Non-pharmacological biological therapies in schizophrenia

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Non-pharmacological biological therapies of schizophrenia have dramatically developed over the last eight decades. Starting from a historical perspective authors aim to give an overview about the development of convulsive therapy. Recommendations of the most influential guidelines and the controversies in the worldwide clinical practice are discussed and clinical conditions responsive to electroconvulsive therapy are reviewed. Finally, the place of the new neurostimulation techniques, particularly TMS is outlined.

(Keywords: electroconvulsive therapy, transcranial magnetic stimulation, schizophrenia, catatonia, post-partum psychosis)

One of the major challenges psychiatry has faced from the very beginning of its history has been finding an effective treatment for schizophrenia (Faludi et al., 2011; Kovacs, 2011). The first encouraging results came in the 1930s when insulin coma, chemical convulsive therapy and lobotomy were introduced in clinical practice nearly at the same time. By now insulin coma and lobotomy have become obsolete but the electrically-induced form of convulsive therapy (ECT) has remained in the therapeutic armamentarium more than 75 years (Baran et al., 2008; Kalman and Kalman, 2011).

Shortly after the success of the first convulsive treatment, it was tried in a variety of diagnostic groups. It became rapidly evident to László Meduna, who called himself its ‘originator’, that convulsive therapy was less effective in the chronic than in acute forms of schizophrenia (Meduna, 1937). It soon became clear that affective patients responded even better to convulsive therapy than those with schizophrenia. In 1938, chemical seizure induction was replaced by electric stimulation (Gazdag, 2006a), and a few years later muscle relaxation was introduced (Bennet, 1940) to avoid serious complications such as fractures or retinal detachment. The last key modification of ECT was brief narcosis aimed to mitigate pre-treatment anxiety and the terrorizing fear associated to the muscle relaxation and electric stimulation.

Methodological limitations prevalent in the literature on ECT in schizophrenia make it difficult to draw firm conclusions about its effectiveness or efficacy. The first main limitation is the diagnostic heterogeneity of the study samples partly due to the changes in the diagnostic criteria of schizophrenia over the last 75 years. The second one is the heterogeneity of the patient populations in terms of the chronicity and that of the study design and the concomitant pharmacotherapy. Current ethical requirements stipulate informed consent for ECT by patients. Limited capacity, a common phenomenon in acute psychotic states, frequently precludes obtaining consent leading to bias in recruiting subjects for prospective studies. Using sham ECT or placebo regarded an unethical practice nowadays hindering randomized controlled trials using ECT.

EFFICACY OF ELECTROCONVULSIVE THERAPY IN SCHIZOPHRENIA

The first randomised controlled trials to confirm the initial clinical experience were conducted in the 1950-60s. ECT did not show superiority over sham ECT, but due to the heterogeneous samples and other methodological limitations these studies can be interpreted only with caution. Three studies conducted in the 1970-80s with more rigorous methodology proved the efficacy of real over sham ECT (Zervas et al., 2011). Meta-analysis of these studies showed earlier improvement on the BPRS with ECT compared to sham treatment, but this difference disappeared 6 months after the treatment (Tharyan and Adams, 2002).
Direct comparison with typical antipsychotic drugs showed equal or inferior efficacy of ECT (Tharyan and Adams, 2002). This may explain why after the introduction of antipsychotic treatment ECT use in schizophrenia decreased dramatically until the 1980s and was restricted to pharmacotherapy-resistant cases. For pharmacotherapy-resistant patients the combination of ECT with pharmacotherapy can be useful (Gazdag, 2006a).

There has been no direct comparison published of the efficacy of ECT against second-generation antipsychotics (SGA). Information on the efficacy of the ECT-pharmacotherapy combination is limited as the available studies have a small sample size. Two studies reported on the successful use of ECT-risperidone combination in patients non-responsive to previous antipsychotic treatment (Tang and Ungvari, 2003; Ravanic et al., 2009). Studies of clozapine-ECT combination in treatment-resistant (TRS) patients confirmed the effectiveness of this treatment strategy. Kupchik and Spiva (2000) found improvement in 67% of their patients with this combination and 8 of 11 patients responded well in another study (Kho et al. 2004). The combined treatment is mainly effective for catatonic and schizoaffective patients (Gazdag et al., 2006b). In a further study involving 18 TRS patients, reduction of the PANSS score was 71% on combined treatment, 46% on clozapine and 40% on ECT monotherapy (Masoudzadeh and Khalilian, 2007).

RECOMMENDATIONS IN THE GUIDELINES

Authoritative international guidelines do not generally recommend the ECT for schizophrenia. Nevertheless, the American guidelines advocate the use of ECT as a first choice if fast clinical improvement is necessary or ECT was effective in a previous episode of the illness (APA, 2001). The Royal College (UK) guidelines, however, suggests ECT in schizophrenia only in the fourth line, in TRS patients non-responsive to clozapine (RCP, 2005). The National Institute for Health and Clinical Excellence (NICE) guidelines are even more restrictive allowing ECT in schizophrenia only in acute, pharmacotherapy-resistant catatonia (NICE, 2003).

ECT IN SCHIZOPHRENIA: A WORLDWIDE PERSPECTIVE

Although the above guidelines propose ECT only in a highly selected segment of schizophrenia patients, clinical practice is in contrast with these recommendations. In several countries, particularly in the developing world, schizophrenia remains the first indication for ECT; e.g. 36.5% of schizophrenia patients are treated with ECT in India (Chanpattana et al, 2005). This implies that a huge number of schizophrenia patients receive ECT underscoring the importance of this topic both for academic psychiatry and clinical practice. Anecdotal evidence suggests that a similarly large number of schizophrenia patients are given ECT in China (YT Xiang, personal information, September, 2011) but exact figures are not yet available. In contrast, in Hong-Kong, where the British guidelines are still influential, ECT is rarely used in the treatment of schizophrenia (Chung, 2003); not surprisingly, an ECT attitude survey detected significant differences in the clinical practices between Hong-Kong and Beijing (Leung et al., 2005).

In some other countries including Thailand (Chanpattana and Kramer, 2004), Fiji Islands (Chanpattana et al, 2010), Japan (Chanpattana et al, 2005), Hungary (Gazdag et al, 2004) and the Chuvash Republic of the Russian Federation (Golenkov et al, 2010), ECT is also mainly used in the treatment of schizophrenia.

Although schizophrenia is not a disease-specific indication for ECT, its certain subtypes however show good clinical response to ECT. In the following part clinical aspects of schizophrenia will be summarized in which ECT and Transcranial Magnetic Stimulation (TMS) are potentially beneficial.

ECT IN CATATONIC SCHIZOPHRENIA

Efficacy of ECT

Already Meduna realized that catatonic states in general, and acute catatonia in particular, improve best with convulsive therapy (Meduna, 1937). Later studies confirmed his observations.

Wells (1973) conducted a retrospective chart review covering 276 schizophrenia patients treated with ECT in a university department between 1960 and 1969. ECT was administered if pharmacotherapy failed to produce improvement or depressive and catatonic symptoms were present. Thirty-three (12%) patients were diagnosed with the catatonic subtype; 18 (55%) of them showed “good” and 9 (27%) “moderate” response to an average of seven bilateral ECT. Catatonic patients responded significantly better to ECT than patients with any other subtype.

The largest and most informative retrospective study also originated from these years. As part of the Iowa 500 project, a chart review of 250 catatonic schiz-
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RELIEF IN SCHIZOPHRENIA PATIENTS was performed relying on detailed case histories (Morrison, 1974). Remission in both psychopathology and social function from a single episode, rather than long-term recovery, was judged blindly. Of the 250 patients, 214 were followed for a median of 2 years. The overall remission rate was 40% as opposed to 53% for patients who did not receive ECT. For all 214 patients, remission correlated only with symptoms of ‘denudativeness’ and ‘stereotypes’ from 26 factors examined for predicting recovery.

In a German university department, 20 patients were diagnosed with catatonic schizophrenia over an 18-month period (Finkbeiner, 1995). ECT was considered first-line treatment for catatonia if a patient was stuporous, resistant to antipsychotics or experienced severe drug side-effects. Only five patients received ECT resulting in complete resolution of catatonia in all cases, while their psychosis also improved.

ECT versus pharmacotherapy

In the only randomized controlled trial published to date (Girish and Gill’s 2003), 14 lorazepam non-responder non-affective patients were randomized to either receiving ECT and oral placebo, or sham ECT and risperidone (4-6 mg) in a 3-week trial. Bilateral ECT was administered three times a week; outcome was measured with the Bush-Francis Catatonia Rating Scale (BFCRS) and the PANSS. Most subjects displayed stupor. Both groups improved markedly, with the ECT-treated subjects showing significantly greater improvement on the sum scores of both rating instruments.

In the other prospective study, 50 catatonic patients, 23 with the diagnosis of schizophrenia, were enrolled (Hatta et al., 2007). The first line treatment was lorazepam; benzodiazepine non-responder patients received either ECT or an antipsychotic drug and if the latter failed, ECT followed. Only 1 of the 41 patients (maximum dose of 3mg/day) responded fully to lorazepam and 19 responded partially. In contrast, all 17 patients who received ECT remitted from catatonia. All 5 schizophrenia patients who received ECT became symptom-free while none of the 18 schizophrenia patients responded lorazepam. The authors concluded that ECT should be used more frequently as a first-line treatment for catatonia.

MALIGNANT CATATONIA

A rare, life-threatening syndrome characterized by extreme motor excitement, followed by stuporous exhaustion, cardiovascular collapse, coma and death as described by Stauder in 1934 as “lethal catatonia”. The clinical presentation also included progressive hyperthermia, autonomic dysfunction, clouding of consciousness and prominent catatonic features. Modern psychiatry prefers the term malignant catatonia (MC) and conceptualizes it as a syndrome rather than a separate disease entity which can develop in association with schizophrenia, bipolar affective disorder as well as a variety of neuromedical conditions.

Although controlled studies are lacking, case reports and case series indicate that ECT is a safe and effective treatment for MC when it occurs as an outgrowth of a major psychotic disorder (Mann et al., 2004). Prior to the mid-1940s, the mortality of MC was reported as 75-100%. Arnold and Stepan (1952) were the first to employ the “shock-block” ECT; 16 (84%) of their 18 patients receiving ECT within the first 5 days after the onset of MC survived. Treatment started with three bilateral stimulations followed by a fourth one within 24 hours. The procedure was continued with one or two daily “electroshocks” for two or three days followed by further single sessions on alternate days or every third days until a total of 12-15 treatment sessions. These authors stressed that early identification and prompt initiation of treatment was critical; all 14 patients starting ECT more than 5 days after the onset of MC died.

More recent publications have reported good treatment response of MC with far fewer ECT sessions. Consistent with the findings of Arnold and Stepan, modern reports underscore that ECT appears effective only if initiated before MC progresses. Sedivec (1981) reported 8 MC cases treated with ECT. In 7 cases, MC remitted after 5-7 treatments; the eighth patient, who was comatose and hyperthermic upon admission, died despite receiving ECT. The author stressed that coma or a temperature in excess of 41 degrees C augurs poorly for MC responding even to ECT. Of the 50 patients reported in four large series, 40 of 41 patients treated with ECT survived (Mann et al. 2003). In contrast, only 5 of 9 patients who received only antipsychotics and supportive care recovered. Similarly, in a review of 18 MC cases, 11 of 13 treated with ECT survived compared with only 1 of 5 patients who did not receive ECT (Philbrick and Rummans, 1994).

ECT IN POST-PARTUM PSYCHOSIS

Postpartum psychotic states show good response to ECT (Herzog and Detre, 1976; Katona, 1982).
Considering alternative treatment options, it is important to bear in mind that to a certain extent all psychopharmacological agents infiltrate into the breast milk (Pons et al, 1994) while drugs used for the anesthesia before ECT pose little risk for the infant. As the absorption of succinylcholine from the gastrointestinal tract is poor, it does enter in the circulation of the infant in a significant amount. The same applies to methohexital: less than one percent of the maternal blood concentration was detected in the blood of the infants (Borgatta et al, 1997).

**NEUROSTIMULATION METHODS IN THE TREATMENT OF SCHIZOPHRENIA**

In the last two decades several new neurostimulation methods have been introduced in psychiatry coming mainly from the field of neurology. These include TMS, vagus nerve stimulation (VNS), deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS). To date, only TMS has been used in the treatment of schizophrenia, all the other new techniques have been applied exclusively in depression.

**TRANSCRANIAL MAGNETIC STIMULATION IN SCHIZOPHRENIA**

TMS refers to the administration of a series of pulsed magnetic stimuli to the brain for the purpose of altering brain function. A stronger and more intense pulse results in more activation of the CNS tissue and a wider area of activation.

Effect of TMS is being actively investigated in two aspects of schizophrenia, negative symptoms and auditory hallucinations. Auditory hallucinations are believed to be connected with the aberrant activation of the language perception area at the junction of the left temporal and parietal cortices (Higgins and George, 2007). Low frequency TMS has been used to inhibit this area to alleviate auditory hallucinations. A recent meta-analysis reviewed the efficacy of low frequency TMS for resistant auditory hallucinations in schizophrenia (Aleman et al. 2007). The conclusion drawn from 10 controlled studies was that TMS is effective in reducing auditory hallucinations, but had no effect on other positive symptoms or the cognitive deficits of schizophrenia.

Several RCTs used intermittent daily prefrontal TMS to treat negative symptoms in patients with schizophrenia. A recent comprehensive review concluded that there is also preliminary but limited evidence that TMS could have a role in reducing the negative symptoms of schizophrenia (Fitzgerald and Daskalakis 2008).

**CONCLUSION**

While ECT in schizophrenia has been significantly restricted in the Western world over the past 30 years it has remained the first indication for this illness in several populous Asian countries. It could be safely assumed that the majority of the ECT-treated patients in Asia suffer from schizophrenia that contradicts the recommendations of current Western guidelines. Owing to the development of more stringent ethical regulation, very few randomized controlled studies were performed in schizophrenia since the 1980s, mainly in India and Africa providing only weak support for the more widespread use of ECT in schizophrenia. On the other hand, there is robust clinical evidence about the exceptional efficacy of ECT in certain clinical conditions such as catatonic stupor, NMS, puerperal psychosis. Investigating the efficacy of ECT in these conditions with randomized controlled trials would be ethically unacceptable, therefore these data reflect well-established clinical wisdom but are not evidence-based. This poses a danger to patients suffering from the above-discussed life-threatening conditions responsive to ECT, as it is expected that with the development of ever stricter guidelines in western countries these patients will miss out on the most effective treatment for their illness.

At this point of their development, new neurostimulation techniques represent no real alternatives for ECT in the treatment of schizophrenia. Only TMS has shown promising result in the treatment of auditory hallucinations.

In conclusion, theoretically there is a clear need for further randomized controlled studies to establish the efficacy of ECT in some clinical conditions loosely linked schizophrenia particularly severe catatonia, NMS, and postpartum psychoses.

**REFERENCES**

A szkizofrénia nem farmakológiai biológiai terápiái

A szkizofrénia nem gyógyszeres biológiai kezelési módszerei drámai fejlődésen mentek keresztül az elmúlt 8 évtized alatt. Történeti perspektívából kiindulva a szerzők bemutatják a görpecskezelés fejlődését. Bemutatásra kerülnek a legjelentősebb nemzetközi protokollok ajánlásai, valamint az ezen ajánlásoktól számos országban jelentősen eltérő klinikai gyakorlat. A szerzők áttekintik a szkizofrénia diagnosztikus kategóriáján belül azokat a tünetegyütteseket, amelyek különösen jól reagálnak elektrokonvulzív kezelésre. Végül megbeszélésre kerül az új neurostimulációs módszerek helye a szkizofrénia kezelésében.

Kulcsszavak: elektrokonvulzív kezelés, transzkranialis mágneses stimuláció, szkizofrénia, katatónia, postpartum pszichózis