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CONCEPTUAL AND METHODOLOGICAL ISSUES IN DESIGNING A RANDOMIZED CONTROLLED TREATMENT TRIAL FOR GERIATRIC BIPOLAR DISORDER: GERI-BD

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Abstract

Aim—This report considers the conceptual and methodological concerns confronting clinical investigators seeking to generate knowledge regarding the tolerability and benefits of pharmacotherapy in geriatric bipolar (BP) patients.

Method—There is continuing need for evidence-based guidelines derived from randomized controlled trials that will enhance drug treatment of geriatric BP patients. We, therefore, present the complex conceptual and methodological choices encountered in designing a multi-site clinical trial and the decisions reached by the investigators with the intention that study findings are pertinent to, and can facilitate, routine treatment decisions.

Results—Guided by a literature review and input from peers, the tolerability and anti-manic effect of lithium and valproate were judged to be the key mood stabilizers to investigate with regard to treating BP I manic, mixed and hypomanic states. The patient selection criteria are intended to generate a sample that experiences common treatment needs but which also represents the variety of older patients seen in university-based clinical settings. The clinical protocol guides titration of lithium and valproate to target serum concentrations, with lower levels allowed when necessitated by limited tolerability. The protocol emphasizes initial monotherapy. However, augmentation with risperidone is permitted after three weeks when indicated by operational criteria.

Conclusions—A randomized controlled trial that both investigates commonly prescribed mood stabilizers and maximizes patient participation can meaningfully address high priority clinical concerns directly relevant to the routine pharmacologic treatment of geriatric BP patients.

The elderly are the fastest growing segment of the US population, and the number of elders with bipolar (BP) disorders is increasing [1]. Aged BP patients have severe episodes [2], and they frequently utilize mental health and other medical services [3,4]. In these patients, physiological changes and co-morbid physical and psychiatric illnesses can increase vulnerability to side effects and limit dosing and benefits [5].

Nevertheless, information needed to guide their clinical management is strikingly limited [6]. Guidelines for pharmacotherapy of younger BP patients cannot be extrapolated directly to their care [7]. Age-specific information on risks and benefits consists, with few exceptions, of case reports and case series concerning retrospective data from open treatment. Clinicians therefore face significant ambiguities in treatment planning.

The complexity of geriatric BP disorders challenges those designing pharmacotherapy studies. The aim of this paper is to present the conceptual concerns and methodological rationale for decisions required in designing the GERI-BD clinical trial focused on these patients.

THE SCOPE OF THE PROBLEM

Although modern pharmacotherapy may have improved the outcomes of BP elders [8], their remission rates may still remain poorer than those of younger BP patients [9]. Earlier studies suggest that among BP manic elders, response to anti-manic, mood stabilizing agents may be attenuated [10,11] and chronicity is relatively frequent [12]. Even those elders displaying a clinical response are at elevated risk for relapse and recurrence [13].

Several additional concerns underscore the need to develop evidence that can guide optimal use of available treatments in elders. First, BP disorder confers significant behavioral disability [14] and compromises quality of life [15]. Disability may worsen the course of BP symptoms [14,15], and even contribute to institutionalization [16] and excess mortality and morbidity [17]. However, in late-life depression treatments directed at mood dysregulation can alleviate disability [18], and may help avoid “behavioral disuse atrophy” [19]. Second, functional limitations in BP elders may be compounded by social factors including lack of social support [20]. These deficits can limit the elder’s management adherence. Third, aged BP patients have a high mortality rate [13]. Fourth, BP elders are at risk for suicide [21,22]. Finally, BP elders with a history of recurrent episodes may be at elevated risk for subsequent dementia [23].

In BP elders, evidence-based treatment approaches for all types of symptomatic episodes require development. Manic and mixed episodes of BP I disorder are debilitating and can be life-threatening in the aged. Hypomanic episodes may evolve into mania or be followed by depression. Episodes of depression can be severe and are prevalent.

It is also of concern that prescribing patterns for the elderly are changing despite the lack of randomized controlled trials-based evidence regarding the risks and benefits in doing so in this population [24]. For example, there has been a relative reduction in first prescriptions of lithium salts despite their low cost, and established acute and long-term efficacy in mixed-age patients.

Given these clinical needs, researchers are challenged by the clinical acuity of presenting symptoms and medical co-morbidity, which can impede recruitment, adherence to protocol

procedures, and retention. An additional practical obstacle to studying pharmacotherapy of BP elders is the relatively low number of such patients presenting for care at individual psychiatric centers. This reality requires that needed clinical trials be designed and conducted within a multi-center strategy. Our collaborative group was established, therefore, at six academic medical centers to undertake a randomized controlled treatment trial that could recruit the number of patients needed to achieve the aims of the study.

GERI-BD's overall study design (Figure 1) is that of a randomized, double-blind parallel group clinical trial which compares lithium and valproate over nine weeks in geriatric patients with BP I manic, mixed, and hypomanic episodes. Participants are patients aged ≥ 60 years recruited from ambulatory and inpatient settings.

GERI-BD has two primary aims (Table 1). The first is to compare the tolerability of lithium and valproate in these BP elders. As discussed below (Outcomes and Analysis), the outcome domains assessed are side effects and tolerated concentration ranges.

The second study aim is to compare the drugs' acute efficacy at the highest tolerated and potentially therapeutic blood levels. The outcome domains assessed are mood signs and symptoms, behavioral function, and quality of life,

WHAT ARE THE PHARMACOLOGICAL DESIGN CHOICES?

Initial Treatment or Inadequate Responders?

We decided to study the initial acute treatment approach for patients with manic and related episodes rather than to study treatment strategies for patients exhibiting an inadequate response to pharmacotherapy. This decision reflected the state of existing evidence, the investigators' sense of current clinical need in treating elder BP patients, and input from the peer review process. A primary focus on optimal strategies for treating inadequate responders with pharmacological augmentations and other interventions should be addressed in future research. We reasoned that findings from an initial acute treatment study would contribute to the design of augmentation studies or studies of switching therapeutic agents.

A Placebo Treatment Arm?

Continuing ambiguities regarding the efficacy of mood stabilizers in treating geriatric BP disorders derive from the lack of placebo-controlled trials. This would suggest the inclusion of a placebo treatment arm in a first clinical trial. Nevertheless, we decided not to include this intervention for several reasons. Placebo treatment carries a particularly high risk/benefit ratio in frail elders. Such persons experiencing acute mania characteristically have significant medical morbidity. They are at risk for "manic exhaustion" and associated mortality as a result of their behavioral problems and related dehydration, orthostatic changes, and metabolic imbalances. A placebo component in the present design would also introduce a selection bias favoring a healthier sample since investigators, clinicians, and families would be reluctant to enter frail BP elders in a clinical trial that might assign them to the placebo arm. A biased sample of "healthy" BP elders, thus, would not address problems associated with the care of frail elders for whom data-driven clinical guidance is critically needed.

Monotherapy or Combined Pharmacotherapy?

Combined pharmacotherapy is advocated for the acute treatment of BP disorder in some patients [25]. The aim of this strategy is to provide more rapid and reliable symptom control, although risk-benefit assessment requires added attention.

Indeed, geropsychiatrists treating BP elders are particularly compelled to follow a strategy of therapeutic parsimony. In this patient population, complex pharmacological regimens often produce adverse consequences, including excessive sedation, falls, confusion, disorientation, delirium, extrapyramidal symptoms, tardive dyskinesia, and metabolic syndromes. Given these potential risks when combining treatments, we considered monotherapy the optimal strategy. We also acknowledge, however, that in the absence of needed research data to guide prescribing practice for BP elders, clinicians do not know whether treatment with a single agent is feasible, what medication doses are likely to be tolerated, and whether blood levels of well-tolerated medication are therapeutically effective in geriatric mania. Additionally, while combination treatment may be indicated in resistant patients, it remains unclear how well such treatment is tolerated by the elderly. In particular, comorbid medical and neurological disorders, prevalent among BP elders, may limit tolerability of combination treatments.

What Class of Drugs Should Be Studied?

Since mood stabilizers are the mainstay of first-line treatment for BP disorder [26,27], this initial randomized controlled acute treatment study of geriatric BP I disorder focuses on this class of drugs. We chose lithium and valproate from the several drugs in this class for several reasons. First, there is strong empirical evidence supporting their efficacy in treating younger BP adults [28]. Second, both drugs already are commonly prescribed in geriatric BP patients. Third, available clinical trial information about the drugs' tolerability and benefits at specified blood concentrations can guide community-based care of this population. Fourth, differences in anticipated dose limitations, necessitated by side effects, make this comparison of the two drugs clinically meaningful.

Lithium, the prototypical mood stabilizer, has the strongest evidence for both acute and long-term efficacy in BP patients [29]. It has protective effects against suicide and other causes of mortality [30], thus favoring its selection for this study given the risks of suicide in elders and increased mortality in elder BP patients. Uncontrolled studies suggest that lithium may be efficacious in BP elders [11,31–34]. Moreover, despite recent declines in the number of newly written prescriptions [24], lithium remains widely prescribed in BP elders [35]. However, lithium may be poorly tolerated at conventional concentrations in some aged patients, including those with dementia [36,37]. Thus, it can be prescribed in GERI-BD at lower concentrations if necessary and as anecdotally suggested [38], despite unclear evidence of efficacy at these concentrations [33,39].

As the comparison drug for this study, we selected valproate given findings with younger BP manic patients that valproate and lithium have equivalent efficacy [28]. Although tolerability of valproate may be impaired in patients with dementia [40], it can be well tolerated by non-demented elders, including patients with neurological and medical comorbid disorders [41], at the same concentrations used in younger patients. Although placebo-controlled data are lacking in BP elders, case series reports suggest that valproate is effective in this population [42–53] as do placebo-controlled data for manic patients aged older than 50 years [54]. Despite the increasing use of valproate in geriatric practice [24], no randomized controlled trials in aged patients have compared this drug to placebo, lithium, or other agents. Moreover, such studies are not a priority for industry. Guidelines, thus, are lacking with regard to both the choice of anti-manic agents and how to prescribe them optimally in aged BP I manic patients.

Since both lithium and valproate are available in various formulations, the decision about formulations of lithium and valproate to be used in this clinical trial was based on tolerability and cost. As regards lithium, the carbonate salt is widely prescribed and is available in generic form. We did not find compelling evidence that delayed release

formulations of this drug are better tolerated [55]. The choice of divalproex sodium formulation was based on prescription patterns and evidence that this form can be associated with less gastrointestinal side effects.

We recognized that atypical antipsychotic agents are increasingly used as primary agents for treating BP disorder. However, there is relatively little systematic information available to guide their use in geriatric BP patients [56–58]. Despite an FDA indication for monotherapy with several atypical antipsychotics in young manic patients, the Expert Consensus Treatment Guidelines have not recommended antipsychotic monotherapy as a first line treatment in either young [59] or elderly patients [56]. We decided against studying antipsychotic medications as a primary agent in this first RCT, pending further emerging preliminary findings in secondary analyses of older adults in industry trials [60,61], and findings from studies of other aged psychiatric populations. Nevertheless, we have included atypical antipsychotic augmentation after three weeks for patients with inadequate response to the initially prescribed mood stabilizer drug.

Other anticonvulsants were considered as a focus for this study but rejected. Lamotrigine lacks evidence for anti-manic efficacy, and information regarding its use in elders has been limited [62]; moreover, the lamotrigine dose must be increased gradually to avoid dermatitis, thereby limiting its use as a monotherapy for acute mania. The side effect profile of carbamazepine, including cardiac conduction changes, limits its use in some aged patients [63]. Additional anticonvulsants were considered to have insufficient evidence for anti-manic activity or lacked age-specific data pertinent to their use as primary agents in this population.

What Patient Eligibility Criteria Should Be Used?

The criteria for recruiting patients clinically eligible for the randomized trial are listed in Table 2. An important factor in the investigators' choice of eligibility criteria was the wish to study a prevalent version of BP disorder that is likely to have common treatment requirements and that is likely to respond to the particular treatment approaches focused upon in this study. Study participants are recruited at both inpatient and outpatient treatment settings. We include the latter since an increasing number of BP elders are treated primarily or even exclusively in ambulatory programs.

The sample's minimum age is 60 years, a threshold consistent with that used by other investigators of geriatric mood disorder. The sample has no upper age limit. The research design, therefore, includes both the "young-old" –patients aged less than 70 years -- and the "older-old", as the limited existing evidence does not support an expectation of benefit attenuation based on age *per se* in geriatric mania [11].

The study design focuses on type I BP disorder since patients experiencing this form of the illness present to psychiatric services and are the predominant subject of the literature describing benefits derived from mood stabilizers. We, therefore, exclude patients experiencing type II BP disorder, about which less is known.

The exclusion of patients with history intolerance of study medication requires comment. We recognize that patients tend to over-interpret adverse effects in prior treatment trials. Therefore we require documented history of intolerance at blood concentrations in the range used in this study. This is intended to minimize unnecessary exclusion of patients with history of mild side effects. It also can allow inclusion of patients with history of side effects that occurred at excess concentrations; changes in concentration/dose ratios with age may not be taken into account in community practice.

We exclude patients with mood disorders related to medical conditions or treatments based on the chronology of mood symptom development since other management approaches may be superior for them. For example, steroid-induced mania may respond to elimination of the provocative agent and not require mood stabilizer treatment. Patients diagnosed with medical conditions that pose contraindications to study medications are also excluded. These conditions include renal insufficiency and hepatic disease. However, patients with stable medical illnesses are included since most BP elders do experience chronic medical illnesses. A limited number of treatments for medical disorders are prohibited, including corticosteroids and stimulants and newly (within three months) prescribed agents that may affect mood, for example antiparkinsonian drugs, cholinesterase inhibitors and estrogen receptor blockers. New prescription or increase in dose of diuretics, angiotensin-related antihypertensive agents, and nonsteroidal anti-inflammatory agents are not prohibited but must be reviewed by the principal investigators. These clinical eligibility decisions are intended to enhance the generalizability and clinical relevance of study findings.

A subgroup of schizoaffective disorder patients present with manic episodes. They are ineligible for the protocol since they may require different treatment approaches than mood stabilizer monotherapy.

We also exclude patients with a pre-existing dementia by DSM-IV criteria [64] to minimize clinical complexity and maximize patient participation in baseline and subsequent study assessments. Patients with pre-existing dementia would also be less appropriate for this study given their possibly lower tolerability of mood stabilizers [11,40]. Nevertheless, given that non-demented patients with manic syndromes can present with cognitive dysfunctions [65], we assess cognitive performance before and during treatment so as to permit secondary analyses of potential relationships between these measures and the study's primary outcomes.

The study does include patients who with substance abuse, given the association of such abuse with BP disorder. However, substance dependence constitutes an exclusion criterion since such dependence requires specialized clinical management procedures and it poses additional risks to participants.

As illustrated by other geropsychiatry investigators [66], we track results of the protocol's screening procedures and the reasons why patients fail to meet established criteria. This information will be particularly useful in determining the feasibility of prescribing lithium and valproate to elderly persons experiencing BP disorder, as well as the generalizability of study findings to this population.

A determination of whether selected demographic and clinical variables influence hypothesized relationships will be included in the data analytic plan. These variables will be deemed covariates in hypothesis testing when this is found to be the case. For example, while age at onset of the index episode is not a selection criterion, this information is recorded given considerable variation in age at onset among BP elders [43,44]. Other demographic and clinical variables that may predict or moderate treatment response and are documented in this study include educational attainment, level of perceived social support, and treatment history.

What Variables Should Be Assessed at Baseline?

Signs and symptoms of mood disorder are assessed using standard instruments including the Young Mania Rating Scale [67], the Clinical Global Impression-Bipolar (CGI-BP) [68] and the Hamilton Depression Rating Scale [69]. The application in geriatric patients of these and other methods employed to assess mood are described elsewhere [70].

Behavioral function and quality of life are assessed through the Independent Activities of Daily Living domain of the World Health Organization- Disability Assessment Schedule- II [71] and the Medical Outcomes Study Short-Form General Health Survey (SF-12) [72], respectively. These instruments are widely used to assess these dimensions in geriatric mood disorder studies.

The majority of patients screened for this study will have had at least some prior exposure to mood stabilizers, and this characteristic requires assessment in order to evaluate the potential impact of prior treatment on outcomes. While first episodes do occur among the aged, most such patients will have at least a 10-year history of mood disorder [73]. Earlier treatment is systematically documented using a modified Treatment History Form [74].

Assessment of medical burden and physical and laboratory evaluations can help identify patients with medical conditions that preclude the use of study medications. These assessment procedures are also consistent with the clinical expectation that when patients experience a mood disorder related to medical conditions and/or treatments, specific medical interventions take therapeutic precedence. In addition, the presence of medical and neurological comorbidities may limit response to mood stabilizer treatments [11,75].

Medical history is obtained, and severity of the resulting burden is scored using the Cumulative Illness Rating Scale – Geriatric CIRS-G) [76], which includes a neurological component. Also, the Framingham Stroke Risk Scale [77] is completed to document vascular burden. Physical complaints are documented at baseline using the Udvalg for Kliniske Undersogelser (UKU) rating scale [78]; this interview-based instrument assesses side effects that include those associated with the study medications, e.g. neurological and gastrointestinal complaints. Finally, participants have a physical examination documented that includes a neurological component.

What Is The Treatment Protocol?

When designing the baseline assessment period we chose not to use a placebo “lead in” given the same concerns discussed above with regard to a placebo treatment arm. During this period antidepressants, other mood stabilizers and antipsychotic agents are eliminated, as well as other unnecessary medications.

During the baseline assessment period we provide lorazepam rescue and if necessary risperidone rescue within operationalized criteria when behavioral interventions are ineffective. Lorazepam is adequately tolerated in elders and can contribute to symptom control in BP disorder.

Although other atypical antipsychotic agents were considered as alternatives when the study was being designed, the choice of risperidone reflected expert opinion among geropsychiatrists [56] who considered metabolic and other dimensions of drug tolerability. We decided against ziprasidone because of insufficient research experience with this drug in the elderly.

While serum concentrations in conventional ranges (e.g. lithium: 0.80 to 1.20 mEq/L or valproate 60 to 100–120 mcg/ml), particularly early in treatment, are often well tolerated and promote favorable outcomes [40,79–81] in younger BP patients, elderly patients may not tolerate the same concentrations, particularly for lithium [82]. Optimal ranges for geriatric patients, thus, are not presently established. The concentration ranges chosen for this study are: lithium (range 0.40 to 0.99mEq/L; target 0.80 mEq/L to 0.99 mEq/L) and valproate (range 40 to 99 mcg/ml; target 80 to 99 mcg/ml). These are based on preliminary experience [9,33] suggesting that such concentrations are well tolerated by a significant

number of elderly patients, and that the drugs can be efficacious at the target values. Study findings will indicate whether these levels have clinical utility, and the results can guide future research.

Treatment with study mood stabilizers is guided by a flexible “guided” dose strategy. This is operationalized based on blood levels obtained on days 4, 9, 15, 21, and thereafter routinely at weeks 6 and 9. Side effects [78] and vital signs are assessed weekly; electrocardiogram and clinical laboratory tests are also assessed at baseline and at weeks 3, 6, and 9. Consideration is given to the number of days that a patient has been receiving the medication to which he/she was randomized, the side effects if any being experienced at a given time point, and the blood level at that time point. Study medication is prescribed in units of 150 mg or 250 mg/capsule for lithium carbonate and divaloprex sodium, respectively. For example, in a participant who at day 9 is experiencing no or minimal side effects and have a blinded concentration reported as 0.60–0.79 mEq/L or 60–79 mcg/ml would have the dose maintained. If however the concentration on that visit is 0.40–0.59 mEq/L or 40–59 mcg/ml the dosage would be increased by one capsule; at that concentration there were significant side effects the dose would be reduced or the medication discontinued, depending on the type of adverse effect.

Randomizing eligible subjects to differing concentrations of lithium and valproate was considered when designing the study. We concluded, however, that clinical findings about dosing to the above concentration ranges based on tolerability would be more relevant to the problems of real world practice. Demonstrating that treatment with high lithium concentrations is the most effective intervention would be of low clinical relevance given potential selection bias, i.e. patients tolerating high lithium concentrations likely were the most medically healthy; hence, findings based on their outcomes may not generalize to a broad geriatric population. The present study uses target plasma concentrations but does allow lower ones based on tolerability. Our clinical trial thus will generate information about the efficacy and side effects of study medications when used in a manner resembling that employed in routine practice.

During the randomized treatment phase, lorazepam and risperidone again can be used as rescue medications by operational criteria if behavioral intervention are not effective; lorazepam: maximum 3 mg/day; risperidone: maximum 1 mg/day in 3 days per week. We recognize that prescribing rescue medication might reduce differences in the efficacy and side effect profiles of lithium and valproate. However, the use of rescue medication is based on medical necessity and thus resembles clinical management procedures in routine practice. Nevertheless, we expect that our protocol will minimize unnecessary prescribing of rescue medications and that lorazepam, and particularly risperidone, will be used infrequently. The use of rescue medications and their clinical impact will be analyzed as secondary outcomes.

While the study design satisfies the need for pharmacological parsimony in treating geriatric patients, it offers the opportunity to study adjunctive pharmacotherapy in patients needing it. Thus, antipsychotic drugs often must be combined with mood stabilizers during the acute treatment of both young [54] and elderly BP patients. Studies of young adults suggest that antipsychotic agents can ameliorate symptoms of hyperactivity and psychosis [5,83] when used as co-therapy [27,84–86]. Atypical antipsychotics have a relatively limited neuromotor toxicity [5,87], and typically are tolerated by elderly patients [5,88]. This study includes risperidone augmentation (maximum 4 mg/day) for patients displaying inadequate response (YMRS $\geq$ 16) after three weeks of pharmacotherapy.

For several reasons, we decided on a longer study duration than the 3–4 weeks often used in acute treatment studies in younger manic patients [89]. First, our preliminary findings in

elder BP manic patients indicated that short-term treatment leaves this group with significant residual symptoms [9]. Second, some aged manic patients respond to treatment only after 3–4 weeks. Thus, three weeks is a usual time frame for decision-making about alternative interventions, including adjunctive treatment, in patients displaying unsatisfactory response. Given these considerations, we judged that a nine-week trial was extensive enough to yield clinically meaningful information.

Patients who discontinue the protocol prematurely are offered follow-up during open treatment. Those accepting it are administered clinical and functional assessments within the regular study schedule. The information so gathered will be used for subsequent intent-to-treat analyses and as-treated analyses.

Outcomes and Analyses

In addressing the first aim of the study, which is to compare tolerability of valproate and lithium, we hypothesize differences in side effects between the two drugs, i.e. that patients treated with valproate as compared to those with lithium will experience greater sedation but less tremor and other side effects during the first three weeks of treatment (see Table 1). Furthermore, we expect that a higher proportion of the valproate compared to lithium-treated patients will achieve the target concentration range. The primary side effect measure is the UKU side effect scale [78], thus the study hypothesis regarding the greater sedating properties of valproate compared to lithium will be tested using the changes in scores on the Sleepiness/Sedation item. Particular attention will also be paid to possible differences in ratings on tremor, gastrointestinal complaints (nausea, diarrhea), and weight gain.

The second study aim is to compare the drugs' acute efficacy at the highest tolerated and potentially therapeutic blood levels; the domains. We hypothesize that patients treated with valproate will display greater improvement in manic psychopathology, behavioral function, and quality of life compared to patients treated with lithium (see Table 1). The primary efficacy outcome measure is the Young Mania Rating Scale (YMRS) [67] score assessed over time, while secondary measures include the Instrumental Activities of Daily Living Scale (IADL) domain of the World Health Organization Disability Assessment Scale (WHO-DAS II) (behavioral function) [71] the 12 item Short-Form Health Survey (SF-12) (quality of life) [72].

The analytic classifications for treatment duration include premature termination, dropout (loss to followup), and protocol completion. Categorical affective outcome criteria planned as secondary measures are consistent with the BP disorder literature [89] and include response (i.e. 50% reduction in YMRS), euthymia, or remission. We considered a composite outcome such as the time to protocol termination utilized in the Clinical Antipsychotic Trial of Intervention Effectiveness [90], but we did not include it in the analysis plan because of lesser specificity and concern for statistical power.

The design considerations discussed above can all be accommodated by applying statistical methodology employed in many clinical trials [91–98]. The primary analyses of randomized groups will be based on the observed primary outcome data of all randomized patients, regardless of whether they missed visits, drop out, discontinue from, change, or violate their treatment protocol.

We intend to follow patients who “prematurely terminate” protocol treatment. These patients are assessed during naturalistic treatment to the end of their follow-up period, even if they are not receiving the treatment assigned to them. This will allow us to analyze the outcomes of these patients with the intent-to-treat approach. The distinction between these patients and “dropout” should be emphasized. The study dropout rate, which is the

proportion of patients who have dropped out of follow-up, is projected to be low. This analytic approach is in accordance with the intent-to-treat (ITT) principle, which while possibly rigid is mandated by the FDA and protects against biases that afflict approaches which drop patients for whom treatment is discontinued [99–101]. However, for the “as-treated” comparison of the direct effects of lithium and valproate, we will analyze data collected while the patient is on the drug until the time it is discontinued, but not after another treatment is started.

There are a variety of longitudinal methods (random effects models; generalized estimating equations) that use all follow-up outcome data to test ITT treatment effect at each follow-up visit (e.g., 3 week and 9 week visits) without last-observation-carried-forward. These methods will allow us to estimate ITT effects at different points of treatment to accommodate the different rates of treatment termination across the visits, such as testing ITT effects at 3 weeks, before which treatment termination is low compared to ITT effects at 9 weeks, before which treatment termination is higher. These models make acceptable missing data assumptions, e.g., missing at random; missing completely at random. They are consistent with the clinical focus on assessing fluctuations of symptoms over time in judging the impact of therapeutics, accommodating treatment differences in dropout, and as a result have been employed for many clinical trials [91–98]. Similar longitudinal models under similar assumptions can be used to test for as-treated effects at each visit using all follow-up data while each patient is on the assigned drug to the time it is discontinued, but not after another treatment is started. However, to control for unmeasured confounding, we will use instrumental variables in the longitudinal analyses, as we have for other studies [102].

The random effects models we employ accommodate “missing at random” data, which includes the case where the dropout rates differ between treatments, given that treatment is included in the random effects model. As a sensitivity analysis to the missing at random assumptions of the primary analyses, we will employ the pattern mixture and shared parameter models as different types of “non-missing at random” model, in order to assess the robustness of our random effects models to non-missing at random data.

CONCLUSION

The GERI-BD study design incorporates many competing scientific and practical factors, with the ultimate choices reflecting the Investigators’ judgment about how best to balance diverse scientific requirements and clinical priorities. In doing so, we have built on the available knowledge base to address issues of high relevance to routine clinical practice. Recruitment of a study sample that is likely to have shared treatment needs and is likely to respond to the treatment protocol were additional paramount considerations. We also have considered that design choices should accommodate specific clinical issues intrinsic to the management of BP elders, e.g. medical co-morbidity makes it unlikely that the majority of elders can tolerate combination therapies, and the risk of suicidality and other excess mortality favors testing lithium, which may reduce these risks.

In designing the treatment protocol, minimizing subject burden, assuring patient safety, and maximizing protocol adherence were given high priority. Accordingly, we have limited the length and duration of the baseline and follow-up assessments. Additional interventions are intended to assure patient safety, i.e. a standardized behavioral intervention followed by lorazepam is available when needed. Risperidone is prescribed within operational criteria as a rescue medication only if clinically indicated. Furthermore, adjunctive treatment with risperidone within operational criteria is offered after three weeks to patients meeting criteria for “inadequate response”.

The study design facilitates additional exploratory analyses. These include examination of possible relationships between cognitive performance and clinical outcomes, and between mood stabilizer concentrations and psychiatric and functional benefits. The impact of augmentation treatment in subgroups of patients can also be explored.

Despite GERI-BD's novel design features, the randomized clinical trial also has limitations. For example, it focuses on a narrow component of the spectrum of BP illness presenting in late life. Drug efficacy could not be directly tested absent a placebo treatment arm. With regard to the clinical issues that must await further studies, BP depression certainly has a high priority.

In summary, the GERI-BD randomized clinical trial addresses questions of high clinical priority and maximizes patient participation. Given major limitations in the current evidence base for treating late-life BP I disorder, the investigators expect this initiative to stimulate interest in and contribute to the development of additional short and long-term studies pertinent to the routine care of this prevalent and disabling psychiatric illness. GERI-BD particularly seeks to foster future multidisciplinary research that utilizes the well-characterized patient sample generated for this pharmacological study. Such future research should include translational strategies using neurobiological measures, such as neuroimaging and genetic characterization, to assess correlates of inter-individual differences in treatment outcomes.

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Figure 1.
GERI-BD Treatment

Table 1**Aims and Hypotheses**

In bipolar I manic, mixed or hypomanic patients aged ≥ 60 years:

Tolerability

Aim: To compare the tolerability of lithium and valproate with a focus on sedation, as well as tremor, gastrointestinal complaints, and weight gain.

Hypothesis: Among patients treated with valproate, compared to those treated with lithium, there will be:

- a. greater sedation (UKU) during the first three weeks of treatment; and
- b. a higher proportion at the target concentration range.

Efficacy

Aim To compare the efficacy of lithium and valproate at highest tolerated concentrations.

Hypothesis: Patients treated with valproate, compared to those treated with lithium, will have greater improvement in manic signs and symptoms (YMRS), behavioral function (IADL subscale, WHO-DAS-II) and quality of life (SF-12).

Table 2**Selection Criteria****Inclusion Criteria:**

- 1 Age $\geq$ 60 years.
- 2 BP Disorder-I: manic or mixed manic episode, or hypomania (DSM -IV).
- 3 YMRS $\geq$ 18.
- 4 Availability of an informant is encouraged but not required for study participation.

Exclusion Criteria

1. Chronic psychotic conditions, ie.schizophrenia, schizoaffective disorder, delusional disorder.
2. Contraindication to lithium or valproate. Examples include renal insufficiency by abnormal serum creatinine (≥ 2.0) for LI; either hepatic disease or thrombocytopenia ($< 100,000$) for valproate.
3. Documented history of intolerance of either lithium or valproate in the study target range (lithium < 1.0 mEq/L; valproate < 100 mcg/ml), lorazepam, or risperidone; Intolerance is defined as the need for discontinuing these drugs for known side effects^a.
4. Patients who have previously failed to respond to at least 4 weeks of treatment with lithium (≥ 0.4 mEq/L) or valproate (≥ 40 ug/ml).
5. Active substance dependence or substance-related safety issues or PI concerns.
6. Mood disorder due to a general medical condition or treatment: Patients with mania associated with use of steroids, L-DOPA use, recent stroke, hyperthyroidism, porphyria, HIV infection, and connective tissue diseases are excluded because the proposed interventions may be insufficient for their treatment^{b,c}.
7. Rapid cycling (DSM-IV).
8. Dementia or delirium (DSM-IV); degenerative brain disease
9. Inability to communicate in English (i.e., interview cannot be conducted without an interpreter; subject largely unable to understand questions and cannot respond in English).
10. Clinically significant sensory impairment, i.e., cannot see well enough to read consent or visually-presented material; cannot hear well enough to cooperate with interview.
12. Recent history of cardiovascular, peripheral vascular events or stroke^d.
13. High risk for suicide, e.g., active suicidal ideation or current intent or plan in an ambulatory patient.

^aWhile many patients may complain of prior lithium toxicity, in order to avoid a skewed sample we require documentation of toxicity of lithium (or valproate) at blood levels in the range used in the study, i.e. that are not excessive, in order to meet this criterion.

^bWhile DSM-IV, and the SCID, give latitude to clinicians to decide whether a manic syndrome is the direct result of a medical disorder, in this study we follow the principles outlined in the DSM-IV and we take into account both the temporal relationship between the onset of a general medical condition and the manic syndrome, and the age at first episode of mania. Cases that are not clear are discussed during a weekly conference call held by the site PI's and a consensus decision is reached.

^cOther medical conditions can be associated with a mood disorder due to a general medical condition and would lead to exclusion of the patient (e.g., onset of mania in an older person with multiple sclerosis). The medical conditions listed are emphasized because, even in one made a clinical judgment that they are not the cause of the manic episode, they would require additional treatment that would confound the interpretation of the effect of the study intervention.

^dOverall, our approach is inclusive rather than etiological or exclusive ("restrictive"). Within the context of a manic syndrome, a manic symptom is considered to be part of a manic episode even when it could be explained by another co-morbid disorder. However, this criterion is meant to exclude patients that are too medically unstable to participate in a randomized clinical trial and in whom recovery from a comorbid medical condition would interfere with the interpretation of the positive or adverse effect of the study intervention. In this context, "recent" could cover a range of 3–12 months depending on the severity of the event.