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Combined use of ECT and psychotropic drugs

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Summary

Electroconvulsive therapy (ECT), despite a significant psychopharmacological development and introduction of modern drugs in recent years, is still an important, biological treatment of proven, high clinical efficacy. In the management algorithms it is still considered as a method of choice in treatment of drug-resistant patients. No wider use of ECT may in part result from fears of potential interactions with pharmacotherapy, or need to interrupt the current treatment. The issue of potential impact of pharmacotherapy on many procedure parameters, including mostly seizure threshold and therefore indirectly clinical effect, is still up-to-date. Systematic studies have revised the existing theories about restrictions in the administration of medications during ECT treatment. Nowadays more often not only the safety of such procedure, but also possibility of synergistic therapeutic effect of ECT and psychopharmacology is highlighted. The authors present previous reports on combined use of pharmacotherapy and ECT, safety or potential risks associated with this treatment and proposals of scientific bodies in this regard. Interpretative limitations of conducted research, including especially case reports or observations of small groups, which requires further studies involving more numerous patient populations is noteworthy.

Key words: electroconvulsive therapy, pharmacotherapy, combined therapy

Introduction

One of the primary indications for the use of electroconvulsive therapy (ECT) still remain: depression, especially severe, drug-resistant episodes and some states in the course of schizophrenia (catatonic syndrome, drug resistance). Due to serious clinical condition of patients treated with ECT, treatments are mostly parallel to psychopharmacotherapy. Before starting ECT series justified concerns arise about possibility and legitimacy of concurrent administration of drugs. Used treatment often affects the sei-

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zure duration, which is one of important efficiency criteria of ECT. Therefore in each case continuation of current treatment or its possible modification should be considered.

In this paper authors present the current literature based on Medline/Pubmed database review. For some drugs, there are only case reports available or studies including a small number of patients. To present a broader problem of combination therapy they were also included in this work. The basic search criterion was concomitant use of ECT and psychotropic drugs belonging to different pharmacological groups.

Earlier recommendations were dominated by the principle of avoiding simultaneous administration of ECT and antidepressant drugs (ADs), mood stabilizers (MS), benzodiazepines (BZDs), and certain antipsychotic drugs (APDs) due to their effect on seizure threshold, circulatory system, and ability to interact with anaesthetic drugs [1]. In recent guidelines the combined use of ADs and ECT is allowed, considering the combination to be safe, but still it is recommended to discontinue treatments with antiepileptic MS and BZDs, which increase seizure threshold, before ECT [2]. In absence of improvement after trials of clozapine potentialising with other APDs, combining it with ECT should be considered [3]. Guidelines from various countries are devoid of strict algorithms and provide general directions, leaving the final decision to the treating team. American Psychiatric Association (APA) recommends an analysis of previously used drugs as an integral part of preparation for ECT, and administration of these drugs, prior to each ECT, which are assigned to have a protective effect in relation to physiological changes induced by ECT, and dose reduction or discontinuation of medications that may adversely affect the therapeutic properties of ECT or cause other side effects. At the same time APA indicates the need to gradually reduce dose of drugs to avoid some withdrawal symptoms [4]. According to authors of British recommendations lack of thorough, randomised study on the combined use of drugs and ECT severely limits the possibilities of interpretation, at the same time they point to the possibility of increasing therapeutic response by ADs or lithium without major risks for patients [5]. Similarly, NICE (National Institute for Health and Care Excellence) recommendations have found possible greater effectiveness of combined application of ECT and drugs, compared to medication alone, but data are not conclusive [6]. In Germany, there are no official guidelines, and position of the Austrian lists possible adverse actions of combined use of pharmacotherapy with ECT [7].

Benzodiazepines

BZDs class of drugs was widely used in daily practice due to anxiolytic and hypnotic action. In psychosis or affective disorders, arousal states, anxiety and sleep disorders are frequent part of the clinical picture hence the problem of concurrent use of BZDs and ECT ceased to be marginal. Due to their characteristics BZDs, increasing the seizure threshold and reducing duration of seizure, reduce the effectiveness of ECT [8–10]. Simultaneously it is known about the advantageous synergistic effect

when combining ECT with BZDs to treat catatonia [11, 12] or unchanged effectiveness of ECT [13].

Recommendations of scientific societies, including APA, suggested discontinuation of BZDs before ECT, especially those with long half-life, or gradual reduction of doses before starting ECT in order to avoid withdrawal symptoms [4, 14]. If there is a need to further use of BZDs, drugs with short half-life i.e. lorazepam, are recommended; it is also recommended to avoid administration of BZDs for eight hours prior to ECT. An alternative solution to problem of sleep disorders and agitation is short-term application of sedative APDs with low doses [14]. Others propose also to interrupt BZDs action during ECT by administration of flumazenil (at a dose of 0.4–0.5 mg) shortly before anaesthetic agents [15–17]. However, when such action appears, it is recommended for addicted people to administrate midazolam after ECT – in order to avoid postictal withdrawal symptoms. In case series study, authors reported the efficacy of flumazenil administration in three patients before ECT as a treatment option for elderly patients with high seizure threshold and low clinical efficacy [18]. The use of zopiclone 7.5–15 mg at night before ECT in two patients resulted in reduction of seizure duration [19].

Antiepileptic mood stabilizers

Antiepileptic mood stabilizers can increase the seizure threshold and thus reduce the effectiveness of ECT or require increased stimulus parameters [20]. Many clinicians reduce their dosage before ECT, while others do so only at "lack of appropriateness of seizure", and lack of clinical response. APA recommendations suggest reducing dose or discontinuation of MS before ECT, while in patients during maintenance treatment omitting one or two doses before ECT. Among patients with epilepsy omission of morning dose or keeping drug concentration at a low serum level is recommended. With the decision of dose reduction risk of phase change should be considered [4]. More conservative British recommendations allow the possibility of MS dose verification with ECT only in situations when it is difficult to induce seizures [5]. In Austrian centres percent of mixed therapy ranges between 0 and 85.7%, while the literature data indicate 46% [21]. In the reviewed literature authors underline the lack of evidence that ECT and MS could not be used at the same time [22]. Valproic acid may prolong the effects of thiopental, and carbamazepine interferes with muscle relaxants [1], but there is no major concern in simultaneous use with ECT. Study of a small group of patients (n = 7) indicate a shorter seizure using unilateral ECT and MS, but it remained without clinical significance [23]. Patients taking MS during ECT achieved symptomatic improvement comparable to those who were treated only with ECT; however, they required a higher number of ECT treatments [24]. Newer MS can be also considered as safe in combination therapy with ECT. Lamotrigine, in a study of 9 patients with diagnosis of depression in bipolar disorder, showed a negligible effect on seizure threshold, duration

of seizures and their clinical appropriateness. At the same time lamotrigine was well tolerated, no somatic adverse effects or cognitive impairment were observed [25]. Other authors have also pointed the safety of the use of lamotrigine with ECT, its good tolerability and lack of clinically significant effect of therapeutic doses of lamotrigine on seizure duration, or stimulus parameters [26]. Similar observations were obtained in studies with gabapentin and topiramate [22].

Lithium

Although lithium probably prolongs seizures and succinylcholine action duration [27], it may lower seizure threshold [1], however, regarding combined application, there are different opinions, which is predominantly related to the lack of large randomised studies. Initially it was reported on risk of a prolonged seizure and delirium after treatment with combined use of lithium and ECT [28–30]. Publication based on description of 3 patients documented occurrence of prolonged seizure, serotonin syndrome and partial seizures after treatment [31]. Possible basis of this mechanism was release of lithium from cells by ECT, resulting in systemic toxicity. In its recommendations, APA states that lithium should be discontinued or its concentration maintained in low therapeutic levels based on analysis of risks and benefits between potential toxicity and recurrence of affective disorders [4]. However, according to British authors lithium intake is not a contraindication for ECT, but due to the possibility of extending seizure duration they recommend to start series with low-power charges [5]. It is also suggested to withdraw lithium up to 48 hours before ECT series and to discontinue administration of the drug for several days after the last treatment. However, newer publications indicate that the use of lithium combined with ECT is safe; there is no increased risk of adverse effects [32, 33]. This is confirmed by results of a prospective study of 27 patients [34] or a retrospective study including 90 patients diagnosed with mania [35].

Antidepressant drugs

Among different ADs risk of combined use with ECT depend on the group. Tricyclic antidepressants (TCAs) lower the seizure threshold and may increase the risk of cardiac arrhythmias, particularly in elderly people and people with cardiac problems (hypotension, bradycardia, ventricular fibrillation and cardiac arrest) [1]. In contrast, selective serotonin reuptake inhibitors (SSRIs) have a negligible effect on the duration of seizure and are considered to be safe, but there is a potential risk of serotonin syndrome [36]. In light of research TCAs are widely used in combination with ECT and, despite recent concerns about combination therapy, it is unlikely to indicate the occurrence of adverse events. Nortriptyline enhances the effects of ECT and reduces negative impact of treatment on cognitive functions [37]. Combined use of TCAs with ECT showed better clinical response [38], superior to combination of paroxetine and

ECT, but paroxetine had greater preventive effect on the recurrence of illness [39]. At the same time, most antidepressants do not affect duration of seizures with exception of some SSRIs, which slightly lengthened them. This phenomenon was observed in studies with fluvoxamine and paroxetine [40], few experiences are described with the use of sertraline and citalopram. Research compatibility with ECT and fluoxetine did not confirm the belief that it increases duration of seizures [41]. In more recent publications, longer duration of seizures after using SSRIs, compared to other ADs, were seen in both small and larger population of patients [42]. Casuistic description of combined therapy with escitalopram indicates good tolerability at 20 mg daily dose [43]. Trazodone aroused concerns due to significant lowering of seizure threshold (risk of status epilepticus) and possibility of arrhythmias [1, 44]. Trazodone in recent studies proved to be safe, but higher doses resulted in orthostatic pressure drops [45]. Bupropion described in a case report caused prolongation of seizure in combination with lithium and venlafaxine [46]. Other authors describe 12-day focal seizures resistant to treatment after 4 ECT treatments with bupropion [47].

In two patients diagnosed with recurrent depression bupropion combined with ECT caused phase change to mania [48]. There are no reports of adverse events with concomitant use of mirtazapine either before, during, or after ECT [49]. Venlafaxine increases ECT effectiveness less than nortriptyline and showed a trend towards adverse effect on cognitive functions [37, 50]. The drug at doses up to 300 mg in combination with propofol is considered to be safe, but the risk of asystole cannot be excluded at higher doses [51, 52]. Ventricular tachycardia has been reported in combination of duloxetine and lithium [53]. To date no publications about combined treatment with reboxetine, tianeptine, vortioxetine or agomelatine and EC have appeared. Monoamine oxidase inhibitors have little effect on seizure duration, but in combination with sympathomimetic drugs can cause hypertensive crisis [1]. Combining them with ECT is considered to be safe [54], similarly selective MAO inhibitors (selegiline, moclobemide) pose a small risk of side effects [55], although some authors advocate the withdrawal of non-selective drugs for 7–14 days prior to ECT. In a retrospective work consisting of 455 patients (including 5,482 ECT treatments), who were treated with ECT monotherapy (18.2%) or with ECT in combination with ADs, significant improvement in efficacy was observed in group receiving TCAs, mirtazapine or SSRIs with absence of annotations for serious adverse reactions [42]. ECT in combination with ADs proved effectiveness in prevention of recurrence of illness compared to ADs alone (32% vs. 61% of patients with relapse of depression in 1-year observation). Cognitive functions and memory remained stable among patients without illness recurrence in both groups [56].

In another study, authors emphasise that commencement of ADs pharmacotherapy (simultaneously with ECT vs. after series of treatments) had no effect on the incidence of relapse, and combination of venlafaxine with lithium compared to nortriptyline with lithium showed no difference both in terms of recurrence risk after ECT series, as well as adverse effects [57].

APA recommends that in case of severe depression, combination therapy should be considered in order to improve the effectiveness of ECT, or to decrease the risk of relapse after cessation of ECT treatment [4]. Sudden discontinuation of antidepressants before ECT, especially those with a short half-life and SSRIs, is not recommended [5]. In older patients with cardiac problems cardiotoxic potential of ADs should determine their choice, while in patients taking SSRIs it is recommended to start series of ECT with smaller loads [5].

Antipsychotic drugs

Simultaneous use of ECT and APDs, known since the 1960s, is considered to be safe, although some reports on causing convulsions as late complication [1]. APDs, especially phenothiazines and clozapine, probably lengthen the seizure duration; hence some have recommended discontinuation prior to treatments [1]. The APA guidelines administered that APDs may be continued due to their probable synergistic effect with ECT, most widely studied in schizophrenia [4]. Risperidone in terms of causing convulsions is placed on the list of minimal risk [58, 59], in further studies no adverse effects of its use with ECT were reported [60]. Despite the weak action for inducing seizures, occurrence of EEG abnormalities in patients treated with risperidone has been emphasised [61]. Casuistic description of patient concerned clinical efficacy and safety of ECT performed simultaneously with risperidone depot [62]. Another study confirmed the efficacy of ECT and risperidone in rapid elimination of aggressive behaviour in patients with schizophrenia [63]. There was a similar high efficacy and good tolerance with concomitant use of ECT with sulpiride, risperidone and olanzapine, despite earlier concerns that olanzapine, similar to clozapine, induces changes in EEG [61]. Casuistic paper reports on the safety of combined use of olanzapine and duloxetine with ECT in patient who achieved a complete remission of symptoms [64]. Anticonvulsant activity of quetiapine has been reported in patients treated with ECT [60]. In a study of 6 patients treated with ECT while taking quetiapine no increase in the value of corrected QTc interval above the norm was observed [65]. So far, there are no published works on the efficacy of quetiapine with ECT. In a retrospective study of Hungarian authors, safety of combined use of amisulpride and ECT was analysed in 20 patients, in whom it was used in the mean dose of 745 mg (range of 200–1200 mg). The combination was well tolerated and side effects were poorly expressed and transient compared to the control group. The addition of amisulpride to previously used APDs during ECT has been considered as safe [66]. Masdrakis et al. provide a description of 8 patients treated with ziprasidone (20–80 mg) during ECT. All patients tolerated the therapy well with minimal side effects and changes in QT without clinical significance [67]. The use of aripiprazole with ECT seems to be similarly safe although the literature data are not extensive. Casuistic description of a man, who had used aripiprazole at a dose of 30 mg, shows both good tolerance and absence of effects on impulse parameters

or seizure threshold and clinical improvement after a series of ECT [68]. Similarly, description of four patients (aripiprazole at a dose of 10–15 mg) indicates the safety of this combination [69]. The use of clozapine in patients treated with ECT is the most controversial. Initially discontinuation of the drug before starting the course of ECT was recommended because of the possibility to extend duration of seizures [1]. Casuistic descriptions actually reported its prolonged duration [70] and the occurrence of supraventricular tachycardia [71], but most contemporary studies do not indicate more serious side effects of this combination. Efficacy of combined use of clozapine and ECT in treatment of treatment-resistant schizophrenia is confirmed [72, 73]. Description of a patient treated with clozapine at a dose of 1600 mg while performing 24 ECT series shows no significant side effects except moderately severe cognitive disorders [74]. Authors emphasise superior efficacy of combined use of clozapine and ECT in comparison to clozapine monotherapy [75, 76], particularly marked in patients with schizoaffective disorder [75]. In a randomised study, Petrides et al., compared clinical response rate of ECT and clozapine combination therapy (n = 20) with clozapine monotherapy (n = 19) in patients with treatment-resistant schizophrenia. In 50% of patients treated with clozapine and ECT improvement was observed, which was not in patients receiving clozapine only (in the second phase of the study inclusion of ECT in this group lead to improvement in 47% of patients). No differences in cognitive functioning were found between those two groups [77].

Finally, a meta-analysis of these studies has demonstrated both the safety and efficacy of ECT used in combination with APDs, including clozapine [78, 79].

Drugs used in cognitive dysfunction associated with ECT

Initially, published case studies reported about patients receiving procognitive drugs who, due to their clinical condition, required ECT treatment. In one study, episode of severe delirium after discharge (there was no extended apnoea or bradyarrhythmia of clinical significance), in a patient receiving donepezil at a dose of 10 mg/day was reported [80]. No significant deterioration of memory and cognition in patients in the early stages of Alzheimer's disease at simultaneous use of rivastigmine and ECT was confirmed [81]. In later years researchers focused on exploring the possibilities of protective effect of procognitive drugs in treatment of cognitive disorders as adverse reaction after ECT. There are few reports on the effectiveness of donepezil in the treatment of cognitive deficits caused by ECT [82]. Donepezil administered at a dose of 5 mg before first treatment and up to three days after the last ECT accelerates cognitive normalisation compared to placebo [83, 84]. A study of 30 patients with schizophrenia treated with ECT and receiving rivastigmine (3–4.5 mg/day for 4 weeks) showed improvement in cognitive functions compared to placebo on Alzheimer's Disease Assessment Scale [85]. Piracetam was not effective in single use [86] or long administration [87]. Thiamine at a dose of 50–200 mg/day resulted in faster resolution of disturbances of consciousness and memory deficits after ECT [88]. Currently, clinical

trials exploring the effect of memantine on cognitive impairment after ECT, are being conducted and their completion is planned for 2015. As APA guidelines suggested, to date there is no pharmacological procedure that would involve reducing cognitive impairment induced by ECT [4].

Recapitulation

In conclusion it should be noted that there are no consistent guidelines regarding combined use of psychotropic drugs during performance of ECT and expert recommendations emphasise to consider each individual benefit/risk of such combination and caution in their use. At the same time, despite earlier concerns associating drugs with ECT, recommendations of dose reduction or complete cessation of drug administration, numerous research works indicate the safety of most antidepressants and APDs during ECT, and their probable synergistic action. However, attention should be paid to limitations of mentioned publications, especially case reports or observations of small groups of patients.

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