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Comparative bioethics in bipolar and epilepsy research*

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Rationale: AEDs are increasingly evaluated for efficacy in bipolar disorders utilizing double-blind, placebo-controlled, randomized clinical trials (RCTs) as required by the FDA. However, the risk to patients is under-estimated in trial design. Bipolar depression has a significant risk for suicide; bipolar episodes can lead to kindling with increased long-term morbidity; rapid regression may occur during the placebo phase or during dose ranging trials with resultant active suicide status. The associated risks mandate that the ethics of FDA-required protocols are addressed.

Method: Comparative analysis and literature review of bipolar and epilepsy research designs.

Results: In psychiatry, all INDs require RCTs for approval. In epilepsy, AEDs are initially approved as add-on agents only. Once AEDs have demonstrated add-on efficacy, cross-over studies comparing active AEDs, sub-optimal dosing paradigms, new-onset, and pre-surgical inpatient placebo trials are utilized to prove efficacy of the new AED in monotherapy. Ethical considerations to avoid seizures and to minimize risks to subjects have led to newer clinical trial designs.

Conclusions: The FDA initially requires add-on studies with new AEDs due to the risk of seizures during the placebo phase. The author argues that bipolar research warrants similar add-on studies to prove efficacy because the risk of suicide and increased long-term morbidity in the bipolar population is as significant as the risk of seizures in the epilepsy population. Although the number of patients needed to prove statistical efficacy would increase, the safety of such research would also markedly increase. The author further concludes that with the risk of suicide during bipolar research, ethical considerations require increased frequency of patient contact with a significant other co-signing the informed consent for research and serving as a contact for the coordinator.

Key words: bipolar disorders; epilepsy; psychotropics; antiepileptic drugs; research; ethics; suicide; treatment.

INTRODUCTION

The concepts of nonmaleficence and beneficence—to do no harm and to do good—are the cornerstones to the ethical practice of clinical medicine[1]. As a profession, we uphold these principles by practicing accepted standards of care, by specifically avoiding malpractice and abandonment, but most importantly by always remembering that the patients' interests come first.

But how do we know what should be appropriate care for patients with specific illnesses? How truly do we know what will be beneficial and what will be detrimental in different patient populations? Herein lies the merit of scientific research. Initially, such research is observational in nature utilizing case studies and case series in uncontrolled patient populations. This leads the clinician to potential hypotheses. Ultimately, with the presence of these hypotheses, the clinical researcher attempts to answer the question of whether a specific intervention is in fact an active and effective medical treatment with maximum benefits and minimum risks.

With the bio-technical explosion of this past century, increasing numbers of pharmaceuticals are being evaluated for efficacy within psychiatric illnesses and specifically for the treatment of affective disorders. Furthermore, original theories of limited episodic

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illness have changed to chronic recurrence leading to the need for long-term psychotropic prophylaxis[2]. But is the efficacy of the newer agent being determined by comparison to known effective agents, to placebos, or as adjunctive treatment? The double-blind, placebo-controlled, randomized trial (RCT) has been utilized for over 50 years[3] and the Food and Drug Administration (FDA) requires such pivotal trials for approval to market[4]. It has been argued that there is a 30–40% placebo effect in psychiatric trials and as such, unless the new agent is compared to placebo, a comparative trial to a known efficacious agent may be relatively meaningless[5,6]. In that sense, to argue that the newer agent is efficacious when it is not may be doing a greater harm to the entire diagnostic population. As such, one could argue that from a societal perspective, there may be a greater risk not to utilize the RCT.

Yet, is there a risk to the patient who partakes in such study and receives only placebo? In light of the Declaration of Helsinki, is it considered ethical or even legal to utilize RCTs when more effective therapeutic agents than placebo are available[7,8]? A recent review of suicide risk in patients treated with placebo during antidepressant clinical trials revealed no significant difference in the rates of suicide and attempted suicide among the drug-treated and placebo-treated groups[9]. However, this review only addressed the issue of suicide during the period of the clinical trial itself; the review did not address the effects on long-term morbidity and mortality that may exist secondary to having taken a placebo during an RCT.

RESEARCH IN BIPOLAR AFFECTIVE DISORDERS

These issues are especially meaningful in research studies applied to bipolar affective disorders. Whereas RCTs are best suited to study homogeneous populations, patients with bipolar disorders are more often heterogeneous (be it secondary to severity of illness, phase of illness, cycling, illness patterns, or comorbidity) resulting in the need for large multicenter studies that may not address the typical clinical bipolar patient[10]. Bipolar depression carries a significant risk for suicide attempts and actual suicides that is increased with psychiatric comorbidity[11,12]. Bipolar episodes can be associated with kindling and increased long-term morbidity from these disorders. Rapid regression can occur during a placebo phase or even with the patient on the active study agent during dose ranging trials, with resultant active suicidal status. The washout process associated with RCTs is very important when addressing bipolar research. There is a differential effect with rapid versus gradual lithium treatment discontinuation on illness recurrence[13,14]. Thus, there is an implication on the validity associated with bipolar research trials wherein lithium was discontinued abruptly[15]. Furthermore, the dramatic effect associated with lithium discontinuation on suicide (a 20-fold increase in suicidal behaviors and a 13-fold increase in mortality during the first year off lithium) is apparently increased with rapid versus gradual discontinuation[16].

Of interest is that the majority of RCTs in treatment of acute bipolar mania and depression used cross-over designs that are not currently considered optimal for discrimination between active drug and placebo response[17]. In fact, there is only one parallel-group RCT demonstrating the effectiveness of lithium over placebo in the treatment of acute mania[18]; there are two parallel-group RCTs demonstrating the effectiveness of divalproex over placebo in the treatment of acute mania[18,19]; and there are two parallel-group RCTs demonstrating the effectiveness of olanzapine over placebo in the treatment of acute mania[20,21]. Furthermore, there is only one positive parallel-group monotherapy RCT demonstrating the effectiveness of a proposed mood stabilizer, lamotrigine, over placebo in the treatment of acute bipolar depression[22].

In a review of seven maintenance bipolar parallel-group RCTs, five lithium studies were done in the early 1970s when the effects of abrupt discontinuation of lithium on illness recurrence were not yet appreciated, and one carbamazepine study used liberal adjunctive medications that obscured the relapse rates between placebo and active agent[23]. Only one study, a recent comparison of divalproex to lithium to placebo incorporated DSM-III-R criteria, rational interventions during the first month to address the effects of discontinuing open-label treatment, and survival analysis[23,24]. However, that study showed no statistical difference in the primary outcome measure, time to recurrence of any mood episode[24].

Thus, not only are there significant bioethical issues that must be addressed when preparing bipolar research designs but also one must be cognizant that there are very few positive parallel-group RCTs that have been done in the bipolar population. There are both societal obligations to approve the most effective agent and individual obligations to do no harm during an RCT in addition to the requirement that there be no long-term morbidity and mortality secondary to having participated in a placebo arm of an RCT.

EVALUATION OF ANTIEPILEPTIC DRUGS (AEDS)

In light of the new wave of anticonvulsant usage in the treatment of bipolar disorders, it was felt appropriate

to look at the research designs currently used in recent AEDs being approved for the treatment of epilepsy as a starting point for re-evaluation of bipolar research.

Specifically, although the parallel-group RCT is considered the gold standard for proving efficacy, ethical considerations in patients with epilepsy have led to the initial evaluation of the study AED in adjunctive therapy[25]. During the past decade, there have been a series of new AEDs evaluated in this way: gabapentin, lamotrigine, tiagabine, topiramate, zonisamide, vigabatrin, oxcarbazepine, levetiracetam, and felbamate[26–35].

In a meta analysis of 29 add-on studies representing 4091 randomized patients on gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin, and zonisamide it was noted that all six AEDs were more effective than placebo; however, the rate of efficacy of the investigated AEDs had a two-fold difference between most effective and least effective and the rate of discontinuation from studies had a four-fold difference. As such, comparative randomized controlled trials were felt to be indicated to allow an evidenced based choice between these drugs[36]. In summary, the add-on studies satisfied registration requirements for adjunctive AED therapy, but these studies were not felt to give the clinician the needed information to make rational treatment decisions as would be garnered from comparative monotherapy trials[37].

In the AED add-on studies, there are no ethical dilemmas, for the patient remains on an active agent. Furthermore, well-designed multicenter placebo-controlled RCTs result in ready registration of adjunctive AED therapy. However, as noted above, the data obtained does not allow for clear comparisons among AEDs. Also, in add-on studies the potential for pharmacokinetic interactions that might influence outcomes of studies must be addressed[38,39].

With the registration of an AED for adjunctive therapy, there would be decreased ethical considerations for use in comparative monotherapy trials. But as different regulatory bodies have different parameters for registration of AEDs for monotherapy, comparative efficacy studies may not be accepted; specifically, European agencies often accept comparative efficacy whereas the FDA requires documented superiority of the investigational AED[25,40]. Yet it is in the direct comparative trials that the clinician may find the most useful data: lack of drug interactions that may obscure findings, treatment similar to that which would be found in the clinic, and the desired evidenced-based comparison of one known efficacious AED to the newer investigated AED.

Thus it is necessary to pursue parallel-group placebo-controlled AED monotherapy RCTs. In such trials, the purest answer to efficacy can be obtained while avoiding pharmacokinetic drug interactions. However, now the ethical dilemma/justification of having a refractory patient off active medication must be considered. There are two designs that have often been utilized to approach this problem: (a) high-dose/low-dose active control monotherapy[41–43] and (b) pre-surgical evaluation placebo-controlled monotherapy[25,44–46]. There are ethical differences between the two approaches. When a suboptimal active medication is used as a control, the patient is not receiving normal antiepileptic treatment and as a pseudo-comparative study, the patient may be unaware that the suboptimal treatment arm may be subtherapeutic for that individual patient. When queried as to why this study design is utilized, researchers have argued that with low dosage divalproex as the active control generalized tonic–clonic seizures will be blocked while still allowing auras and partial seizures to occur. However, this may not be the case with all study patients nor would it necessarily be the case were alternative suboptimal AEDs to be utilized[47]. To permit such studies to be done, very specific informed consents explaining the role of the low-dose active control would be required. In presurgical evaluation placebo-controlled monotherapy there is a rationale for the patient being on placebo—the need to be thoroughly evaluated for a surgical intervention. Yet, once video monitoring has identified the focus, is it ethical to keep the patient off a known effective AED? This design presents the cleanest approach in an inpatient setting with fixed and easily monitored exit criteria. In both designs the emphasis should be placed upon limiting total time in study and utilizing a combination of fixed number of seizures, percentage seizure frequency increase, and severity of seizures (serial seizures or status) as strict criteria in order to maximize the benefits from the study while minimizing the potential adverse effects to the study patient. With the introduction of preset exit criteria based on seizure activity, researchers have argued that ethical considerations in these two study designs are minimized[48,49].

These novel monotherapy trial designs lead to registration of the investigated AED for monotherapy; but these trials do not tell the clinician which AED to utilize. For this, one requires comparative monotherapy trials with optimal doses of standard AEDs[37]. Some argue that significant ethical questions remain with these monotherapy trial designs and that the gold standard in AED evaluation should be randomized, long-term comparative trials[50].

DISCUSSION

In psychiatry, all investigational new drugs (INDs) require RCTs. To date, no psychotropics have been registered as adjunctive agents only. In the treatment of epilepsy, AEDs are initially approved as add-on agents after undergoing parallel-group placebo-controlled RCTs. Once AEDs have demonstrated efficacy as add-on agents, novel monotherapy trials including suboptimal dosing paradigms (low-dose active control) and presurgical inpatient placebo trials are utilized to prove the efficacy of the new agent in monotherapy followed by comparative monotherapy trials against optimal doses of standard AEDs. Nonetheless, ethical issues exist in epilepsy research just as in bipolar research: should the IND be tested against a placebo and will there be harm to the patient under such circumstances; specifically, is the risk/benefit ratio too great to allow placebo controls.

The new monotherapy AED trial designs were created in order to minimize ethical concerns while maximizing assessment of efficacy. Unfortunately, in any clinical study that involves placebo controls there will always be an inherent risk; similarly with the use of a low-dose active control the issue of the pseudo-comparative trial must be considered. It is true that even with low serum concentrations of standard AEDs there can be some anticonvulsant effect, but it may not be generalizable to the entire study group and the study patients need to clearly appreciate that from a well-crafted informed consent. But the critical change in the newer AED monotherapy designs is strict exit criteria based on seizure activity. What can bipolar research learn from AED development and especially from these newer AED designs?

There is a glaring need for parallel-group placebo-controlled add-on RCTs in bipolar research. Such trials could be performed in either inpatient or outpatient settings. With such design, the ethical dilemmas faced by pure placebo trials would be obviated, for all patients would remain on active agents with one arm receiving the study agent and the other placebo. Furthermore, although the add-on study may be more expensive, secondary to the presumed need for a greater N to power the study, enrollment into such study should be much easier. Based on the outcome of these add-on trials, enrichment continuation (maintenance) studies could be designed[10, 51]. With the knowledge that the study agent is effective in adjunctive treatment of bipolar disorders, the ethical concerns in further acute and maintenance comparative studies would be decreased. Nonetheless, the FDA still requires the placebo-controlled RCT for registration of psychotropics.

How then to pursue such studies while minimizing patient risk? Taking a lesson from the presurgical evaluation AED trials, the effective bipolar adjunctive agent should be studied in acute hospitalized patients where the greatest change would be noted in the shortest time period while permitting the greatest safety for the study patients. In such parallel-group placebo-controlled RCTs, there must be multiple outcome measures utilized with strict exit criteria if there are any signs of a worsening in illness status in addition to the presence of rational rescue medications.

In addition, rapid cycling and ultra rapid cycling patients should be studied. Although these patients are often refractory to treatment, the severity and frequency of symptoms should permit an easier discrimination between the efficacy of placebo and study agent[10].

Inpatient settings would be appropriate for manic episodes and for severe depression with active suicidal ideation; however, not all bipolar patients that need to be studied would be so severely ill. How would one study hypomanic or moderately depressed bipolar patients without suicidal ideation, especially in outpatient maintenance trials? There are several concerns with outpatient studies: is the patient too ill to participate in such a study (i.e. too suicidal); does the patient truly understand the risks involved and as such is the consent an informed consent; does the consent clearly explore long-term consequences of being in an RCT (including the potential for long-term morbidity and mortality for having been in the placebo arm of the RCT); is there sufficient supervision of this patient in the outpatient setting; are there appropriate exit criteria. For these reasons, there should be tight inclusion/exclusion criteria with specific emphasis placed on suicidal ideation. Furthermore, in bipolar disorders where the risk of suicide attempt is so great, a significant other should witness the consent and agree to be the independent contact to the study team regarding any regression between study visits. Finally, the frequency of study visits should be increased.

Perhaps the most important steps to be taken concern the methodology of assessing treatment responses. For example, in the lamotrigine study for bipolar depression the Montgomery–Asberg Depression Rating Scale (MADRS) appeared to be more sensitive than the Hamilton Depression Rating Scale (HAMDRS) in discriminating response from placebo[17, 22]. Thus multiple outcome measures and survival analysis should be included[23, 52]. Furthermore, it has been suggested that the Life Chart Method (LCM) is utilized as a rating instrument to measure severity of episodes and subsyndromal symptoms[23, 52, 53].

As noted in the epilepsy literature, comparative studies are most needed in order to allow evidenced-based clinical decisions between medications. In

bipolar research, the Stanley Foundation Bipolar Treatment Outcome Network monitors the continuous daily longitudinal follow-up of >500 outpatients and enrolls these patients in open-label add-on, placebo-controlled add-on, and randomized active comparator add-on studies in the presence of existing mood stabilizers resulting in significant clinical findings while minimizing any patient risks[10, 54–57].

There are many similarities between AED and bipolar research—both in trial designs and in ethical dilemmas. That both epileptologists and psychiatrists are addressing these issues is noteworthy. It is expected that these issues will be revisited frequently. As a template, seven requirements for clinical ethical research have been proposed: value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects[58]. These should be adhered to as further research designs are created. Although research is performed in order to improve clinical insight into treating the diagnostic category, the individual and the individual's rights must never be forgotten[59].

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