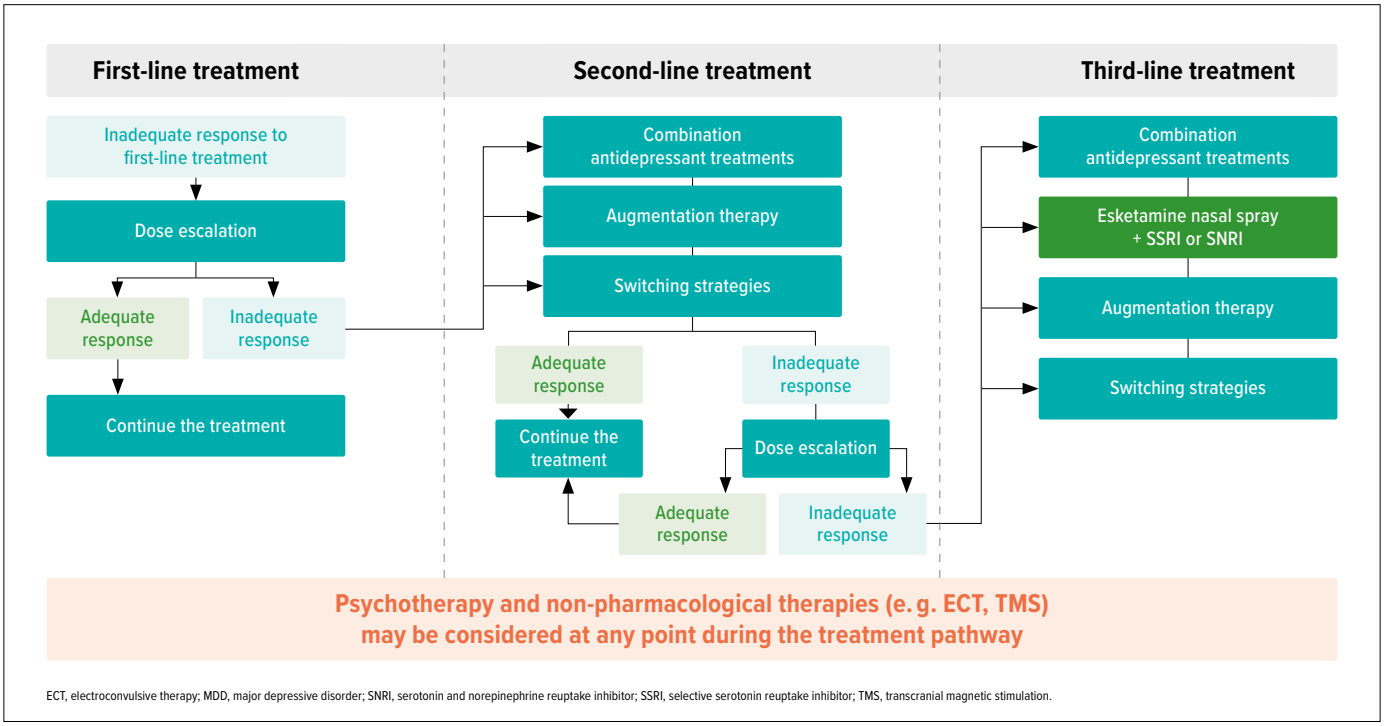

Figure 5: Treatment algorithm for major depressive disorder including the treatment with esketamine nasal spray (according to Kasper et al. 2020)

In the future, light therapy, TMS, add-on strategies such as nutritional interventions (O'Neil et al. 2014), and improved psychotherapy techniques that should be further developed for children, such as also CBT brief interventions or low-threshold digital therapy services, could be used. However, as with adults, the biggest problem is the high rate of undetected and untreated depression.

13 Summary

TRD is not uncommon and represents a significant challenge for both patients and practitioners. In this context, the patient's adherence is of particular importance. This is promoted by open discussion between practitioner and patient. Potential advantages and disadvantages of the various therapies must be clearly communicated. In everyday clinical practice, treatment should be based on the algorithms recommended by the international professional societies.

These include close monitoring of therapy and recommendations based on published evidence regarding appropriate dose optimization, possible augmentation and add-on strategies, and switching to other medications. Under no circumstances should the importance of non-pharmacological therapy methods for the treatment of TRD, such as ECT, be underestimated. Among the various methods of psychotherapy, CBT and its further developments currently have by far the most data available for this clinical picture. They show efficacy, especially when psychotherapy is used in addition to antidepressant medication.

A sequential approach is likely to prove effective, i. e., psychopharmacotherapy first and psychotherapy added later. As the basis of any treatment, a modification of lifestyle factors such as diet and exercise should also be sought as part of a multimodal, biopsychosocial therapy in order to achieve an optimal outcome. ■

Substance group	Agent	Anticholinergic effect	Sedation	Insomnia/ agitation	Orthostasis	ECG change	Gastrointestinal issues	Weight gain	Sexual dysfunctions
SSRI	Citalopram	0,5	0,5	0,5	0	0,5	1,5	0	2
	Fluoxetine	0	0,5	2	0	0,5	3	0	3
	Paroxetine	2	0,5	1	0	0,5	3	0–0,5	3
	Sertraline	0	0,5	1	0	0,5	3	0	2
ASRI	Escitalopram	0,5	0,5	0,5	0	0	1	0	2
SNRI	Duloxetine	0,5[1]	0	2	0	0,5	2	0	1
	Milnacipran	0,5[1]	0	2	0	0,5	2	0	0
	Venlafaxine retard	0,5[1]	0,5	2	0	0,5	3	0	1
Others	Agomelatine	0	0	0	0	0	2[2]	0	0
	Bupropion	0	0	2	0	0,5	1	0	0
	Mirtazapin	0,5–1	4	0,5	0,5	0	0	4	0
	Trazodone	0	3	0	2	0,5	1	0	0
	Venlafaxine	0,5	0,5	2	0	0,5	3	0	1
	Amitriptyline	4	4	0,5	4	3	0,5	4	2
TZA	Nortriptyline	1	2	0,5	1	2	0,5	2	2

[1] Pseudocholinergic noradrenergic effect (dry mouth, obstipation, transpiration), [2] Transaminase elevation
Legend: 0 not detectable, 0,5 minimal, 1 moderate, 1,5 medium, 2 significant, 3 moderately increased, 4 high
SSRI, Serotonin-re-uptake inhibitors, ASRI, alloosteric serotonin-re-uptake inhibitor, SNRI, serotonin-noradrenalin-re-uptake inhibitor, TZA: tricyclic antidepressants

Table 7: Relative side effect severity of selective antidepressants in the elderly patient (according to Pies RW et al. 2005)

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