

Evidence-Based Pharmacological Treatment of Geriatric Bipolar Disorder

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Elderly individuals who have bipolar (BP) disorder present a particular challenge to clinicians, health care services, and caregivers. They are a complex and heterogeneous group of patients who frequently have comorbidities and poor outcomes, including a high mortality rate.

BP elders represent 5% to 19% of patients presenting for acute treatment at geriatric psychiatry services [1,2]. They use health services heavily [3,4]. The psychopathology associated with their illness episodes (ie, mania, mixed mania, hypomania, and depression) can be severe; their signs and symptoms resemble those in younger patients [5]. Elderly BP patients who are treated for manic and mixed episodes often have incomplete response [6,7], further episodes [8–10], and high mortality rate [8,9].

Beyond recognition and careful diagnostic assessment, pharmacotherapy is the cornerstone of their management. This article addresses the current evidence regarding drug treatment of BP disorder in old age. In particular:

- What are the side effects and toxicity of relevant psychotropic agents?
- What is the evidence for their efficacy for acute and continuation/maintenance treatment?
- What age-associated factors may modify these risks and benefits?

The therapeutic armamentarium in BP patients also includes education, other psychosocial interventions, and electroconvulsive therapy. Although these are pertinent to both older and younger BP patients, they will be mentioned only briefly here, because the age-specific literature related to elderly BP individuals is sparse.

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The following discussion of the evidence base emphasizes its limitations, as well as its implications for clinical management and public health. This review also suggests strategies and priorities for research.

Methods

Data sources

Articles written in English on the pharmacologic treatment of BP disorder in the elderly between 1966 and May 2005 were identified through a search of the MEDLINE database. Material used in a recent review [11] was updated. Additional data sources included reference lists of the identified articles, other reviews, the author's files, and textbook articles when appropriate.

Selection criteria

"Elderly" was defined as being 60 years of age or older. The keywords "aged" and "geriatric" were combined with words indicating pharmacologic treatments (ie, "pharmacotherapy"), classes of medications (eg, lithium, anti-convulsants, antidepressants), and names of selected individual medications (eg, valproate, divalproex, carbamazepine) with or without names of diagnostic terms (bipolar disorder, mania, hypomania, bipolar depression, depression).

A few articles on "older adults" in which the lower age limits were 50 to 55 years were included for heuristic value and possible extrapolation of their results to the geriatric population. Seminal articles on pharmacotherapy of BP disorder in mixed-age patients were included for evaluation of age effects. All identified original articles were reviewed and reported. Conclusions regarding therapeutics were drawn primarily from studies of more than 10 patients. Case reports and smaller case series were described regarding benefit as appropriate for their heuristic value and when reviewing toxicity issues.

Results

First, the side effects and tolerability in elders of psychotropic agents used in the treatment of BP disorder, and potential modifiers of these effects, are discussed in this article. Thereafter, their efficacy, and potential modifiers of efficacy, are considered. The rationale for this sequence is that tolerability informs drug selection and influences the dose and duration of therapeutic trials. Side effects also determine, in part, adherence to treatment. Side effects and tolerability therefore are important determinants of benefit in these patients.

Overall, the main limitation of the literature is the lack of randomized controlled trials in elderly individuals. The existing evidence is derived mainly from small case series or case reports.

Side effects and toxicity

In the elderly, side effects and toxicity of psychotropics are of particular concern. The medical consequences of specific side effects (eg, falls [12]) may be more severe than the consequences in younger patients. Side effects can also interfere with the quality of remission [13]. The risks of side effects and toxicity of psychotropics may be increased in elders as a result of age-related pharmacokinetic changes. Pharmacodynamic changes that may contribute to increased risks will be outlined separately.

Lithium salts

LI has been widely prescribed in the elderly [14,15]. Among community-based BP patients from Western Pennsylvania in the late 1990s, close to two thirds of those over the age of 65 were treated with LI, and only 31% were receiving anticonvulsants; the proportion of older patients treated with LI was significantly higher than the proportion of younger patients [14].

Table 1 lists 12 studies that include assessment of LI side effects. These reports dealt with more than 10 cases each.

Cognitive and neuromotor impairments. Cognitive and neuromotor impairments range from mild tremor and other “nuisance” effects to life-threatening conditions such as delirium. Neurocognitive side effects were assessed in 9 of these studies [7,16–23]. Although some investigators have suggested that LI can dull cognitive performance [24,25], this has not been examined in the elderly. In aged patients, recovery from LI-induced delirium can be prolonged [26]. However, in a recent study, the incidence of hospitalization for delirium in elderly patients initiated on LI was equivalent to those initiated on valproate [20], and was less than that for benztropine treatment.

Cardiovascular effects. Sick sinus syndrome [27] can occur at moderate LI concentrations in older patients with compromised sinus node function. In a cross-sectional study [28], 58% of elderly BP patients receiving maintenance LI treatment had electrocardiographic abnormalities; interpretation of these findings is limited by the study design.

Other side effects. LI antagonizes thyroid function. In one cross-sectional study, 32% of aged patients treated with LI were prescribed thyroxine replacement or had elevated thyroid stimulating hormone levels [29]. In another study, almost 6% of elderly patients recently initiated on LI treatment received new thyroxine prescriptions, compared with half that rate among elders initiated on VAL [30].

In one report [21], polyuria and polydipsia occurred during LI treatment in approximately 40% of elderly patient visits. Polyuria and polydipsia, weight gain, and edema were categorized as mild side effects in another study, and these occurred at a rate of 46% in patients aged 50 years or older

Table 1
Side effects/toxicity of pharmacotherapy of older adult and elderly BP patients

| Agent | Reference | Study design | n | Mean age in years (range) | Dx | Mean dose in mg/d (range) | Mean concentration in mEq/L (range) | Neurocognitive toxicity | Other toxicity | Comment |
|-------|----------------------|--------------|----------|---------------------------|---------------------------------|---------------------------|-------------------------------------|---------------------------------|---|---|
| LI | Hewick et al [22] | R | 23 23 | NA (50–59) (60–84) | BP, 82%; UP, 9%; other-9% | NA (NA) | NA (NA) | Fine tremor included as “minor” | 21/46 (46%) had minor side effects versus 15/36 (42%) of younger patients aged 21–49 yr | Lower concentrations in patients aged ≥60 yr |
| LI | Roose et al [28] | P | 31 | 67 (60–79) | Primary affective disorder | NA (NA) | NA (0.60–0.70) | NA | 4 episodes of toxicity in 18 mo (versus 2/164 younger patients over 18 mo (chi square = 8.32; $P < .01$); 5 had arrhythmias; 14 had conduction abnormality on ECG; hypothyroidism in 1 | Concentration in younger group not specified |
| LI | Himmelhoch et al [7] | R | 81 | 63 (55–) | BP I 74; BP II 7 | NA (NA) | NA (NA) | 13 (16%) | NA | Predicted by dementiform features and/or extrapyramidal syndrome; not age |

| | | | | | | | | | | |
|----|--------------------------|---|----|---------------|-----------------|---------|-------------------|---|------------------------|--|
| LI | Smith and Helms [17] | R | 15 | 70 (65–80) | BP 8; UP 7 | NA (NA) | NA (NA) | 7 (47%) had moderate to severe side effects – primarily neurotoxicity | NA | LI concentration 1.2–1.5 mEq/L in 5 of those with moderate to severe side effects; in younger group (n = 41) aged 19–61 yr, 12% had moderate to severe side effects (chi square = 5.84; $P < .02$) |
| LI | Murray et al [21] | P | 37 | NA (60–78) | BP 25; UP 12 | P (NA) | NA (NA) | Tremor about 40% of visits in BP aged 70–78 (graph) | Graphical presentation | Cross-sectional assessment; no difference in LI concentration with age in BP patients; tremor about 20% of visits in patients aged 20–29 yr, 30% in those aged 30–69 yr; polyuria and polydipsia not greater with age. |
| LI | Schaffer and Garvey [19] | P | 14 | 67 (65–77) | BP, manic | NA (NA) | NA (0.50-1.10) | 3 (21%) | NA | LI discontinued in 2 with toxicity at 0.5–0.8 mEq/L; 1 other when level increased to 1.1 mEq/L |

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Table 1 (continued)

| Agent | Reference | Study design | n | Mean age in years (range) | Dx | Mean dose in mg/d (range) | Mean concentration in mEq/L (range) | Neurocognitive toxicity | Other toxicity | Comment |
|-------|----------------------|--------------|-----|---------------------------|-----------------------|---------------------------|-------------------------------------|-----------------------------------|---|--|
| LI | Chacko et al [16] | P | 19 | 68 (59–84) | BP | NA (NA) | 0.70 (0.30–1.10) | 11 (58%) tremor, 8 (42%) sedation | 14 (74%) polydipsia, 11 (58%) polyuria; 10 (53%) dry mouth; 6 (32%) weight gain | Only 3 monotherapy; mean duration LI = 3.9 yr; side effects related to number of other psychotropics (r = 0.60, P < .01) |
| LI | Stone 1989 [18] | R | 43 | NA (65–) | BP, manic | NA (NA) | NA (NA) | 11 (26%) | One developed goiter | LI levels in 9 toxic patients were 1.4–2.6 mEq/L; LI discontinued in 2 others with tremor vomiting and ataxia |
| LI | Head and Dening [29] | R | 148 | NA (65–85 +) | BP 83; UP 57; other 7 | 482 (100–1400) | 0.64 (0.00–1.50) | NA | 47 (32%) were on thyroid replacement or had elevated TSH | Cross sectional |
| VAL | Puryear et al [141] | R | 13 | 70 (63–77) | BP, manic | 1000 (100–1750) | 57 (34–82) | 1 (8%) delirium; 3 (23%) tremor | 2 (15%) weight gain; 5 (38%) dry mouth | VAL discontinued in pt with delirium, also was receiving phenytoin |

| | | | | | | | | | | |
|--------------|--|---|-------|---------------|------------------------|---------------------|-------------|--|---|---|
| VAL | Kando [142] | R | 35 | 71 (63–85) | BP, manic; other | 743 (250– 2000) | 53 (11–102) | 2 (6%) sedation; 1 (3%) c/o confusion | 2 (6%) nausea; 1 transient leukopenia | VAL was discontinued in 1 pt with nausea |
| VAL | Noaguil et al [140] | R | 21 | 71 (60–82) | BP, manic | 1405 (500– 3000) | 72 (31–106) | 2 (10%) with sedation | NA | Responded to dose reduction |
| VAL | Niedermier and Nasrallah [91] | R | 39 | 67 (60–86) | BP | 1029 (500– 2250) | 72 (36–111) | 2 (5%) sedation; 1 (3%) slurred speech, 1 confusion; 1 ataxia | 1 (3%) nausea; 1 diarrhea; 1 rash; | None required discontinuation; improved with lowering of dose |
| LI or VAL | Shulman et al [20] | R; population- based cohort study | 4,111 | 73.4 (>65) | NA | NA | NA | NA | Over 18 mo new prescription for thyroxine: 5.65/100 person years in new LI treatment group versus 2.70 in new VAL group | Near 6% treatment in LI group |
| LI or VAL | Shulman et al [31] | R; as above | 5,340 | 74.7 (>65) | Mood disorder | NA | NA | Over 8 years, hospitalization for delirium at equivalent rates in patients newly treated with LI (2.8 per 100 person years) versus; VAL (4.1 per 100 person years) | NA | Benztropine comparator group had higher rate of delirium than LI group |

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Table 1 (continued)

| Agent | Reference | Study design | n | Mean age in years (range) | Dx | Mean dose in mg/d (range) | Mean concentration in mEq/L (range) | Neurocognitive toxicity | Other toxicity | Comment |
|-----------|----------------------|---|---------------|---------------------------|------|---|-------------------------------------|--|---|---|
| LI or LTG | Sajatovic et al [23] | P, secondary analysis: following open label phase; randomized, double blind, placebo controlled | 98 randomized | 61 (55–82) | BP I | LI (n = 34): modal 750 mg/d; LTG (n = 33): modal 240 mg/d (100–400 mg/d); PBO, n = 31 | LI (0.8–1.1 mEq/L) | LI adverse events included dypraxia, tremor, amnesia | No cases of serious rash in randomized phase; back pain and headache most common adverse events associated with LTG. Other LI adverse events included xerostomia, headache, infection, dizziness, nausea, fatigue | Adverse events leading to premature withdrawal: LI (29%); LTG (18%); PBO (13%). |

Abbreviations: BP, bipolar; ECG, electrocardiogram; LI, lithium; LTG, lamotrigine; NA, not available; P, prospective; PBO, placebo; R, retrospective; VAL, valproate; UP, unipolar.

[22]. In another report [17], mild side effects occurred in 27% of elderly patients. In a randomized control trial of stabilized patients, adverse events lead to premature discontinuation in 29% of LI-treated patients compared with 13% for placebo [38].

Dose/concentration and effects. Although case reports in elderly subjects indicate that LI toxicity can occur at moderate blood levels (eg, 0.5–0.8 mEq/L [19]), the relationship of LI concentrations to side effects in the elderly has remained poorly defined. In mixed-age patients, LI concentrations are positively related to side effects, and these increase greatly above 1.0 to 1.5 mEq/L.

Pharmacokinetic distortions in elderly BP patients that lead to increased LI dose/concentration ratios put them at increased risk for side effects. Renal clearance of LI decreases with age, the elimination half-life of LI in the elderly is twice as long as in younger patients [31], and amount of time after which stable concentrations are achieved at a given dose is prolonged. Renal disease and cardiac insufficiency can further reduce LI clearance, and increase in fat/lean body mass ratio may also contribute to higher concentration/dose ratios [31,32]. Finally, medications and special diets for medical disorders, such as thiazide diuretics, nonsteroidal anti-inflammatory agents, angiotension-converting enzyme inhibitors, and sodium restriction, can increase LI dose/concentration ratios, while theophylline can decrease these ratios [33,34].

These pharmacokinetic issues were underscored by Strayhorn and Nash [35]; toxicity in the six elderly subjects in their series occurred in the context of high LI levels (1.58–2.45 mEq/L). In aged patients, brain/peripheral LI concentration ratio can be increased [36], and this may also increase vulnerability to central nervous system toxicity. The relationship of erythrocyte LI concentrations to side effects has not been systematically assessed in elders [37].

Anticonvulsants

Clinicians increasingly prescribe valproate (VAL) for elderly individuals who have BP disorder. Divalproex sodium is more commonly prescribed than valproic acid. In the province of Ontario, VAL has surpassed LI salts as a new prescription for elderly patients with a mood disorder [15].

Table 1 lists six reports concerning VAL in elderly patients that included examination of side effects. Each involves more than 10 patients treated with that agent.

Cognitive and neuromotor impairments. VAL is often well tolerated in elderly individuals [38]. Unimpaired neuropsychologic test performance was reported in geriatric patients with seizure disorder treated with valproate [39]. Neurocognitive side effects including sedation, tremor, and gait disturbance, were noted in a subgroup of patients.

Other anticonvulsants, ie, carbamazepine (CBZ), oxcarbazepine, topiramate, gabapentin and lamotrigine (LTG) have been described in fewer reports as part of the management of geriatric BP disorder. Systematic data

on cognitive and other side effects of these agents in nondemented elderly subjects is sparse.

Cardiovascular effects. CBZ can cause bradycardia and atrioventricular conduction delays [40].

Other side effects. VAL and CBZ are associated with blood dyskrasias. VAL is associated with more leukopenia than CBZ. Combined treatment with CBZ in 16 treatment refractory-depressed patients with a mean age of 63 years had to be discontinued in 7 patients due to gastrointestinal complaints, hepatic toxicity, hyponatremia, or rash [41]. Stevens-Johnson syndrome can occur with LTG; it is not known whether advanced aged alters the risk of Stevens-Johnson syndrome, although serious rash did not occur in BP patients aged 55 years of age or older who were randomized to LTG, LI, or placebo [23].

Dose/concentration and effects. The relationship between VAL concentrations and side effects in elderly patients is not well described. In one study, CBZ concentrations in elderly patients presenting with bradyarrhythmia or conduction delay were often moderate, while tachyarrhythmias in younger patients were often associated with substantially elevated concentrations, including those reflecting intentional overdose [40].

With increased age, the elimination half-life of VAL can be prolonged [42], and the free fraction of plasma concentrations increases [43]. Aspirin can increase the VAL free fraction [44]. The ratio of total VAL concentration to dose is decreased by phenytoin and CBZ. For example, VAL itself inhibits metabolism of LTG, which may necessitate use of lower LTG doses to minimize its side effects.

Pharmacokinetic characteristics of CBZ are not well described in aged patients. Drug interactions with phenytoin and barbiturates can decrease CBZ dose/concentration ratios [44]. CBZ itself increases hepatic enzyme activity [45] and decreases levels of VAL and LTG; relatively high doses of those drugs may therefore be necessary to obtain their full benefit when they are used in combination with CBZ.

Antipsychotic agents

Side effects of antipsychotic agents are probably not specific to BP diagnosis. However, they will be discussed briefly.

Antipsychotic agents may be used alone or in combination with mood stabilizers in elderly BP patients [46]. Atypical agents have generally supplanted conventional agents as first-line antipsychotics in geriatric clinical practice [47]. They are used as adjuncts or as primary agents.

Cognitive and neuromotor impairments. Conventional antipsychotic drugs can cause sedation and impair cognition, which are particularly problematic when they occur in the elderly. Some atypical agents such as clozapine,

olanzapine and quetiapine, also can cause somnolence [48]. On the other hand, atypical antipsychotic treatment may enhance cognition in some elderly patients who are treated for psychosis [49].

Elderly patients are more vulnerable than younger patients to the parkinsonian side effects of antipsychotics, although they may experience acute dystonic reactions less often; their rate of akathisia may be equivalent to that seen in younger patients. The risk of tardive dyskinesia increases with age at first exposure and with cumulative treatment; female patients and patients who have affective disorders may also be at increased risk [50–52]. Atypical antipsychotics, compared with conventional agents, have reduced liability for acute motor side effects [53]; some atypical antipsychotics also may be associated with lower risk for tardive dyskinesia.

Cardiovascular effects. Antipsychotics can prolong QT interval (QTc), which can lead to life-threatening arrhythmia. Pretreatment conduction abnormalities are a risk factor for such changes [54]. Thioridazine and butyrophenones have been particularly implicated in QTc prolongation and arrhythmia [55]; QTc prolongation by ziprasidone is of unknown clinical significance [56].

Both conventional and atypical antipsychotics have anticholinergic effects that can contribute to problematic side effects in the elderly—these include tachycardia, constipation, and urinary hesitancy or obstruction, as well as cognitive toxicity. Lower potency conventional agents and olanzapine, in particular, have such anticholinergic properties. Alpha-1 adrenergic receptor antagonism by antipsychotic drugs, including atypical agents, may contribute to treatment emergent orthostatic hypotension.

Atypical antipsychotics can cause metabolic effects including weight gain, glucose intolerance, and hyperlipidemia in mixed-age populations [57]. Olanzapine and clozapine appear to have the greatest potential for such effects [58]. Although analysis of these effects in geriatric patients is not yet available, preliminary evidence has suggested that advanced age attenuates these effects [59].

Excess mortality has been reported in subgroups of elderly patients treated with atypical antipsychotics [60]. This issue is discussed below under “Neurological and Medical Comorbidities” as modifiers of toxicity.

Doses and effects. Side effects of antipsychotic medications can be dose-dependent. Examples include cognitive toxicity and neuromotor effects such as akathisia.

Antipsychotic dose/concentration ratios can be increased by age-associated factors. This has been reported with risperidone [61] and clozapine [62].

Benzodiazepines

Benzodiazepines have limited, adjunctive use in elderly BP patients.

Cognitive and neuromotor impairments. Benzodiazepines can decrease memory consolidation [63,64]; even short-acting compounds cause memory impairment [64]. There is a pharmacodynamic component to the sensitivity of some elders to diazepam [65]. Benzodiazepines, in particular long-acting drugs such as clonazepam, can also increase disability [66], and risk for falls and fractures [67].

Long-acting benzodiazepines are metabolized to active products by cytochrome P-450-3A4 enzymes, and concentrations of these drugs can accumulate with age [68].

Antidepressants

Antidepressants can be used to treat BP depressed elderly individuals (see below). Their use in unipolar depression in old age, including pharmacokinetics and tolerability, is reviewed elsewhere in this issue. Several types of side effects are only briefly summarized here.

Cognitive and neuromotor impairments. Antidepressants can cause sedation in the elderly. Successful treatment is often associated with improved cognitive performance in elders; however, treatment with selective serotonin reuptake inhibitors (SSRIs) can cause neuromotor side effects.

Cardiovascular effects. Recent practice has favored the use of SSRIs or bupropion in elderly patients, including BP patients. These lack quinidine-like effects and have minimal orthostatic hypotensive effects. SSRIs can, however, cause bradycardia. Dose-related hypertension can occur with venlafaxine. Nonspecific monoamine oxidase inhibitors require dietary restriction to avoid tyramine reaction; phenelzine is associated with delayed orthostatic hypotension [69].

Other side effects. SSRI treatment can cause hyponatremia in elderly individuals.

Pharmacodynamic modifiers of toxicity

In addition to pharmacokinetic changes with age, pharmacodynamic differences may contribute to vulnerability to side effects. To assess pharmacodynamic factors requires accounting for pharmacokinetic differences, when appropriate, using therapeutic drug monitoring. It is difficult to interpret studies of agents where this information is relevant, but is lacking, or in which there are differences in concentrations between patient groups of interest.

Age

Evidence regarding the influence of age on side effects of medications used in the management of BP disorders is sparse. Such influences have

been examined in some studies of LI treatment. Although they did not find greater overall side effects in elderly patients compared with younger patients, Smith and Helms [17] did find greater moderate to severe LI side effects in aged patients. Murray and colleagues [21] reported greater tremor but not greater polydipsia/polyuria in aged compared with younger patients. Although Roose and colleagues [28] observed that overall LI toxicity was greater in older patients, no age effect was found in two other studies [7,22]. Himmelhoch and colleagues [7] included only patients aged more than 55 years, and differences in LI concentration limit interpretation of findings from another study [22].

Patterns of carbamazepine cardiotoxicity may differ by age and sex [40]. In that study, young men with cardiotoxicity often have tachyarrhythmias and high drug concentrations and overdose; elderly women more often have bradyarrhythmias and conduction delay without excessive drug exposure.

Neurological and medical comorbidity

As illustrated by the following reports, comorbid dementia in particular may increase vulnerability to side effects of psychotropics. Thus, the central nervous system side effects of LI may be greater in aged patients with dementia. Himmelhoch [7] reported, for example, that among elderly patients, LI was poorly tolerated in those with dementia and in those with parkinsonian features. Anticonvulsant side effects may also be greater in elders with dementia, but, as is the case for LI [7], available reports have not included nondemented patients [70,71]. In a randomized double blind, placebo-controlled study of VAL, elderly patients with dementia and manic features had a discontinuation rate due to adverse events, primarily sedation, of 22% during initiation of treatment at doses greater than 15 mg/kg [70]; this suggests that demented patients tolerate lower doses than do nondemented patients. Also, CBZ caused diplopia or ataxia in 23% of elders with dementia [71].

Excess mortality associated with atypical antipsychotic agents has been reported in a subgroup of geriatric patients. Excess cerebrovascular accidents and deaths have been reported in patients with dementia; other risk factors appear to include advanced age and vascular disease [60].

Cardiovascular disorders are a potential modifier of side effects of other psychotropics in the elderly. Thus, they can increase vulnerability to orthostatic hypotensive, and quinidine-like effects [72].

Pharmacodynamic drug–drug interactions

Polypharmacy is liable to be associated with high side effect burden as a result of pharmacodynamic as well as pharmacokinetic interactions. Examples of pharmacodynamic effects include the potentiation of extrapyramidal side effects of antipsychotic agents used in conjunction with LI [73], and

the potentiation of anticholinergic effects by combining agents with that property [74]. However, such interactions can also be used for clinical benefit—for example, potentiation of sedative effects.

What is the evidence for efficacy in the elderly?

Treatment of manic states

Lithium. The efficacy of lithium (LI) in mania has been demonstrated in placebo-controlled studies of mixed-age patients [75]. Cade [76] reported efficacy of LI in ten patients; of these three were elderly and they responded. However, there have been no placebo-controlled acute efficacy trials of LI in the geriatric population. Studies of efficacy in purely geriatric samples have been primarily retrospective; they have described outcomes of naturalistic treatment of differing duration. Table 2 includes five studies that involved more than 10 elders treated with LI. LI dose and levels were not reported in all of these.

In addition, Wylie and colleagues [77] included 39 manic patients in a group of 62 elderly BP patients assessed for outcome of naturalistic treatment; 37 of these patients were treated with LI. Although the patients fared well overall, the authors did not evaluate the outcomes of treatment with LI separately. Gildengers and colleagues [78] reported the feasibility of protocol-based treatment, primarily with LI or VAL, of BP elderly subjects in various clinical states; they noted that most patients did not experience sustained recovery. In another study, LI was more efficacious than chlorpromazine in a sample of manic patients with a mean age of 56 years [79].

The relationship between plasma LI concentrations and acute antimanic response has not been defined in elderly patients. Case series [19,28] have suggested that geriatric patients may respond to levels of LI that are lower (0.5–0.8 mEq/L) than those considered optimal (0.8–1.2 mEq/L) in mixed-age adults [80]. However, other reports have suggested that geriatric patients benefit best from conventional LI levels when tolerated [81,82]. Studies that can identify subgroups of elderly individuals who benefit from low concentration of LI and other psychotropic drugs are needed; concentration-dependent side effects could be avoided in these patients.

Monotherapy with mood stabilizers, together with elimination of other unnecessary psychotropics, is considered an optimal first step in the management of elderly patients. Monotherapy, if efficacious, can avoid the additional side effect burden of combined treatment. Nevertheless, the time course of antimanic response to LI or other monotherapy, under particular dosing conditions, has not been described in aged manic patients. Defining adequate trials of antimanic agents such as LI in elderly patients requires considering both treatment duration and dose.

Anticonvulsants. Whereas placebo-controlled studies of VAL (divalproex) in mixed-age patients support its efficacy in mania [83], there are no

published data comparing VAL to placebo or to LI in the elderly. Nevertheless, retrospective and open studies indicate that VAL can have antimanic effects in geriatric patients [38,84–86]. Table 2 includes five studies that included more than 10 elders treated with VAL. A total of 137 elderly patients were studied. The doses ranged between 250 and 2250 mg/d. The total VAL concentrations were 25 to 120 $\mu\text{g}/\text{mL}$. Overall, 59% of patients met various improvement criteria. Other reports regarding VAL treatment were consistent with these findings [38,84–87].

One retrospective report [88] compared VAL with LI treatment in manic BP elders; the therapeutic benefits of the two agents were comparable. In another report, although either VAL or LI were mainly prescribed, the limited number of manic patients precluded such comparison [71].

The relationship between blood levels of VAL and antimanic response is not established in the elderly. Bowden [89] recommended total concentrations between 50 and 120 $\mu\text{g}/\text{mL}$ based on data from a mixed-age sample with an average age of 39 years. Findings from retrospective naturalistic series are difficult to interpret [88,90]. However, Chen and colleagues [88] found that manic elders with VAL concentrations of 65 to 90 $\mu\text{g}/\text{mL}$ improved more than patients who had levels of 45 to 65 $\mu\text{g}/\text{mL}$. Recently, VAL administered intravenously reduced psychopathology in three geriatric patients with concentrations between 44 and 87 $\mu\text{g}/\text{mL}$ [91]. While the proportion of VAL not bound to proteins is higher with increased age [43]; the clinical significance of these differences in protein binding is not known.

Information is limited regarding therapeutic benefit of VAL in combination with LI in aged BP patients. This combination was reportedly beneficial for elderly patients who were only partially responsive to LI [92,93], and it can also be useful in rapid cycling BP elders [93,94].

The antimanic effect of CBZ has not been a focus of controlled trials in the elderly [95]. Okuma and colleagues [96], in their double-blind comparison of the efficacy of CBZ and LI, included 7 elderly manic patients out of 50 in the CBZ arm, treated with a mean level of 8 $\mu\text{g}/\text{mL}$, and 6 out of 51 patients in the LI arm. Overall, both drugs were efficacious.

With regard to other anticonvulsants (eg, oxcarbazepine, gabapentin, and topiramate) in elderly manic patients, information is limited to case reports and case series. For example, gabapentin in combination with an antipsychotic or VAL was associated with reduction in manic symptoms in 7 elderly patients [97]. Thus, the role of these agents in geriatric practice is not established.

Antipsychotic agents. There is little data regarding the efficacy of atypical antipsychotic medications in aged BP patients. Although newer agents such as aripiprazole may have particular advantages in elders, the broadest experience for mixed-age BP patients relates to risperidone and olanzapine as adjunct therapy [98,99] or as monotherapy [100]. Risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone have US Food and Drug

Table 2
Acute efficacy of pharmacotherapy in older adult and elderly BP patients

| Agent | Reference | Study design | n | Mean age in years (range) | Dx | Mean dose in mg/d (range) | Mean concentration in mEq/L (range) | Outcome measures | Duration (wk) | Benefit | Comments |
|-------|--------------------------|--------------|----|---------------------------|-----------------------------|---------------------------|-------------------------------------|--|----------------|-------------------------------|--|
| LI | van der Velde [6] | R | 12 | 67 (60–74) | BP, manic | NA (700–2100) | NA (0.60–2.00) | Global improvement (–4 severe depression, + 4 severe mania) | 2 | 4 (33%) improved | 51/63 (81%) of younger (age 17–59 yr) BP manic patients responded |
| LI | Himmelhoch et al [7] | R | 81 | 63 (55–88) | BP I 74; BP II 7 | NA (NA) | (NA) | Global efficacy/improvement scale: 1–6 (1 = optimum, 6 = none) | 3–8 | 56 (69%) improved | 23/25 of the poor responders had dementia, intermittent confusion, and/or extrapyramidal syndromes; drug abuse also was a negative predictor |
| LI | Schaffer and Garvey [19] | P | 14 | 69 (65–77) | BP, manic | NA (NA) | NA (0.50–0.90) | Discharge | > 2 | 11 (71%) improved | |
| VAL | Puryear et al [141] | R | 13 | 70 (63–77) | 7 BP, manic; mixed; 6 other | 1000 (100–1750) | 57 (34–82) | BPRS, Cohen Mansfield Agitation Inventory | NA (inpatient) | Reduction in BPRS in 12 (92%) | |

| | | | | | | | | | | |
|--------------|-------------------------------|---|------------------|---|--------------------|---|---|----------|---|---|
| VAL | Kando et al [142] | R | 35 71 (63–85) | 24 BP I, manic, 11 other affective disorder | 743 (250–2000) | 53 (11–102) | Global McElroy scale 0-3 (0 no improvement, 3 complete remission) | 0.5–21 | 18/29 (62%) improved with adequate trial | No data for inadequate trial group; 27 patients had past trial with LI, 19% did not respond |
| VAL | Noaguil et al [140] | R | 21 71 (60–82) | BP, manic | 1405 (500–3000) | 72 (31–106) | Improvement of CGI (responders: CGI 1 and 2) | 1–7 | 19 (90%) improved | 20 patients received neuroleptics |
| VAL | Niedermier and Nasrallah [91] | R | 39 67 (60–86) | 16 BP, 7 BP and dementia | 1029 (500–2250) | 72 (36–111) | CGI | ≥1 | 14/16 (88%) BP responded; 7 (100%) BP and dementia responded | |
| LI or VAL | Chen et al [89] | R | 59 69 (NA) | BP, manic | NA | LI (n = 30): 0.30–1.30 mEq/L; VAL (n = 29): 25–116 µg/mL) | Improvement of CGI (score of 1 and 2) | Mean 2.3 | LI: 20 (67%) improved overall; 9/11 (82%) improved with ≥ 0.8 mEq/L (CGI = 2 ± 0.6). VAL: 11 (38%) improved overall; 6/8 (75%) with 65-90 µg/mL (CGI = 2.1 ± 0.6) | Response rates to LI better than VAL for classic mania; similar efficacy for mixed mania |

Abbreviations: BP, bipolar; BPRS, Brief Psychiatric Rating Scale; CGI, clinical global impression; LI, lithium; NA, not available; P, prospective; PBO, placebo; R, retrospective; VAL, valproate.

Administration—approved indications for use in BP disorder. A preliminary analysis of manic patients aged 50 years or more suggests efficacy of olanzapine monotherapy [101]. Also, preliminary experience has suggested a role for quetiapine in management of BP elders [102,103]. In addition, Shulman and colleagues [104] and Frye [105] noted response to clozapine in geriatric manic patients.

Relationships between antipsychotic dose or serum/plasma concentrations to efficacy in the elderly are not defined.

Benzodiazepines. The benefits of benzodiazepines, such as lorazepam, as adjuncts in elderly manic patients have not been studied. Clinicians must weigh their potential benefits against associated risks.

Treatment of BP depression

There is no systematic literature focused on the treatment of elderly patients who have BP depression [106]. Indeed, the pharmacotherapy of acute BP depression has not been adequately studied in mixed-age populations. The pharmacologic strategies used in BP depression differ from those used in unipolar depression in their focus on mood stabilizers and on combination treatments [107]. In a series of five elderly BP depressed patients, LTG (75–100 mg/d) augmentation of LI or VAL led to remission [106].

The efficacy of antidepressant pharmacotherapy in aged BP patients has not been tested. Nemeroff and colleagues [108] found that the combination of paroxetine and LI, at a concentration of 0.8 mEq/L or less, was more efficacious than LI alone in patients aged 21 to 71 years. No age dependence of response was reported.

In elderly patients, “switching” to mania during pharmacotherapy with tricyclic and other antidepressant agents can occur [109,110]. Comparisons of treatment-emergent mania related to alternative antidepressants in the elderly are needed.

Monoamine oxidase inhibitors can benefit younger BP depressed patients [111], and they are effective in geriatric unipolar depression [69]. They have not been studied in elderly individuals who have BP.

What factors may modify acute efficacy?

Age-associated factors may modify benefit from pharmacotherapy in elderly individuals who have BP. The evidence for such effects is summarized as follows:

Age. There are limited findings regarding the influence of age on acute treatment outcomes in BP disorders. Van der Velde [6] noted poorer acute benefit of LI in elderly BP patients compared with younger patients (Table 2). One study of naturalistic LI treatment in mixed-age manic patients suggested that benefit was attenuated by increased age [112]; however, only four

patients in this study were elderly. No age effect was reported in a placebo-controlled study of the efficacy of LI in mixed-age manic patients, 18% of whom were 60 years of age or older [113]. Apparently, no analyses address age effects on VAL or CBZ efficacy in mania. Cycling into a depressive episode may occur more often during treatment of mania in elders than in younger patients [114]. The effects of age on treatment outcomes in BP depression are not known.

Age at onset. There is little information regarding the relationship of age at onset and treatment outcome in geriatric BP patients [115]. No effect of age at onset on outcome at end point was found in one naturalistic study [116], or in one retrospective report [117]. In BP patients, both age at first affective episode and at first manic episode may be pertinent. The reliability of course assessment in geriatric patients is a limiting factor in research, and multiple sources of information must be used.

Neurological comorbidity/cognitive impairment. Elderly manic patients with neurological compromise may have relatively poor therapeutic outcomes. Berrios and Bakshi [118] reported an association between higher Hachinski scores, indicating cerebrovascular disease, and worse acute outcome. Himmelhoeh [7] observed chronic mania in 19 elderly subjects despite treatment with LI; 12 of these subjects had extrapyramidal syndromes, and 5 had dementia.

Cognitive impairments may be associated with attenuated acute treatment outcomes in older BP patients. Executive impairments, for example, are prevalent in BP disorders, particularly in late life [119–121]; these are often associated with frontostriatal pathology. These impairments were associated with limited acute response to LI pharmacotherapy in a preliminary study of elderly manic patients [122]. Comorbid dementia may also be associated with worse antimanic outcomes of LI treatment [7]. In a randomized, placebo-controlled trial in demented patients with manic symptoms, VAL reduced agitation but not mania ratings [70].

Acute treatment can improve cognitive performance in geriatric BP patients [77]; however, one mechanism for such improvement is alleviation of affective psychopathology, sometimes referred to as “reversible dementia.” In addition, mood stabilizers may have neuroprotective effects [123,124], and may promote regeneration of cortical gray matter [125]. However, cognitive impairments may also persist despite successful treatment of BP patients [126], and these impairments may have implications for long-term management.

Comorbid medical conditions. Comorbid medical conditions are prevalent among elderly BP patients [7] and may also predict poor LI response. In a mixed-age sample, patients with medical comorbidity had higher age (mean 51 yr) and poorer response to naturalistic LI treatment compared with patients without such comorbidity [127]. Studies focusing on the implications of specific medical disorders in the elderly are needed.

Substance abuse. Substance abuse may be relatively prevalent in aged BP patients. It was associated with poor antimanic response to LI in elderly manic patients in one report [7].

Symptom profile. The relationship between symptom profile and treatment outcome in geriatric mania has received little study. For example, the presence of mixed features or psychosis and outcomes await investigation in the elderly. In a retrospective report, LI treatment was associated with better therapeutic effect than VAL treatment in patients with classic mania compared with those with mixed mania; drug levels were not provided in this comparison. Treatments for hypomania and rapid cycling also have not been systematically studied in late life.

Continuation/maintenance treatment

Because BP patients, including the elderly, are at risk for repeated episodes requiring treatment, continuation and maintenance pharmacotherapy is critical to their care. The literature regarding the long-term treatment of elderly BP patients is even more limited than for acute management.

Information concerning long-term treatment of elderly BP patients is primarily derived from naturalistic treatment in mixed-age samples. Table 3 presents five studies that each included at least 10 elderly BP patients. All of these studies included LI treatment. Stone [18] did not find fewer psychiatric rehospitalizations in patients naturalistically maintained on LI compared with those who were not. These studies do not allow assessment of the efficacy of LI.

In a secondary analysis of BP I patients 55 years of age or older treated in randomized double-blind studies after open-label stabilization, LTG delayed time to intervention for any mood episode and for depressive episode, while LI delayed time to intervention for manic, hypomanic, and mixed episodes [23].

Clinical experience suggests that many elders with BP disorder receive combined psychotropic regimens [77,103]. The optimal duration of adjunctive agents, ie, antidepressants or antipsychotic agents, after successful treatment is not defined in elderly BP patients.

There is no adequate information to guide mood stabilizer dosing in the context of continuation and maintenance treatment in BP elders. The patients followed by Stone [18] were treated with LI at concentrations of 0.5 to 1.00 mEq/L, and those of Sajatovic and colleagues [23] at 0.8 to 1.1 mEq/L.

Studies in mixed-age patients have suggested that LI treatment can have an antisuicide effect [128]. Although BP patients are at risk for suicide [129], BP elderly individuals have yet to be studied from this perspective.

Nonsuicide mortality rates on follow-up of manic elders are greater than those of same-age patients who have major depression [8]. The effect of psychiatric interventions on mortality in BP elderly individuals is not known.

What factors may modify efficacy of continuation-maintenance treatment?

Age. There has been conflicting evidence whether advanced age has adverse implications for long-term affective outcomes, and this evidence is limited to LI treatment. Three of the studies listed in Table 3 included younger patients treated with LI. While one of these studies indicated more recurrent affective episodes in elderly subjects [6], another [21] found only trends for greater manic psychopathology but not more frequent hospitalizations. Interpretation of the third report [22] was confounded by differing LI concentrations with age. Other studies of LI maintenance treatment in mixed-age populations that have examined age as a predictor have included few elderly subjects, or, despite a wide age range, did not indicate the number of elderly subjects; these reported no age effect on various outcome measures [130–133].

Course of illness. In the naturalistic follow-up of geriatric mania by Stone [18], patients with prior episodes had a greater rate of recurrence. Schurhoff and colleagues [133] did find differences in outcome of LI treatment in mixed-age BP patients with illness onset after age 40 years compared with those with earlier age at onset.

Neurological status/cognitive impairment. Elderly BP patients with neurologic comorbidity had higher risk of psychiatric rehospitalization and institutionalization in one study. Also, enduring cognitive impairments, despite acute control of affective symptoms, may have adverse implications for long-term treatment outcomes. In geriatric BP patients, cognitive deficits have been limited to poor community living skills and deficits in performing activities of daily living, as well as with nursing home placement [134], but not greater relapse with hospitalization [9].

Thus, factors that alter acute treatment outcomes in elderly BP patients may also influence outcomes of long-term management information. However, controlled treatment trials are needed.

Discussion

The results noted in this article provide limited direction for clinical practice and have implications for health care delivery. They also highlight the need for clinical investigation and suggest directions for such research.

Limitations of the search strategy need to be kept in mind in considering the literature reviewed. Few articles published before 1966 were identified, only English language literature was searched, and abstracts and reports at research meetings are not identified by MEDLINE. The challenges of using unfiltered databases such as MEDLINE have been emphasized by Bartels and colleagues [135].

Table 3
Efficacy of continuation-maintenance treatment in older adult and elderly BP patients

| Agent | Reference | Study design | n | Mean age in years (range) | Dx | Mean dose in mg/d (range) | Mean concentration in mEq/L (range) | Outcome measures | Duration (yr) | Results | Comments |
|-------|-------------------|--------------|----------|---------------------------|-------------------------------|---------------------------|-------------------------------------|--|-------------------------------------|---|---|
| LI | Van der Velde [6] | R | 12 | 67 (60–74) | BP, manic | NA (900–2100) | NA (0.60–2.00) | Recurrence of affective episodes | 3 years after acute inpatient phase | 2 /12 (17%) had no recurrence in 1 year, 1 (8%) in 2 and 3 years | Younger patients (n = 63; age 17 - 59) remained better during follow-up. |
| LI | Hewick et al [22] | R | 23 23 | NA (50–59) (60–84) | BP 82%; UP 9%; other 9% | NA (NA) | NA (NA) | Global (0–3) after > 3 mo of treatment | NA | 13/46 (28%) not optimally controlled (rating > 0) versus 6/36 (17%) of younger patients | Lower concentrations in elders |
| LI | Murray et al [21] | P | 37 | NA (60–78) | BP 25; UP 12 | NA (NA) | NA (NA) | Global (0–3) | 2 | Trend for more severe and prolonged mania in elders | Similar LI levels in elderly and younger patients (n = 129; range 25–59 yr); 69% of patients on LI for at least 12 mo |
| LI | Stone [18] | R | 43 | NA (65–) | BP, manic | NA (NA) | NA (0.50–1.00) | No. of readmissions | Mean 3.2 | 1.1 on LI versus 1.6 not on LI (n = 44) | |

| | | | | | | | | | | |
|--------------|----------------------------|--|------------------|---------------|---|---|--------------------------|-------------------------|----------------|--|
| LI or LTG | Sajatovic et al [23] | P; secondary analysis: following open label phase; randomized, double- blind, placebo- controlled | 98 randomized | 61 (55–82) | BP I; stabilization criteria after 8–16 weeks open label phase | LI (n = 34), modal 750 mg/d; LTG (n = 33), modal 240 mg/d (100– 400 mg/day); PBO, n = 31 | LI (0.8–1.1 mEq/L) | Time to intervention | Up to 18 mo | LTG delayed time to intervention for any mood episode (median 201 d) and for depressive but not mania/ hypomania/ mixed episode; LI delayed time to intervention for mania/hypomania/ mixed episode, but not depression or any episode (median 138 d); for PBO the median was 98 d for any episode. |
|--------------|----------------------------|--|------------------|---------------|---|---|--------------------------|-------------------------|----------------|--|

Abbreviations: BP, bipolar; LI, lithium; LTG, lamotrigine; NA, not available; P, prospective; PBO, placebo; R, retrospective; UP, unipolar.

Implications for clinical practice and health care delivery

The tolerability of specific agents is a major determinant guiding treatment selection and dosing in elderly BP patients. Central clinical tasks are to obtain and critically review history of adverse response, benefit, and drug levels where appropriate. The initial clinical and laboratory evaluation needs to focus not only on excluding aggravating or causative factors, but also on identification of conditions that can influence drug selection. Lying and standing blood pressure and pulse, an electrocardiogram, neurologic examination, and cognitive assessment are important in management of aged patients. In considering acute treatment, clinicians should be sensitive to the potential role of nonadherence in patients with limited benefit, relapse, or recurrence. Geropsychiatrists, while choosing from among alternatives based on side effect profile and treatment history, should avoid unnecessary abandonment of previously effective agents—for example, when side effect history is given without corroboration or when associated drug concentrations were documented as excessive.

LI remains one of the treatments of choice for BP manic episodes. Clinicians should target concentration ranges from 0.4 to 1.0 mEq/L and expect that concentrations at the upper end may be necessary. LI dose should be titrated gradually because of the higher dose/concentration ratio and longer time to steady state levels compared with younger patients. Diseases and treatments that increase dose/concentration ratio require more conservative dosing. In the presence of brain pathology, more conservative LI concentrations may be warranted. Worsening of cognitive status, coarse tremor, and hypothyroidism are important side effects to avoid.

VAL is a rational alternative to LI in elderly manic patients. It can be used as a first-line mood stabilizer in most cases. It may replace LI in patients who develop adverse effects of LI. Given the state of the evidence, clinicians should expect to use concentrations in the range of 40 to 100 µg/mL. The most clinically important side effects are sedation, gait disturbance, and thrombocytopenia.

CBZ can be considered a second-line agent for the treatment of mania in the elderly. The role of other anticonvulsants as antimanic agents in elderly individuals is unclear. In using CBZ, the preinitiation workup should place particular emphasis on the electrocardiogram, liver function tests and hematology. Adverse reactions include cardiovascular effects and hematologic effects.

Monotherapy with mood stabilizer, together with elimination of unnecessary psychotropic agents, is considered a reasonable first approach.

The optimal timing of treatment changes for manic elders with partial response or nonresponse—that is, augmentation or change to alternative treatment, respectively—remains to be clarified. In the absence of evidence-based guidelines, clinical experience suggests a duration of several weeks to assess the initial strategy.

Partial response to initial monotherapy suggests addition of atypical antipsychotic or another mood stabilizer. Clinicians have virtually no age-specific systematic information to guide atypical antipsychotic use. The greatest amount of experience has come with olanzapine and risperidone as adjunctive agents for manic and mixed states in late life. The potential metabolic effects of atypical agents mean that laboratory monitoring is needed.

The treatment of BP depression in the elderly is guided only by sporadic age-specific reports and extrapolation from other age and diagnostic groups. Initial mood stabilizer treatment has potential advantages, and LI may be used when feasible, in anticipation of its use either as a primary agent or in later combination with antidepressants. LTG is a promising medication for BP depression, especially because the risk of Stevens-Johnson syndrome appears to be low in older patients. The dosing schedule for LTG should follow the same guidelines as in younger patients.

When an antidepressant is needed in addition to a mood stabilizer, the treatment history and toxicity profile of particular agents should guide treatment selection. Electroconvulsive therapy (ECT) is effective in BP depression and should be considered in refractory elderly patients in addition to elderly patients who exhibit suicidality or inadequate nutritional intake. ECT should also be considered in patients with mania or mood states refractory to pharmacotherapy. However, there are no systematic data comparing ECT and pharmacotherapy in elderly BP patients.

Pharmacotherapy that has proved to be efficacious for acute treatment of mania or BP depression should be continued for 6 to 12 months. After that period of continuation treatment, if remission is sustained, slow discontinuation of adjunctive antidepressants, antipsychotics, or antianxiety agents can be attempted under close monitoring.

Clinicians should expect to provide maintenance pharmacologic management despite the absence of clear guidelines for this in BP elders; mood stabilizers should in general be continued indefinitely. Although acute and long-term treatment benefits may be attenuated in some elders, in particular those with comorbid brain disease, this should not preclude attempts to provide adequate treatment trials in these patients.

Directions for research

The development of evidence-based treatment of late-life BP disorders has been limited by several factors. First, a relatively small numbers of patients can be studied prospectively at individual academic centers, as is reflected by the fact that the existing literature consists primarily of small sample case series. Additional challenges include the rigors of working with these patients, and the complex design issues that must be faced in such research.

Recently, these challenges are being met through new strategies, including analysis of clinical administrative databases, and collaborative

multicenter studies in which investigators with expertise in studying young BP patients are participating. The elderly BP population was recognized as a priority for funding at the National Institute of Mental Health Depression and BP Support Alliance Consensus Conference 2001 and its report [136].

The existing literature in elderly patients can help formulate further hypotheses for systematic and controlled efficacy and safety trials. Randomized controlled trials comparing available agents are needed. Initial studies of acute treatment can provide a basis for designing continuation and maintenance treatment studies. Research should focus on defining those dosing and duration conditions for first-line drugs (eg, LI and VAL) that provide the best balance between benefit and side effects. New agents (eg, LTG and atypical antipsychotic medications) also need to be studied systematically in these patients.

Given the significance of side effects in elders, one important agenda for research in this population is the identification of patients who respond adequately to monotherapy to minimize side effects. For the same reason, characterization of patients who respond to low exposure (ie, relatively low drug blood levels) is an important aim. Further, such research provides a focus for examination of the utility of experimental measures related to drug distribution—for example, VAL not bound to peripheral protein, and central or erythrocyte LI concentrations.

Another major research need is to define rationale alternative approaches in patients who receive limited benefit from initial treatments and to explore the heuristic opportunities presented by such patients. In partially responsive elderly patients, the efficacies of standard augmentation regimens need to be tested. Dementia, cognitive impairments, and other neurologic dysfunction may characterize patients who require such augmentation. Specific features such as these can provide a framework for selection from among innovative augmentation approaches that are particularly relevant to particular elderly BP patients and may be adequately tolerated. One example is the use of cholinesterase inhibitors [137].

Given the prevalence of various comorbid conditions in BP elders, patients who have stable comorbid medical conditions or mild cognitive impairment need to be included in initial studies so that their findings can influence practice. In addition to symptom measures, the assessment of outcome in geriatric BP treatment studies should include other dimensions, including measures of side effects, behavioral and cognitive function, and medical status.

The management of type II BP disorder and of schizoaffective BP disorder [138] needs to be studied separately in the elderly.

Effectiveness studies become a higher priority as information regarding efficacy becomes available. For example, nonadherence is a particularly important issue in the elderly; laboratory monitoring of treatment can be improved by nurse intervention programs [139].

Summary

In BP elders, there is a clear disparity between the sparse age-specific evidence base that can contribute to rational treatment approaches and their illness severity, high mortality, vulnerability to side effects, chronicity and relapse/recurrence, high services use, and potential caregiver burden. Pressure from managed care providers to minimize inpatient management increases the need for timely symptom reduction and the prevention of relapse and recurrence. Yet extrapolations regarding the efficacy of medications used in younger BP patients are not yet supported by data from aged patients.

Case series suggest differences in side effect profile between lithium salts and anticonvulsants, and between atypical compared with conventional antipsychotics. Dementia and other comorbidities may exacerbate side effects. Case series also indicate that lithium and valproate both can have efficacy in manic states. Age-associated factors including dementia and cognitive impairment may attenuate benefit.

Research priorities include the need for randomized controlled trials of both acute and continuation/maintenance treatments. Elderly BP patients highlight the issues of monotherapy and timing of augmentation strategies and offer opportunities for investigation of the mechanisms of attenuation of response and testing innovative interventions.

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