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Assessing bipolar disorder in the older adult: the GERI-BD toolbox

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Abstract

Introduction—The evidence base regarding characteristics of older adults with bipolar disorder (BD) remains limited. The NIH-funded multicenter study Acute Pharmacotherapy of Late-Life Mania (GERI-BD) assessed various clinical domains before and during mood stabilizer treatment in older adults participating in a 9-week, double-blind randomized controlled trial. We describe the rationale for selecting these instruments.

Methods—Domains and instruments were selected on the basis of the study design and the participants. The investigators' experience in clinical trials involving young adults with BD or older adults with major depressive disorder, along with open studies of older adults with BD, contributed to the selection process.

Results—We identified domains and selected instruments that could be used to assess the participants given their diagnostic, treatment history, and medical and mood state characteristics. They were also intended to measure tolerability and efficacy and permit examination of potential moderating and mediating factors.

Conclusions—Decisions regarding the assessment domains to be included in the clinical trial highlight the challenges facing researchers studying drug treatments for older adults with BD, or more generally, mood disorders. We suggest that the domains and instruments selected by GERI-BD investigators constitute a “toolbox” that can be customized for other investigators.

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Conflict of interest

None declared.

Keywords

assessment; bipolar disorder; mania; older adult

Introduction

Bipolar disorder (BD) is highly prevalent among older adults admitted for inpatient psychiatric treatment, accounting for at least 8–10% of hospital admissions in this age group (Depp and Jeste, 2004). Although the number of older adults with BD may be increasing as the population ages (Jeste *et al.*, 1999; Sajatovic *et al.*, 2015b), the evidence base guiding treatment remains limited. Pharmacotherapy guidelines for younger patients with BD cannot be extrapolated directly to older adults (Snowdon, 2000; Young *et al.*, 2004). Although acute BD affective states may present with similar profiles and severity in older and young patient (Al Jurdi, *et al.*, 2012), guideline recommendations for the treatment of older adults with BD need to be further developed to meet the growing need of older adults and clinical heterogeneity in BD across the life span (Dols *et al.*, 2016).

The GERI-BD study sought to characterize responses to mood stabilizer treatments in older adults experiencing mania (Young *et al.*, 2010). As the first study of its kind to focus on older adults with BD, GERI-BD recruited patients with BD I aged 60 years and older with manic, mixed, or hypomanic episodes. The subjects were randomly assigned to treatment with either lithium or divalproex. The study was designed to test the following: (1) differences in side effects of lithium and divalproex and (2) their acute efficacy at the highest tolerated, potentially therapeutic blood levels.

Because most treatment research in BD, including pharmacological studies, has been conducted in young adult patients, we selected assessment domains and instruments for this study by reviewing the literature in mixed-age patients with BD and by considering investigator experience with pharmacotherapy in studies of late-life mood disorders. This paper describes the investigators' selection of domains and instruments.

We selected domains and assessments to evaluate the primary clinical outcomes of tolerability and efficacy. Additionally, we chose measures that could foster generation of new hypotheses by examining potential moderators and mediators of treatment outcomes (Kraemer *et al.*, 2002; Papakostas and Fava, 2008).

Given these objectives, this paper presents a “toolbox” of instruments for assessing participants in a geriatric BD treatment study. We also discuss challenges in the application of these instruments in this population.

Methods

Sample selection

The GERI-BD study focused on BD type I, the predominant psychopathology benefiting from mood stabilizers. GERI-BD, therefore, recruited clinically eligible inpatients and outpatients aged ≥ 60 years with BD I currently meeting the Diagnostic and Statistical

Manual of Mental Disorder, Fourth Edition (DSM IV) criteria for manic, hypomanic, or mixed episode. There was no upper age limit and no exclusion criteria regarding sex, race, or ethnicity. Patients who had a diagnosis of dementia were excluded.

Assessment selection

Study measures were selected on the basis of the experience of the principal investigators and their research teams. We considered prior experience with the measures in assessing older adults and patients with BD as well as their pertinence to the study's domains; the domains included diagnosis, clinical and laboratory tests, treatment history, medical comorbidity, side effects, mood state, behavioral function and quality of life, social support, cognition, and mood stabilizer concentration.

Although this study's aims guided specific instrument selection, the assessment package can be utilized in other studies of older adults with BD. We also considered the psychometric properties of the measures.

At baseline, the assessed domains pertained to sample selection requirements, patient safety, and initial information related to drug tolerability and efficacy. Repeated assessments generated data regarding the domains of mood state, side effects, and other variables (Table 1).

Outcomes—The primary hypotheses in GERI-BD pertained to differences in tolerability and efficacy of the study drugs lithium and divalproex. Several assessment domains, therefore, were central to examining outcomes.

Potential predictors, moderators, and mediators—We selected additional assessments with potential utility as predictors, moderators, or mediators by review of studies of mixed-age patients with BD and studies of late-life mood disorders. Potential moderators, assessed at baseline, include social support (Beyer *et al.*, 2014), cognition (Gildengers *et al.*, 2008), medical comorbidity (Sajatovic *et al.*, 2015b), functioning (Michalak *et al.*, 2005; Sanchez-Moreno *et al.*, 2009), and treatment history (Sackeim, 2001b); these may affect treatment outcomes in mixed-age patients with BD and depressed older adults. Potential mediators, assessed post-baseline, including mood states and mood stabilizer concentrations (Dols *et al.*, 2016), are suggested by mix-aged BD and older adult depression research. Careful distinction is needed between potential moderators and mediators of treatment effect because the latter needs to be measured post-baseline. Selecting a broader list of potential mediators and moderators, so that moderating and mediating effects can be determined in a data-driven way, could result in increased type I error (or false positives) and reduce the statistical power to detect such associations.

Meeting challenges to assessment of older adults with bipolar disorder—Bipolar manic patients typically display signs and symptoms that challenge the assessment process. Restlessness and distractibility reduce attention to tasks. Excessive rate, volume, amount, and abnormal form of speech can interfere with communication. Elated mood, irritability, delusional ideas, and poor insight each can complicate subject–staff interaction

and preclude subject motivation for needed cooperation; similar challenges are true when depressive features are present in manic patients.

Age-related factors also create potential challenges to instrument administration and cooperation with the protocol. The physical challenge of sitting through extended interviews can fatigue frail older adults. Cognitive limitations can interfere with the subject's attending to the interview. Participants followed on an outpatient basis, and inadequate social support can obstruct adherence to protocol.

Standardization of assessments—Shared scoring conventions and assessment of inter-rater reliability in clinical trials are essential, particularly in multisite studies. Training and monitoring procedures were established, therefore, to evaluate the administration of selected measures and to ensure continued inter-rater reliability and consistency. Written training materials were employed to guide and monitor the administration of assessment instruments.

Results

Within each domain, we selected instruments from available options. These choices followed the scientific and protocol considerations previously noted, and they are specified in what follows.

Diagnosis and demographics

Diagnosis and demographics were confirmed through administration of the Structured Clinical Interview for DSM-IV (SCID-IV; First *et al.*, 1995), a semi-structured clinical instrument. The selection criteria generated a sample of participants who were half inpatient at recruitment, averaged 68 years of age, had an equal proportion of men and women, and had representation of minority groups (Young and GERI-BD Study Group, 2015). They had an average of 13 years of education.

Medical status

The baseline laboratory and physical assessments were performed to evaluate medical status. Blood tests included chemistries, complete blood count, thyroid stimulating hormone, vitamin B12 and folate measures, electrocardiogram, and physical examination. We obtained sitting and standing heart rate, blood pressure, and body weight at baseline, at weeks 3 and 6, and at study termination.

Medical burden

Comorbid medical conditions are prevalent in older adults with BD (Depp and Jeste, 2004; McIntyre *et al.*, 2006; Gildengers *et al.*, 2008; Sajatovic *et al.*, 2015b). Older adults with BD experience higher rates of chronic medical diseases (e.g., cardiovascular disease, diabetes mellitus, and chronic obstructive pulmonary disease) compared with mentally healthy persons of similar age, as well as higher levels of obesity, endocrine/metabolic, and respiratory disease compared with older adults with major depressive disorder (MDD; Gildengers *et al.*, 2008; Sajatovic *et al.*, 2015b). Some comorbid medical disorders may be viewed as a consequence of mood disorder, while others may contribute to the pathogenesis

(Leboyer *et al.*, 2012). Furthermore, treatments for medical disorders may contribute to mood disorder symptoms, and some mood disorder treatments, such as antipsychotic medications, may contribute to or exacerbate medical conditions (Leboyer and Kupfer, 2010). Thus, medical disorders and their related treatments may interact with the mood disorder treatments evaluated in GERI-BD.

In this study, overall medical burden was evaluated using the Cumulative Illness Rating Scale-Geriatric (Miller *et al.*, 1992). The Cumulative Illness Rating Scale-Geriatric assesses 14 systems; morbidity in each system is rated on a 0–4 scale. We also administered the Framingham Stroke Risk Profile (Wolf *et al.*, 1991). The Framingham Stroke Risk Profile consists of eight items including demographic measures, medical diagnoses, and health behaviors.

Treatment history

A systematic history of pharmacological treatments is important in several ways. First, it established whether study medications had been used in the current or prior episodes. Second, information about past drug dose, duration, blood concentrations when relevant, and response could be used to judge current drug tolerability and adequacy. Third, number of prior adequate drug trials may relate to varied responses to further treatment.

We acknowledge limitations to feasible and reliable methods for systematically collecting BD treatment history. While instruments are available to determine past use of antidepressants for MDD, for example, the Antidepressant Treatment History Form (Sackeim, 2001a; Dew *et al.*, 2005), they are inadequate when used for BD. We, therefore, modified the Antidepressant Treatment History Form to develop and use a Bipolar Treatment History Form. The resulting categories of medication treatment were as follows: mood stabilizers, antipsychotics, benzodiazepines, and antidepressants. Pharmacotherapy was recorded, including dose, duration, blood levels, and adherence; reasons for discontinuation were indicated. The chronology of combined treatments was documented. We used multiple specified sources of information including patient report, medical record, and family and pharmacy records.

Side effects

The Udvalg for Kliniske Undersøgelser (UKU; Lingjaerde *et al.*, 1987) constitutes the primary measure of drug tolerability, as it has been widely used in geriatric depression studies (Drayer *et al.*, 2005) including treatment studies (Allard *et al.*, 2004). This scale has 46 items, which rate multiple domains such as psychic, neurological, and autonomic functioning. Items evaluating gait, alopecia, and edema were added for this study. Each item is scored 0–3, according to defined descriptors.

Psychopathology

Meeting diagnostic criteria for manic or mixed-manic state was an inclusion criterion for the study. Manic states can range in severity from mild (hypomanic) to severe and can include psychotic symptoms, that is, delusions and hallucinations. Mixed-manic states include depressive symptoms.

Mania

The Young Mania Rating Scale (YMRS) (Young *et al.*, 1978) has been commonly used both as a clinical status and primary outcome measure in studies of BD. It rates each of 11 mania-related behaviors on a 5-point scale. A minimum total baseline score of 18 was required.

There has been conflicting clinical impression and limited evidence regarding potential differences in severity levels and symptom profile in older mania BD patients compared with younger patients (Slater and Roth, 1977; Broadhead and Jacoby, 1990; Young *et al.*, 2007; Oostervink *et al.*, 2009; Al Jurdi *et al.*, 2012).

Depression

The Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979) has been widely used in studies of BD (Sajatovic *et al.*, 2015a) and of MDD in young and older adults (Parker *et al.*, 2003; Heo *et al.*, 2007). It consists of 10 items scored 0–8 assessing signs and symptoms of depression. The Montgomery–Asberg Depression Rating does not assess depression’s somatic symptoms but rather focuses on sadness, tension, lassitude, pessimistic thoughts, and suicidal thoughts.

The 24-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) was also administered in the GERI-BD clinical trial given its wide usage to assess depression severity in treatment studies. We used the GRID HAM-D-17 as a component of scoring the HAMD-24 (Kalali *et al.*, 2002) because it operationalizes the intensity and frequency of symptoms and provides an overall severity score for individual items.

The Clinical Global Impression-Bipolar Disorder (Spearing *et al.*, 1997) is a widely administered clinician-rated scale that assesses clinical status in three domains: mania, depression, and overall mood presentation. Domain rating includes cross-sectional severity and change from baseline.

Cognitive function

Bipolar disorder has been associated with impaired cognitive function. This impairment can be associated with illness episodes and may be present even when patients are euthymic (Weisenbach *et al.*, 2014). In early onset BD, patterns of cognitive impairment appear in early life and are present in first-degree non-affective relatives (Arts *et al.*, 2008). Further cognitive dysfunction in BD may also be acquired during the course of the illness, perhaps as a consequence of BD or other factors (e.g., iatrogenic effects of medications or substance use). In older adults with BD, cognitive status may be confounded by the effects of other age-related factors. BD patients may also develop dementias more rapidly than other individuals (Kessing and Nilsson, 2003; Kessing *et al.*, 2004). Not surprisingly, cognitive impairments may have clinical consequences such as functional disabilities (Gildengers *et al.*, 2008; Gildengers *et al.*, 2013; Dols *et al.*, 2014).

The GERI-BD trial assessed global cognitive performance with both the Mini-Mental State Examination (MMSE) and the Dementia Rating Scale (Mattis, 1989). The MMSE (Folstein *et al.*, 1975) has been extensively utilized in research protocols (Gildengers *et al.*, 2004). A

limitation of the MMSE for research purposes, however, is its potentially low sensitivity (Rajji *et al.*, 2009).

The Dementia Rating Scale (Mattis, 1989) provides a broader and more sensitive measure of cognitive function by assessing five distinct domains: attention, initiation-perseveration, construction, conceptualization, and memory. It too has been widely used in geriatric mood disorder studies (Rajji *et al.*, 2009).

Behavior functioning

The adverse impact of BD on everyday life activities is well recognized (Michalak *et al.*, 2005; Sanchez-Moreno *et al.*, 2009). The World Health Organization (World Health Organization, 2001) has long identified BD as one of the 10 leading causes of disability worldwide. Patients with BD experience difficulties in their functioning, including work impairment and interpersonal disturbances (Sanchez-Moreno *et al.*, 2009).

We assessed behavioral functioning with the 12-item World Health Organization Disability Assessment Schedule II (WHODAS II; Epping-Jordan and Ustun, 2000). It is used across all diseases and ages (Banerjee *et al.*, 2008; Yuen *et al.*, 2015), is cross-culturally applicable, and assesses disability level and overall functioning. The WHODAS II addresses functioning in six domains: (1) understanding and communicating; (2) getting around; (3) self-care; (4) getting along with others; (5) household and work activities; and (6) participation in society. The WHODAS II total score summarizes overall functioning. We supplemented the WHODAS II self-report scoring format with a version incorporating all available information, an approach similarly used by others (Schlote *et al.*, 2008).

Health-related quality of life

Although impaired health-related quality of life has been linked to BD in both young adults and the older adults (Depp *et al.*, 2006; Weisenbach *et al.*, 2014), research in this area remains relatively limited (Michalak *et al.*, 2013). Additionally, findings regarding the impact of manic states on quality of life are mixed (Vojta *et al.*, 2001; Zhang *et al.*, 2006; Gazalle *et al.*, 2007). Challenges to such research include the lack of disease-specific measures of quality of life and reliability concerns (Michalak *et al.*, 2005).

We assessed health-related quality of life using the Medical Outcomes Survey Short Form (SF-12; Stewart *et al.*, 1988). It is a widely used general indicator of health status, and it evaluates functional health, well-being, and general health perception. The SF-12 is an abbreviated version of the SF-36, frequently used in BD studies, and has been validated in this population (Leidy *et al.*, 1998). The SF-12 assesses eight health-related domains: physical functioning, role limitations due to physical health, bodily pain, social functioning, general mental health, role limitations due to emotional problems, vitality, energy or fatigue, and general health perception.

Social support

Social support influences the course of BD illness and its management (Beyer *et al.*, 2014). To assess the size and utilization of a person's social network, we administered the

abbreviated and widely used version of the Duke Social Support Index (Koenig *et al.*, 1993). It assesses four dimensions: network size, social interaction frequency, instrumental support, and subjective support (George *et al.*, 1989). The Duke Social Support Index has been widely used to evaluate social support among a wide range of ages and psychopathology.

Other factors to be considered by researchers when assembling a tool kit for assessing late-life BD beyond the assessment instruments per se include the following:

Rater training

Reliability is essential to hypothesis testing, a psychometric property especially important in multicenter studies (Mulsant *et al.*, 2002). GERI-BD research staff were trained and certified in the administration of protocol instruments prior to their interactions with study subjects. A manual of operations and a study training manual were developed to facilitate standardized organization and implementation of the protocol across all research sites. Additionally, the weekly teleconferences led by the coordinating center regularly reviewed study practices and administration of these instruments so as to maintain needed adherence and standardization.

To certify study site interviewers in the administration of the SCID-IV, YMRS, GRID HAM-D, and the UKU, these staff initially reviewed written materials provided by the coordinating center. They then viewed videotaped vignettes of interviews illustrating a range of symptom severity. Raters' scores were compared with standard scores established by experienced clinicians at the coordinating center. Raters achieved good agreement with the standard ratings (Spearman $r = 0.85\text{--}0.98$). Finally, raters videotaped themselves administering the YMRS and UKU to patients for review and certification. Raters completed training on the GRID HAM-D using a web-based training program. We have reported our experience using the GRID HAM D (Rosen *et al.*, 2008).

To achieve certification in administration of the SCID-IV, raters observed 11 h of the instrument's DVD training program (Ventura *et al.*, 1998). Raters then role played the administration of the SCID and videotaped themselves doing so. These materials subsequently were reviewed by coordinating center personnel.

With regard to the cognitive measures, co-investigators at the University of Pennsylvania's Brain Behavior Laboratory trained raters to administer these instruments. These co-investigators developed written materials to facilitate this process. Trainees videotaped their administration of the cognitive measures, and these videos were reviewed.

To detect rater drift and evaluate accuracy over time, study site interviewers annually rated videotaped vignettes for comparison with expert standard ratings of the UKU and YMRS. The interviewers were also periodically videotaped administering and scoring the YMRS, UKU, SCID-IV, GRID HAM-D, and cognitive measures.

Facilitating patient assessments

We used multiple strategies to minimize constraints on protocol participation related to illness effects and age-related factors. We minimized subject burden to the degree possible

by administering limited number of instruments. We scheduled sessions of brief duration and offered flexibility in the timing of protocol assessments. We prioritized the administration of instruments incorporating observer judgments in addition to patient self-reports. We communicated with family, other physicians, and caregivers so as to encourage their support for the patient's continued participation (Young *et al.*, 2010).

Discussion

Our experience with designing the GERI-BD study highlights several critical points. First, multiple challenges arise in selecting instruments pertinent to assessing our domains of interest when treating late-life BD given the role of aging, cognition, function, and physical health in this population. Despite the limited literature on geriatric BD, we nevertheless successfully integrated clinical experience, studies of geriatric depression, and the findings with younger adults with mania to reach needed assessment decisions. Second, we addressed the possible confounds of medical illness and cognitive change by evaluating all subjects for variables that potentially affect accurate measurement of mood state, excluding subjects experiencing severe medical illness or dementia. Third, in designing the assessment protocol, priority was given to minimizing subject burden, assuring patient safety and maximizing protocol adherence (Young *et al.*, 2010).

We suggest that the selected assessments are concise and adapted to specific study goals such as evaluating outcomes and generating new hypotheses. Potential moderators should be selected on the premise that the magnitude of their presence at baseline influences the relative likelihood of a particular outcome (Papakostas and Fava, 2008). Pertinent moderators when studying BD in older adults may include mood state, illness course, medical comorbidity and treatment history, social support, medical burden, psychopathology, cognition, everyday function and quality of life, and physiological measures.

Treatment mediators represent possible mechanisms through which the drug interventions achieve or are impeded from achieving their intended outcome (Kraemer *et al.*, 2002). Mediating variables should be selected, therefore, to measure changes that occur during treatment and that are correlated with treatment outcome (Papakostas and Fava, 2008). Such mediators should be assessed throughout the course of the intervention and can include measures that also serve as moderators, for example, of psychopathology.

The selection of assessment domains and instruments in clinical trials in geriatric BD is determined both by inherent characteristics of this population and the investigator's scientific objectives. Meeting special challenges to the construction of a relevant tool kit is informed by the investigator's experience with other aged mood disorder populations.

We hope that this initiative will help to stimulate interest in, and contribute to the development of, additional short-term and long-term treatment studies in older adults with BD and related conditions. An example of this is seen in a related report in aged BD-depressed patients (Sajatovic *et al.*, 2011). Consequently, the assessment issues emphasized

in this report and the “toolbox” of instruments reviewed here are directed at fellow investigators who design and conduct related treatment studies.

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Key points

- Our experience with designing the GERI-BD randomized controlled trial in older adults with BD emphasizes several critical points with regard to selecting and administering pertinent assessment instruments.
- Multiple challenges arise in selecting instruments pertinent to assessing our domains of interest when treating late-life BD given the role of aging, cognition, function, and physical health in this population.
- We addressed the possible confounds of medical illness and cognitive change by evaluating all subjects for variables that potentially affect accurate measurement of mood state.
- We hope that this initiative's design and findings will stimulate interest in, and contribute to the development of, additional short-term and long-term treatment studies in older adults with BD and related conditions.

Table 1

Domains and instruments in GERI-BD toolbox

Domains	Instruments/Measures	Schedule	Applications
Diagnosis	SCID	B	Mod
Clinical and laboratory tests	Vitals signs and weight	B, R	Mod
	Clinical blood tests, ECG; physical examination	B, R	Mod
Treatment history	BTHF	B	Mod
Medical comorbidity	CVD	B	Mod
	CIRS-G	B	Mod
Side effects	UKU	B, R	O
Mood state	YMRS	B, R	Mod/Med/O
	CGI-BP	B, R	Mod/Med/O
	HDRS	B, R	Mod/Med/O
	MADRS	B, R	Mod/Med/O
Behavioral function/QOL	WHO-DAS II	B, R	Mod
	SF-20	B, R	Mod
Social support	SSI	B	Mod
Cognition	MMSE	B, R	Mod
	DRS	B, R	Mod
Mood stabilizer concentrations	LI/valproate levels	R	Med

B, baseline; BTHF, Bipolar Treatment History Form; CGI-BD, Clinical Global Impression-Bipolar Disorder; CIRS-G, Cumulative Illness Rating Scale-Geriatric; DRS, Dementia Rating Scale; CVD, cardiovascular disease; ECG, electrocardiogram; HDRS, Hamilton Depression Rating Scale; LI, lithium; MADRS, Montgomery–Asberg Depression Rating Scale; Med, possible mediator; MMSE, Mini-Mental State Examination; Mod, possible moderator; O, Outcome; QOL, quality of life; R, repeat; SCID, Structured Clinical Interview for DSM-IV; SSI, social support inventory; UKU, Udvalg for Kliniske Undersøgelser; YMRS, Young Mania Rating Scale.