Clinical research

Electroconvulsive therapy and its different indications

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In spite of recent developments in the pharmacotherapy of depressive disorders, the delay until clinical improvement can be achieved, and the considerable rate of non-response and nonremission, are major problems which remain unresolved. Electroconvulsive therapy (ECT) is a nonpharmacologic biological treatment which has been proven to be a highly effective treatment option, predominantly for depression, but also for schizophrenia and other indications. Though there is a lack of controlled investigations on long-term treatments, ECT can also be used for relapse prevention during maintenance therapies. The safety and tolerability of electroconvulsive treatment have been enhanced by the use of modified stimulation techniques and by progress in modern anesthesia. Thus, today a safe treatment can also be offered to patients with higher somatic risks. ECT still represents an important option, especially in the therapy of treatment-resistant psychiatric disorders after medication treatment failures. Earlier consideration of ECT may reduce the rate of chronic and difficult-to-treat psychiatric disorders.

Electroconvulsive therapy (ECT) is the safe induction of a series of generalized epileptic seizures for therapeutic purposes, using brief-pulse stimulation techniques under anesthesia and muscle paralysis. Informed consent of the patient or the responsible legal guardian is mandatory. In cases of life-threatening diseases where there is no possibility of obtaining informed consent due to the character of the mental illness, ECT can also be administered after legal authorization and the informed consent of the patients' legal representatives. Patients in stupor, manic excitement, catatonic mutism, and acute paranoid states may not be able to provide written consent, and alternative consent processes which vary with jurisdictions in different countries must be applied. It is useful for physicians, who are responsible for the more acute and severely ill psychiatric patients, to consider ECT as a primary indication, and to be acquainted with all the means for proper consent for treatment within their jurisdiction. *Table I* shows the WHO recommendations on administration of ECT.

Since the earliest publications on the subject, the excellent therapeutic effectiveness of this method in the treatment of depression and other psychiatric disorders has been described in a variety of reviews and meta-analyses.[2-4] However, although the technique and practice of ECT has improved considerably in the last decades, the crucial neurobiological mechanisms contributing to the therapeutic efficacy in distinct psychiatric disorders are still under investigation.

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Putative mechanisms of action of ECT

Although decades of research and clinical experience have improved the technique and practice of ECT, the underlying crucial mechanisms which contribute to the superior therapeutic effects of ECT are still under investigation. Most research investigating the neurobiological effects of ECT focused on the antidepressant potential of ECT, and revealed that ECT particularly affects neurotransmitter systems which may be involved in the pathophysiology of depression.[5] In accordance with the monoamine deficiency hypothesis in depression, several studies indicated that ECT attenuates serotonergic and noradrenergic neurotransmission. However, animal studies revealed conflicting results, such as an enhanced sensitivity of presynaptic hippocampal serotonin $(5-HT)_{1A}$ receptors,[6] but also a decreased sensitivity of hippocampal $5-HT_{1A}$ receptors,[7] have been described after electroconvulsive shocks (ECS) in rats. However, in patients suffering from major depression, ECT has been shown to increase tryptophan plasma levels[8,9] suggesting that an increased availability of the serotonin precursor may contribute to the therapeutic effects of ECT.[9]

In addition, a compensatory increase in γ-aminobutyric acid (GABA) neurotransmission has been suggested as a possible mechanism of ECT. In line with the anticonvulsant effects of ECT and the GABA-deficit hypothesis of depression,[10] a proton magnetic resonance spectroscopy study showed that occipital cortex GABA concentrations[11] are increased in depressed patients treated with ECT. Furthermore, an iomazenil-single-photon emission computer tomography (SPECT) study suggested an enhanced GABAergic neurotransmission as a possible mechanism of ECT.[12] Recently, ECT has been shown to enhance activity of inhibitory circuits in human motor cortex, further indicating that ECT has marked effects on GABAergic neurotransmission.[13]

Due to the fact that ECT increased glutamate plasma levels[9] and normalized reduced glutamate/glutamine levels in the left cingulum in depressed patients responding to ECT,[14] effects on glutamate, an excitatory neurotransmitter, may also play a role.

In addition to effects on neurotransmitter systems, therapeutic effects of ECT have also been attributed to its influence on the hypothalamic-pituitary-adrenal (HPA) axis. A dysregulation of the HPA axis comprising elevated levels of corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol during depressive episodes, which normalizes after clinical remission, is one of the most consistent biological findings in depressive disorders.[15] Acute elevations of ACTH and cortisol plasma levels have been observed immediately after ECT,[16,17] and might be interpreted as a physiological stress response. However, during the course of ECT, ACTH and cortisol plasma levels have been found to decrease, suggesting that a downregulation of the HPA axis[18] might comprise a therapeutic effect of ECT in major depression.

In recent decades, considerable evidence has emerged that neuroactive steroids, which alter neuronal excitability via nongenomic mechanisms, might be involved in the pathophysiology of depression, and might contribute to the therapeutic effects of antidepressants.[19] Although no alterations of positive GABAergic 3α-reduced neuroactive steroids have been detected in depressed patients after treatment with ECT,[20] elevated plasma levels of dehydroepiandrosterone sulfate (DHEAS), which is a potent negative modulator of the GABA-A receptor, have been found in psychotic depressed patients and were associated with nonresponse to ECT these patients.[21] Therefore, it has been suggested that DHEAS plasma levels might serve as a predictive marker of nonresponsiveness to ECT.[21] In a genetic rat model of depression, DHEAS pretreatment abolished the antidepressant effects of ECS, suggesting that a pharmacologically induced decrease in DHEAS levels might serve

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- According to WHO recommendations, as with any other treatment, ECT should only be administered after obtaining informed consent.
- ECT should only be administered in the so-called "modified form" (which to date represents a standard procedure), ie, with the use of anesthesia and muscle relaxation.
- The practice of using unmodified ECT should be stopped, but currently this method still is in use in some countries, due to local habits and financial resources.

Table I. The administration of ECT according to WHO recommendations.[1]

as a putative intervention to restore the treatment response in depressed patients resistant to ECT.[22]

Recently, growing evidence has emerged for a major role of downstream signal transduction pathways, eg, the cyclo-adenosine monophosphate (AMP)-responsive element binding protein (CREB) cascade, and their effects on neurotrophic factors such as brain-derived neurotrophic factor (BDNF) in the pathogenesis and treatment of depressive disorders.[23] In this context, in vivo and animal studies suggested that the antidepressant effects of ECS may be attributed to its putative effects on neurogenesis and neuroplasticity. Single ECS have been shown to increase BDNF mRNA[24-26] and tyrosine kinase B (TrkB) mRNA, which is an effector of BDNF.[25] Furthermore, comparable to the observations after pharmacological antidepressant treatment,[27] BDNF mRNA and TrkB mRNA are continuously increased after a course of ECS.[28] Moreover, several studies have indicated that ECS increase synaptic connectivity. Chronic ECS induce mossy fiber sprouting in the hippocampus[29,30] and in other brain regions such as amygdala and frontal areas.[31] In addition, ECS are followed by an increase in neuron formation in the hippocampus,[30,32,33] an effect that was already observed after a single ECS[33] but which was even more pronounced after a series of ECS,[32,33] suggesting a dose-dependent mechanism of ECT on neurogenesis.[32] In addition, increased levels of CREB and an enhanced transcription mediated by CREB have been detected in hippocampus after ECS in experimental animals.[27]

SPECT studies in depressed patients indicated a reduced cerebral blood flow (CBF) in frontal areas briefly after ECT.[34] In contrast to these acute effects, CBF has been shown to increase and therefore to normalize in depressed patients after a course of ECT.[12,35] In frontal and parietal cortex, and in anterior and posterior cingulate gyrus of depressed patients, a decreased regional cerebral glucose metabolism has been observed after ECT.[36,37] Responders compared with nonresponders had reduced cerebral glucose metabolism in frontal regions,[38] suggesting that the decrease in glucose metabolism might contribute to the therapeutic effects of ECT.[36]

Nevertheless, in spite of the increasing knowledge about the central nervous system effects, the single or combined mechanisms crucial for therapeutic efficacy of ECT in divergent psychiatric disorders are not yet known.

The priority of ECT in the treatment of psychiatric disorders

ECT as first-line treatment

Depressive stupor and inanition, as in melancholic, catatonic, or psychotic depression, can be a first-line indication for ECT before other treatments are prescribed. Because ECT has been shown to be associated with a fast relief of symptoms,[39] this is essential in case of severe psychomotor retardation or refusal of food and drink. In case of severe psychotic symptoms and high suicide risk, ECT should be considered earlier than other therapeutic options.[40] In psychotic depression, the remission rate for ECT approaches 90%, with relief experienced within 10 to 14 days.[41,42] The risks of suicide that mark severe psychiatric illnesses are quickly relieved by ECT, although attention to continuation treatments is essential to sustain the benefit.[43] Also other acute psychiatric syndromes such as severe excitement, eg, in delirious mania, malignant catatonia, and neuroleptic malignant syndrome (NMS) may require ECT as a first-line treatment.[2,3] This is especially true if the clinical differentiation between NMS and malignant catatonia is not possible. Intensive ECT, usually administered daily (en bloc), relieves the high rates of mortality associated with malignant catatonia and delirious mania.[44,45] In addition, when depression, mania, and psychotic symptoms accompany systemic illnesses or are present during early pregnancy or the postpartum breast-feeding period, the administration of medications is often precluded, and ECT becomes a useful treatment option. In the case of severe and life-threatening adverse events of medication, ECT monotherapy can be a safe first-line treatment. This is also true for patients suffering from severe somatic diseases with a risk of worsening due to antidepressant or antipsychotic pharmacotherapy.[46-48]

Long duration and a chronic course of psychiatric disorders are negative outcome variables predicting higher risks for treatment resistance against both medication and ECT.[46,49] More patients should therefore be informed about enhanced response rates in case of ECT administration in comparison with pharmacotherapy alone to be involved properly in shared decision-making concerning their treatment. Nevertheless, the primary use of ECT is handicapped by the severe stigma and even legal restrictions against its use in some jurisdictions.[41] It is useful for practitioners who are responsible for the more acute and severely ill psychiatric patients to consider ECT as a pri-

mary indication and to be acquainted with all the means for proper consent for treatment within their jurisdiction.

ECT as second-line treatment

Even if patients receive ECT only in rare cases immediately after attaining criteria for pharmacotherapy resistance, those treatment failures are the most frequent ECT indication.[50-53] The utilization of ECT enhances response rates significantly.[54-56] This is especially true in patients suffering from psychotic depression, even if antipsychotic therapies have been adequately applied.[40,57] Intolerable side effects of antidepressant medications, somatic comorbidities emerging during the pharmacological treatment,[40,58] or worsening of depressive symptoms, including severe suicidality during antidepressant pharmacotherapy, can be also the cause of initiating an ECT treatment course.[40]

ECT as "last-resort" treatment

For rare *last-resort* indications, no scientific evidence derived from randomized controlled trials (RCTs) demonstrating the efficacy of ECT can be found in the scientific literature. Nevertheless anecdotal case reports, case series, and retrospective reviews suggest the clinical effectiveness of ECT in obsessive-compulsive disorder (OCD) after multiple treatment failures utilizing pharmacotherapeutic and psychotherapeutic approaches. Also, in a patient suffering from Tourette's syndrome, a rapid and sustained relief of symptoms has been reported.[59] In the case of treatment-resistant epilepsy, ECT can be utilized for rapid symptom relief in the case of present[60] or absent[61] concomitant depression. Not only depressive symptoms but also impaired motor function in Parkinson's disease show amelioration after a course of electroconvulsive treatment (for review see ref 62).

Of course, particularly in such rare cases with last-resort indications, an individual benefit/risk estimation, including the complete evaluation of prior treatment failures, has to be done for each patient.

First- and second-line indications and rare last resort indications are summarized in *Table II*.

ECT in the treatment of depressive disorders

Efficacy of ECT in the acute treatment of depression under specific diagnostic, comorbid, and somatic conditions

Unipolar depression

The general efficacy and superiority of ECT in comparison with antidepressant pharmacotherapy has been

Category of ECT indications	Indication
ECT as a first-line treatment	• febrile catatonia* • malignant neuroleptic syndrome* • severe depressive episode** • schizoaffective psychosis** • schizophrenia**, *** • in case of life-threatening or intolerable side effects of psychopharmacological treatments
ECT as a second-line treatment	medication treatment failures in: • depression • schizoaffective psychosis • schizophrenia • mania • depression or psychotic symptoms in case of organic diseases
ECT as a last-resort treatment	• treatment-resistant obsessive compulsive disorder (OCD) • treatment-resistant dyskinesias • treatment-resistant Gilles de la Tourette syndrome • treatment resistant epilepsy • Parkinson's disease (treatment-resistant)

Table II. Indications for electroconvulsive therapy (ECT). *, ref 45; **, with suicidality which can not be handled even on protected wards, psychotic symptoms, depressive stupor, with positive symptoms or acute danger of self-harm or harm of others, or with severe reduction in oral intake; ***, ref 63

described in controlled clinical trials and meta-analyses.[4] Response rates between 80% and 90%[49,51] and even 100%,[64] have been reported. Also, lower response rates of about 50% to 60% have been described in patients receiving unilateral ECT after several medication treatment failures.[64] Nevertheless, in a recent study, sustained response rates of 80%, superior to pharmacotherapy response rates (up to 70%), and remission rates of 75% (up to 87% for study completers suffering from psychotic depression) have been found in major depressed patients treated with optimized ECT.[42,43,65,66]

A 20% improvement in comparison with tricyclic antidepressants and a 45% improvement in comparison with monoamine oxidase inhibitors (MAOIs),[67] as well as a better improvement in comparison with the selective serotonin reuptake inhibitor (SSRI) paroxetine,[57] have been described. In addition, a more rapid improvement in comparison with pharmacotherapeutic approaches has been reported.[2,14,42,68] Most patients show a faster treatment response during ECT in comparison with pharmacotherapy.[69] An advantage concerning speed of response in similar efficacious pharmacotherapeutic approaches such as lithium augmentation[68] after tricyclic antidepressant (TCA) treatment failures has also been described. In particular, in patients receiving ECT after pharmacotherapy treatment failures, longer treatment intervals until complete remission have to be expected.

In former studies in which lower stimulation energy has been used, bilateral ECT has been shown to be more effective than unilateral ECT.[4,68,69] In addition, unilateral ECT may achieve efficacy rates equal to those of bilateral ECT if the dose regime is 6 to 8 times above the titrated seizure threshold.[64,70] In this case the requirement of a calibration session, probably ineffective for antidepressant treatment, can slow down the decrease in depressive symptoms. In addition, cognitive adverse events are identical to those of bilateral ECT.

Bipolar disorder

Bipolar depression

ECT is an effective antidepressant therapy, regardless of whether depressive episodes occur due to major depressive disorder (MDD) or bipolar disorder.[2,40] An enhanced switch risk, including the occurrence of hypomania or mania, can be observed during every highly effective antidepressant treatment. Infrequent switches from

depression to mania may also occur during the course of ECT,[40,71] but due to missing randomized controlled trials and switch rates of up to 30% regardless of antidepressant therapies, this clinical observation also has been discussed as an artifact.[72] Contrary to antidepressant pharmacotherapy, the treatment does not have to be stopped, due to the antimanic properties of ECT. Furthermore ECT may be combined with lithium treatment to augment lithium effects and to prevent the switch to mania in high-risk patients. In this case an enhanced risk for cognitive and medical side effects has to be taken into account.[73] Even a combined use of ECT and anticonvulsants in case of urgent indications for mood stabilizers is possible, and may yield clinical advantages.[73,74,55]

Mania

Due to the availability of lithium, other mood stabilizers, classical neuroleptics, and atypical antipsychotics which exert good antimanic effectiveness, the primary treatment of mania using ECT nowadays is a rare event. This is true even if good efficacy has been shown in several RCTs[76] and the treatment has been recommended in several reviews (eg, ref 77). A high remission or improvement rate of 80%[77] has been reported, even if prior pharmacotherapeutic approaches have shown only poor response. Moreover, superiority of ECT in comparison with lithium or antipsychotics has been reported.[78,79] Concerning the treatment modalities, predominantly a superiority of bilateral ECT in comparison with unilateral stimulation techniques has been reported.[80,81]

Dysthymia and double depression

Chronic depression in case of dysthymia alone is not an indication for ECT treatment. Nevertheless, if the diagnostic criteria for MDD or double depression are present, dysthymia is not a predictor of a poor ECT response.[2,40]

Depressive syndromes in OCD

In patients suffering from OCD not responsive to pharmacotherapy, response after ECT may be expected, predominantly if OCD is accompanied by depressive symptoms,[40] which is often the case. In addition, in case of treatment-refractory OCD, improvements occurred independently of depression scores and were long-lasting in

some patients.[82] Also, the beneficial use of ECT during OCD continuation therapy has been reported.[40]

Comorbid personality disorder

Comorbid personality disorder is a predictor of poor response to ECT, and the recommendation for ECT should be cautious in such cases.[2,64] Nevertheless, ECT should not be withheld from patients suffering from MDD with comorbid personality disorders in case of pharmacotherapy resistance.[40] The information about lower response rates has to be included in the patient information about the estimated treatment outcome.

Organic depression due to somatic disorders

Patients suffering from secondary depression associated with somatic diseases show lower response rates to biological therapies such as pharmacotherapy or ECT[83-85] in comparison with MDD. Nevertheless ECT is clinical effective in patients suffering from depression after cerebral infarction ("poststroke depression").[64,69,84] However, particularly in this patient group, organic risk factors have to be considered thoroughly during interdisciplinary neurologic and psychiatric evaluations.

ECT in old age

ECT has also been shown to have excellent effectiveness in geriatric patients. Response rates were better in younger than in older geriatric patients.[2,86,87] Despite specific side effects such as greater cognitive impairment, efficacy was generally greater in geriatric than in young patients, and a reduced mortality in comparison with other treatments has been shown.[88] Further progression in understanding of ECT and anesthesia has reduced the risks of ECT. So some authors now are of the opinion that the use of modified ECT in geriatric patients, particularly in patients at medical risk, can be encouraged now.[2,44]

Combination of ECT and antidepressants

Clinical effectiveness

In spite of the greater efficacy and clinical effectiveness of ECT in comparison with pharmacotherapy, not all patients respond to conventional ECT monotherapy.

The majority of patients referred for ECT have had multiple trials of medication; this may reduce the response rate to ECT. The use of bilateral or high-dose unilateral stimulation can enhance the effectiveness of ECT.[64,65] A further option to augment an ECT treatment course may be the concomitant prescription of antidepressants. This may be necessary due to possible nonresponsiveness to ECT in 15% to 25% of depressed patients.[65] However, study results on a putative benefit combining ECT with tricyclic antidepressants,[89,90] and the lack of advantages of other concomitant medication like selective serotonin reuptake inhibitors (SSRIs) are still controversial.[89] In particular, the efficacy of modern antidepressants in combination with ECT, eg, the dually acting substances mirtazapine and venlafaxine, has never been investigated in controlled studies. Nevertheless, retrospective chart analyses suggest beneficial effects during an ECT/antidepressant combination treatment.[91]

In patients after medication treatment failures, the clinical recommendation is to combine ECT with antidepressants at moderate doses. This is possible during the whole treatment course or at least during the last 2 weeks of ECT treatment to prevent an exacerbation of depression immediately after stopping ECT.

Safety and tolerability

The combination of ECT with TCAs and SSRIs has been described as a safe procedure.[89,90] Safety data about the combination of modern antidepressants with ECT are available: in a recent study venlafaxine at dosages lower than 300 mg/day has been shown to be safe in combination with ECT. In high-dose treatments above 300 mg/d, side effects of cardiovascular nature such as transient asystolia or bradycardia were more frequent if ECT was combined with propofol anesthesia.[92] The combination of ECT with MAOIs should be treated with particular caution. It should be avoided if possible, due to the enhanced risk of possibly lethal complications, especially shortly after starting the pharmacological treatment.[93] At least the condition of a 2-week washout period should be retained. The combination of ECT with lithium enhances anesthesia risks,[94-96] the risk of prolonged seizures,[97] and the risk of cognitive disturbances, but represents only a relative contraindication due to reports of a safe use of this combination and the specific risks of discontinuing the lithium treatment.[98]

Continuation ECT (C-ECT) in the long-term treatment of MDD

The terms *continuation treatment* and continuation ECT (C-ECT) are predominantly used to characterize the maintenance treatment after successful treatment of the index phase. It is sometimes distinguished from *maintenance treatment* and maintenance ECT (M-ECT)[99] due to theoretical considerations about a switch to prophylactic treatment preventing new episodes of depression. This time point cannot be defined precisely in an individual patient; therefore, in the following section only the term C-ECT is used.

Besides pharmacologic and psychotherapeutic continuation therapies, especially after pharmacotherapy treatment failures, ECT is also an effective continuation treatment,[43,99-101] even if the scientific evidence for use of ECT as a maintenance treatment is limited due to an absence of controlled studies. Continuation ECT should be considered in cases of recurrence of depressive symptoms despite adequate pharmacologic continuation therapy or in case of patients' preference. Especially if the prior history of an individual patient shows an enhanced risk for recurrence of depression during continued pharmacotherapy including both antidepressants and mood stabilizers, C-ECT should be part of the treatment plan.[102-104] The usual clinical procedure is to prolong the treatment intervals according to individual clinical requirements. During the acute treatment, a patient usually receives two or three treatments per week. Afterwards usually one treatment per week is applied for 4 to 8 weeks, then one treatment every 2 weeks, and then one treatment every 4 weeks. This frequency should be maintained for at least 6 months. A frequently used alternative strategy (the so-called *cafeteria style*) is the individual decision as to whether an C-ECT treatment is administered when the first signs of recurrence of depressive symptoms are reported.[2,100] Regular weekly evaluations help to judge the necessity of shortening the treatment-free intervals on an individual basis. The same evaluation is necessary during the attempt to stop ECT treatment after 6 months. As soon as depressive symptoms reoccur, a prolongation of the C-ECT should be applied.

ECT in the treatment of schizophrenia and schizoaffective disorders

Electroconvulsive treatment of acute schizophrenia

ECT was introduced firstly as a treatment for schizophrenia (for review see ref 105). Due to the subsequent availability of antipsychotic medication, the use of ECT in schizophrenic patients was notably reduced, in spite of sufficient evidence for the efficacy of ECT in the acute treatment reported in a variety of reviews and meta-analyses.[106-108] According to these reports, ECT may be considered for schizophrenic patients, especially when rapid improvement and symptom reduction is desired.

In an extensive Cochrane review compared with simulated ECT (sham ECT) as a placebo condition, more patients showed improvement after receiving ECT.[108] In the short term fewer relapses and a greater likelihood of an earlier discharge from the hospital have also been reported. Unfortunately insufficient evidence exists as to whether this early advantage of ECT can be maintained over the medium to long term.

Similar to other reports[103] limited evidence suggests that greater improvement can be obtained combining ECT with antipsychotic drugs. The combination of ECT with antipsychotics was superior to either treatment alone.[106,108] Clozapine in particular seems to exert synergistic effects with electroconvulsive treatment.[109-111]

Comparing unilateral and bilateral stimulus administration, no clear advantage of bilateral ECT could be found. An advantage of a longer treatment series with 20 electroconvulsive treatments being more effective than 12 treatments has been reported.[108]

Therefore, even though initial beneficial effects may not last beyond the short term in each patient, ECT as an additional treatment option can be recommended in combination with an antipsychotic medication in treatment-resistant schizophrenia.

Electroconvulsive treatment of acute schizoaffective disorders

With regard to response to pharmacologic treatments, schizoaffective disorders are similar to the primary affective disorders.[112] Similar to the switch risk in bipolar disorders, in schizoaffective disorders mania may also be induced by highly effective antidepressant treatments including ECT.[70] Because a high rate of rapid treatment response to electroconvulsive treatment of mania has been reported,[78,113] ECT is suitable in both bipolar manic and schizomanic episodes. In spite of the reported rapid relief of symptoms,[113] ECT in schizoaffective disorders has also been associated with poorer outcome in com-

parison with the treatment of affective disorders.[114] Nevertheless, good clinical effectiveness in both schizophrenia and schizoaffective disorders has been reported in case series.[115,116] In addition, in very large Cochrane reviews, the effectiveness of ECT in schizoaffective disorders has been confirmed.[108] Again in case of nonresponsiveness to clozapine due to good effectiveness, the combination with ECT has been recommended for the treatment of schizoaffective disorders.[109]

Continuation ECT (C-ECT) in the long-term treatment of schizophrenia and schizoaffective disorders

Due to high relapse rates, even in cases of sufficient relapse prevention using adequate neuroleptic treatment[117] continuation (and maintenance) ECT should be considered as an effective treatment option in case of schizophrenia[103,118] or schizoaffective disorders.[119] Even if the lack of sufficient evidence for cost-effectiveness and superiority of ECT over neuroleptic continuation treatment has been considered,[120] and resource-intensive C-ECT may not be a practical solution for some patients,[103] it is still an option in preventing relapse in patients not responding sufficiently to pharmacotherapeutic relapse prevention. It should therefore be offered to this selected patient collective.[103,118] Patients referred for C-ECT should have been responsive to ECT during the acute treatment

of their index episode and C-ECT should be considered especially in the case of patients preference or in the case of treatment resistance or intolerance to pharmacotherapeutic continuation treatment.[40]

The safety of ECT

In general, ECT is one of the best-tolerated biological therapies with low risk for severe complications, even lower than during the application of TCA.[2;40] The mortality rate during ECT varies between 1:50 000 and 1:25 000 treatments.[2;40] In less than one in 10 000 treatments severe complications are seen that warrant special attention.[40] ECT therefore is considered to be one of the safest medical procedures under anesthesia. Clinical conditions requiring special attention before and during ECT, described in refs 2,3, are summarized in *Table III*.

Side effects

Somatic side effects

The most frequent immediate unpleasant effects of ECT are headache, nausea, and vomiting (varying with anesthetic). Up to 45% of patients report headache which can be treated symptomatically using analgesics such as acetylsalicylic acid or paracetamol and, if severe, by

Category	Clinical condition
Enhanced intracerebral pressure*	at present
Cerebral infarction*	not older than 3 months
Myocardial infarction*	not older than 3 months
Intracerebral tumor*	including intracerebral edema
Any life-threatening anesthesia risk*	at present
Cardiovascular disorders	cardiac arrhythmias, coronary artery disease and instable angina pectoris, myocardial infarction (older than 3 months), myocardial insufficiency, heart valve abnormalities, not sufficiently treated hyper-or hypotonia, aortal aneurysm
Medical disorders	disturbance of blood coagulation, severe liver diseases, severe pulmonal diseases, pheochromocytoma
Neurological disorders	intracerebral neoplasias, intracranial bleeding, intracerebral vascular malformations, cerebral ischemia, cerebral inflammations, hydrocephalus (also normal pressure hydrocephalus with risk for herniation), dementias, diseases of the basal ganglia, craniotomies, severe cerebral traumas
Orthopedic disorders	osteoporosis
Esophageal hernia	increased aspiration risk; intubation recommended
Concomitant pharmacological treatment	if enhancing the ECT risks or reducing ECT efficacy

Table III. Relative contraindications—clinical conditions requiring special attention before and during ECT. ***bold**: previously considered as absolute contraindications; today an individual risk/benefit-analysis is necessary

changing the induction medications. Patients suffering from regular migraine attacks are predisposed to postictal headache after ECT. In this case triptans, eg, sumatriptan, can be applied orally or intranasally.[121] Nausea occurs rarely after anesthesia, and can be treated using metoclopramide. Other rare complications of ECT can be cardiovascular events emerging from anesthesia. On rare occasions, the seizure is prolonged beyond the anticipated 30 to 180 seconds.[40] This risk is considerably enhanced in patients receiving theophylline.[97,122,123] The treating anesthesiologist or psychiatrist will end the seizure by the administration of intravenous benzodiazepines (eg diazepam), anesthetics, or other anticonvulsants. This event is best managed by ictal and postictal electroencephalographic (EEG) monitoring,[123] which can be of use also in the treatment of nonconvulsive seizures which rarely occur after ECT.[122,123]

In case of prolonged effectiveness of muscle relaxants due to predisposition or lithium therapy[95,96] longer assisted respiration and subsequent measurement of oxygen saturation using finger or toe pulse oxymetry is necessary to prevent hypoxia. Aching muscles are prevented by adequate muscle relaxation, and were reported rarely. In patients suffering from bipolar depression ECT like any other antidepressant agent[121] can induce hypomania or mania ("switch").[121] Concomitant lithium therapy[73] can be used despite the higher risk of side effects such as prolonged muscle relaxation and confusional states. The use of mood stabilizers such as lamotrigine, valproate, or carbamazepine is possible despite the anticonvulsant properties of these agents.[73] Both methods can reduce the switch risk significantly.

Cognitive side effects

All patients are confused on awakening after a seizure. The duration and the severity of the post-seizure delirium vary with patient age (older patients have more severe and more prolonged periods of confusion), dosage and type of anesthetic, and the characteristics of the medications, both psychoactive and systemic, which may be prescribed for the patients. Special attention is paid to sedatives and anxiolytics, antipsychotics, and lithium that may augment the confusional syndrome.

Typical side effects which are more prominent in bilateral than in unilateral and in high-dose than in lower dose ECT[4] are transient cognitive disturbances. These include short-term memory disturbances in up to 30% of the treated patients.[124] Postictal delirium including a prolonged reorientation period and memory disturbances including anterograde or retrograde amnesia can be differentiated from rarely occurring effects on the autobiographic long-term memory.[125] In addition, cognitive deficits not emerging from memory disturbances, such as concentration or attention deficits, can occur. It can be difficult in an individual patient to differentiate the cognitive side effects of an ECT treatment from cognitive disturbances caused by depression itself.[126] Therefore a variety of patients report amelioration of cognitive impairment after an ECT treatment course.[127]

As described, the rate of cognitive disturbances is dependent on dose and application of electrical stimulation.[85,127] Sometimes patients experience profound and sustained memory loss, sufficient to interfere with their ability to return to work. Such instances are rare, but are the principal burden of the complaints against the use of ECT.[2;41]

Nevertheless, recent improvements in the use of ECT include methods to maintain good therapeutic efficacy together with a better tolerability concerning cognitive disturbances. Using modified ECT techniques,[128] including unilateral or bifrontal pulse wave stimulation, anesthesia with muscle relaxation, and sufficient oxygenation, these risks could be reduced substantially.[64,68,128]

If, in spite of these precautions, cognitive disturbances occur, a rapid improvement within 1 and up to 4 weeks can be observed in most cases.[128] Follow-up investigations showed a complete reversibility of cognitive side effects after an ECT course[128,129] or even an improvement in comparison with the time interval before ECT treatment.[3,129] A variety of case reports, case series, and controlled studies confirm that ECT does not cause long-lasting functional[54] or any structural damage of the central nervous system.[127,129,130]

Clinical precautions and special considerations

After many decades of research and clinical experience, clinicians have developed protocols for the safe treatment of patients warranting ECT regardless of age, medical status, or physical state. In the long term, after adequate treatment of medical conditions enhancing somatic risks, no absolute contraindications are acknowledged (conditions including higher somatic risks are described in *Table II*). In addition, every other untreated severe medical and life-threatening anesthesiological risk has to

be taken into account. If treated insufficiently, these conditions become relative contraindications, and an individual and interdisciplinary benefit/risk analysis has to be performed for each patient. In general, each factor enhancing the risk for ECT or anesthesia should be taken into consideration. In case of the described specific risks interdisciplinary counseling may be necessary. Afterwards the higher somatic risk has to be compared with the risk of an insufficiently treated or prolonged psychiatric illness. Patients and relatives or responsible legal guardians have to be informed about risk:benefit ratios to contribute to a shared decision.

Conclusion

ECT is a nonpharmacologic biological treatment which has been proven to be a highly effective treatment option predominantly for depression, but also for schizophrenia in a variety of controlled investigations. This is not only true in acute treatments; ECT can also be used for relapse prevention during maintenance therapies.

In addition, the safety and tolerability of electroconvul-sive treatment have been enhanced by using modified stimulation techniques and by progress in modern anesthesia. During recent years, clinical conditions considered as absolute contraindications for ECT in former times became relative contraindications. Thus, today a safe treatment can also be offered to patients with higher somatic risks.

Recent research has contributed to an enhancement of the knowledge of possible mechanisms of action of ECT and to a safe and well tolerated treatment, but unfortunately the final clarification of the underlying crucial mechanisms still remains unresolved. Nevertheless, this highly effective therapeutic option should not kept back, especially from patients suffering from psychiatric illnesses which are unresponsive to other treatments. ECT still represents an important option in the therapy of treatment-resistant depression.

Thorough information provision in hospitals, and also the growing objective and unbiased information in the press and other media, could contribute to fighting the prejudice and stigma of psychiatric disorders and specific therapies such as ECT. ❏

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Terapia electroconvulsiva y sus diferentes indicaciones

A pesar de los recientes progresos en la farmacoterapia de los trastornos depresivos aun persisten sin resolverse dos importantes problemas: la latencia hasta alcanzar la mejoría clínica, y la alta frecuencia de falta de respuesta y de remisión. La terapia electroconvulsiva (TEC) es un tratamiento biológico no farmacológico que ha probado ser una opción terapéutica altamente efectiva, preferentemente para la depresión, pero también para la esquizofrenia y otras indicaciones. Aunque faltan investigaciones controladas en tratamientos a largo plazo, la TEC también puede ser empleada en prevención de recaídas durante las terapias de mantenimiento. La seguridad y tolerabilidad del tratamiento electroconvulsivo han aumentado con el uso de técnicas de estimulación modificadas y por el progreso de la moderna anestesia. De esta manera hoy en día también se puede ofrecer un tratamiento seguro a pacientes que tienen mayores riesgos somáticos. La TEC aun representa una importante opción, especialmente en el manejo de pacientes con trastornos psiquiátricos resistentes al tratamiento después de fallar la terapia medicamentosa. Con las consideraciones anteriores la TEC puede reducir la frecuencia de trastornos psiquiátricos crónicos y difíciles de tratar.

L'électroconvulsivothérapie et ses différentes indications

Malgré les récents développements dans le domaine de la pharmachothérapie de la dépression, la latence de survenue de l'amélioration clinique et le taux considérable d'absence de réponse et de rémission sont des problèmes majeurs non résolus à ce jour. L'électroconvulsivothérapie (ECT) est un traitement biologique non pharmacologique qui a prouvé sa grande efficacité thérapeutique surtout dans la dépression mais aussi dans la schizophrénie et d'autres indications. En dépit d'un manque d'études contrôlées sur les traitements à long terme, l'ECT peut être également utilisé dans la prévention des rechutes au cours des traitements d'entretien. Les progrès de l'anesthésie moderne et les techniques de stimulation dites modifiées ont amélioré la tolérance et la sécurité d'emploi de l'ECT. Aujourd'hui, un traitement sûr peut donc être proposé aux patients à risque somatique plus élevé. L'ECT reste une alternative importante surtout dans le traitement des troubles psychiatriques résistants au traitement en cas d'échec thérapeutique antérieur. Envisager l'ECT de façon précoce pourrait diminuer le taux de troubles psychiatriques chroniques difficiles à traiter.

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