Chapter 1

Introduction

The field of brain stimulation in psychiatry is advancing at a rapid pace. Practitioners, researchers, and educators have a need to stay informed about the latest advances in these therapeutic modalities. This manual summarizes the information about the brain stimulation techniques currently used for the treatment of psychiatric illness. It covers the scientific basis for the efficacy of each modality, describes the technique itself, and explains the clinical conditions for which each is indicated. Likely future directions for each of the stimulation techniques are discussed.

ECT has by far the longest track record of use as well as the largest medical and scientific evidence base supporting its efficacy and safety. It remains a standard treatment in the psychiatric armamentarium around the world. It is important for psychiatrists to be aware of the most recent advances in technique and clinical indications that allow ECT to be effective and better tolerated than ever before.

DBS is a fascinating brain stimulation modality that has recently crossed into psychiatry from neurology, where its principal use is in Parkinson's disease. While approved currently in psychiatry only for refractory OCD, it is being studied for use in refractory depression, an indication that is likely to greatly expand its use. Because DBS involves direct stimulation of brain tissue, it has promise as a powerful investigative tool in neuroscience.

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation modality that has been approved for the treatment of depression in the United States and Canada, as well as several European countries. It is in its clinical infancy and is still only modestly effective for the treatment of depression. It has wide appeal, however, because of its non-invasive nature and excellent safety profile.

Other, less widely used, or experimental, brain stimulation techniques such as vagus nerve stimulation (VNS) and magnetic seizure therapy (MST), among others, are described and assessed as to their likely roles in future clinical practice.

With the citations at the end of each chapter of the manual, the reader will find a concise reference guide to the state-of-the-art of the medical literature for each modality.

Brain Stimulation in Psychiatry: ECT, DBS, TMS, and Other Modalities, Charles H. Kellner. Published by Cambridge University Press.

Chapter 2

Electroconvulsive Therapy (ECT): Basic Concepts

Basic Concepts

Electroconvulsive therapy (ECT) is a safe, reliably effective procedure; it requires that the practitioner have a theoretical and practical background to perform it well. Our hope is that this book will assist the practitioner in the application of previously acquired knowledge of ECT. Our intent is that this book should complement the existing, comprehensive texts on ECT, including the report of the American Psychiatric Association (APA) Task Force on Electroconvulsive Therapy (2001) (American Psychiatric Association, 2001), *Electroconvulsive Therapy* by Richard Abrams (Abrams, 2002), and *Electroconvulsive and Neuromodulation Therapies* by Conrad Swartz (Swartz, 2009). *Electroconvulsive therapy: a guide for professionals and their patients* by Max Fink (Fink, 2009) is also recommended.

Our belief is that ECT is a well-standardized procedure that can be learned quite easily. The body of knowledge that the practitioner must master is circumscribed and not overly complex. Of course, as in any clinical endeavor, situations arise that require expert judgment and some modification of standard technique. There is no substitute for clinical experience, and consultation with experts is recommended in difficult cases.

The goal of this text is to provide a practical and useful outline of the basics of the treatment and to assist the reader in developing a well-informed, commonsense attitude to approaching the patient who needs ECT. At all times, technical excellence and patient comfort should be foremost considerations.

Overview

ECT remains the most reliably effective treatment for serious depression (Lisanby, 2007). Its efficacy and speed of response compare favorably to those of antidepressant medications (Husain et al., 2004). For these reasons, it must be considered a mainstream treatment in modern psychiatric practice, not one that is optional or "on the fringe." In the past two decades, there has been a steady

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increase in ECT research, as evidenced by the growing number of ECT-related citations in the scientific literature. In addition, renewed clinical interest in ECT has led to the growth of professional societies dedicated to the advancement of ECT including the International Society for ECT and Neurostimulation (ISEN, formerly the Association for Convulsive Therapy [ACT]) and the European Forum for ECT (EFFECT), among others worldwide. Innovations in technique (e.g., the electrical dose-titration method of estimating seizure threshold) (Sackeim et al., 1987), the use of ultrabrief pulse stimuli (Sienaert et al., 2009), as well as new information about the use of ECT in catatonia (Fink and Taylor, 2006) and as a continuation/maintenance treatment for affective disorders (Kellner et al., 2006), have been exciting recent developments.

Despite the ongoing barrage of criticism of the treatment (based largely on either outdated or incorrect information), ECT has remained in continuous use since its introduction in Rome in 1938. But modern ECT is so far removed from that primitive procedure that it should hardly be considered the same treatment. Just as it would be unreasonable to equate surgery as performed in 1938 with surgery as performed in 2010, so old-fashioned ECT is now of purely historical interest. The remarkable popularity of the movie *One Flew Over the Cuckoo's Nest* is largely responsible for the continued public perception of ECT as a barbaric, coercive procedure. Two recent books for the lay public, *Shock Therapy: a History of Electroconvulsive Treatment in Mental Illness* by Edward Shorter and David Healy (Shorter and Healy, 2007), and *Shock: the Healing Power of Electroconvulsive Therapy* by Kitty Dukakis and Larry Tye (Dukakis and Tye, 2006) are both informative and factually accurate; they paint a realistic and positive picture of contemporary ECT.

Although ECT is an essential part of psychiatric practice, it remains a very small part. According to data from the National Institute of Mental Health (NIMH), in 1980, approximately 32,000 psychiatric inpatients received ECT in the United States; in 1986, the number increased to approximately 37,000 (Thompson et al., 1994). The current figure of patients who receive ECT annually in the United States is almost certainly greater, although, surprisingly, precise data are unavailable. Hermann et al. estimated that 100,000 patients received ECT in the United States in 1995 (Hermann et al., 1995); Abrams estimated that 1–2 million patients per year receive ECT worldwide (Abrams, 2002).

Health care reform has led to more frequent use of ECT and a greater emphasis on the ability to offer the treatment to outpatients. Because ECT is likely to be more effective than antidepressant medications for many patients (Janicak et al., 1985), it stands to reason that it would be viewed favorably in an increasingly cost- and efficiency-conscious environment.

The old assumption that a course of ECT necessitates being in the hospital is no longer valid. Of course, some patients will be so severely ill as to require hospitalization. Many, however, with adequate family support and close attention to the logistics of treatment, for example, explicit written instructions

about concurrent medications, nothing by mouth (NPO) status, proscription of driving, can be safely and comfortably treated as outpatients (Jaffe et al., 1990; Fink et al., 1996).

Because ECT requires specialized knowledge and technical skill, it is likely to be performed by only a small minority of psychiatrists. Thus, local ECT experts, to whom other practitioners refer patients, may be the norm.

Although there may be some controversy about what level of ECT expertise should be required of all psychiatric residents, there can be little disagreement that all psychiatrists should know enough about ECT to make informed referrals to ECT practitioners. Furthermore, the report of the APA Task Force on Electroconvulsive Therapy (American Psychiatric Association, 2001) makes specific recommendations about minimum didactic and practical experiences for psychiatric residents and practitioners who want to be privileged by a hospital to perform ECT.

ECT should be performed only by qualified personnel in an appropriate setting. This setting is generally in a hospital or clinic where access to the equipment and personnel necessary to handle cardiopulmonary emergencies is available. Close cooperation with the staff who provide anesthesia support is essential for optimal ECT. As in all medicine, the goal of scientific and technical advancement remains improved patient care. Our approach to the patient referred for ECT (i.e., the ECT consultation) is quite simple. We require that three questions be answered:

1. Does the patient have an ECT-responsive illness?
2. Does the patient have any medical problems that might require modifications of technique or increase the risks of the procedure?
3. Has appropriate informed consent been obtained?

Each of these questions and many other related issues are covered in subsequent chapters.

Theories of Mechanism of Action

ECT has multiple, profound effects on brain systems, and hypotheses about its mechanism(s) of action are plentiful. Patients and practitioners, understandably, would be comforted by knowing exactly how ECT exerts its therapeutic effects. We are not yet able to explain this in an accurate and comprehensive way. However, rather than settle for a stark "we don't know" response to the question of how it works, it may be more reasonable to invoke one of the better-supported theories of mechanism of action (see below). In truth, we know nearly as much about how ECT works as we do about how antidepressant medications work. A full understanding of how ECT (and other antidepressant treatments) works may need to await a more thorough understanding of the etiology of the major psychiatric illnesses.

Research over the last several decades has provided a wealth of information about specific changes in neurobiology induced by ECT (Sackeim, 1989; Swartz, 2009; Mann, 1998). The classic research of Ottosson (Ottosson, 1960, 1962) using lidocaine-modified ECT helped to establish the seizure as crucial to the efficacy of ECT. The finding that low-dose right unilateral ECT produces suboptimal clinical outcomes despite adequate seizure duration confirmed that not all ECT seizures are equivalent (Sackeim et al., 1987). It appears that both the anatomic location of seizure initiation as well as intensity of the electrical stimulus affect both therapeutic efficacy and cognitive effects (Nobler et al., 2000). A search has begun for more sophisticated measures of seizure therapeutic adequacy other than seizure duration (e.g., postictal electroencephalographic [EEG] suppression) (Nobler et al., 1993; Krystal and Weiner, 1994), but, as yet, no reliable, clinically useful measure has been validated. In short we still lack a definitive understanding of how ECT results in antidepressant and antipsychotic effects. Four main theories are summarized below:

Classical (Monoamine) Neurotransmitter Theory

This theory suggests that ECT works in a way similar to that of antidepressant medications – that it enhances deficient neurotransmission in relevant brain systems. This is a corollary of the classical monoamine depletion theory of depression, a theory that has been updated to include the possibility of a modulatory role for monoamine systems, rather than a simple deficit-adequacy model (Heninger et al., 1996). Specifically, ECT is known to enhance dopaminergic, serotonergic, and adrenergic neurotransmission. Animal studies using ECS (electroconvulsive shock, the term for ECT in animals) have demonstrated increases in dopamine-related behaviors (Fochtmann, 1994). The exact mechanism for this dopaminergic enhancement is as yet unclear; however, it may involve increased dopamine release, receptor changes, and/or changes in the blood-brain barrier (Fall et al., 2000). The fact that ECT has clear antiparkinsonian effects argues strongly for dopaminergic enhancement (Popeo and Kellner, 2009). That ECT also has profoundly antipsychotic effects (and we would expect decreases in dopamine function to be associated with antipsychotic effects) argues against a single theory of increased dopamine availability throughout the brain.

Numerous studies of the serotonin system in both animals (ECS) and humans (ECT) have revealed a complex pattern of changes to pre- and postsynaptic receptors, the serotonin transporter and serotonin metabolites in the cerebrospinal fluid, not all of which are consistent with a simple theory of serotonin enhancement with ECT (Swartz, 2009). For many years, based on animal studies, the serotonin system was believed to be the only monoaminergic system in which ECT had opposite effects from most antidepressant drugs. ECS increases 5-HT_2 receptor number, whereas antidepressant drugs decrease 5-HT_2 receptor number (Mann and Kapur, 1992). A recent

PET scan investigation found, in contrast to the ECS studies, that ECT reduces brain 5-HT_2 receptors in depressed patients (Yatham et al., 2010). These authors speculated, "the ability of ECT to further down-regulate brain 5-HT_2 receptors in antidepressant non-responsive individuals may explain its efficacy in those people with antidepressant refractory depression." Rudorfer et al. (1988) demonstrated that 5-hydroxyindoleacetic acid (5HIAA), the major metabolite of serotonin, was increased in the spinal fluid of patients after ECT.

The adrenergic system is also affected by ECT; here, too, numerous preclinical, as well as clinical studies have yielded complex, sometimes contradictory findings. As with other antidepressant drugs, down regulation of beta-adrenergic receptors has been a consistent finding in ECS studies. More recent studies suggest that ECS results in increased cortical norepinephrine transmission as a result of postsynaptic effects (Newman et al., 1998). However, human studies have failed to find consistent alterations in norepinephrine turnover with ECT (Rudorfer et al., 1988).

Other neurotransmitter systems, including glutamate and GABA have been implicated in the mechanism of action of ECT. Studies of glutamate, in both animals and human subjects, have yielded conflicting results. Pfleiderer et al. (2003) showed reduced glutamate with magnetic resonance spectroscopy in the anterior cingulate of depressed patients; glutamate levels normalized with successful ECT. A more recent study showed the opposite in the rat hippocampus, with glutamate levels decreasing after ECS (Dong et al., 2010). Glutamate may be involved in both the antidepressant and the cognitive effects of ECT.

The GABA system has been implicated in the antidepressant and anticonvulsant properties of ECT (Swartz, 2009). Both animal (Ferraro et al., 1990) and human studies (Esel et al., 2008) have demonstrated increases in GABA levels after ECS or ECT. As a major inhibitory neurotransmitter that is measurable in human serum, GABA is likely to be the focus of further investigations of ECT's mechanism of action in the future.

Neuroendocrine Theory

This theory suggests that ECT-induced release of hypothalamic or pituitary hormones results in antidepressant effects. The specific hormone(s) responsible for this therapeutic effect has yet to be isolated. ECT results in release of prolactin, thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and endorphins, among other neurohumoral substances (Kamil and Joffe, 1991). A putative antidepressant neuropeptide, "antidepressin" or "euthymesin," has been theorized to be released from the hypothalamus during the ECT seizure, exerting beneficial effects on mood disorders in a way similar to that in the diabetes/insulin model (Fink and Nemeroff, 1989).

Many investigations have confirmed both the dysregulation of the hypothalamic-pituitary-adrenal (HPA) in melancholic depression and the

correction of this abnormality with successful antidepressant treatment, most notably, ECT (Carroll, 1986). The dexamethasone suppression test (DST), the endocrine test that identifies the HPA abnormality, has also been used as a marker of the adequacy of continuation ECT; failure to normalize has been shown to be an indication of the need for ongoing continuation ECT (for review, see Bourgon and Kellner, 2000).

Anticonvulsant Theory

This theory suggests that the antidepressant effect of ECT is related to the fact that ECT itself exerts a profound anticonvulsant effect on the brain. Several lines of evidence indicate that this is so, including the facts that seizure threshold rises (and seizure duration decreases) over a course of ECT and that some patients with epilepsy have fewer seizures after ECT (Griesemer et al., 1997; Sackeim, 1999). ECT has even been used to treat resistant status epilepticus (Lisanby et al., 2001). Neurohormones have been postulated to mediate this anticonvulsant effect. The cerebrospinal fluid of animals receiving ECS is anticonvulsant when given intraventricularly to recipient animals, possibly as a result of endogenous opioids (Holaday et al., 1986). GABA has also been proposed as a key mediator of ECT's anticonvulsant effect (see above).

Neurotrophic Theory

A substantial amount of recent evidence suggests that ECT, like other antidepressant treatments has neurotrophic properties: the effects of ECT, in contradistinction to those of prolonged depression, may be beneficial for the brain. Animal studies show that ECS (the animal analog of ECT) results in increased neurogenesis and mossy fiber sprouting in the dentate gyrus of the hippocampus (Madsen et al., 2000; Lamont et al., 2005; Bolwig and Madsen, 2007). It is possible that neuroimaging techniques, such as magnetic resonance spectroscopy (MRS), may soon be able to provide evidence for neurogenesis in humans after ECT. Preliminary evidence suggests that ECT may lead to increases in neurotrophic factors such as brain-derived neurotrophic factor (BDNF) in depressed patients (Piccinni et al., 2009).

Basics of Electricity

The ECT practitioner should know the following basic facts about electricity in ECT:

Stimulus Characteristics

Modern ECT devices use alternating current that delivers a stimulus in the form of a series of bidirectional square-wave pulses. This is referred to as a brief pulse or ultra brief pulse (when the pulse width is below 0.5 ms) stimulus. Older

ECT devices delivered a sine-wave stimulus. The brief pulse or ultra brief pulse stimulus is more efficient at inducing seizures and consequently can produce seizures with a lower "dose" of electricity. This results in less cognitive impairment. Emerging data are promising that ultra brief pulse stimuli will be much less cognitively impairing, yet preserve efficacy (Sienaert et al., 2010).

Charge

Charge refers to the total number of electrons flowing through a conductor. Many ECT experts agree that the dose of electricity used in ECT should be expressed in terms of charge. The setting dials on some ECT devices vary the charge (by increasing stimulus duration), despite the fact that they are labeled "energy." The equation for charge is

$$\text{charge} = \text{current} \times \text{time}$$

Charge is expressed in millicoulombs (mC).

Energy

Energy adds a term for voltage to the equation for charge. Thus:

$$\text{energy} = \text{voltage} \times \text{current} \times \text{time}$$

Voltage can be thought of as the pressure with which the electrons are "pushed" through the conductor.

By rearranging the above equation with the substitution of an expanded term for voltage

$$(\text{voltage} = \text{current} \times \text{resistance [Ohm's law]}),$$

we arrive at

$$\text{energy} = \text{current}^2 \times \text{resistance} \times \text{time}$$

Thus, as resistance increases, if current and time are kept constant, energy also increases. Because modern ECT devices are mostly of the constant-current type, a patient with a higher resistance will have more energy delivered than a patient with lower resistance treated at the same setting. The constant-current ECT device is designed to increase the voltage automatically (up to a predetermined safe maximum limit) to deliver the desired charge despite high resistance. Because a patient's resistance (impedance) during the delivery of a stimulus is unknown until the stimulus is delivered, settings on an ECT device in terms of joules (J) must necessarily be estimates based on an arbitrary fixed "standard" impedance (e.g., 200 or 220 ohms). Remember that the dial on the ECT device that controls the length of the stimulus is actually setting the charge and only indirectly setting the energy.

Energy is expressed in terms of joules. Note that the number of joules used in ECT is generally considerably smaller than that used in cardiac defibrillation. ECT devices available in the United States deliver an allowable maximum of 101.4 J. Joules may be converted to millicoulombs by multiplying by 5.7 (assuming fixed impedance of 220 ohms and current of 0.8 A).

Impedance may be highly variable between individual patients. The primary contributor to the impedance of the electrical circuit is not the brain, but rather the skin, the underlying scalp soft tissues, and the skull. The contribution of these elements to the interindividual variability of seizure threshold for ECT requires further research (Coffey et al., 1995; Beale et al., 1994; Sackeim et al., 1994; Petrides et al., 2009).

Electrical Safety

The risk of injury to the patient or the practitioner from being shocked is very small. Theoretically, if the patient's impedance is too high, a skin burn at the electrode site can occur. This possibility is virtually eliminated by the provision of electrical self-test features in modern ECT devices, which allow the psychiatrist to check impedance before delivering the stimulus (see section, "Electrode Site Preparation," in Chapter 3). The person delivering the stimulus is at no risk for getting shocked unless he or she actually touches the metal or the conducting surface of one of the stimulus electrodes. The patient's scalp may be touched (e.g., to provide counterpressure on the left side of the forehead during a right unilateral treatment) during the delivery of the stimulus without fear of being shocked. Calls of "Stand clear!" are unnecessary. However, it is prudent to ensure that anesthesia personnel or other personnel do not touch the electrodes during the delivery of the stimulus.

Medical Physiology

Of greatest importance to the clinician are the physiological effects of ECT on the central nervous and cardiovascular systems. As described in later sections, modifications in ECT technique may be required in patients with neurological or cardiovascular disease.

Cerebral Physiology of ECT

Seizure Induction

ECT involves the use of an electrical stimulus to depolarize cerebral neurons and thereby produce a generalized seizure. The more completely generalized the seizure, the more powerful the antidepressant effect is thought to be. The mechanism by which ECT seizures are propagated is not well understood (Enev et al., 2007). However, important differences between bilateral and unilateral