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Comparison of the Usefulness of Lithium and Valproate

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ABSTRACT

This review shows that lithium and valproate have comparable anti-manic effects. However, manic patients who respond well to lithium are euphoric but manic patients who respond poorly to lithium have more than 10 past recurrences, are in a mixed state and/or have dysphoric mood and mood-incongruent psychotic features such as delusions of persecution. Valproate exhibits greater anti-manic efficacy than lithium in manic patients with a higher number of past recurrences and may be effective for patients with mixed conditions and rapid cycling. The antidepressant effects of both lithium and valproate are modest, and may necessitate concomitant lamotrigine and/or switching. Lithium may afford more prophylactic efficacy than valproate. Positive predictors for lithium prophylaxis are an episodic pattern of mania-depression-interval and a high age of illness onset, while negative predictors are a high number of previous hospitalizations, an episodic pattern of depression-mania-interval, and continuous cycling. Checking these predictors in order to determine whether lithium or valproate should be selected would appear to be useful. In addition, even very low levels of lithium in drinking water may contribute to a reduction in suicide risk in the general population. In conclusion, both lithium and valproate are useful in the treatment of bipolar disorders, and several measures exist for differentiating their clinical positioning.

Keywords: bipolar disorders, lithium, valproate

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INTRODUCTION

It is widely accepted that lithium and valproate are mood stabilizers for bipolar disorders, but their clinical positioning has not been established based on sufficient evidence. At present, there are several different therapeutic guidelines for bipolar disorders that psychiatrists may use, or they may simply follow their own experience and intuition. In this review, the author presents several measures that will make it possible to differentiate the clinical positioning of lithium and valproate in the treatment of bipolar disorders.

METHODS

This review is not a quantitative analysis such as a meta-analysis, but rather a qualitative analysis. Relevant articles on lithium and valproate were reviewed, and a selection of these have been cited at the author's discretion.

RESULTS

1) Manic Episodes

Cade in Australia discovered the anti-manic action of lithium in 1949 [1]. Since that time, more than 60 years ago, lithium has remained the first-line treatment for manic episodes. Recently, Cipriani et al. [2] conducted a systematic review of 68 randomized controlled trials (RCTs) encompassing a total of 16,073 participants from January 1, 1980 to November 25, 2010 that compared the following drugs in their respective therapeutic dosage ranges for the treatment of acute mania in adults: aripiprazole, asenapine, carbamazepine, valproate, gabapentin,

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haloperidol, lamotrigine, lithium, olanzapine, quetiapine, risperidone, topiramate, and ziprasidone. One of the primary outcome measures was the mean change on mania rating scales. The results showed that haloperidol (standardized mean difference [SMD]: –0.56 [95% CI: –0.69 to –0.43]), risperidone (–0.50 [–0.63 to –0.38]), olanzapine (–0.43 [–0.54 to –0.32], lithium (–0.37 [–0.63 to –0.11]), quetiapine (–0.37 [–0.51 to –0.23]), aripiprazole (–0.37 [–0.51 to –0.23]), carbamazepine (–0.36 [–0.60 to –0.11], asenapine (–0.30 [–0.53 to –0.07]), valproate (–0.20 [–0.37 to –0.04]), and ziprasidone (–0.20 [–0.37 to –0.03]) were significantly more effective than placebo, whereas gabapentin, lamotrigine, and topiramate were not. Although the antimanic efficacy of lithium appeared to be greater than that of valproate (-0.37 vs. -0.20), the difference was not significant. Although these results suggest that antipsychotic drugs may be significantly more effective than mood stabilizers, the only assessment time point was at 3 weeks, and the effects of mood stabilizers may gradually catch up to those of antipsychotic drugs after 3 weeks, although this has not yet been determined. In any case, this meta-analysis suggests that the anti-manic effects of lithium and valproate may be comparable.

Manic patients who respond well to lithium are euphoric but manic patients who respond poorly to lithium have more than 10 past recurrences [3], are in a mixed state, and/or have dysphoric mood and mood-incongruent psychotic features such as delusions of persecution. Common adverse reactions to lithium include fine tremors of the hand and fingers (27%), excessive urination (30–35%), thyroid hypofunction (5–35%), memory disturbance (28%), weight gain (19%), sedation (12%), and digestive symptoms (10%) [4]. In addition, bradycardia, sinus node dysfunction syndrome, or renal dysfunction are rare but may occur. It should be noted that a teratogenic effect specific to lithium is Ebstein's anomaly, and administration to pregnant women is therefore contraindicated.

Although the therapeutic level of lithium (0.4-1.0 mEq/L) is very close to the intoxication level (more than 1.5 mEq/L), a high lithium level of around 1.0 mEq/L needs to be maintained for manic patients. Lithium levels should be measured once a week in the initial stages of treatment, or when the dose is going to be increased. Lithium levels should also be measured before the drug is taken in the morning (at its lowest, or trough, level). It is therefore convenient to administer lithium in the evening and/or just before bedtime. As a rule, non-steroidal anti-inflammatory drugs (NSAIDs) should not be combined with lithium, because NSAIDs inhibit lithium excretion from the kidneys, which may increase lithium levels and hence the risk of lithium intoxication [5].

Valproate was originally administered as an anti-epileptic drug, but has been classified as a mood stabilizer by Lambert [6]. Meta-analyses have confirmed that valproate exerts significantly greater anti-manic effects than placebo [7,8]. Compared to lithium, valproate exhibits anti-manic efficacy in manic patients with a higher number of past recurrences [3]. It may be effective for patients with mixed conditions and rapid cycling. Nausea (7–34%), excessive sedation (7–16%), thrombocytopenia (27%), and headache (10%) are the most commonly reported adverse reactions [4]. Other side effects requiring caution include leukopenia, polycystic follicular syndrome, hyperammonemia, pancreatitis, and drug eruption. Valproate has relatively high teratogenicity. Because valproate inhibits drug-metabolizing enzymes, the concentrations of drugs administered in combination with it may be increased.

The therapeutic and toxic levels of valproate are not as close together as they are with lithium. However, to avoid toxicity while achieving therapeutic levels, valproate levels should be measured in the morning (at the lowest, or trough, value). The therapeutic level for manic episodes has been reported to be 70 μg/mL or higher, at which dose levels valproate exhibits greater anti-manic efficacy than either lower dose levels or placebo [9]. In certain cases, a level exceeding 100 μg/mL may be needed. Care should be taken, however, to avoid levels exceeding 120 μg/mL.

2) Depressive Episodes

Although several RCTs with small sample sizes were conducted in the 1970s showing that lithium exhibited greater antidepressant efficacy in acute bipolar depression than placebo, the antidepressant effect is modest and may take 6 to 8 weeks to achieve.

Nierenberg et al. [10] conducted a study of efficacy that was designed to determine if medium-dose lithium added to an optimized personalized treatment (OPT) regimen achieves a better clinical outcome for bipolar patients. Patients were randomly assigned to receive either OPT (requiring treatment with at least one mood stabilizer other than lithium) or OPT plus a fixed lithium dosage of 600 mg/day for the first 2 months, with subsequent dosage adjustments as clinically indicated. The results showed that there was no statistically significant advantage for lithium plus OPT on the Clinical Global Impression Scale for Bipolar Disorder–Severity (CGI-BP-S) scores, necessary clinical adjustments, or proportion of

subjects with sustained remission. These findings suggest that adding moderate dose lithium does not help patients with bipolar disorder [11].

However, the results hint at another possibility. The patients were mostly depressed, with 87% meeting DSM-IV criteria for recurrent major depressive episodes. For these depressive patients, lamotrigine might have been administered as OPT, because OPT is an empirically supported strategy largely based on the Texas Implementation of Medication Algorithm [12], which recommends the use of lamotrigine as the first-line treatment for acute depressive episodes in patients with bipolar I disorder. In fact, a meta-analysis showed that lamotrigine has a modest but statistically significant effect on the depressive symptoms of bipolar depression [13], and a pooled analysis showed that lamotrigine is effective against depression relapse and mania relapse, with more robust activity against depression relapse, whereas lithium was effective against mania relapse [14]. Therefore, in their study, the use of lamotrigine might have improved depression and prevented depression and/or mania relapse in those patients who received OPT alone. Moreover, the absence of a significant difference between OPT plus moderate dose lithium and OPT alone suggests that the addition of moderate dose lithium may be as effective as lamotrigine in some bipolar patients.

The efficacy of valproate for bipolar depression has been shown only in reports from small studies. Valproate was ineffective for bipolar depression in one recent meta-analysis [15], but was effective in another meta-analysis [16]. Therefore, no definite conclusions have yet been reached.

3) Prophylaxis

The prophylactic effects of lithium have been shown in many clinical studies [17,18]. The BALANCE investigators [19] aimed to establish whether lithium plus valproate was better than monotherapy with either drug alone for relapse prevention in bipolar I disorder. They enrolled 330 patients aged 16 years and older with bipolar I disorder at 41 sites in the UK, France, USA, and Italy. The patients were randomly allocated to open-label lithium monotherapy (0.4-1.0 mEq/L, n = 110), valproate monotherapy (750-1,250 mg/day, n = 110), or both agents in combination (n = 110), after an active run-in period of 4–8 weeks on the combination. Participants were followed for up to 24 months. The primary outcome was initiation of new intervention for an emergent mood episode. The results showed that 59 (54%) of 110 people in the combination therapy group, 65 (59%) of 110 in the lithium group, and 76 (69%) of 110 in the valproate group had a primary outcome event during follow-up. Hazard ratios for the primary outcome were 0.59 (95% CI 0.42–0.83, p = 0.0023) for combination therapy versus valproate, 0.82 (0.58–1.17, p = 0.27) for combination therapy versus lithium, and 0.71 (0.51–1.00, p = 0.0472) for lithium versus valproate. Although the results suggested that the BALANCE study could neither reliably confirm nor refute the benefits of combination therapy compared to lithium monotherapy, it seems likely that lithium monotherapy is as effective as combination therapy, and that both are more effective than valproate monotherapy.

Kessing et al. [20] compared the effects of valproate vs. lithium in the treatment of bipolar disorder in the clinical setting. They performed an observational cohort study based on the national registration of all people receiving a diagnosis of bipolar disorder in psychiatric hospital settings who were prescribed valproate or lithium in Denmark from 1995 to 2006. As a result, a total of 4,268 participants were included in the study, of whom 719 received valproate and 3,549 received lithium after receiving a diagnosis of bipolar disorder. The proportion of patients switching to the opposite drug (lithium or valproate) or receiving antidepressants, antipsychotics, or anticonvulsants other than valproate was higher for valproate than for lithium (hazard ratio [HR] = 1.86, 95% CI 1.59–2.16). The rate of psychiatric hospital admissions was increased for valproate compared to lithium (HR = 1.33, 95% CI 1.18–1.48), regardless of the type of episode leading to admission (depressive or manic/mixed). These results suggest that in daily clinical practice, treatment with lithium seems in general to be superior to treatment with valproate. This study also showed the advantages of lithium compared to valproate.

Kleindienst et al. [21] systematically integrated the available evidence on the prediction of response to prophylactic lithium based on clinical factors. As a result, of 42 potential clinical predictors investigated, two were identified as positive predictors of prophylactic lithium: an episodic pattern of mania-depression-interval, and a high age of illness onset. Three variables were also identified as negative predictors: a high number of previous hospitalizations, an episodic pattern of depression-mania-interval, and continuous cycling. Checking these predictors when deciding whether lithium or valproate should be administered would appear to be useful.

Although lithium is known to prevent suicide in

people with mood disorders [22], it is unknown if lithium in drinking water could also help lower the risk in the general population. To investigate this, Ohgami et al. [23] examined lithium levels in tap water in the 18 municipalities of Oita prefecture in Japan in relation to the suicide standardized mortality ratio (SMR) in each municipality. They found that lithium levels were significantly and negatively associated with SMR averages for 2002–2006. These findings suggest that even very low levels of lithium in drinking water may play a role in reducing suicide risk within the general population.

DISCUSSION

This review shows that, although lithium and valproate have comparable anti-manic effects, manic patients who respond well to lithium are euphoric but manic patients who respond poorly to lithium have more than 10 past recurrences, and are in a mixed state and/or have dysphoric mood and mood-incongruent psychotic features such as delusions of persecution. Compared to lithium, valproate exhibits anti-manic efficacy in manic patients with more past recurrences and may be more effective in patients with mixed conditions and rapid cycling.

Both lithium and valproate exhibit modest anti-depressant effects that are sufficient in some depressive patients but not sufficient in others. In the latter, an antidepressant might have to be added when the use of these mood-stabilizers fails to achieve remission. Alternatively, such patients may benefit from being switched to lamotrigine or receiving it concomitantly. Lamotrigine, however, may cause critical skin disorders such as mucocutaneous ocular syndrome (Stevens–Johnson syndrome) or toxic epidermal necrolysis (Lyell syndrome), and it is therefore recommended that treatment be initiated at a low dose, and that the dose be increased gradually, with much caution.

Lithium may have more prophylactic efficacy than valproate. An episodic pattern of mania-depression-interval, and a high age of illness onset may be positive predictors for lithium prophylaxis, whereas a high number of previous hospitalizations, an episodic pattern of depression-mania-interval, and continuous cycling may be negative predictors.

Even very low levels of lithium in drinking water may contribute to a reduction in suicide risk in the general population.

In conclusion, both lithium and valproate are useful for treating bipolar disorders, and there are several measures that can be used to differentiate their clinical positioning.

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