CONTINUING MEDICAL EDUCATION

Chronic and Treatment Resistant Depression

Diagnosis and Stepwise Therapy

Tom Bschor, Michael Bauer, Mazda Adli

SUMMARY

Background: The 12-month prevalence of depression in Europe is approximately 7%; depression becomes chronic in 15–25% of sufferers. One-third to one-half do not respond to an initial trial of drug therapy lasting several weeks.

Methods: Selective literature review, including consideration of the German National Disease Management Guideline Unipolar Depression.

Results: At the end of an initial trial of treatment with an antidepressant drug, usually lasting four weeks, its efficacy should be evaluated systematically. In case of non-response, the following options have been found useful: measurement of the serum drug level, dose escalation (but not for selective serotonin reuptake inhibitors [SSRIs]), lithium augmentation, the addition of a second-generation antipsychotic (atypical neuroleptic), and any one of several defined combinations of antidepressants. There is no empirical evidence for switching to another antidepressant. Electroconvulsive therapy is the most effective treatment for refractory depression. Cognitive behavioral therapy, interpersonal psychotherapy, psychoanalysis and psychodynamic psychotherapy have also been found useful. The cognitive behavioral analysis system of psychotherapy (CBASP) was developed specifically for the treatment of chronic depression.

Conclusion: The structured application of treatments of documented efficacy, in a stepwise treatment algorithm that gives equal weight to drugs and psychotherapy, is the best way to prevent or overcome treatment resistance and chronification.

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Depression is a common condition that often takes a chronic course and fails to respond to treatment (*Box 1*). The 12-month prevalence of depression in Europe is 6.9%, according to the largest and best study of the subject to date (1). Depression is thus one of the most common diseases of any kind. It has not, however, become more common in recent years (1). Although it classically takes an episodic course, depression becomes chronic in 15–25% of sufferers (2). 50% of the depressed patients in a longitudinal study were well again six months later (e1), but 7% were still depressed ten years later (e2). Resistance to treatment is also common: in the approval and efficacy trials of various antidepressants, one-third to one-half of the patients did not respond to several weeks of treatment (2–4). The largest-ever study of the treatment of depression was the STAR*D trial (Sequenced Treatment Alternatives to Relieve Depression), carried out in the USA and involving over 4000 participants: only 37% were in remission after an initial 12-week treatment trial with citalopram, and 67% after four treatment trials (5).

Learning aims

In this article, we answer the following questions:

- What distinguishes true treatment resistance from pseudoresistance?
- What treatment options are available—drugs, psychotherapy, other—that can prevent or overcome treatment resistance and chronification?
- What scientific evidence underlies these treatment strategies, and how are they applied in practice?

Methods

This article is based on a selective literature search making use of the authors' personal experience, as well as on the most up-to-date German-language guideline

Psychiatric Department, Schlosspark-Klinik Berlin: Prof. Dr. med. Bschor

Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden: Prof. Dr. med. Bschor, Prof. Dr. rer. nat. Dr. med. Dipl.-Biol. Bauer

Fliedner Hospital Berlin and Department of Psychiatry and Psychotherapy, University Hospital Charité Campus Mitte, Berlin: PD Dr. med. Adli

Prevalence

The 12-month prevalence of depression in Europe is 6.9%, according to the largest and best study of this subject to date. Depression is thus one of the most common diseases of any kind.

for the treatment of depression: the S3 Guideline (German National Disease Management Guideline) Unipolar Depression (6). The S3 Guideline is, in turn, based on a systematic analysis of the literature.

Diagnostic evaluation

Often, when depression does not respond to treatment, the resistance to treatment is only apparent, because either the diagnostic evaluation or the trial of treatment was not properly conducted. This is called “pseudoresistance”; possible causes are listed in *Box 2*.

As there are many somatic and psychiatric diseases and comorbidities in the differential diagnosis of depression (9), only a systematic diagnostic approach can ensure that the diagnosis is correct. To be both scientifically well-founded and cost-efficient, the diagnostic evaluation should be performed in stepwise fashion, i.e., according to an algorithm (10). A basic evaluation should be done before any treatment is started; thereafter, if the patient does not respond to two properly conducted trials of treatment, the evaluation should be supplemented by a further diagnostic step to rule out pseudoresistance (*Figure 1*). Many of the treatment options require further diagnostic testing before they can be initiated, for reasons of safety (e.g., an ECG before treatment with selective serotonin reuptake inhibitors [SSRIs] or tricyclic antidepressants [TCAs]).

Many drugs can cause depression (*eBox 2*). Pharmacogenic depression should be suspected if there is a close correlation between the beginning of drug treatment and the onset of depressive manifestations; such suspicions should be confirmed, whenever possible, by a trial of drug cessation or substitution.

Pharmacotherapy

First step

Key elements in the successful treatment of depression are the following:

- adherence to a clear treatment strategy,
- treatment for an adequate period of time, and
- systematic evaluation of efficacy at predetermined time points.

Antidepressant drugs are the mainstay of pharmacotherapy for depression. About 30 drugs in this class are now approved for use in Germany. They all have a number of features in common: The rate of non-

BOX 1

Definitions: chronic/treatment resistant depression, dysthymia

- “Chronic” means that the depressive syndrome has been present for a long time, whether or not treatment has been attempted. The time at which depression becomes “chronic,” by definition, has been set (more or less arbitrarily) at two years. For chronification factors, see *eSupplement* and *eBox 1*.
- “Treatment resistance” means, not that depression is untreatable, but that it does not immediately respond to standard treatment. In a common definition, “treatment resistance” is taken to mean non-response to standard drug treatment, even though drug treatment is only one of the available therapeutic options. Depression is called treatment resistant if two trials of drug treatment, each of them at an adequate dose and for a long enough period of time, have had no beneficial effect. This definition, too, is partly arbitrary; more specific definitions grade treatment resistance according to the number of failed treatment attempts.
- “Dysthymia,” according to ICD-10, is a state consisting of a depressive syndrome, lasting for several years, with lesser severity than in depression as strictly defined (including chronic depression). The latter can also be called “major” depression to distinguish it from less severe conditions such as dysthymia. In the DSM-5 (the new standard US-American classification of mental illness, issued in May 2013), the once separate diagnoses “dysthymia” and “chronic major depression” are grouped together under the term “persistent depressive disorder”: the authors concluded that the diagnostic and therapeutic differences between the two entities were too small to warrant separate classification.

response is similar for all antidepressants. No antidepressant works immediately; as a clinical rule of thumb, one should wait three to four weeks from the beginning of treatment before judging whether a drug is effective, or up to six weeks in older patients (6). Nearly all antidepressants are thought to exert their clinical effect by increasing the intrasynaptic concentration of serotonin and/or norepinephrine in the central nervous system (CNS), through a variety of mechanisms (reuptake inhibition in the case of SSRIs, serotonin-norepinephrine reuptake inhibitors [SNRIs], and TCAs; inhibition of monoamine oxidase [MAO]; presynaptic α_2 -receptor antagonism by mirtazapine and mianserin).

Treatment resistance

“Treatment resistance” does not mean that depression is untreatable, but rather that it does not respond immediately to standard treatment.

Pseudoresistance to treatment

The resistance to treatment is only apparent (pseudoresistance) if either the diagnostic evaluation or the trial of treatment was improperly conducted.

BOX 2

Potential causes of pseudoresistance to treatment

- Incorrectly conducted antidepressant treatment
- Non-compliance
- Secondary gain from illness
- Unrecognized psychosocial factors causing or maintaining depression
- Unrecognized somatic comorbidity, or misdiagnosis of a somatic disease as depression
- Unrecognized psychiatric comorbidity, or misdiagnosis of another psychiatric disease as depression
- Drug-induced depression (see eBox 2)

Antidepressants vary considerably, however, in their side-effect profiles.

In the initial phase of treatment, an antidepressant should be selected on the basis of the patient's history, the side-effect profile, potential interactions with other drugs the patient is taking, and the physician's experience. It should be given in a standard dose. Suitable review articles should be consulted for information on standard dosages, side effects, and interactions (for example, References [6] and [11] are freely available).

For some antidepressants, notably TCAs and venlafaxine, the standard dose should not be given at the very beginning of treatment. A dose-escalation phase is needed to ensure tolerability and compliance, but it should be kept as short as possible. The latency period for the effect commences only when the standard dose has been reached. As soon as treatment with an antidepressant is begun, a particular date should be chosen by the physician and patient as the "decision day" on which they will jointly assess the efficacy of the drug (Figure 2). To make this assessment as reliable as possible, the patient's depressive manifestations should be meticulously documented before the treatment is

begun (psychopathological evaluation; standardized, observer based depression scales, e.g., the Hamilton Rating Scale for Depression [e4]; and self-assessment scales, e.g., the Beck Depression Inventory [e5]).

If the patient responds positively to the drug, the treatment is maintained as continuation therapy for six to twelve months after the remission of depressive manifestations. Clinical trials have clearly shown a very high risk of recurrence in this period; it is, therefore, recommended that antidepressant medication should be maintained for its entire duration, in an unchanged dose if possible (e6). An even longer, temporally open-ended administration of antidepressants is indicated for recurrence prophylaxis in patients who display a recurrent course of disease (as a rule of thumb, two or more episodes in five years, or three or more episodes overall).

If, on decision day, the response is judged to have been inadequate, drug treatment should be changed to a second-step strategy, as will be discussed in the next section.

Second step

Therapeutic Drug Monitoring (TDM)—For most antidepressants, adequate information is now available about the optimal range of the serum drug level for clinical efficacy. In case of non-response to any of these drugs, a serum level measurement is advisable, followed by upward or downward dose adjustment if indicated. A comprehensive overview of the recommended serum levels can be found in the consensus guidelines for therapeutic drug monitoring in psychiatry that have been issued by the German Working Group for Neuropsychopharmacology and Pharmacopsychiatry (*Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie*, AGNP) (12).

On the other hand, the determination of serum levels is not recommended for the following antidepressants, either because inadequate information is available or for pharmacological reasons: agomelatine, bupropion, moclobemide, paroxetine, and tranylcypromine.

Serum levels should be measured at their trough, i.e., blood should be drawn just before the next dose is taken. If the serum level is not in the therapeutic range despite the administration of a standard dose, the possible reasons include non-compliance, (rarely) inadequate resorption, and genetic variability of the cytochrome P₄₅₀ system, by which most antidepressants are metabolized. Moreover, concomitantly administered drugs frequently cause either inhibition (e.g., by

Evaluation of efficacy

The efficacy of antidepressant therapy must be systematically evaluated on a day that has been preset by the patient and therapist, usually about four weeks after the start of treatment.

Continuation therapy

If the patient responds positively to the drug, the treatment is maintained as continuation therapy for six to twelve months after the remission of depressive manifestations.

FIGURE 1

Steps in an algorithm for the diagnostic evaluation of depression.

The recommended tests serve to rule out somatic disease; they do not include prerequisite tests for particular treatment options (e.g., ECG before treatment with serotonin reuptake inhibitors or tricyclic antidepressants). Any of the tests listed may be omitted if it is clear, in the individual patient, that a pathological finding on that test is not to be expected.

CBC, complete blood count

CRP, c-reactive protein

CT, computed tomography

MRI, magnetic resonance imaging

TSH, thyroid-stimulating hormone

EEG, electroencephalography

TPHA, treponema pallidum hemagglutination assay

fluoxetine, fluvoxamine, and paroxetine) or stimulation (e.g., by carbamazepine); for further information, see the website www.drug-interactions.com.

Switching to another antidepressant—A switch to another antidepressant is perhaps the strategy that is most commonly used at present, despite a lack of scientific validation. The fact that all approved antidepressants were effective in placebo-controlled trials does not, in itself, justify switching to another one in case of non-response. A benefit from switching cannot be expected *a priori*, for at least two reasons: the approval trials did not specifically study patients who had failed to respond to a previously administered antidepressant, and the available antidepressants,

numerous as they are, still tend to have very similar effects.

Any symptomatic improvement after switching to another antidepressant might simply be due to the longer duration of treatment. Thus, in a properly designed trial, non-responders to initial monotherapy should be randomized either to further treatment with the same antidepressant or to a switch to another one. This should be done in double-blind fashion.

A systematic, computer-assisted search yielded only three trials that were designed in this way. None of them showed the switching strategy to be superior to further treatment with the same antidepressant; neither did a meta-analysis taking all three trials into account (13).

Serum levels

In case of non-response to an antidepressant, measurement of serum levels enables detection of non-compliance and metabolic changes due to concomitantly administered drugs or genetic variation.

No evidence in favor of switching drugs

Switching to another antidepressant is a common but scientifically unfounded strategy and should be done no more than once in a patient's course of treatment.

Time course of treatment with an antidepressant
(first step in treatment algorithm)

FIGURE 2

One of two further, recently published trials on this question showed no difference between the switching and continuation strategies (e7); in the other trial, the patients who were switched to a different antidepressant actually did significantly worse (e8).

There is thus a notable discrepancy between the frequency with which the switching strategy is applied and the meager scientific evidence for it. Further trials are needed; at least until more evidence is available, antidepressants should not be prescribed serially.

Lithium augmentation—This strategy was specifically developed for the treatment of refractory depression. Lithium can be added if the patient has not responded to at least one trial of antidepressant monotherapy of adequate duration (14–16). The purpose of this is to convert a non-response into a response. Ten randomized, double-blinded trials have shown that lithium augmentation is more than twice as likely to bring about a response than placebo augmentation (odds ratio 3.1, 95% confidence interval [CI] 1.8–5.4, number needed to treat [NNT] 5) (17). There is some evidence indicating that the addition of lithium to an antidepressant that has no serotonergic component is unlikely to help (e9, e10). Lithium augmentation therapy should be given in a rapidly escalating dose, with due attention to the necessary preliminary tests and contraindications (6, 18); serum lithium levels should be checked regularly, with a therapeutic target range of

0.6–0.9 mmol/L. Once the serum level is in this range, the effect should be observed for two weeks; if there is no response, lithium treatment should be terminated (as long as there is no other indication for it). In the event of a response, the combination of lithium and the antidepressant should be given for a further six to twelve months of continuation therapy (19, 20).

The following are arguments in favor of lithium augmentation: that the antidepressant taken till now has been well tolerated and need not be discontinued, that prophylactic lithium treatment is indicated anyway because of a recurrent course, or that the patient is recurrently suicidal (21). The independent benefit of lithium in reducing suicidality has been consistently shown, not only in multiple analyses of published efficacy trials (22), but also in a prospective, controlled trial with the reduction of suicidality as its primary end point (e11).

Augmentation with a second-generation antipsychotic—Recent controlled trials have shown that augmentation of an antidepressant with a second-generation antipsychotic (alternative term: atypical neuroleptic) can convert a non-response to a response. A meta-analysis of such trials yielded an overall odds ratio of 1.69 (95% CI 1.46–1.95, NNT 9) compared to placebo (23). Quetiapine is the only drug approved for this indication in Germany. Weight gain, with the risk of metabolic syndrome, is a common side effect. In a

Lithium augmentation

This strategy was specifically developed for the treatment of refractory depression. Studies have shown that lithium augmentation is three times as likely to bring about a response as placebo augmentation.

Lithium dose escalation

Lithium for add-on therapy should be given in a rapidly escalating dose, with due attention to the necessary preliminary tests and contraindications and with regular checking of serum lithium levels.

randomized trial comparing lithium augmentation to quetiapine augmentation, sponsored by the manufacturer of quetiapine, the two drugs were found to be of comparable benefit (24).

High-dose antidepressant medication—It was concluded in a systematic review (25) that the principle “more is better” holds for some, but not all, antidepressants. Clinical trials have consistently shown high-dose treatment with SSRIs to be no more effective than treatment at the standard dose; there is thus no indication for dose escalation in the event of non-response. A SPECT study showed that treatment with paroxetine, an SSRI, at the standard dose of 20 mg/d already causes blockage of roughly 80% of serotonin transporters in the CNS, without any further increase in patients treated with a high dose of the drug (mean, 47 mg/d) (e12).

On the other hand, for TCA, tranylcypromine, and venlafaxine, doses in the high therapeutic range have been found to be more effective than doses in the low therapeutic range. Dose escalation would be a reasonable next step in case of non-response to one of these drugs at the standard dose (25), as long as the standard dose has been well tolerated and the patient has a positive attitude to the drug in question.

Combinations of two antidepressants—Randomized clinical trials demonstrating the greater efficacy of a combination of two antidepressants compared to a single antidepressant combined with placebo are available only for combinations that involve a reuptake inhibitor (i.e., an SSRI, SNRI, or TCA) paired with a presynaptic autoreceptor blocker (mianserin, mirtazapine, or trazodone) (26). Such combinations have been more extensively studied than others because drugs in these two classes given together can be expected, on theoretical grounds, to exert a synergistic effect. With only a single exception, nearly all trials have shown such combinations to be effective. They clearly can be recommended as a treatment strategy in case of non-response to monotherapy (6). Clinicians welcome such combinations, because mirtazapine, mianserin, and trazodone have a sedating effect (unlike the SSRIs) and can therefore be usefully given in the evening.

It is unclear from the available evidence whether each of the two drugs in such combinations should be given in the standard dose used for monotherapy, or whether lower doses might suffice. It is presumed, though not yet documented, that standard doses are more effective. It is important to note that combinations

FIGURE 3

Algorithm: drug treatment for refractory depression.

From: German S3 Guideline / National Disease Management Guideline Unipolar Depression (6). Each treatment step should be applied for four weeks (six weeks in older patients). The color of each box indicates how well the efficacy of each treatment strategy has been documented in controlled trials. TCA, tricyclic antidepressant; SSRI, serotonin reuptake inhibitor

High-dose treatment

There is no indication for dose escalation in the event of non-response to a standard dose of an SSRI.

Combinations of two antidepressants

Trials have shown the greater efficacy of a combination of two antidepressants, compared to a single one combined with placebo, only for combinations that pair a reuptake inhibitor (i.e., an SSRI, SNRI, or TCA) with mianserin, mirtazapine, or trazodone.

of MAO inhibitors with serotonergic antidepressants are contraindicated and that fluoxetine, fluvoxamine, and paroxetine inhibit the cytochrome P₄₅₀ system.

Third step

Irreversible MAO inhibitors—Refractory depression is now the main indication for irreversible MAO inhibitors (in Germany: tranylcypromine), which are considered to be more effective against refractory depression than the reversible MAO inhibitor moclobemide (27). Although this conclusion was drawn mainly from older studies that do not meet current methodological standards, most experts still consider it correct. As a result, treatment with an irreversible MAO inhibitor occupies a step all by itself in current algorithms for the treatment of depression.

Irreversible MAO inhibitors are no longer drugs of first choice, however, because patients who take them must adhere to a low-tyramine diet to obviate the risk of a hypertensive crisis (28). Experience has shown that patients generally adhere to a low-tyramine diet without difficulty, and the diet has even been said to have an independently beneficial placebo effect. Because of the dose-dependence of the response to tranylcypromine in patients with refractory depression, the target dose is usually set in the high range, at roughly 60 mg/d (the dose should be escalated slowly, with the drug being given in the morning and at midday) (29). Irreversible MAO inhibitors must not be given in combination with serotonergic drugs such as SSRIs, SNRIs, or clomipramine, or too soon after these drugs have been discontinued.

Electroconvulsive therapy (ECT)—ECT is the most effective treatment for refractory depression, with a response rate of 50% to 85% in general and 50% to 75% among non-responders to antidepressant medication (30). Contemporary ECT has minimal risks and side effects. General anesthesia and pharmacological muscle relaxation, administered by an anesthesiologist, prevent tonic-clonic muscle activity and the injuries that might result; ventilation with oxygen prevents cerebral hypoxia; and cerebral electrical stimulation with intermittent square-wave pulses reduces the quantity of energy required for provoking a grand mal seizure (31).

Cognitive impairment, mainly involving short-term memory, is seen relatively often after ECT, but it is transient and no longer demonstrable four days after the end of treatment (e13). The main clinical drawback is the high rate of early recurrence after an initially suc-

cessful course of ECT—up to 80% within six months. This figure applies if no drug treatment is given after ECT; it can be markedly lowered by antidepressant medication. The best clinical trial on this subject showed that a combination of nortriptyline and lithium is significantly better for this purpose than nortriptyline alone, which is, in turn, better than placebo (e14).

Treatment algorithm for depression

With so many treatment options available, the question arises in what order they should be used. A scientifically grounded treatment algorithm would be desirable, as the indiscriminate serial administration of multiple drugs in inadequate doses is now considered an important cause of treatment resistance (or pseudoresistance) (32). Better results ought to be obtainable with a treatment algorithm in which the improvement of depressive manifestations is assessed in standardized fashion at predetermined intervals and the findings of the assessment then determine whether the treatment should be changed (i.e., whether the algorithm should proceed to the next step). Such algorithms are already in existence for pharmacotherapy and ECT but, in principle, would be useful for psychotherapy as well. The algorithm of the German S3 Guideline / National Disease Management Guideline Unipolar Depression is shown in *Figure 3* (6).

Large-scale randomized controlled trials have repeatedly shown that treatment according to an algorithm brings about a response more often and more rapidly than conventional treatment at the discretion of the treating physician (33, 34). In one trial, the patients in the algorithm group achieved remission in a mean of 7.0 weeks, compared to 12.3 weeks in the control group (33). They also took less medication and underwent less frequent changes in their treatment strategy. It can be concluded that the use of algorithms prevents unnecessary scattershot therapies and premature switching of treatment measures (33).

Psychotherapy

Controlled trials have shown that interpersonal psychotherapy (IPT), behavioral therapy, and cognitive therapy are effective treatments for non-refractory and non-chronic depression; moreover, large-scale observational studies and clinical trials in groups of patients with mixed diagnoses provide evidence of efficacy for psychoanalysis and psychodynamic short-term therapy. The potential efficacy of psychotherapeutic methods in

Irreversible MAO inhibitors

Irreversible MAO inhibitors such as tranylcypromine are thought to be especially effective against refractory depression.

Electroconvulsive therapy

Electroconvulsive therapy is the most effective treatment for depression.

the treatment of refractory depression has been very little studied, but some types of psychotherapy were specifically developed to treat chronified depression. Psychotherapy seems to have the advantage of longer persistence of its beneficial effect after the end of treatment, compared to drug treatment (35, e15). Psychotherapy improves compliance with drug treatment and thus leads to better efficacy when these two modes of treatment are used in combination.

Cognitive behavioral therapy (CBT)

The aim of cognitive behavioral therapy (CBT) is to make patients aware of their illness-promoting, depressive-negative modes of perception and automatic thoughts so that they can rid themselves of them. CBT is based on the assumption that dysfunctional cognitions disturb the patient's emotions and behavior. Important treatment strategies for chronified depression include overcoming the patient's social withdrawal, supposed helplessness, and lack of positive reinforcement. CBT is intended to correct these dysfunctional cognitions. A ten-phase CBT manual has been specifically devised for the treatment of chronic depression, in order to do justice to the special features of this patient group (36).

Interpersonal psychotherapy (IPT)

Interpersonal psychotherapy is a type of short-term therapy that was developed specifically for the treatment of acutely depressed patients, based on the idea that depression typically arises in a particular interpersonal or psychosocial context. IPT is therefore oriented toward current problems in the patient's life, usually in one or more of four problem areas: role changes, interpersonal conflicts, social deficits, and grief (37).

Adaptations of IPT for chronic depression are now being developed and tested. It should be noted that depression, once it becomes chronic, is less closely connected to current life events than acute depression. Patients who have been depressed for years often have negative expectations of treatment, a poor social network, and chronified interpersonal conflicts; these are the areas in which IPT for chronic depression might usefully intervene.

Psychodynamic psychotherapy

In psychodynamic psychotherapy, the therapist–patient relationship gives the patient an opportunity to

emotionally re-experience unfavorable relationship experiences of the past in a sheltered setting. At the beginning of treatment, refractory depression is addressed with what can be thought of as “environmental protection measures”: the empathic attitude that is so important to depressed patients, along with an emotional resonance that patients can appreciate, are best assured by a psychotherapeutic attitude of acceptance with constant attention to countertransference on the part of the therapist.

Person-centered therapy (PCT)

PCT, which was developed on the basis of humanistic psychology, proceeds from the assumption that anyone seeking help from a psychotherapist already has the capacity to heal him- or herself. The goal of psychotherapy is, therefore, to create favorable conditions that enable self-healing. The therapist must understand what the patient is feeling (empathy), and the therapist's attitude toward the patient must be characterized by genuineness (congruence) and acceptance (unconditional positive regard).

Cognitive behavioral analysis system of psychotherapy (CBASP)

The only psychotherapeutic method developed specifically for the treatment of chronic depression is rather awkwardly known as CBASP (38). It is a manual-based method that incorporates behavioral, cognitive, and interpersonal strategies and takes account of the psychological trauma to which many chronically depressed patients were exposed early in life. CBASP is intended to help the patient become aware of the consequences of his or her own behavior, acquire empathy, learn problem-solving skills and coping strategies, and benefit from an interpersonal process for the healing of prior trauma. The main techniques for achieving these goals in CBASP are so-called situational analysis and special interpersonal strategies. Large-scale randomized trials have yielded both positive (39) and negative (40) evidence concerning the putative efficacy of CBASP.

Overview

Treatment resistant depression is not an untreatable disease. Considering the wide diversity of depressive manifestations, disease courses, and chronification factors, no single method or small battery of methods can be expected to overcome treatment resistance and chronification in every case. Rather, what is needed is

Interpersonal psychotherapy

Interpersonal psychotherapy (IPT) is a type of short-term therapy that was developed specifically for the treatment of acutely depressed patients.

Cognitive behavioral analysis system of psychotherapy (CBASP)

CBASP is the only psychotherapeutic method developed specifically for the treatment of chronic depression.

the structured application of a variety of treatment options that have been validated by the available scientific evidence, with drug treatment and psychotherapy playing equally important roles.

Conflict of interest statement

Prof. Bschor has received reimbursement of meeting participation fees and of travel and accommodation expenses from Lundbeck and AstraZeneca. He has received honoraria for lectures at continuing medical education events from Lilly, BMS, esparma (Aristo), Servier, AstraZeneca, Sanofi, and Lundbeck. Prof. Bschor is a regular member of the Drug Commission of the German Medical Association and also the spokesman for the psychiatric working group within it. He is a board member of IGSLI and President of the Berlin Society for Psychiatry and Neurology.

Prof. Bauer has served as a paid consultant for Alkermes, AstraZeneca, BristolMyersSquibb, Ferrer Internacional, Janssen, Lilly, Lundbeck, Otsuka, Servier, and Takeda. He has received honoraria from UNI MED Verlag, Elsevier, Kohlhammer, and Springer for authorship of publications relating to the topic of this article. He has received reimbursement of meeting participation fees from Servier. He has received payment for the preparation of continuing medical education events from AstraZeneca, BristolMyers Squibb, Ferrer Internacional, Lilly, Lundbeck, Otsuka, Pfizer, and Servier. He has also received payment for carrying out clinical trials on behalf of Lilly, Servier, and AstraZeneca.

Dr Adli has served as a paid consultant for Lundbeck, esparma (Aristo), and Merz and has received reimbursement of meeting participation fees and of travel and accommodation expenses from Lundbeck and Servier. He has received payment for the preparation of continuing medical education events from Lundbeck, Servier, and esparma (Aristo).

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Corresponding author

Prof. Dr. med. Tom Bschor
Abteilung für Psychiatrie, Schlosspark-Klinik
Heubnerweg 2, D-14059 Berlin, Germany
bschor@schlosspark-klinik.de

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Question 1

Which of the following is a common definition of “treatment-resistant depression”?

- a) depression that does not respond to two trials of drug treatment of adequate dosage and duration
- b) depression that does not respond to electroconvulsive therapy
- c) depression of at least two years' duration
- d) a depressive episode with documented organic brain disease
- e) depression that does not respond to any evidence-based treatment

Question 2

What is dysthymia?

- a) the onset of depression
- b) a period lasting several years in which depressive manifestations are mild
- c) depression that does not respond immediately to standard treatments
- d) diminished self-esteem
- e) certified high intelligence

Question 3

Which of the following is a potential cause of so-called pseudo-resistance to treatment?

- a) misdiagnosis of a somatic disease as depression
- b) high patient compliance
- c) non-response to two weeks of monotherapy with an antidepressant in a standard dose
- d) simultaneous homeopathic treatment
- e) familial predisposition

Question 4

What difference did clinical trials show between the treatment of depression by a stepwise treatment algorithm and conventional treatment by the physician's choice?

- a) On average, the time to remission was longer under algorithm-based treatment.
- b) Algorithm-based treatment involved more frequent changes of the treatment strategy.
- c) The clinical benefit of algorithm-based treatment was largely due to combinations of antidepressants.
- d) Both types of treatment had the same response rate.
- e) Patients treated by algorithm took fewer psychoactive drugs, on average, than those treated conventionally.

Question 5

A 44-year-old, male bus driver in whom you diagnosed a depressive episode has not responded to four weeks of treatment with citalopram (an SSRI) in the standard dose of 20 mg/d. What is recommended as a possible next step?

- a) augmentation with venlafaxine
- b) raising the dose to 40 mg/d
- c) the addition of mirtazapine
- d) switching to an antipsychotic drug
- e) the addition of St. John's wort extract

Question 6

A 53-year-old, female branch manager in whom you diagnosed a depressive episode has not responded to four weeks of treatment with amitriptyline (a tricyclic antidepressant) in the standard dose of 150 mg/d. Which of the following is a recommended next step of scientifically documented efficacy?

- a) augmentation with lithium
- b) the addition of a monoamine oxidase inhibitor
- c) monotherapy with amisulpride (a second-generation antipsychotic drug)
- d) switching to sertraline (an SSRI)
- e) switching to a combination of quetiapine and lithium

Question 7

You have diagnosed a severe depressive episode in a 32-year-old male office worker and are considering treatment with tranylcypromine. Which of the following is an especially important consideration?

- a) If this patient is to be treated with tranylcypromine, he must go on a low-serotonin diet.
- b) Tranylcypromine must not be combined with serotonergic medications such as SSRIs for this patient.
- c) Dose titration can be based on serum drug levels, as the therapeutic range for tranylcypromine is well established.
- d) Tranylcypromine is a tricyclic antidepressant, and you must, therefore, rule out glaucoma (a contraindication) before initiating treatment.
- e) Tranylcypromine is an antidepressant of first choice and can thus be considered even if this patient has not yet been treated with any drug.

Question 8

What psychotherapeutic technique was developed specifically for the treatment of chronic depression?

- a) cognitive behavioral analysis system of psychotherapy (CBASP)
- b) interpersonal psychotherapy (IPT)
- c) cognitive behavioral therapy (CBT)
- d) psychoanalysis
- e) psychodynamic psychotherapy

Question 9

What psychotherapeutic technique was developed specifically for the short-term treatment of acutely depressed patients?

- a) cognitive behavioral analysis system of psychotherapy (CBASP)
- b) person-centered therapy (PCT)
- c) interpersonal psychotherapy (IPT)
- d) cognitive behavioral therapy (CBT)
- e) psychodynamic psychotherapy

Question 10

Which of the following is a major clinical problem of electroconvulsive therapy (ECT)?

- a) bodily injury due to tonic-clonic convulsions
- b) cerebral hypoxia
- c) low response rate
- d) hallucinations
- e) high rate of early recurrences

CONTINUING MEDICAL EDUCATION

Chronic and Treatment Resistant Depression

Diagnosis and Stepwise Therapy

Tom Bschor, Michael Bauer, Mazda Adli

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eSUPPLEMENT

Chronic and Treatment Resistant Depression

Diagnosis and Stepwise Therapy

Tom Bschor, Michael Bauer, Mazda Adli

Risk factors for chronification

Many factors of different kinds can make it more likely that a depressive episode will persist and become difficult to treat. Usually, multiple factors are present and synergistically exert an unfavorable effect. In a recent, comprehensive, systematic review (7), 25 primary studies of risk factors for the chronification of depression were evaluated. Only factors that were clearly present before the chronification of depression were designated as risk factors. Aside from these, there were other factors that were found to be correlated with chronic depression, but for which it was unclear whether they were the cause or the effect of chronification, or else perhaps a common effect of some other underlying cause. Such factors were called associated factors (*eBox 1*).

Chronified depressive manifestations themselves tend to promote the persistence of psychopathology, as the lives of chronically depressed persons are typically characterized by social isolation, a lack of activity and emotionally positive events, and fixation on the patient role (e.g., with visits to the doctor becoming the main event of the day) (8). Although chronic or treatment resistant depression has the same basic manifestations as an acute depressive episode, the following manifestations tend to be most prominent: low affective variability, anhedonia, lack of drive, social withdrawal, lack of self-esteem, hopelessness, loss of libido, sleep disturbances, cognitive impairment, and chronic suicidality (e3).

eBOX 1

Risk factors for a chronic course of depression (from [7])

Consistent evidence

- Risk factors
 - family history of affective disorders
 - early onset of depression
 - long duration of depressive episode
- Associated factors
 - comorbidity with anxiety disorders
 - comorbidity with personality disorders
 - comorbidity with substance dependence or abuse
 - poor social integration
 - negative social interaction
 - less intense depressive manifestations

Inconsistent evidence

- Risk factors
 - female sex
 - family history of substance dependence or abuse
 - many (>3) prior depressive episodes
- Associated factors
 - low socioeconomic status
 - low educational attainment
 - no partner (never married, without partner, separated, divorced, widowed)
 - stressful life events
 - advanced age

eBOX 2

Drugs that can cause depression

- antihypertensive drugs, especially reserpine and hydralazine
- beta-blockers, e.g., propranolol
- ACE inhibitors, e.g., enalapril
- Ca²⁺ channel blockers: verapamil, clonidine, thiazide diuretics
- α-methyldopamine
- other cardiac drugs
- digitalis preparations
- lidocaine
- salbutamol
- corticosteroids
- anabolic steroids
- baclofen
- bromocriptine and levodopamine
- high-potency conventional neuroleptic drugs, e.g., haloperidol
- metoclopramide
- antibiotic, virostatic, & antimycotic drugs, e.g., gyrase inhibitors, isoniazid, acyclovir, amantadine, zidovudine, amphotericin B
- immunosuppressants: azathioprine, cytostatic drugs, interferon
- analgetic and anti-inflammatory drugs, e.g., indomethacin, ibuprofen, opiates
- oral contraceptive drugs
- antihistamine drugs, e.g., cimetidine
- antiepileptic drugs, e.g., carbamazepine, barbiturates, phenytoin, vigabatrin, disulfiram
- isotretinoin (vitamine A derivative)