Update on electroconvulsive therapy dosing strategies

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Abstract
Electroconvulsive Therapy (ECT) remains a controversial treatment modality, with a wide range of clinical practice and application. Recently significant advances in the technique of application of ECT have been made. These new approaches incorporate a variety of advances in ECT dosing strategies and techniques, including stimulus dosing and high-dose delivery mechanisms. The purpose of this paper is to review the various advances in ECT dosing strategies and to review the impact of these changes on the delivery of ECT as a treatment modality.

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Introduction

The impetus for developing new techniques of electroconvulsive therapy (ECT) administration comes from the problems associated with this treatment modality. Today these problems consist largely of the neuro-cognitive deficits associated with bifronto-temporal ECT techniques. In order to overcome these problems, ECT clinicians have undertaken research looking for the factors responsible for these adverse effects and mechanisms to overcome or minimise them.

ECT dosing techniques

The search for an ECT dosing technique that limits the number and severity of the neurocognitive deficits associated with the treatment, but retains all of the therapeutic benefits, has resulted in the development of various modifications to the practice over the decades. It is well recognised that there are a host of factors associated with the development of ECT related cognitive deficits. The most critical amongst these include the electrical "dose" and pattern of electrode placement (right unilateral RUL ECT versus bilateral BL ECT). Other factors include the number of treatments administered, frequency of ECT administration and the concomitant pharmacotherapy used.[1-10] So how does the clinician decide on the "dose" of ECT to administer for each individual patient on the commencement of treatment?

There are a number of techniques available, varying in complexity and accuracy. The method of stimulus dose selection is a topic of much heated debate in the modern ECT literature. So much so, that it may boil down to what technique one is a proponent of, or is familiar with, that will be chosen, regardless of evidence base. Charles Kellner, Editor-in-Chief of the Journal of ECT recently highlighted the situation just described.[11]

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Which technique

In order to make an "evidence based" decision on the stimulus dose question here are some dosing techniques one could consider. Each technique has a reasonable evidence based data pool to support its use and of course, each has its own set of unique strengths, weaknesses and controversies.

The "Age Rule" (*also called the age method*)

It has been known for decades that there is an inverse relationship between seizure duration and age. That is, seizure duration decreases with increasing age.[6] It was also known that seizure duration was not specifically related to seizure threshold per say, but rather to the magnitude by which the ECT stimulus was given above this point.[6] This means that the higher the administered ECT dose above threshold, the longer the resulting seizure. It has also been known since the 1940's that there is a positive correlation between age and seizure threshold, with older patients having a higher threshold than younger patients. These relationships were confirmed in studies in the 1980,s using the then new, brief-pulse ECT machines such as we use today.[2,3,6] Data from the 1990,s then showed that this age-threshold correlation was indeed present.[10,12,13]

The "age rule" came into being as a result of an ongoing search for a simple and reliable means of predicting a patients threshold so as to commence treatment without the need for stimulus titration, or precise threshold elicitation. The "age rule" has been the recommended dosing procedure with the Thymatron DGxTM ECT device training manual.14 The age rule states "just set to the patients age and treat".[14] For example, a 50 year old patient will have the energy dial set at 50% (252 mC charge) and treatment will proceed. The justification for this approach, is it "...saves time while automatically providing a stimulus dose that averages about 2.5 times the minimum required to induce a seizure".[14] It is also claimed that "setting Thymatron to patient's age gives correct dose for ECT".[14]

The data quoted to justify this approach in the training manual text is given as original work conducted by Weiner [6] and

Sackeim.[2,3] This clinical data deserves some dissection. On review of these articles nowhere is it suggested by these authors that one must just "set to the patients age and treat". The aim of the Weiner article was to "help resolve the effects of stimulus wave form and electrode placement upon seizure threshold in a clinical setting."[6] The study was not designed to correlate age with ECT "dose". The study involved 48 patients suffering with depression and schizophrenia. All except one was male and 17 received a sine wave stimulus, an ECT practice that no longer exists. The patients were divided into two groups, one group treated with brief pulse UL ECT and the other with BL ECT. The mean age of the UL ECT group was 53 yrs and their mean threshold was very approximately, 100mC or 20% energy on the Thymatron DGxTM machine. The mean age for the BL ECT group was 47.4 yrs and their mean threshold was approximately the same. The authors were unable to show a significant difference in threshold between the two groups based on electrode placement due to the small numbers of cases involved. They did, however, show a statistically significant correlation between age and threshold.[6] However, no data was presented to show therapeutic outcome based on ECT dose as all the treatments were given at or near threshold. In other words, none of this data can be used to support the "age rule", except to show that there was a positive correlation between age and threshold.

The two studies by Sackeim[2,3] were both based on data extracted form the same group of 52 depressed patients. In the first study the aim was to examine the "relationships between seizure threshold, age, sex, electrode placement and cumulative treatment number".[2] Again in this study, as in the Weiner study,[6] there was indeed a weak correlation between seizure threshold and age (0.32, $p<0.05$), as there was with sex and electrode placement. However, the authors point out the critical finding that " the majority of the variance in seizure threshold was still unaccounted for". Of significant importance was the huge (12 times) variance in seizure threshold in their group, ranging from 36mC to 459mC (between approximately 5% and 90% on the Thymatron DGxTm machine) with a mean of 154 mC (30% on the Thymatron DGxTm machine). These findings are certainly not in favour of the "age rule".

In the second Sackeim study, there were two aims. Firstly to evaluate the cognitive consequences of a "low-dose" ECT titration procedure and the second being to "contrast the relative therapeutic properties of the two treatment modalities" that being "low-dose" RUL ECT versus "low-dose" BL-ECT.3 The "low-dose" pertains to ECT energy just sufficient to produce a threshold seizure lasting approximately 25 seconds clinically. Only 55% of the total group showed a response to the low-dose ECT, with a full 70 % of those in the BL ECT group, and only 28% in the RUL ECT group. The authors concluded "the degree to which dose exceeds seizure threshold may contribute more to the efficacy of UL ECT than to BL ECT." The findings in this study seem to fly in the face of the "age rule", especially for the BL ECT groups as these patients showed a clinical response to low "dose" threshold energies.

There is recent data that are sometimes quoted as being supportive of the "age rule" that also deserve some scrutiny. In the Coffey et al study, age, gender and electrode placement accounted for 50% of the initial seizure threshold variance.[10] However, in terms of predictors of initial seizure threshold, age accounted for only 15% of the variance.[10] Across the group of the 111 depressed patients used in the study, the average initial seizure threshold was 60mC (between 10% and 15% on the Thymatron DGxTM machine). However, the authors comment that 55% of their sample had a seizure at the initial starting dose, which was only 32mC (between 5% and 10% Thymatron DGxTM machine). Their interpretation of this data was that for many of these patient the threshold would have bee even lower! Also of interest is the fact that these patients had thresholds noticeably lower than those of the Weiner and Sackeim studies above.[2,3,6]

The mean age of the sample was 57.5 years. Using the "age rule" then the patient would have to be treated with 60% on the energy dial (Thymatron DGxTM machine). Had this been the case the "average patient" would have received an initial dose of ECT 4 to 6 times threshold. For many patients this figure would have been even higher as their thresholds were below the minimum stimulus used. If these patients had BL ECT using the "age rule" many of them would have been "over dosed", thus possibly exposing them to side effects. However, had they all received UL ECT they would have been adequately treated.

In the Beale et al paper there was a positive correlation between threshold and age and BL ECT electrode placement, but interestingly these authors found no correlation with patient gender.[13] The aim of this study was to demonstrate the clinical viability of a dose titration method, and to examine patient seizure threshold characteristics. Of their 134 patients, the mean threshold was found to be 134.4mC (between 25% and 30% on the Tymatron DGxTM machine) for the BL ECT group (N=82), and 74.8 mC (approximately 15% on the Tymatron DGxTM machine) for the RUL ECT group (N= 52).[13] In the BL ECT group the authors compared their threshold titration results to the "age method".[13] The authors found that across the 3 age groups, the dose titrated mean threshold (134 mC) was found to be 39.8% of the age method recommendation. In other words, an "age rule" recommended dose of approximately 337 mC, or 2.5 times threshold. These are precisely the figures that would be suggested in the Thymatron DGx TM instruction manual and seems, on the surface, to strongly support this age method for the BL ECT group.[14] However, consider the following problems with the data. An age-based "dose" of 337 mC would equate to between 65% and 70% on the Thymatron DGxTm machine, with the implication being that the BL ECT group had an age between these values as well. However, the authors also state that there was a statistically significant difference between the seizure threshold for the age group over 65 years, compared to both the other two groups, with the oldest group having by far the highest threshold of 138.3mC, compared to 98,6mC and 74.3mC respectively for the other two groups.[13] In fact, the oldest group had a mean threshold almost double (1.9 times) that of the youngest group. Further confounding the statistical analysis was the small numbers in the under 40 years age group (N=22), compared to the 40-65 years age group (N=57) and the over 65 years age group (N= 55). As can be deduced from this the mean values would be positively skewed towards the older groups who had the higher seizure thresholds. In illustration of this point, the mean threshold dose for the BL ECT group (134.4mC) was almost identical to that of the oldest age group of over 65 years (138.3mc), and almost double that of the youngest age group (74.3mC). It thus stands to reason, that the age based model would more accurately have dosed the older patients with the statistically higher mean threshold value, than it

would have for the younger patients who would have been overdosed. As such this data cannot be used to justify the accuracy or the utility of an age-based method ("age rule"). Indeed the authors indirectly concede this point when they state that, "using age-based dosing estimates may lead to doses far in excess of seizure threshold in many patients", and that "age-based estimates are likely to be inaccurate".[13] No equivalent results were given for the RUL ECT group.

The "Half-Age Rule" (HASS15 half age stimulation strategy)

Petrides and Fink originally advocated this method of stimulus dosing in 1996.[15] The rational behind this study was the search for a reliable and simple method of stimulus dosing that would at the same time minimise the cognitive deficits associated with higher dosing methods. Using this method, one sets the "percent energy dial" to that of half the chronological age of the patient, or "rounded –up" to the next highest available setting. For example, a 44 year-old patient would be treated with a "rounded-up" setting of 25% on the Thymatron DGxTM machine. Their suggestions were based on two studies involving a total of 55 patients. Their findings were that with this dosing schedule, the patients were treated with energies 45-50% closer to their elicited thresholds than they were using the age method. Also the half-age "dose" resulted in treatments that were at about 30% above threshold. Overall the authors found this method far easier to apply and safer for their group of patients than the threshold titration method used in the study. Their technique is recommended for BL ECT only. To date, rigorous empirical data supporting their approach is still lacking, and as such its performance in terms of efficacy and side effects relative to the "age rule" above is unconfirmed. The technique has been endorsed under certain specific situations, in particular when "staffing or patient issues make stimulus titration less desirable", and when the patient is "ill enough" to require BL ECT.[16]

Aged based dosing methods suffer from one critical methodological limitation. The correlation between age and threshold is not robust. As indicated above, various studies have confirmed the association, but age accounts for a small percentage of the threshold variability, in the region of 10-15%. That means that for the majority of cases other factors dictate the threshold. So if age, or a percentage thereof, is used to estimate ECT dose, the other factors and the influence they have, are ignored. This will inevitably result in some patients receiving the wrong ECT "dose", being either too much (most likely), or too little. If too small a "dose" is given, then the patient will not have a seizure (or an "adequate" seizure), and the treating clinician will then resort to some type of dose titration and restimulate the patient at a higher "dose". However, if too high a "dose" is given, then the patient is subjected to an increased risk of ECT induced neuro-cognitive side effects. Using an age based method, even if the patient has an "adequate" seizure, the clinician has no way of knowing by how much the given "dose" exceeds threshold and as a result has no way of knowing if the treatment was therapeutic or not. Ultimately, the only "way of knowing if the treatment was therapeutic or not" is to observe the clinical response of the patient, and measure this as accurately as possible.

Stimulus dosing tables

Another large ECT machine manufacturer, MECTA Corporation, recommends this method of stimulus selection with the use of their machines.[16] This method is simple to use, as the settings are simply read off a chart, as determined by the patients age, sex and electrode placement (RUL or BL ECT). Some tables neglect to take age into account.[16] The settings used are based on the empirical data of Sackeim, Weiner and others.[2,3,4,6] The criticism with this methodology is that these charts do not take individual variables in threshold levels into account and a result the short comings are similar to those mentioned above for age based methods.

Stimulus dose titration

Stimulus dosing protocols emerged from early studies in the 1980's.[2,6] Since that time a number of different titration sequences and protocols have been published and used with anecdotal success in various ECT centres.[4,10,16] It is a technique that provides for the most accurate and individualised establishment of a patients seizure threshold. This enables precise ECT "dosing" to be established regardless of the induction agent used, concomitant medications taken or the electrode placement. It thus has advantages over the other methodologies described above. However, some of the titration protocols do not take the patients age into account, and as such may result in older patients receiving numerous subconvulsive stimulations prior to threshold being found. As highlighted, age is one of the predictors of seizure threshold. Beale has developed a stimulus dosing strategy that takes age into account, by dividing the patients into two broad groups, one below the age of fifty years and the other above fifty years.[16] The theory here being that with older patients, the dosing strategy should start at higher levels and the increments should be greater to ensure threshold achievement within a reasonable number of stimulations, like four to five. According to Beale using their titration methods results in threshold being found in less than 3 subconvulsive stimulations on average.[16] The protocol looks like this:-

Under 50 years: 5%, 10%, 20%, 40% and 80%.
Over 50years: 10%, 20%, 40%, 80% and 100%.[16]

There is little other controlled data to support this approach. However, one could argue that with big percentage energy jumps, the threshold value found may well be more of a "rough estimation" than an actual reflection of the patient's true threshold.

Stimulus dose titration is gradually being implemented on a regular basis in clinical practice and in many centres is now the dosing method of choice.[4,16] A decade ago, 49% of American ECT practitioners were still using an age-based method for dose estimation. Stimulus titration methods were used by 39% and a "fixed high-dose" protocol used by 12%.[17] However, more recent publications suspect that stimulus titration protocols are now being used far more commonly.[16]

Stimulus dose titration has not been universally adopted as the technique has its shortcomings. These include difficulty in implementing the process as it is time consuming, and it requires a lot more staff training and upgraded equipment than age-based or fixed high-dose methods. From an anaesthetic point of view there are also added challenges. The procedure requires a longer anaesthetic with added atropine or glycopyrrolate, and at times top-up doses of induction agent are needed if the titration is particularly lengthy. Indeed many of these problems have been reported in the literature[15] and have been experienced in our ECT unit as well. Also there have been reports of cardio-

vascular events associated with the multiple subconvulsive stimuli that the patient is expose to, although this does not appear to be especially problematic. Most reports suggest that bradycardia is the main complication, and pre-treatment with atropine during anaesthetic induction appears to all but eliminate this problem.[18] It is also commonly experienced that the post titration recovery phase can be prolonged and stormy, with increased confusion and sedation. One last complication that has been described is the delayed seizure. This is a seizure that occurs several seconds (delays of up to 35 seconds being reported) after the sub-threshold stimulus has been given.[15] This appears to be a very rare complication, and its impact on the therapeutic process is unknown. There is some data from animal models to show that repeated subthreshold stimuli are associated with kindling phenomena that lower the seizure threshold.[19] Whether this is applicable to human subthreshold titrations is unknown.

Opposition to stimulus dose titration methods also comes from the "fixed high-dose" school of thought, of which Abrams is a significant contributor.[10,14,20,21] It is important to note however, that both Abrams and Swartz are on the Board of Directors of Somatic Inc, the company that manufactures the Thymatron DGxTM ECT machine.[14,21] In their study of UL ECT, all patients (N=38) were commenced on 378mC charge (75% energy setting on the ThymatronTM machine) regardless of age or sex, or electrode placement, with twenty patients receiving UL ECT and eighteen receiving BL ECT.[20] As such these authors did not follow the "age rule" as outlined previously, despite the fact that the patients in their study group ranged in age from 34 to 75 years. The energy setting used was based on the following presumption, "according to published data, this dose should be about 2.5 times the average expected seizure threshold" and is an example of "fixed high-dose" dosing methods. The published data mentioned was in fact the Sackeim study discussed previously.[3] To remind the reader, in that study the mean threshold was found to be 154 mC (30% on the ThymatronTm machine), but the range was a huge 12 times (36mC to 459mC). So in essence, a 2.5 times threshold dose of the group mean would equate to 385mC, of which the closest is the 378mC on the ThymatronTm machine used in the study.[20] It is also interesting to note that cognitive effects were not assessed in the study. The two groups, RUL and BL ECT showed no statistically significant difference in their response rates.[20]

Other dosing techniques

Kellner has given his own suggestions for dose selection, and his recommendations were very straight forward indeed.[11] For RUL ECT, set the machine to 75% of its maximum dose and treat. For BL ECT set the machine to 30-60% of its maximum dose and treat.[11] This approach could be considered an example of a "fixed high-dose" dosing protocol. There is however no controlled data to support this particular approach. Abrams appears to be more supportive of this approach compared to titration methods.[21] Recently, there have been attempts at estimating seizure thresholds using "threshold estimation formulas". Again the problem with a formula method (as with the table methods) is that they are really little better than educated guesses when estimating the threshold of a particular patient. The authors of a recent paper concluded that titration methods remain the preferred choice over the formula methods.[22]

New dosing techniques

As a result of the ongoing and seemingly irreconcilable difference between the two schools of thought, new approaches for assessing seizure adequacy are being sought. The theory goes something like this. If we had markers of what constituted an "antidepressant seizure" (clinically effective) then we could titrate our ECT "dose" according to these markers rather than according to items that appear to be unrelated to clinical outcome, as we are currently doing using age or threshold. There are a number of potential candidate markers that are coming to light, amongst them a variety of EEG markers. Some of the most promising seem to be postictal suppression, ictal power, interictal coherence and peak heart rate. Much more controlled data is still needed to clarify the potential use of these tools.[21,23]

Discussion

Abrams and the rest of the "fixed high-dose" school claim that the arguments over seizure threshold are a waste of energy and that there is little if any evidence to support a better outcome for the patients that have undergone threshold estimations using stimulus titration methods.[21] Indeed they argue that it may be more dangerous, certainly from a cardiac perspective.[4] More recently, Abrams has highlighted that there is no consistent relationship between the therapeutic response to ECT and the seizure threshold, or to the duration of the induced seizure.[21] He feels that these facts expose an irremediable flaw in the stimulus titration methodology and the arguments used to support its use, in particular when applied to the treatment of clinically depressed patients. He also insists that "better results" are obtained using "fixed high-dose" or age-based dosing methods.[21]

On the other hand, the proponents of stimulus titration methods would argue that there is data to show that when comparing RUL and BL ECT there are sound reasons to establish the patients' threshold. If RUL ECT is to be administered, then it is critical that high doses be used in order for the procedure to be as clinically effective as BL ETC, and still afford the therapeutic advantages of less cognitive side-effects.[8] In order for this to be given safely stimulus dosing techniques and threshold estimations should be mastered by the treating practitioner. This is highlighted by Rasmussen in his review, when he states that if unilateral ECT is to be used, seizure threshold should be measured at the first session.[24] For high dose RUL ECT the majority of patients will need energies at 3-5 times seizure threshold. Rasmussen claims that six times threshold should be used (ultra high-dose).[24] However, should BL ECT be administered it is probably reasonable to assume based on Sackeim's data mentioned above, that doses of only 1.5 – 2.5 times threshold are sufficient. Indeed patients respond to threshold doses as well.[2,3] Higher doses may precipitate neurocognitive side-effects that could outweigh the clinical benefits. Stimulus titration supporters use this argument to support their approach when using BL ECT. The patient's seizure threshold may increase during the course of ECT. As such it may be necessary to repeat the stimulus titration to re-establish the patients threshold during the course of the ECT. This exercise is critical if converting a patient from RUL ECT to another electrode placement. This electrode placement conversion occurs typically if the patient has failed to respond to the RUL ECT trial and requires a course of bitemporal ECT.[24] The practice of RUL ECT brings other problems with it. If high doses of RUL ECT are to be considered then it is incumbent upon the ECT practitioner to ensure that the ECT machine they use is capable of admin-

istering the doses required. For example, should a patient's threshold be established to be 100.8 mc energy (20% on a Thymatron DGxTM machine) then high dose RUL ECT would equate to around 302.4mc-504 mc (60% to 100% on a Thymatron DGxTM machine) depending on whether 3 or 5 times seizure threshold was decided upon by the treating doctor. Clearly then, during the course of the ECT, should the patients threshold increase, it will soon be discovered that the machine is no longer capable of administering the doses needed to stay above threshold at the necessary levels. This situation results in inadequate treatments being given to the patient and undermines the therapeutic efficacy of the ECT. So in order to overcome this situation many of the more modern ECT machines have the capacity to deliver over 1000mc (up to 200% on a Thymatron DGx TM machine). These machines are not yet available in the USA but are available here in South Africa and other countries like Australia. Unless the clinician has had extensive training and supervision with these converted ECT machines there is potential for greater cognitive side-effects should such high doses be used in an inappropriate manner. On the other hand there is certainly sufficient data to show that low dose RUL ECT is clinically useless and should be abandoned.[7] Low dose RUL ECT would be considered to be at levels of, or near to, threshold and possibly up to levels as high as 2.5 times threshold, because even at these levels the response rates are unacceptably low.[2,7] It is thus highly recommended that should RUL ECT be considered, the correct equipment should be available and the treating clinician adequately trained and supervised to administer this type of ECT. In the South African context there are many significant hurdles to "best clinical practice" that are not readily overcome. Examples here include lack of funding for equipment, training, and other facilities. Also poor teaching methods, a general lack of supervision and interest, further compounded by professional ambivalence towards ECT, perpetuate the status quo. This unfortunately appears to be an international trend.[25] It is also important to note that this author was unable to find published data on South African threshold values.

Conclusion

So which dosing protocol should the ECT practitioner follow? The answer will probably be different for each clinician and each ECT unit. As there are no set recommendations in the international literature regarding electrode placement, stimulus titration or other dosing methods, the clinician will have to be guided by the overall clinical response of the patient, with very careful documentation of both clinical efficacy and overall side effect profile. Until our level of knowledge of ECT is such that definitive recommendations can be made regarding these issues the individual practitioner will have to formulate an approach that they are comfortable with and which will ensure a satisfactory clinical outcome for the patient. Hopefully this paper will provide some guidance for the embattled clinician at the coalface when it comes to making these difficult decisions.

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