

Review Article

Syndromes that may be Particularly Responsive to Electroconvulsive Therapy

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Abstract

Electroconvulsive Therapy (ECT) has become a treatment of last resort for many reasons including that it is an invasive therapy utilizing anesthesia based on inducing modified seizures; therefore, there are risks, particularly cognitive. Stigma about its use and misrepresentations by the media and literature have contributed to its underuse.

A few psychiatric and medical disorders appear to be particularly responsive to ECT with higher response/remission rates and efficacy occurring earlier in treatment. We review 4 such disorders- catatonia (due to medical and psychiatric conditions), suicidal behavior, Parkinson's Disease (PD) and Bipolar Disorder (BPD).

Our review clearly demonstrates that catatonia and suicidal behavior in general respond early to ECT; the latter not only is effective but decreases the high morbidity and mortality of these conditions compared to non-ECT methodologies. Although ECT is usually used in PD with comorbid depression, it has also been effective in PD without comorbid psychiatric disorders; it appears to increase the "on phase" of the "on-off syndrome". Since medication treatments frequently lose efficacy in PD, alternative treatments such as ECT are important to explore. Lastly, BPD, particularly bipolar depression, also appears to be highly responsive to ECT.

Keywords: Electroconvulsive therapy (ECT); Catatonia; Suicidal Behaviors; Parkinson's Disease; Bipolar Disorders

Introduction

Electroconvulsive Therapy (ECT) is a highly successful treatment for Major Depressive Disorder (MDD), other mood disorders-e.g., Bipolar Disorder (BPD), various non-mood psychiatric disorders, e.g., schizophrenia, as well as catatonia associated with another mental disorder; it may also be effective in the treatment of some medical disorders such as Parkinson's Disease (PD), catatonia "due to another medical condition" and refractory status epilepticus [1-6]. Despite its clear efficacy-considered the gold standard in the treatment of MDD-the use of ECT has decreased, due to potential deleterious effects on memory, marked stigma about its use, and misrepresentations in the media and literature [7]. This has led to restrictive use, imposed by state and institutional regulations [8-10]. Currently, ECT is usually reserved for medication resistant mood disorders, (predominantly with the diagnosis of MDD or BPD). It is almost always considered a "treatment of last resort" [11]. Occasionally, it is considered as a first line treatment for patients who are acutely suicidal, and for those who have a history of not being able to tolerate psychopharmacological treatments [2-6]. The current paper highlights that a small number of psychiatric/medical disorders respond particularly well to ECT including responding significantly early in treatment (an "early response"). Therefore, ECT should be considered more often and earlier in the course of treatment for at least these indications.

Methodology

The author focused on 4 psychiatric and medical conditions/

behaviors- catatonia (secondary to either psychiatric or medical syndromes), PD, suicidal behavior and BPD that are unusually sensitive to the therapeutic effects of ECT based upon a literature review and the author's own expertise and experience in the behavioral health field. A literature search included Pubmed as well as other databases such as Embase and Psyc NET. The MESH terms used were PD, Catatonia, Suicidal Behaviors (Attempted Suicide), BPD, ECT, and treatment efficacy. There was no restriction on the time period assessed and concluded in October 2019.

Proposed ECT sensitive disorders

Catatonia: Catatonia is a neuropsychiatric disorder consisting of autonomic, behavioral and psychomotor symptoms. It is mainly manifested by symptoms of immobility ("retarded type") and/or excessive motor activity ("excited type"); its symptoms can quickly shift from one extreme to another or occur together (e.g., negativity, and mutism co-occurring with agitation) [12]; at least 3 of 12 symptoms (cataplexy, waxy flexibility, stupor, agitation, mutism, negativism, posturing, mannerisms, stereotypies, grimacing, echolalia, or echopraxia) listed by the Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5) must be present for a diagnosis to be made. DSM-5 has defined catatonia into 3 categories- "catatonia due to another medical condition", "catatonia due to a mental disorder" where it is a specifier, and "catatonia not otherwise specified" (unspecified catatonia) [1]. Catatonia is usually associated with psychiatric and/or medical conditions, including mood disorders, schizophrenia, and autistic spectrum disorder, as well

as neurological disorders (e.g., dementia, anti-N-methyl-D-aspartate encephalitis), infections (e.g., H.I.V., typhoid), substance abuse (e.g., opiates, marijuana), drug withdrawal (e.g., benzodiazepine, clozapine), and endocrinopathies (e.g., hypothyroidism) [13-20].

Catatonia is readily treatable no matter what its origin or whatever it is associated with, be it a psychiatric or medical disorder. Benzodiazepines, particularly lorazepam, are considered one of the most effective and safe treatments for this diverse disorder. Most patients experience at least a partial response after the first dose [21]. Success rates reach over 80% except possibly in schizophrenia which may have a lower recovery rate ranging from 20-30% [18-22]. Therefore, benzodiazepines are recommended as the first line treatment unless there is a need for an emergency intervention. In the case of the latter or when benzodiazepines fail to relieve this clinical state, ECT should be actively considered as a treatment [23]. Most reports have found that ECT was highly successful in 80-100%, even in cases which were refractory to benzodiazepines; one Dutch study demonstrated a response rate of only 59% [24]. Some investigators have suggested that this outlier study had a lower ECT response rate due to the delay in these patients receiving treatment, the presence of psychosis, the concurrent use of antipsychotic medication and the presence of a co-morbid neurological condition- all factors associated with a poorer response to ECT [13]. Bush et al (1996) particularly noted that catatonic patients were highly responsive to ECT treatment (all 4 catatonic patients that failed a course of lorazepam treatment were successfully treated with ECT) [25]. Most notable was that they responded unusually early in treatment. By the end of the first treatment, there was over a 30% reduction of the patients' catatonic symptom severity (as assessed with a catatonic rating scale) and over 70% by the end of the second treatment. Furthermore, the catatonia fully remitted by the second or third treatments in 3 of the 4 cases [25]. Philbrick and Rummans (1994) reported on 4 catatonic patients being treated with ECT; 3 of the 4 cases responded by the end of the first ECT with 1 patient responding by the third treatment [26]. Raveendranathan et al (2012) reported in a retrospective study of 63 catatonic patients being treated with ECT that approximately 50% had a fast response (receiving less than or equal to 4 ECT treatments); as a group, improvement was seen by the second treatment (mean 1.82 SD 0.92 treatments). Interestingly, fast responders tended to be more severely ill and had a shorter duration of illness; in addition, fast responders tended to have particular catatonic symptoms, e.g., waxy flexibility and gegenhalten (increase in muscle tone in response to passive movement) [23]. Similar results were reported by Cristancho et al., (2014) in a retrospective series of 5 catatonic patient being treated with ECT; 2 of the 5 cases demonstrated a "fast response"- one case responding after the first treatment and the others by the second treatment [27]. Recently, Honings et al., (2016), and Ratzlaff et al., (2018), both reported in a single case study that their catatonic patient had a rapid ECT response, with one having a full remission after the third treatment [28] and the other having a significant response by the end of the second treatment [29].

This unusual sensitivity to responding to ECT in catatonia is further supported by data demonstrating that not infrequently, these patients experience a delay and/or lack of response of non-catatonic features to ECT (e.g., psychotic symptoms of schizophrenia or depressive symptoms in mood disorders) in contrast to their highly

responsive catatonic symptoms [12,13,15,17,30-32].

PD: PD is one of the most common neurodegenerative disorders, clinically consisting of symptoms of a resting tremor, rigidity, bradykinesia with gait and/or balance problems [3,5]. Although PD affects multiple neurotransmitters and regions of the brain, its motor symptoms predominantly derive from a pathophysiological loss of dopaminergic neurons in the substantia nigra [33]. Most treatments have focused on increasing or normalizing the dopamine system. Unfortunately, PD is usually progressive and frequently becomes resistant to pharmacotherapy [33]. Therefore, exploring alternative treatment strategies including non-pharmacological ones would be helpful. For example, ECT appears to be an effective treatment for PD with and without comorbid depression despite being underutilized for this indication [2-6].

Lebensohn (1975) treated 2 depressed patients with comorbid PD with a course of 4 ECT treatments; both PD and depression significantly improved. The most notable finding was the rather early response regarding neurological symptoms with one patient having a response after the first treatment and the other a response by the second ECT treatment [34]. Asnis (1977) treated a patient with MDD with comorbid PD with ECT for his severe depression. Interestingly, the patient's extrapyramidal syndrome, i.e., PD responded by the second ECT treatment as assessed by neurological rating scales and writing sample assessments. Although the mood disorder also significantly improved, it was delayed in comparison to PD, taking a total of 5 ECT treatments to respond [35].

A review by Faber and Trimble (1991) which included 78 patients with PD highlights that ECT had a significant ameliorating effect on PD in 50% of cases which lasted for at least 2 weeks; this effect of ECT on PD frequently preceded its antidepressant effect in PD patients with comorbid depression. Furthermore, the beneficial effect on PD commonly occurred early (from 1-3 treatments) [36]. Most patients with PD who were treated with ECT were treated for their severe MDD (approximately 40% of PD patients develop a comorbid depression) [37]. ECT was also reported to be effective in patients with PD without co-morbid depressive or psychiatric disorders [36].

Borisovskaya and colleagues (2016) conducted a metaanalysis (including both case reports and clinical trials) reporting on the effect of ECT in PD with concomitant depression). The studies in the review were published between 1975 through 2015, consisting of 43 articles and totaling 116 patients. The results were that 93% of the patients had improvement of their depression and 83% had improvement of their PD. ECT was well tolerated with most patients (93%) not having any deleterious cognitive effects; Furthermore, clinical response was seen early in treatment, often preceding antidepressant effects [3]. It is possible that the benefits of ECT on PD might be related to an interaction with ECT's antidepressant effect; nonetheless, the authors suggest that ECT may have a direct antiparkinsonian effect [3]. Supporting their latter hypothesis is that ECT is a potent releaser of dopamine, a central neurotransmitter in the pathology of PD [38]. In addition, the antiparkinsonian effect of ECT frequently preceded its antidepressant effect. Furthermore, some reported cases had a marked antiparkinsonian effect with only a negligible antidepressant effect. Lastly, and perhaps the most interestingly data supporting their hypothesis was that ECT was effective in patients with PD without depression or any other comorbid psychiatric disorder

ameliorating the motor symptoms and prolonging the “on phase” of the “on-off syndrome”) [5]. Impressed by the data, some investigators have advocated for a course of ECT for all patients whose PD was intractable or drug resistant [39].

Suicidal Behaviors

Suicidal behavior and ideation particularly when associated with MDD is known to be highly responsive to ECT; in reviewing the effect of ECT on suicidal behavior, response frequently occurs early, usually during the first 3 treatments and frequently even prior to its antidepressant effect [40]. Kobeissi et al, (2011) [41], Fligelman et al, (2016) [42] and Tran et al, (2017) [43] each reported on a different single patient whose suicidal ideation fully responded after only a single ECT treatment. In one of the largest ECT collaborative studies, the Consortium for Research on Electroconvulsive therapy (CORE), evaluated 444 depressed patients being treated with ECT with 131 having active suicidal ideation at baseline; 76.3% had a full remission of their suicidal ideation by the end of treatment (approximately, 9 treatments); most notable was an early response occurred in 15.3% by the end of the first ECT treatment and an additional 38.2% by the fourth ECT treatment [44,45]. Interestingly, the dramatic effect on suicidal ideation frequently occurs even prior to depression lifting. Furthermore, the reduction of suicidal ideation scores as noted in the Hamilton Depression (HAMD) Rating Scale) from baseline were greater than the reduction of total HAMD scores after a full course of ECT [46]. Surprisingly, ECT was associated with a quicker anti-suicidal effect than pharmacotherapy [47]; in addition, ECT had a greater anti-suicidal effect at least for UP and BP depressives [48]. Depressed patients who had significant suicidal ideation had a greater ECT response than depressed non-suicidal patients [49]. Thus, the presence of suicidal behavior is highly responsive to ECT and may also increase the responsiveness of comorbid depression to the antidepressant effects of ECT.

BPD

BPD is a mood disorder consisting of a depressive episode as well as a manic/hypomanic episode or a mixture of both episodes over the course of the illness [1]. The lifetime prevalence rate is approximately 2.4% and is considered to be a chronic illness [50,51]; thus, treatment not only has to deal with the acute episode but also maintenance therapy to prevent relapses and/or recurrences from occurring [52]. Amongst psychiatric disorders, BPD has the highest morbidity and mortality rates [53,54].

Most BP cases respond to mood stabilizers such as lithium or valproic acid although many need adjunctive antipsychotic medication, antidepressants and/or benzodiazepines) [52]. ECT also is an alternate treatment to be used by itself or in combination with medications that patients failed to respond to alone. The use of ECT in BPD is usually reserved for drug refractory patients, those with “life-threatening manic excitement” or those that have significant suicidal behavior [3,4].

In reviewing the efficacy of ECT in BP depressive disorder, it is clear that ECT is highly effective in treating both BP depressive disorder and Unipolar (UP) depressive disorder (UP depressive disorder is used in this manuscript interchangeably with MDD) with response rates of 77.1% and 74.2% respectively) [55]; nonetheless, as reviewed recently by Bahji et al., (2019), with a large meta-analysis

(19 studies were included) using sophisticated meta-analysis software in 2422 depressed patients (BP=553 and UP=1803) undergoing ECT, reported that the response rate and speed of response were significantly greater in BP depression group *versus* UP depression group (OR=0.73, 95% CI: 0.56-0.95, p=0.02 and SMD=-0.023, p=0.03 respectively); the increased responsiveness in BP depression *vs* UP depression to ECT was further supported by the significant finding that BP depressives *vs* UP depressives needed fewer ECT treatments to achieve response (SMD=-0.23, 95% CI:-0.44-0.023, p=0.03). Interestingly, the remission rate was similar for BP and UP depression (OR=0.91, 95 % CI: 0.65-1.26, p=0.56) [55].

In a large review by Agarkar et al (2018) (including 10 studies, consisting of a total of 461 BP depressives and 1190 UP depressives), ECT was highly effective in both groups without significant differences in outcome measures (final response and remission rates) [56]; nonetheless, 5 studies in this review found that BP depression responded faster than UP depression requiring fewer treatments- 4 studies reached significance (Daly et al., 2001; Sackheim and Prudic, 2005; Sienaert et al., 2009; Agarkar et al., 2012) [57-60] while 1 study showed a trend (Perris and d’Elia, 1966) [61].

In contrast to the above cited studies, Baline et al. (2010) and Fink (2014), each reported on the same data base from the Consortium for Research on Electroconvulsive Therapy (CORE) studies (n=220 depressed patients-170 UP’s and 50 BP’s) finding that the BP group had an 80% response rate to ECT, similar to the 78.8% response rate from the UP group. Regarding the remission rate to ECT, the BP group had a 64% remission rate *versus* a remission rate for the UP group of 61.4%. The authors noted that ECT was highly effective in the treatment of both the BP and UP depressed groups with polarity of illness having no bearing on ECT response nor remission [47,62]. This study stands in contrast to the studies reviewed above. A replication regarding whether polarity is an important variable to a course of ECT treatment awaits.

The effects of ECT in BP mania and particularly BP mixed states have been much less studied in comparison to BP and UP depression [63]. Nonetheless, ECT also appears to be highly effective in BP mania and mixed states; Perugi et al (2017) found the ECT response rate to be equivalent for BP manic group and BP mixed state group (75.0% *versus* 72.9%, respectively) even though mixed states do more poorly to pharmacotherapy than non-mixed state BP mania or BP depressives [63]. Mukherjee et al (1994) estimated that approximately 80% of 589 manic patients (including data from retrospective and prospective studies) had a significant clinical response or remission to ECT [64]. Furthermore, ECT for BP mania might be more efficacious than pharmacotherapy; Black et al., (1987) reported that manic patients responded well to both ECT and lithium carbonate with the ECT group having a significantly greater response rate (78%) than the lithium carbonate alone group (60%) [65]. Similar results were reported by Small et al., (1988) [66].

Thus, not only does BP mania respond well to ECT, they may respond particularly early, needing fewer ECT treatments than other diagnostic groups. A report by Sidorov et al., (2017) of 4 patients with acute mania found that all responded to ultra-brief pulse of ECT with 3 of the 4 obtaining a rapid response (total course of ECT of 5 or less treatments) [67]. Mohan et al. (2009) evaluated 50 manic

patients with ECT and found that 92% had a significant response and 88% achieved remission. Most noteworthy though was the speed of response; the mean number of ECT treatments for clinical response (50% improvement on the mania scale, the Young Mania Rating Scale (YMRS) scale was 2.8 SD 1.3 and for remission (YMRS score < 10) was 3.4 SD 1.7 [68]. To confirm that patients with BP mania may have a particularly fast response to ECT, studies must compare the BP manic group to other disorders.

The review on the effect of ECT on BPD demonstrates that ECT is highly effective for both BP and UP disorders. Whether BPD is particularly sensitive to the effect of ECT (speed of response, response rate, remission rate, number of treatments, etc.) awaits further clarification. One potential complicating factor that might help explain some of the disparate findings regarding this topic is that over the longitudinal course of UP disorder, greater than 20% of patients will have a manic or hypomanic episode; thus, a significant number of patients in the UP group will get re-diagnosed in time as having a BPD [69]. It appears that the presence of mixed features and/or subsyndromal hypomanic symptoms during a patients' UP illness are linked to conversion of their diagnosis from MDD (or UP depression) to BP depression [70]. Another complicating factor is that the criteria used to make a diagnosis of BPD has been undergoing significant changes which could have a serious effect on data analysis. Thus, Machado-Vieira et al., (2017) found that only 52% of patients diagnosed as BPD by DSM-IV were able to be re-diagnosed as BPD when using DSM-V criteria [71]. These potential complications must be better understood to truly know that BP is a separate and perhaps more responsive disorder to ECT than UP depressives.

Discussion

Although the review is highly suggestive that these syndromes (catatonia, BPD, suicidal behavior/suicidal ideation, and PD) are particularly responsive to ECT, further research must be done to be fully confirmatory. The timing of response to ECT treatment in general (particularly an early response), has received minimal focus in the literature. One article by Husain et al. (2004) evaluated 253 severely depressed patients with MDD treated with ECT targeting speed of response; 13.4% demonstrated an early response after the first treatment while a total of 54% demonstrated an early response by the end of the third treatment [72]. Similar results have been cited in earlier studies of Barton (1973) [73] and Rich (1984) [74]. Unfortunately, these above studies did not assess what effect catatonia, BPD, suicidal behavior or PD may have had on the findings. It is possible that early response or remission to ECT is not so selective for the groups that we suggest and may be seen frequently in general. A rare event (7 reported cases in the literature) in ECT treatment is a clinical remission after only a single ECT treatment (one case cited by Keisling (1984) [75], Figelman, (2016), Kobeissi, (2011), Thomas, (2003), and Tran, (2017) as well as 2 cases cited by Rich, (1984) [41-43,72-76]; all 7 cases had a diagnosis of MDD but 3 also had comorbid suicidal behavior [41-43] and 1 of these suicidal patients also had a BPD [43]. The status of the other 4 patients regarding catatonia, suicidal behavior, BPD or PD was not stated which might have also contributed to this rapid response [74-76].

We believe that the syndromes/symptoms reviewed in this manuscript (catatonia, BPD, particularly BP depression, PD and

suicidal behavior) tend to be particularly responsive to ECT treatment and frequently show an early response. Nonetheless, Randomized Control Trials (RCT's) must be employed with studies incorporating a suitable placebo such as a sham ECT group to support these findings. Data analysis of the responsiveness of BPD to ECT has been fairly consistent demonstrating that BPD (both BP depressed, BP manic and BP mixed state) responded earlier and needed fewer treatments than their unipolar counterparts [55,56,67,68]. Regarding ECT response for patients with catatonia, suicidal ideation, and PD (in most cases the main clinical reason for treatment was a comorbid MDD), improvement frequently preceded response of their depressed mood, occurred when there was a lack of response to their mood disorder, or even independently of response to non-catatonic features [5,12,13,15,17,30-32].

In addition, such RCT studies must ensure that concomitant medications are controlled for since they might have bearing on the efficacy of ECT. For example, concomitant antipsychotic medications may be depressogenic as was recently demonstrated in healthy controls [77]. In contrast, antipsychotic medication can also be synergistic to ECT as has been noted in treating schizophrenia [2,10,78] or have antidepressant properties with many being FDA approved for refractory mood disorders [79-81]. Use of benzodiazepines and/or anticonvulsants (which include many of the mood stabilizers used concurrently with ECT) might affect various parameters of the seizure (such as duration and magnitude of the seizure threshold); therefore, these concomitant medications might have a negative potential effect on the outcome to ECT treatment [82]. Patients with MDD treated with some concomitant antidepressants such as tricyclic antidepressants may raise the remission rate over ECT alone [4,83]. Lastly, the ECT methodology must be controlled for such as electrode placement (bilateral vs unilateral), frequency of administration, and total stimulus charge, all factors that also may have bearing on outcome [2,4,84,85]. To minimize possible cognitive side effects from ECT, many investigators have recommended the use of unilateral over bilateral electrode placement, reduced frequency of administration (twice a week instead of three times a week) as well as using ultra-brief and low total stimulus charge [2,4-6]. Fink (2014) and Fink et al (2016) have suggested that these modifications may in fact decrease the efficacy of ECT [32,45]. Thus, ECT methodology must be also be standardized in these RCT studies.

Conclusion

In summary, the manuscript increases the awareness of clinicians that certain medical and psychiatric disorders (catatonia, PD, suicidal behavior and BPD) respond particularly well and quickly to ECT, frequently needing only a minimal number of actual treatments or interventions (sometimes only 1-3 treatments) for a significant clinical response. Thus, this information may be extremely useful and potentially lifesaving, particularly regarding catatonia and suicidal behaviors. It has been demonstrated that the longer a catatonic patient is symptomatic, the more likely he will become refractory to treatment and develop malignant catatonia with its highly associated morbidity and mortality [86-88]. Regarding "Suicidal Behaviors", the likelihood of a suicide attempt or completed suicide rises as one remains symptomatic. In fact, emergency ECT is usually reserved to bring relief of severe suicidal ideation and depression as soon as possible [2,4,46]. Unfortunately, alternate non-ECT treatments

[e.g., FDA approved antidepressant medication] take a minimum of weeks to months to get a significant clinical response [89]; recently, a ketamine-like agent, esketamine, was just FDA approved for “drug refractory depression” [90] but may offer a faster onset of action for suicidal ideation and depression even in non-refractory MDD. Regarding PD, ECT can provide a useful and fast onset clinical response in those patients with co-morbid depression but is frequently successful in PD without comorbid psychiatric disorder [36]. It appears that ECT can prolong the “on phase” the “on-off syndrome” [5]. The possible usefulness of a non-pharmacotherapy treatment to help PD is a promising treatment for such patients since PD is a serious, chronic, and frequently a progressive illness that often becomes drug refractory [52]. Lastly, ECT appears to also provide highly effective treatment in BPD with a faster onset of action than that seen in non-BPD. Due to some inconsistent findings described above, further studies are needed to validate these latter findings. Although pharmacotherapy is highly effective during the acute treatment phase, not infrequently, BP patients can have a delayed or only a partial response to pharmacotherapy where an intervention with ECT can provide an alternate treatment with a fast response [52].

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