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General Discussion and future directions

Electroconvulsive therapy (ECT) is the transcutaneous application of small electrical stimuli to the brain to produce generalized seizure for the treatment of selected psychiatric disorders, typically. ECT owes its current acceptance to modern anesthesia. Indeed, a cornerstone of the periprocedural management of patients receiving ECT is the proper selection and use of anesthetic drugs and techniques tailored to mitigate the associated physiological response and potential complications, without interfering with its beneficial effects. [1] A combination of a short acting induction agent (e.g. propofol), neuromuscular blocking agent (i.e. succinylcholine) and hemodynamic monitoring under supervision of anesthesiologist and in collaboration with psychiatrists has favorably yielded more safety for this short treatment procedure. Furthermore, anesthesia medications applied during ECT could augment the response to induced seizure (e.g. the NMDA receptor antagonist ketamine) as well as increasing the safety of the procedure.

Safety of ECT increases the efficacy of therapy and provides fulfillment of a series of required treatments resulting in longer treatment effect of ECT. Over the decades many efforts have been made to reduce the special risks in ECT. As a result, the safety and efficacy of ECT has been improved and its indications have been relatively defined to increase the efficiency of outcome of therapy.

While there has been considerable improvement in safety features, further investigation have been done to promote both the safety and efficacy of the treatment. These investigations take on greater significance by considering that some aspects of ECT safety (e.g. memory and cognitive effects) could partly be inherent to unknown induced biological mechanisms correlating with transmitters involved in the outcome of treatment (efficacy). However, this correlation is not the same in all patients suggesting a more prominent role of pharmacogenetics in ECT. Neurotransmitters such as dopamine, norepinephrine, and serotonin systems are more involved with depression. These neurotransmitter systems along with multitude of other neurochemicals such as endorphins, enkephalins and prolactin, GABA, glutamate and acetylcholine play role in the behavioral manifestations of other psychiatric illnesses. Yet it is unknown which induced neurobiological system(s) by ECT stimulation might be more involved with impairment of memory than efficacy treatment response.

Accordingly, in this dissertation we investigated several important aspects of safety and efficacy of ECT from looking into the current literature to conducting clinical research studies. We attempted to contribute to the existing literature and clinical principals in application of ECT and understanding of the role of pharmacogenetics in ECT.

Neuromuscular blockers in ECT and optimal seizure activity (safety improves efficacy)

Neuromuscular blocking agents (NMBAs) dramatically revolutionized the practice of anesthesia during procedural treatments, particularly in ECT. Neuromuscular transmission blockade mitigates the tonic-clonic motor activity during ECT sessions and provides an effective mean to reduce the physical and psychological trauma associated with uncontrolled tetanic muscle contractions.

Anesthetic drugs and neuromuscular blocking agents (NMBAs) are administered to ensure patient comfort and safety, but need also be titrated to provide optimal conditions for the induced seizure activity during the treatment, while allowing a rapid recovery upon its completion. [2] As an ideal neuromuscular blocker, what is needed is an agent that is rapidly acting, non-cumulative, independent of renal or hepatic function for its elimination, easily and rapidly reversed and free from side effects. While waiting for new muscle relaxants to be developed, we need to opt for optimization of available NMBAs and improvement of neuromuscular transmission (NMT) monitoring. In order to optimize the dose of NMBAs, important pharmacological characteristics of each agent have to be considered, including its potency, speed of onset, duration of action and the muscle-dependent effects. This optimization takes on greater significance as it has been shown that the quality and duration of the induced seizure by ECT is associated with the efficacy of the procedure. [2]

In *chapter two* of this dissertation we reviewed the current applied neuromuscular blocking agents in ECT. We showed that succinylcholine, due to the short onset time and duration of action is the first choice for ECT procedure, however, all the currently available NMB agents have their own limitations and the quest continues for an ideal drug. There were some points to be considered for the application of succinylcholine. The recommended dose range of succinylcholine during ECT had been reported to be 0.5-1.5 mg/kg that is a relatively large range of dose and no clinical guideline for the application of succinylcholine during ECT was identified. [3-6] Furthermore, there are some clinical indications, which application of succinylcholine could be contraindicated or using an alternative is recommended, e.g. elderly patients with risk of hyperkalemia and long length of stay in hospital. [7] The individual and variability in response to succinylcholine and other NMB agents is also another point of consideration. [8, 9] Owing to these factors, and based on the systematic review conducted in *chapter two,* we conclusively suggested seeking an alternative such as rocuronium to be applied for ECT in patients with absolute or relative contraindication of succinylcholine usage. [10, 11] We also showed that similar to succinylcholine, a wide range of rocuronium doses for ECT, i.e. 0.3-0.6 mg/kg has been administered for ECT and no clinical guideline has been recommended for rocuronium application in ECT. Doses beyond 0.4 $mg.kg^{-1}$, for ECT, have

been used in combination with the reversal agent sugammadex, a selective relaxant-binding agent (currently not available in the USA) that has also been used to reverse profound rocuronium-induced neuromuscular blockade in adult surgical patients.[3] Rocuronium and succinylcholine had satisfactorily been compared for other clinical indications such as rapid-sequence induction of anesthesia and the required dose, onset times and clinical duration of actions had been defined. [12, 13]

In pursuit of our suggestion, we designed a randomized crossover clinical trial (*chapter three*) and investigated the optimal doses of succinylcholine and rocuronium for ECT and compare their clinical significance. Consistent with the report from Murali and his colleagues [14], our acquired data suggest that succinylcholine doses closer to one $mg.kg^{-1}$ may provide acceptable ECT conditions and also highlight the importance to avoid early application of ECT after the administration of succinylcholine, i.e. less than 1.4 min even in the absence of a twitch response to nerve stimulation. The 1 $mg.kg^{-1}$ dose is the 90^{th} percentile of optimal effective dose equal to 3.5 × ED_{95} of succinylcholine. Furthermore, in our study an induced twitch height suppression of almost null (0-4%) for acceptable motor seizure modification are in line with findings by Murali and his colleagues, who recommended a dose of 1.0 $mg.kg^{-1}$ and twitch suppression to 0-5% of baseline.[14] This dose has also been applied for rapid sequence intubation (1 $mg.kg^{-1}$of succinylcholine, 3.5 × ED_{95}). [15-17] However our study suggests longer time to achieve adequate muscle relaxation for ECT is required (60 sec for rapid sequence intubation). This observation is also consistent with previous finding by Beale and colleagues [18] that the muscle response to ulnar nerve stimulation can be extinguished long before cessation of muscle fasciculation. This difference in time to obtain acceptable ECT conditions as compared to that for endotracheal intubation may be attributed to a difference in sensitivity to succinylcholine in different muscle groups (e.g. oropharynx versus extremities), but can also indicate that a deeper neuromuscular blockade is needed for acceptable ECT conditions as compared to endotracheal intubation.

Rocuronium 0.57 $mg.kg^{-1}$ (≈ 2 × ED_{95}) was the 90^{th} percentile estimated dose to produce acceptable level of muscle relaxation. This dose has already shown its efficacy in inducing more than > 95% block in almost 98% of subjects.[19, 20] The onset time from NMBA injection to acceptable ECT conditions is hence approximately 2.3 minutes longer with rocuronium as compared to succinylcholine. While we did not identify any difference in major clinical characteristics during seizures such as hemodynamic variables or oxygen saturation between rocuronium and succinylcholine, the recovery time of recuronium was substantially longer than succinylcholine (8 min). However, rocuronium application showed some other qualities not observed by succinylcholine. Consistent with other studies seizure duration was longer in patients who received rocuronium as NMB agent. [21] As there is an association

between clinical effectiveness of ECT and the duration of induced seizure [22], the American Psychiatric Association task force advocates seizure lengths more than 20 sec for effective ECT treatment.[23] This recommendation not only underscores the importance of titrating the dose of the NMBA to achieve an adequate and optimized neuromuscular blockade, but also this quality might be of interest for potential role in the efficacy of ECT in set of treatments (i.e. cumulative seizure time). Further clinical investigation is warranted.

In *chapter three,* we defined the optimal doses of rocuronium and succinylcholine and demonstrated that even in absence of this selective reversal agent, in patients with contraindications to the use of succinylcholine, [2] the rocuronium-neostigmine combination can provide a safe and relatively time-effective alternative to other available non-depolarizing NMBAs and reversal agents. Rocuronium is increasingly employed as an alternative to succinylcholine for neuromuscular blockade during ECT, primarily in the elderly and patients with cardiovascular and neurological comorbidities. On the other hand, ECT is highly effective and is increasingly applied in the elderly and those with increased incidence of prolonged immobilization, prone to higher risk of hyperkalemia. [3] Nondepolarizing NMBAs do not cause hyperkalemia and can be given to these patients and those with susceptibility to malignant hyperthermia or contraindications to succinylcholine, but are often avoided because of their relatively long duration of action, typically exceeding the ECT time. Our study demonstrated that even in absence of selective reversal agents such as sugammadex, in patients with contraindications to the use of succinylcholine, [2] the rocuronium-neostigmine combination can provide a safe and relatively time-effective alternative to other available non-depolarizing NMBAs and reversal agents.

As compared to rocuronium, succinylcholine showed relatively higher inter-individual variability for the applied effective doses that resulted in acceptable neuromuscular blockade and controlled ECT induced seizure. This fact reemphasized the role of pharmacogenetics in ECT (discussed more in *chapter five*) and how the variability in expression and activity of butyrylcholinesterase enzyme resulting in different observed degradation quality of succinylcholine might have caused this observation. The lower variability in the applied rocuronium doses to identify individualized optimal dose might take on greater significance if achieving the optimized induced motor activity is required to rapidly maximize the therapeutic effect of sequential ECTs, particularly if alternative for succinylcholine is advisable. However after initial dose, if increments are required, less predictable and longer recovery time than increment of succinylcholine doses should be considered. [24, 25]

In general, complete paralysis is neither necessary nor desirable since it may be associated with prolonged apnea. As previously mentioned, currently, no guideline has been described for application of rocuronium during ECT and according to the guidelines of the Nederlandse Vereniging voor Psychiatrie (Richtlijnen Nederlandse Vereniging voor Psychiatrie, tweede, herziene versie, 2010), succinlycholine 0.5-1 mg/kg is recommended for ECT. This ECT guideline also suggests measurement of serum potassium in certain patients i.e. age>60 or use of diuretics, digoxin, corticosteroids, laxatives, antihypertensive drugs, decrease renal function, hypertension and diabetes, as increased potassium levels are a contra-indication for ECT. The guideline does however does not recommend any alternative to succinylcholine, if needed.

In *chapter three*, we tried to provide some clinical suggestions for clinicians for how to apply these two NMB agents. According to our experimental randomized crossover trial for ECT, the optimal dose of succinylcholine and rocuronium mostly oscillates by 0.1 mg.kg, up to 0.2 mg/kg around their optimal effective dose of 50 ($OED_{50\text{-}ECT}$). Therefore we suggest administration of OED50 of either of the NMB agents (succinylcholine 0.85 mg.kg^{-}and rocuronium 0.4 mg.kg^{-}) with dose adjustments based on the quality of the observed motor seizure activity for each individual during subsequent treatments. 0.1-0.2 mg.kg^{-1} increment or decrement in the initial dose should be considered if the corresponding motor activity is insufficient or excessive, respectively. Due to short duration of action and fastest recovery from induced neuromuscular block, succinylcholine is recommended as the first choice with consideration of rocuronium as an alternative. Consistently, Bryson et al. recommended the single bolus dose of succinylcholine 0.9 mg.kg^{-1} for ECT, however they observed high variability among their subjects the fact that highlights our suggested clinical guideline. [9] To improve the perioperative and anesthesia recommendations for ECT provided by the guidelines of the Nederlandse Vereniging voor Psychiatrie (Richtlijnen Nederlandse Vereniging voor Psychiatrie, tweede, herziene versie, 2010), our data suggest using succinylcholine 0.6-0.8 mg/kg for those who might have relative risk of hyperkalemia as initial dose and adjustment of the dose based on the clinical outcome, i.e. any adverse effect due to hyperkalemia and induced level of neuromuscular blockade. For those who have absolute contraindication to succinylcholine or if anesthesiologist in care advise so, e.g. elderly at high risk of developing hyperkalemia due to immobilization or their medications, we suggest using rocuronium 0.4 mg/kg as an alternative initial dose with subsequent dose adjustment as needed. We also recommended applying neurotransmission monitoring to facilitate inducing the optimal seizure activity. Furthermore, quantitative NMT monitoring is highly recommended to evaluate adequate level of relaxation and safe recovery of patients undergoing ECT. NMT monitoring helps to avoid increased risk of adverse respiratory events and overcome the potential inter-individual variability in time to recovery. [3, 26] ECT should be applied after observing

stabilized twitch suppression more that 90% or 1.4 or 3 min (succinylcholine and rocuronium, respectively) for achieving more than 90% peak effect, if monitoring is not available. In the absence of monitoring, clinicians should ensure that patients stay under close observations by appropriately trained personnel in using bedside tests such as tongue depressor test to assess the adequate recovery of neuromuscular function until complete recovery of the neuromuscular transmission. [27] Our study also provided the gourd for a prospective clinical trial using the ED50, OED90 and OED95 of succincylcholine and rocuronium to achieve a better estimation of EC90 and ED95 of these two neuromuscular blockers for application in ECT.

In the follow-up PK-PD study on the ECT data and in *chapter four*, we identified similar pharmacokinetic-pharmacodynamic parameters (k_{e0} and Ce50) for succinylcholine during ECT as previously investigated. For rocuronium the estimated k_{e0} is consistent with others' finding, while we identified higher Ce50 at adductor pollicis that might justify the faster observed recovery from rocuronium induced NMB in this study. This observation warrants further investigation for PK-PD investigation of rocurnium during ECT in a prospective clinical trial.

Pharmacogenetics in ECT: From safety to efficacy

Variation of treatment response and adverse effects of treatment are dependent on genetic factors. The aim of pharmacogenetics is to help to predict an individual's drug response (*prediction of efficacy*), unraveling the potential genetic association *(mechanisms in efficiency of ECT*) while minimizing the side effects (*improvement of safety*). Investigating the effect of treatment on neurotransmitter concentration or receptor function might help in better understanding of the mechanism of ECT treatment. However, the addition of functional genomics by considering the interactive biological effect of genes as well as their protein expressions in response to ECT treatment, may lead to the development of novel and safer medications that mimic the effect of ECT. In *chapter five,* we discussed this point of view for safety of ECT and explored the potential interaction of genes that has been investigated in association with the efficacy of ECT.

Earlier in this section, we discussed in *chapter three* that the inter-individual variability in *BCHE* expression might cause higher variability in applied optimal doses as compared to a non-depolarizing NMB agent such as rocuronium with a different metabolic degradation pathway. Polymorphisms could be clinically important when a medication is dependent on a polymorphic enzyme for metabolism. In *chapter five,* we discussed how genetic variation in the *BCHE1* gene leads to variant enzyme forms, which affects the substrate behavior and results in reduced or absence of the enzyme BCHE activity. This deficiency results in

prolonged post-succinlycholine apnea due to markedly decrease in plasma cholinesterase activity. [28] While clinicians should be aware of this adverse event, currently routine test due to low prevalence of the clinically deficient subjects is not recommended. However, for those patients who exhibit prolonged apnea to succinylcholine, it is important to screen other family members to determine their risk of atypical serum cholinesterase. From the safety perspective of ECT, in this chapter, we also explored other genes such as *CACNA2D1* and C*ACNA1S*, and *RYR1* that are associated with malignant hyperthermia and safe practice of anesthesia in ECT. The reported incidence of MH during ECT has been less than other procedures requiring general anesthesia, a report that requires further investigation.

The neural and the molecular pathway alterations induced by ECT stimulus might explain the mediation of the behavioral changes by this procedural treatment. These alterations are both acute and chronic. While the acute neurotransmitter changes cause the rapid response to treatment, the duration of therapy outcome is in part dependent on the continuation of at least some those acutely induced neurobiological effects. In *chapter five,* we reviewed the evidences that support these neurobiological responses and how the pharmacogenetics or pharmacogenomics might contribute in identifying the neural and the biological pathways involved in the efficacy of ECT or even safety of ECT (e.g. cognitive side effects) as well as predicting the outcome of the therapy. Accordingly, we showed that few studies had investigated gene expression signatures (co-expression of several genes) in response to ECT stimulus. Altar et al.'s pre-clinical investigation, on the effects of single versus repeated electroconvulsive seizure (ECS) exposure on gene transcription to identify genes and potentially associated biochemical pathways with response ECT, was the major study to show the overlap of regionally expressed genes in acute and chronic treatments. [29] They showed that almost one hundred and twenty hippocampal and frontal genes were differentially expressed (e.g. BDNF-MAP kinase) within distinct pathways in response to acute and chronic ECS. Of those, only nineteen genes showed similar expression in response to acute or chronic ECS. In contrast with this approach of investigation, several other studies used a prior knowledge on a gene which directly or in directly may play a role in neurobiological mechanisms to investigate their role in efficacy of ECT response. These studies used either gene polymorphism to predict the therapeutic outcome of ECT or altered transcriptional expression of gene of interest to infer the potentially involved neurobiological pathway. This way, we identified several investigated genes in association with response to ECT treatment. These genes include *BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB* and NMDA receptor. Accordingly these genes could be assumed as set genes that their potential co-expressions in specific regions of brain might contribute to treatment response. We examined this hypothesis by building the regulatory network of these genes and test if these genes are significantly enriched in a specific region of brain and as part of the known brain functional

regulatory networks. Accordingly, we identified our genes of interest to be prominently enriched in frontal functional regulatory networks. We also consistent with prior studies found that AP-1 transcriptional complex could play an important role in such regulatory networks associated with ECT therapeutic responses, particularly the long-term response. [30] Acquiring such knowledge on the biological mechanisms involved in ECT will provide clues to unraveling the neurobiological alterations that are linked to treatment response and identification of potential targets for novel psychotropic treatments. This attempt is important knowing that ECT is still a physical intervention and more cumbersome than medications with higher efficacy. Although all the above conclusions have to be clinically validated in further studies, there is no doubt that by improvement of the growing technology of functional genomics, large-scale gene and protein expression could provide new insights in how ECT might differently help in treatment psychiatric disorders and which neurotransmitters are more related to the efficacy of treatments. Such detailed knowledge will have profound effects on the diagnosis of psychological disease subtypes, prevention, and treatment of these diseases. In agreement with Palfreyman et al. [31], in *chapter five,* we suggested the comparison of the disease and treatment gene signatures (e.g. antidepressants, ECT, depression) to identify genes or their potential biologically relevant functional pathways which are common between phenotypes of interest. The comparison of the spotted genes could identify a set of targets whose alteration might be a better predictor of disease and the effect of treatment, either by procedure or drug. This approach also provides the opportunity of simultaneously studying the disease, medication used for its treatment and the effective procedural treatment when those medications are not effective. Ultimately, such overlapping genes could be used to identify drug compounds that show similarity in inducing the gene expressions, which consequently mimic the therapeutic response of ECT. As our investigation demonstrates, most of the ECT studies on efficacy of ECT are pre-clinical and further well-designed longitudinal clinical studies are required to increase our knowledge of the mechanisms underlying the efficacy of ECT.

The variability in drug response is highly complex however, and genetic factors has been recognized as one the factors that might influence both the efficacy of a drug and the likelihood of adverse reactions. Applications of pharmacogenetics include the identification of new drug targets, prediction of efficacy and toxicity for new drug therapy, testing for the direct influence of an agent on a specific pathway, and identification of drug responders, nonresponders, and toxic responders within a population. With the advent of pharmacogenetics 'the melding of sciences, including genetics, biochemistry, and molecular pharmacology' has come the hope of personalized medicine in the future. Although medicine may be far from realizing that goal, there has been much scientific progress leading to the hope of one day attaining personalized medicine.

Owing to its importance, CYP2D6 is the most extensively studied P-450 isoenzyme in psychiatry. CYP2D6 enzyme, in part, executes the oxidative metabolism of most of antidepressants (ADs), depending on the metabolizing categories and type of drug. The presence of allelic variants in CYP enzymes with varying degrees of functional significance may result in three main phenotypes, poor metabolizers (PMs), normal metabolizers (NMs), and extensive metabolizers (EMs). The PMs lack an active form of the expressed enzyme due to an inactivating allelic variant; NMs have at least one copy of an active gene; and EMs contain duplicated or amplified gene copies, thus leading to either increased (maybe toxic) or decreased (maybe ineffective) concentrations of the drug. [32] Hence, in *chapter six* we investigated the CYP2D6 enzyme phenotype in prediction of patients underwent ECT. In this study, frequency of CYP2D6 phenotypes was not associated with failure of antidepressant treatment response. CYP2D6 enzyme, in part, executes the oxidative metabolism of most of SSRIs, depending on the metabolizing categories and drug-by-drug basis. The observed frequency of UM phenotype was 0 as opposed to the previously reported prevalence of 3% o in the Dutch population. [33] The prevalence of PMs in ECT patients and patients with single episode of depression were 5.3% and 6.4%, consistent with previous reports (5.5%-9%) in healthy Dutch volunteers. [34-36] The frequencies of IMs in both ECT patients and those with single episode disorders of depression were higher than healthy subjects. [36] Consistently, Haber et al. demonstrated that Hungarian patients with difficult-to-treat depression did not exhibit an increased frequency of aberrant CYP2D6 phenotypes. [37]

Several studies have demonstrated that poor, intermediate and ultra-rapid CYP2D6 metabolizers might have a higher incidence of adverse effects when taking CYP2D6-dependent AD and more risk of TRD. [38] However, an almost equal number of studies did not find significant evidence to support these findings. [38] In line with these evidences, our study does not support the routine application of *CYP2D6* genotyping prior to treatment to reduce the risk of non-responsiveness to the CYP2D6-dependent ADs. Our study has the advantage that the unipolar and bipolar depressive patients in each of the study groups represent extreme clinical outcomes of depression, i.e., one group of patients with severe and recurrent episodes who had received several prior trial treatments, eventually indicated for ECT, and the other with only a single episode of depression. However, this fact should also be considered that lack of the CYP2D6 phenotype correlation with failure of AD treatment response might be due to unreported smaller effect size affecting the study power. Accordingly, a large sample size may be required to capture substantial number of CYP2D6 phenotypes and such a presumptive effect size ($N \approx 1000$ for $df=2$ or 3, effect size of 0.1 at $\alpha=0.05$ and $\beta=0.20$). While our results are suggestive that preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in depressed patients undergoing ECT, further large-scale prospective clinical trials are warranted to validate this suggestion.

It is noted that the guidelines of the Nederlandse Vereniging voor Psychiatrie (Richtlijnen Nederlandse Vereniging voor Psychiatrie, tweede, herziene versie, 2010) does not currently provide any recommendation on the impact of pharmacogenomics (PGx), particularly the utility of *CYP2D6* genotyping, in patients with treatment-resistant depression undergoing ECT. An update on the standpoint according to the current evidences is suggested.

The variability in drug response is highly complex however, and genetic factors has been recognized as one the factors that might influence both the efficacy of a drug and the likelihood of adverse reactions. In *chapter six* no increase in prevalence of aberrant genotype-predicted CYP2D6 phenotypes was observed among patients who received ECT for continuation of depression treatment as compared to patients with single episode of depression. However, we found that some clinical characteristics of patients are associated with the indication of ECT for treatment resistant depression. The failure of gender to be associated with the depression recurrence and preferential response to SSRI medication in our results are consistent with previous studies. [39] Older adults might have higher likelihood of receiving ECT for treatment of depression. [40] Similarly, Our data show that patients who received ECT for the treatment of resistant and recurrent depression were older than patients with single episode of depression. Our data also suggest that patients with bipolar depression have a higher risk of receiving ECT than those with unipolar depression. Relevantly, Ghaemi and colleagues studied the outcomes of antidepressant trials for 41 patients with bipolar depression and 37 with unipolar depression matched by age and sex distribution. They found that short-term nonresponse was more frequent in bipolar (51.3%) than unipolar (31.6%) depression. [41] While our results are suggestive that preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in depressed patients undergoing ECT, further large-scale prospective clinical trials are warranted to validate this suggestion.

Advancement of safety of anesthetics for ambulatory procedures

After the introduction of propofol (2,6-di-isopropylphenol), this anesthetic became widely used for induction of general anesthesia and for sedation in intensive-care patients. In recent years, propofol has increasingly been administered for sedation during short diagnostic or treatment procedures such as gastrointestinal endoscopy ECT procedures. In comparison with conventional sedation using short acting central nervous system sedatives such as midazolam, propofol has attractive characteristics to be applied for short procedural sedations; namely a considerably more rapid onset of minimum residual sedation after the procedure. [42]

Although propofol results in a rapid recovery time and widely used in ECT and other medical procedures, adverse hemodynamic and respiratory effects are observed. [43] Sedation with

propofol is often associated with a significant decrease in arterial blood pressure especially in patients with advanced age, higher ASA (American Society of Anesthesiologist) physical status class>II and prior hypotension. [44] Adverse effects on hemodynamic function may occur whenever sedative and analgesic agents are administered.

ECT plays an important role in the treatment of late life depression and other psychiatric conditions in the elderly. Compared to pharmacologic treatments, ECT is administered in high proportion of elderly patients. [45] Therefore, any potential drug-drug interaction that might exacerbate the propofol-induced hypotension during induction of anesthesia could be of high importance for clinicians and should be assessed. Practitioners providing procedural sedation should have a thorough knowledge of the pharmacology of the applied agents and always be cautious on observation of anesthetic adverse effect exacerbation. Potential adverse effects of these agents on airway patency, respiratory function, and hemodynamic balance should be fully appreciated. As an example of such exacerbated adverse events, in *chapter seven,* we introduced a new drug-drug interaction, i.e. propofol induced profound hypotension during induction of anesthesia in patients with rifampin pre-treatment. We demonstrated that the risk of a prolonged hypotensive episode increased almost three-fold when propofol was used for induction in patients who received rifampin. In 40% of subjects, this exaggerated hemodynamic response required vigorous treatment with vasopressors and fluids as well as repeated doses of vasopressors. In our appropriately designed study with control groups, we also considered several other factors such as the duration of fluid abstinence among subjects [46], the dose or type of pre-induction anxiolytic agent, and applied fentanyl doses that might affect the investigation. However, the observed hemodynamic response was significantly greater in the propofol-rifampin group, suggesting a drug-drug interaction as the cause. Hemodynamic instability was not seen when rifampin was given with thiopental, indicating that the interaction is unique to propofol. The potential mechanisms to explain this observation needs to be further investigated. Intravenous administration of rifampin alone can induce hypotension by a direct, dose-dependent reduction of vascular tone and SVR, [47] and propofol-induced hypotension is largely due to venodilation. [48] One potential mechanism might be rifampin augmentation of the venodilating effect of propofol through an increased endothelial production and release of nitric oxide (NO). [49] This may occur as a result of increased NO production by upregulating iNOS mRNA transcription. [50] Rifampin is commonly used for treatment of tuberculosis and less often for prophylaxis of staphylococcal infections and nisseria meningitidis infections. Clinicians should be aware of this potentially dangerous interaction and if patient who is taking rifampin is necessary to undergo medical procedures and consider using alternative agents for induction of anesthesia. A prospective study is desirable to investigate the mechanism of this drug-drug interaction.

Procedural sedation, which includes medications and monitoring, aims to facilitate the performance of the procedures that might cause discomfort such as pain, anxiety, unpleasant memories associated with such procedures. In the ambulatory setting, the optimal anesthetic techniques would provide ideal procedural conditions and rapid recovery with minimizing the side effects of anesthetics. An optimal ambulatory anesthesia will increase the efficiency and reduce the preoperative complications as well as the healthcare costs. Several clinical factors causes delays in post anesthesia care unit (PACU) discharge that significantly increase the cost of ambulatory procedure. [51] In the purview of ambulatory anesthesia efficiency, in *chapter eight*, we investigated the postoperative hemodynamic adverse events and potential contributors to the prolonged PACU discharge after spinal anesthesia. While recovery from the residual motor and sympathetic blockade is primary factor for discharge delay after spinal anesthesia, back pain, post-dural ponctural headache and radicular irritation have been other concerns. [52] Hypotension has been reported to be present after spinal anesthesia in almost in 5.4% patients. [53] The incidence of bradycardia has been shown to be associated with position that the spinal anesthesia was inserted. In one study the incidence of severe bradycardia in the PACU was significantly higher in patients in the Trendelenburg position (60%) than in the horizontal (20%) or hammock (10%) position. [54] The combination of bradycardia and hypotension could cause potential life-threatening hemodynamic instability after spinal anesthesia. Therefor in *chapter eight*, we attempted to determine the coincidence of hypotension and baradycardia after spinal anesthesia as well as to identify factors associated with these hemodynamic changes. We further examined the association of potential dependent variables with increased PACU length of stay and its duration. The coincidence of bardycardia and hypotension was 5% of the patients recovering from spinal anesthesia and was associated with a prolonged PACU length of stay. Among the potential associated factors, the patient's position during spinal placement and the postoperative opioid dose were correlated with the events.

Discharge criteria for patients after spinal anesthesia should minimize the risk of central nervous system or cardio-respiratory depression after discharge. After spinal anesthesia patients are often discharged from the PACU after recovery for motor and sensory function. In this study the severe hemodynamic events occurred even in the absence of profound motor block. Accordingly, this observation on late occurrence of severe hemodynamic instability is suggestive of considering the addition of the orthostatic stability discharge criteria [55, 56] to recovery of sensory and motor function. Modifications of procedural sedation guidelines for patients with high risk of developing such events after spinal anesthesia are also recommended as a preventive measure. Further studies are required to define and test optimal clinical criteria for safe transfer of patients after spinal anesthesia.

FUTURE DIRECTIONS

Safety

In this dissertation we investigated several safety aspects of ECT as a procedural treatment. We defined the minimal effective doses (MEDs) of two NMBA, i.e. succinylcholine and rocuronium for ECT. Accordingly, we suggested a guideline for clinicians how to use ED_{50ECT} (50% effect dose for ECT) of these two NMBA to attain the optimal effective dose (OED) for each patient resulting in an acceptable induced seizure during his/her ECT. We also provided the 90^{th} and 95^{th} percentiles of MEDs for succinylcholine and rocuronium in our results. In our study ED_{50}s were calculated with averaging the mid-point doses of all independent pairs of patients involving a crossover as per methodology of up-and-down adjustment. When using the up-and-down methodology the starting dose should ideally be the minimum dose expected to result in a positive response, i.e., close to the expected ED_{50}, what we considered in our study. This approach results in a obtaining a more precise estimation of ED_{50ECT}, however, any estimated ED_{95ECT} by probit regression using the obtained data from this approach could be inaccurate. A future clinical study could address this issue by applying some fix doses (e.g. $ED_{25ECT,}$ ED_{50ECT}, 90^{th} and 95^{th} percentiles of MED_{ECT}s) using the obtained knowledge from our study to precisely define the ED_{95ECT} of succinylcholine and rocuromium. Furthermore, the observed faster recovery time after using rocuronium during ECT and higher estimated Ce50 for rocuronium in our PK-PD analysis is a matter of further investigation to understand the potential involved mechanisms and other potential factors such as longer duration of seizure or different effect of increased CO during ECT on rocuronium Ce50.

To Advance the safety of anesthetics for ambulatory procedure such as ECT, we investigated severe hemodynamic changes resulted from a newly introduced drug-drug interaction (rifampin-propofol) and factors related to the type of procedures. While clinicians should be aware of these potential drug-drug or periprocedural side effects, the findings require more rigorous future investigation for the validity and mechanisms involved.

Efficacy

To investigate the role of pharmacogenetics in the efficacy of ECT, we searched for the studies used either gene polymorphism to predict the therapeutic outcome of ECT or altered transcriptional expression of genes of interest to infer the potentially involved neurobiological pathway. We identified several genes in association with response to ECT treatment. These genes include *BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB* and NMDA receptor. Using the network analysis, we showed that the potential co-expressions of these genes in specific regions of brain might contribute to treatment response through building

the functional regulatory network. We also consistent with prior studies found that AP-1 transcriptional complex could play an important role in the identified regulatory networks associated with ECT therapeutic responses. All these genes and their potential co-regulation by common transcriptional factors should be further investigated in future preclinical and clinical studies. There is no doubt that by improvement of the growing technology of functional genomics, large-scale gene and protein expression could provide new insights in how ECT might differently help in treatment psychiatric disorders and which neurotransmitters are more related to the efficacy of treatments. We also studied the application of *CYP2D6* genotyping prior to treatment and its potential role to reduce the risk of non-responsiveness to the CYP2D6-dependent medications. Our study does not support the routine application of this test prior to treatment. However, this observation should be further investigated in a larger prospective randomized trial to satisfy the possibility of unmeasured confounders as well as the potentially smaller effect size of aberrancy of *CYP2D6.* Such a study also provides the opportunity of validating the effect of clinical characteristics such as age and type of depression in prediction of the treatment outcome.

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