

# The Use of Anticonvulsants to Augment Antidepressant Medication

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Combination therapy that couples classical antidepressants with other psychoactive compounds is one of the major therapeutic strategies in therapy-resistant depression. The authors review reports on the antidepressive effects of the mood stabilizers carbamazepine and valproate and focus on the pharmacodynamic and clinical aspects of combining these compounds with antidepressant drugs. In addition, a pivotal study (N = 10 outpatients) demonstrates the use and efficacy of a low-dose combination therapy of carbamazepine and amitriptyline. It is concluded that low-dose combination of classical antidepressants and mood stabilizers appears to be well tolerated and highly effective.

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Therapeutic strategies in the augmentation of antidepressant effects of thymoleptics may be regarded from the point of view of systemic considerations about neurobiological interactions between subsystems, relevant in the regulation of mood. As a matter of fact, several modes of interaction play a role in fortifying antidepressant actions: (1) pure constitutional effects, e.g., by hormonal actions; (2) molecular interactions as one site of targeting the neuronal system, e.g., by combining primary, secondary, and tertiary neurotransmission effects; (3) co-transmission and neuromodulation; and (4) systemic interactions between distant, macroscopically coupled subsystems of the central nervous system (CNS).

With the concept of augmentation, the traditional conviction, which has dominated classical psychopharmacology for some time, that *one* disease has to be treated simply by *one* drug, is given up. The complexity and autoregulatory of the CNS requires a more complex and multimodal targeting of depression.

From a practical clinical point of view, the acute treatment and prophylaxis of depression may require the recognition of the following four factors:

1. constitutional factors, such as the compensation for hormonal deficits, which may be present regarding, e.g., estrogens or thyroid functions
2. chronobiological aspects (Recognition has to be given to chronological aspects—the time course of an individual case history. How does the phase-chart look? What are the predictions, to be derived from the phase-calendar, that are the chronobiological “rules” of the disease-process?)
3. psychiatric and medical history (Which specific combinations or alternatives—e.g., opioids, sleep deprivation, electroconvulsive therapy [ECT]—may be useful with regard to the patient’s psychiatric and medical history?)
4. other factors (Is the personality of the patient understood with regard to the “melancholic subtype of personality”? What are the psychic circumstances the patient has been living in?)

## MOOD-STABILIZING ACTION OF ANTICONVULSANTS

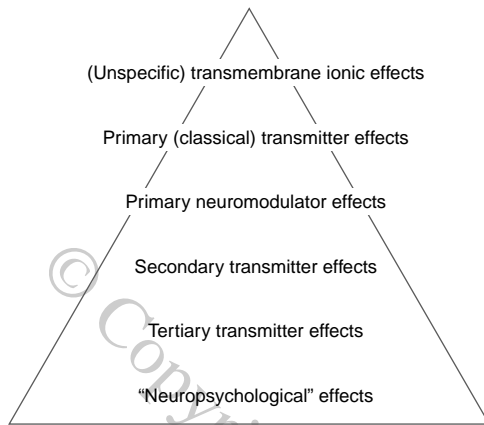
From a neurobiological point of view, the psychopharmacologic effects of different mood stabilizers, especially the anticonvulsants carbamazepine and valproate, represent a challenging problem, as the different modes of action of these compounds have to be attributed to a common mechanism regarding the regulation of affect. An elucidation of this would require an understanding of the basic neurobiological mechanisms underlying the pathogenesis of affective disorders and also would imply an elucidation of the modes of action of the different compounds. Though we are far removed from such an understanding, it appears important to outline the basic mechanisms relevant to the

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**Figure 1. Hierarchy of Mood-Stabilizing Mechanisms\***

\*Adapted from reference 91. Figure 1 shows a hierarchy of the neurobiological organization levels indicating different mechanisms of mood-stabilizing action.

interpretation of the effects of combination therapies that pair mood stabilizers with antidepressants.

The representation of the different organizational levels on which the actions of mood stabilizers may be understood is provided in Figure 1. These levels, moreover, have to be synoptically considered from the perspectives of (1) neurons as representing autoregulative units, and (2) system neurobiology of the CNS as a whole.

### Neurobiology of Mood-Stabilizing Effects of Anticonvulsants

Primary modes of action of mood stabilizers are considered to be transmembrane ionic effects on sodium, potassium, and calcium conductance (e.g., Heinemann et al.,<sup>15</sup> Macdonald<sup>17</sup>). Other possible mechanisms of action are the classical primary neurotransmission (e.g., Post et al.,<sup>18</sup> Schmutz et al.<sup>19</sup>) and the secondary neurotransmission with its cyclase, inositol mechanisms, calcium antagonism, and actions at G-protein functions (e.g., Avissar et al.,<sup>20</sup> Schubert et al.,<sup>21</sup> and Walden et al.<sup>22</sup>). Carbamazepine has been found to modulate tertiary neurotransmission, namely the release of genetic information from the DNA library, by upregulating the  $\beta$ -receptor mRNA.<sup>23</sup>

An integrative view of the organizational levels of neurons requires an understanding of neuronal cells as representing autoregulatory units in which the different (electrical, ionic, and neurobiochemical) processes are functionally coupled in a self-referential way; the intracellular calcium concentration seems to be at the center of each neuronal cell.<sup>24</sup>

Therefore, calcium is regarded as an important factor in mediating mood-stabilizing action.<sup>25</sup> Investigations have been conducted on the calcium turnover influenced by lithium (e.g., Aldenhoff and Lux<sup>26</sup>) and also on calcium-antagonistic effects of carbamazepine.<sup>27,28</sup> In a review,

Schmutz et al.<sup>19</sup> summarized the following effects of valproate and carbamazepine: a voltage-dependent sodium-inwards current is seen as inhibited and a potassium-outwards current as facilitated. In addition, a possibly crucial calcium-influx impairment is described.

Within the field of primary neurotransmission, the GABA hypothesis of affective disorders, put forward by Emrich et al.<sup>25</sup> in 1980, claims that cortical GABA efficacy is insufficient in relation to other neurochemical activities of the brain in patients with affective disorders. This speculation was based on the acute antimanic and bipolar-prophylactic effects of sodium valproate, which was at that time accepted as being a GABAergic anticonvulsant. In further studies, an inhibitory effect of valproate<sup>29</sup> and of carbamazepine<sup>30</sup> on GABA turnover with a consecutive activation of GABA transmission was shown, as was, furthermore, a similar effect on dopamine turnover of both compounds. Concerning carbamazepine, they<sup>30</sup> additionally described a reduced action of the excitatory ligands glutamate and aspartate.

Summarizing the neurobiological effects of valproate and carbamazepine, one may conclude that the mood stabilizers exert a sizable number of relatively complex actions on different subsystems of neurons that influence neuronal excitability.

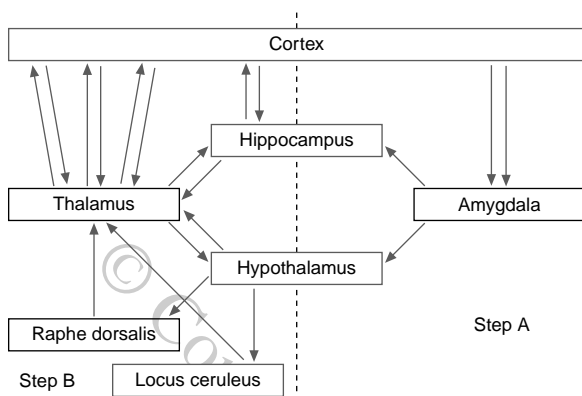
### Neuropsychological Considerations Regarding the Action of Mood Stabilizers

The most complex level of understanding of the mode of action of mood-stabilizing compounds is the neuropsychological level. The following perspectives are relevant here: how is the relation between cognitive and/or sensory semantic contents and the concomitant affective "tone" established?

Within this context, two steps of transference—that is, two types of translation procedures—have to be anticipated: step A is the transduction from cognition/perception into emotional processes, and step B is the translation of emotional activations into activity/inhibition of cognitive and sensory semantic contents (Figure 2).

According to the work of Aggleton and Mishkin,<sup>31</sup> the gating entrance area for transference of sensory and cognitive semantic contents to the limbic brain is the amygdala nuclei. The effects of the anticonvulsants valproate and carbamazepine on amygdala kindling (e.g., Post et al.<sup>32,33</sup>) may shed some light on the pharmacopsychiatry of these compounds in respect to the Aggleton/Mishkin concept.<sup>31</sup> Since these anticonvulsants appear to prophylactically suppress manic and depressive episodes, one may interpret this action as being due to an inhibition of cognition/emotion coupling (step A); i.e., it is assumed that cognitive and sensory semantic contents tend to be to a reduced extent effective in releasing concomitant emotional behavior. Several clinical observations support this concept: symptoms such as episodic dyscontrol,

**Figure 2. Scheme of the Functional Organization of the Brain\***



\*Divergence modulation is exerted from the locus ceruleus and raphe dorsalis to subcortical areas, whereas the amygdala nuclei are interpreted as gating areas in the regulation of the coupling between emotion and cognition/perception, representing major aspects of step A.

outbursts of rage, and affective symptoms of patients with borderline personalities (cf. Stein,<sup>34</sup> Garbutt and Loosen<sup>35</sup>) also respond to low dosages of carbamazepine, which reduces the concomitant emotional activation within these types of disorders.

Concerning step B, namely, the coupling between emotion and cognition/perception, one may refer to a concept by Synder,<sup>36</sup> the divergence principle: 3000 locus ceruleus cells in humans reach nearly 30% to 50% of all cortical neurons, shifting their state of activation to higher levels. Classical unidirectionally acting psychoactive compounds like amphetamines, cocaine, tranlycypromine, and possibly the classical antidepressants, may be interpreted as acting on step B by such a mode of divergence modulation (Figure 2).

This divergence modulation activates the interaction between thalamic and cortical neurons. According to Mumford,<sup>37</sup> this interaction is characteristic for a thalamo-cortical feedback loop, which is assumed to represent a process of conceptualization. As a consequence, it may be anticipated that brain stem-derived activating divergence modulation increases the activity of conceptualizing systems, generating increased activity of sensory processes as well as of cognitive activities. From this point of view, the step A/step B interaction of the coupling between emotion and cognition/perception appears to represent an interactive self-referential feedback system that can, to some extent, selectively be influenced by mood stabilizers, especially anticonvulsants.

### HISTORICAL AND CLINICAL ASPECTS OF ANTICONVULSANTS IN AFFECTIVE DISORDERS

Therapeutically, one of the most fruitful discoveries in pharmacopsychiatry was the prophylactic effect of chronic

lithium administration in patients with affective and schizoaffective disorders. Although this therapy represents an important step, several problems remained unresolved: one was the partial or nonresponse of approximately 30% of patients with affective psychoses and of approximately 50% of patients with schizoaffective psychoses; another was the problem of side effects and, resulting from this, noncompliance. For this reason, the introduction of the anticonvulsants valproate and carbamazepine for pharmacologic treatment of affective and schizoaffective disorders was important, as these compounds apparently have a lithium-like clinical profile of action.

Historically, the first anticonvulsant medication used in psychoses was diphenylhydantoin. The psychotropic, especially mood-stabilizing, effect of diphenylhydantoin—in contrast to bromide and phenobarbital—was observed in the 1930s. In the first clinical trials carried out by Kalinowsky and Putnam,<sup>38</sup> a pronounced result was seen in manic patients with affective psychoses compared with those with schizophrenic psychoses. Following a lack of interest in the therapeutic efficacy of diphenylhydantoin during the next years, another anticonvulsant was introduced for the treatment of affective psychoses: dipropylacetamide (an amide of valproate) was used by Lambert et al.,<sup>39,40</sup> who found an antimanic efficacy and a supportive effect with neuroleptics. In contrast to a rather poor antidepressant effect, a sizable prophylactic efficacy of dipropylacetamide was seen, especially if combined with lithium, a finding that was supported by other investigators.<sup>41,42</sup>

After the first reports of Lambert et al.,<sup>39</sup> Takezaki and Hanaoka<sup>43</sup> found that the anticonvulsant carbamazepine was clinically effective in manic states in patients with organic psychoses. Also, patients with endogenous mania improved with carbamazepine treatment. Following these years, Okuma et al.<sup>44</sup> reported a strong effect of carbamazepine on acute manic symptoms as well as a prophylactic efficacy in patients with bipolar affective disorders. In addition, the antimanic, as well as the prophylactic, effect of carbamazepine was much better than the antidepressant.<sup>45</sup> However, international attention to these findings was raised in 1980 after a placebo-controlled, double-blind study by Ballenger and Post<sup>46</sup> replicated the antimanic properties of carbamazepine under controlled circumstances. During the next years, the development of carbamazepine as a therapeutic and prophylactic drug in affective and schizoaffective psychoses took place. In addition, oxcarbazepine, the ketoderivative of carbamazepine, was shown to have anticonvulsant as well as antimanic and prophylactic effects with regard to affective disorders.<sup>47,48</sup>

When the possible role of valproate in treating mania was investigated by Emrich et al.<sup>25</sup> under double-blind conditions, acute antimanic efficacy was shown. Patients

with no or partial response to lithium had a chance to receive effective prophylactic therapy by coadministration of valproate while the serum lithium level was reduced. In addition, patients with schizoaffective psychoses improved significantly using this combination,<sup>49</sup> although the prophylactic effect was superior in the patients with affective disorders compared with that in the schizoaffective patients.

### ANTIDEPRESSANT ACTIONS OF CARBAMAZEPINE AND VALPROATE

Irrespective of the possible therapeutic effects of anti-convulsants as adjuncts to thymoleptic compounds, carbamazepine and valproate have been used alone as atypical antidepressants under several circumstances.

#### Carbamazepine as an Antidepressant

The first to report antidepressant effects of carbamazepine were Ballenger and Post,<sup>46</sup> who investigated 13 depressed patients using a controlled single-blind ABAB-design. Seven patients showed a sizable or only partial antidepressant response to carbamazepine treatment. In further studies, Ballenger<sup>50</sup> supported this evidence under double-blind and placebo-controlled conditions.

Compared with other antidepressants (e.g., trimipramine), carbamazepine has been reported to produce the same response rate<sup>51</sup> after 4 weeks of treatment and to have an earlier onset of the antidepressant effect including a reduction of fear, psychomotor restlessness, autoaggression, and hypochondriac symptoms.

Sethi and Tiwari<sup>52</sup> compared the antidepressant effect of carbamazepine with that of imipramine in 10 patients and found a stronger antidepressant effect of carbamazepine (compared with imipramine) after 1 week but a superior efficacy of imipramine after 4 weeks of treatment. One reason for this difference was hypothesized to be the autoinductive effect on cytochrome P450 associated with a consecutive reduction of carbamazepine.<sup>53</sup> In open studies, Wunderlich et al.<sup>54,55</sup> reported an improvement in 6 (55%) of 11 major depressive and bipolar patients, and a response-rate of 11 of 13 patients in an additional study.<sup>56</sup>

In therapy-resistant chronic depressed patients, Prasad<sup>57</sup> found a response to carbamazepine in 11 of 12 cases. Emrich et al.<sup>58</sup> described 3 patients with extremely severe, and up to then therapy-resistant, courses of affective/schizoaffective psychoses; a remarkable and stable improvement was noticed in all patients, after several months of carbamazepine treatment.

Concerning the onset of the antidepressant effect, it should be noted that the patients treated by Emrich et al.,<sup>58</sup> Frankenburg et al.,<sup>59</sup> and Post<sup>60</sup>—who found a late onset of antidepressant effect of carbamazepine compared with the onset of the antimanic effect—were more chronically ill than the patients treated by Neumann et al.<sup>51</sup> and by Sethi

and Tiwari,<sup>52</sup> who showed an earlier onset of antidepressant action.

Concerning its efficacy in certain subtypes of affective disorders, carbamazepine (like lithium) seems to have more antidepressant effect in bipolar than in unipolar depressive disorders.<sup>50</sup> On the basis of the findings of these and other studies that also point to a certain antidepressant efficacy of carbamazepine,<sup>61–63</sup> the use of carbamazepine as an antidepressant may be most effective in the treatment of bipolar and therapy-resistant and/or chronically depressed patients, especially patients with somatic symptoms. The dopaminergic as well as GABAergic effects were reported as being possible major reasons for the antidepressant (as well as antimanic) effects of carbamazepine.<sup>64–67</sup>

#### Valproate as an Antidepressant

No placebo-controlled studies exist examining the efficacy of valproate in the treatment of acute depressive episodes. However, some studies report on antidepressant effects; for example, Lambert et al.<sup>39</sup> described an antidepressant efficacy of dipropylacetamide (an amide of valproate) in an open study of psychiatric patients with melancholia. Since some patients also received small doses of antidepressants and/or neuroleptics, it appears difficult to determine the antidepressant effect of dipropylacetamide in this study. Others,<sup>68–73</sup> while describing certain antidepressant effects, reported chiefly on antimanic effects of valproate. In these open studies, the overall rate of acute antidepressant response was only about 20% to 40%. Comparing this with the results of McElroy et al.,<sup>74</sup> who reported a response rate for valproate of about 60% in acute manic patients, the antidepressant effect of valproate appears rather poor. However, valproate appeared to be more effective in the treatment of depression over a long period of time and in the prophylaxis of depressive and especially manic episodes<sup>72,73</sup> in patients with bipolar I disorders and in schizoaffective patients. There have also been reports on successful valproate treatment of cyclothymia or bipolar II disorders<sup>69,75</sup> and of rapid-cycling unipolar affective disorders.<sup>76</sup> The latest study by Davis et al.<sup>77</sup> was an open and systematic trial on the efficacy of valproate monotherapy in patients with major depressive disorder who had no history of mania or hypomania; Davis and colleagues described a 66% response rate after 8 weeks of treatment (with a dosage of 1200–1500 mg/day), which is comparable with the response to standard antidepressant treatment of major depressive disorders. Therefore, the antidepressant effect of valproate in this study was superior to the 30% to 40% response rate of other mood stabilizers such as lithium<sup>78</sup> and the 30% to 60% response rate of carbamazepine.<sup>79,80</sup> In line with carbamazepine, one major mode of antidepressant action for valproate was also assumed to be the GABAergic effect (Davis et al.<sup>77</sup>).

## PHARMACOLOGIC INTERACTIONS BETWEEN ANTIDEPRESSANTS AND ANTICONVULSANTS

Due to the long-term use of carbamazepine and valproate in epilepsy, various potential pharmacokinetic and pharmacodynamic interactions of these drugs have been described. In contrast, only a limited number of studies or case reports have focused on the pharmacologic interactions of anticonvulsant and antidepressant medication. Carbamazepine is highly protein-bound and induces a metabolism of other drugs that are metabolized by the liver. Therefore, it may show important interactions with other drugs stemming from changes in hepatic metabolism and protein binding.<sup>81-83</sup> It decreases the plasma levels, for example, of neuroleptics, benzodiazepines, other anticonvulsants, hormonal contraceptives, thyroid hormones, and tricyclic antidepressants (as shown below). In contrast, the serum carbamazepine concentration may be increased by drugs that inhibit carbamazepine metabolism, such as the calcium channel blockers verapamil and diltiazem and, potentially, the serotonin selective reuptake inhibitors (SSRIs). Carbamazepine is structurally related to tricyclic antidepressants (TCAs), and the peak levels of the single dose are obtained about 1 to 6 hours after ingestion depending on the type of preparation (suspension or tablet). The maximum blood levels are reached in about 2 to 4 days, and the elimination half-life of carbamazepine ranges from 18 to 55 hours after acute administration and 5 to 25 hours after long-term use. As carbamazepine stimulates its own metabolism, upward dose adjustment may be required after a few weeks.

The general drug interactions of valproate are partly different from those of carbamazepine. Because valproate is also metabolized by the liver and highly protein-bound, interactions may occur with other hepatically metabolized or protein-bound drugs.<sup>84</sup> Serum concentrations of drugs that are oxidatively metabolized (e.g., phenobarbital, phenytoin, and TCAs) can be increased when coadministered with valproate. Serum valproate concentration itself can be decreased by coadministration of microsomal enzyme-inducing drugs (e.g., carbamazepine) and may be increased by drugs inhibiting this metabolism (e.g., fluoxetine). Substances that can interact with valproate protein binding (e.g., aspirin) may increase the free serum valproate concentration and toxicity. Valproate is rapidly absorbed after ingestion and reaches peak plasma levels in 1 to 4 hours and peak serum concentration within 3 to 8 hours. The plasma half-life ranges from 5 to 20 hours (e.g., Bezchlibnyk-Butler and Jeffries<sup>85</sup>).

Contraindications for carbamazepine are a history of hepatic and cardiovascular disease or a blood dyscrasia or a hypersensitivity to any tricyclic compound. For valproate, the major contraindications are liver dysfunctions. Further pharmacokinetic information and side effects concerning carbamazepine and/or valproate are described in a

substantial literature (e.g., Rall and Schleifer,<sup>81</sup> Ketter et al.,<sup>82,83</sup> Janicak et al.,<sup>86</sup> Smith and Bleck,<sup>87</sup> Penry and Dean,<sup>88</sup> Gilman et al.<sup>89</sup>).

The results of different studies concerning the pharmacologic drug-drug interactions of anticonvulsant and antidepressant medication are shown in Table 1. In summarizing the findings of these studies, it could be noted that serum levels of TCAs may be reduced up to 50% by a carbamazepine coadministration due to enzyme induction and may be increased by 50% if combined with valproate. For monoamine oxidase inhibitors (MAOIs), one group reports a reduction of serum carbamazepine levels, whereas two other authors did not find a significant interaction with carbamazepine. Data show no significant change of serum carbamazepine level related to the SSRIs (fluoxetine and fluvoxamine). With regard to valproate, the only study on the combination with fluoxetine reported an increased serum valproate level.

## CLINICAL ASPECTS OF COMBINING ANTICONVULSANTS WITH THYMOLEPTICS

In an open pivotal study in 10 outpatients (6 men, 4 women) with major depression (DSM-IV criteria), carbamazepine was combined with low doses of amitriptyline (the doses ranged from 100 to 400 mg for carbamazepine and 25 to 65 mg for amitriptyline), as shown in Table 2. In most of the patients, carbamazepine and amitriptyline were given in a single dose at night (between 8 and 11 p.m.). No patient had a severe medical illness or a neurologic history. Five (50%) patients showed a very good therapeutic effect, 4 patients showed a good or moderate improvement of their depression, and 1 patient showed only a slight improvement. No patient mentioned severe side effects, and the overall compliance was excellent. However, this observation requires further corroboration by operationalized investigations.

From a theoretical point of view, this result may be interpreted as being due to a combination of two types of mechanisms, described earlier in this article, pointing to the idea that the observed enhancement of thymoleptic efficacy by anticonvulsants may be due to the presence of two completely neuropsychologically distinct functional subsystems in the mood regulation of the CNS (see Figure 2): (1) on the one side, the amygdaloid-temporal lobe regulatory mechanisms, which have been elucidated by Davis<sup>90</sup> and, neuropsychologically, by Aggleton and Mishkin<sup>31</sup>; and (2) on the other side, the major mechanisms of thymoleptic therapy on, e.g., brain stem and such cortical neurons and neurotransmitter systems such as the norepinephrine, dopamine, and serotonin systems, which are assumed to directly be involved in endogenous depression. The combination of targeting these two types of modes of action in the regulation of affect may be of great advantage; one advantage may be the multimodal targeting of

**Table 1. Studies Reporting on the Pharmacodynamic Aspects of the Combination of Antidepressants and Anticonvulsants\***

| Antidepressant               | Anticonvulsant           | Study   | Comment   | Effect   |
|------------------------------|--------------------------|---|---|--|
| <b>TCA</b>                   |                          |   |   |  |
| Amitriptyline                | Carbamazepine            | Leinonen et al. <sup>1</sup> (1991)           | (N = 8)   | Amitriptyline (and nortriptyline) ↓ (~40%)   |
| Nortriptyline                | Carbamazepine            | Brøsen and Kragh-Sorenson <sup>2</sup> (1993) | Case report                                     | Nortriptyline ↓  |
| Doxepin                      | Carbamazepine            | Leinonen et al. <sup>1</sup> (1991)           | (N = 17)  | Doxepin ↓ (~45%)   |
| Imipramine                   | Carbamazepine            | Brown et al. <sup>3</sup> (1990)              | Treatment of children with attentional deficits | Imipramine, desipramine ↓  |
| Amitriptyline, nortriptyline | Valproate                | Vandel et al. <sup>4</sup> (1988)             | Amitriptyline (N = 10)                          | Amitriptyline, nortriptyline ↑ (~50%)  |
| Nortriptyline                | Valproate                | Fu et al. <sup>5</sup> (1994)                 |   | Nortriptyline ↑  |
| Desipramine                  | Valproate                | Joseph and Wroblewski <sup>6</sup> (1993)     | Case report (patient after brain injury)        | Desipramine ↑ after valproate discontinuation  |
| <b>MAOI</b>                  |                          |   |   |  |
| Tranlycypromine              | Carbamazepine            | Joffe et al. <sup>7</sup> (1985)              |   | No significant interaction   |
| Tranlycypromine              | Carbamazepine            | Barklage et al. <sup>8</sup> (1992)           | (N = 5)   | Carbamazepine ↓  |
| Tranlycypromine, phenelzine  | Carbamazepine            | Ketter et al. <sup>9</sup> (1995)             | Tranlycypromine (N = 6), phenelzine (N = 4)     | For both: no significant interaction   |
| <b>SSRI</b>                  |                          |   |   |  |
| Fluoxetine                   | Carbamazepine            | Pearson <sup>10</sup> (1990)                  | 2 case reports                                  | Carbamazepine ↑  |
| Fluoxetine                   | Carbamazepine            | Grimsley et al. <sup>11</sup> (1991)          |   | Carbamazepine ↑ (~30%)   |
| Fluoxetine, fluvoxamine      | Carbamazepine            | Spina et al. <sup>12</sup> (1993)             | Epileptic patients (N = 15)                     | No significant change of carbamazepine levels  |
| Fluoxetine                   | Valproate                | Soyner and Davis <sup>13</sup> (1991)         |   | Valproate ↑  |
| <b>Other</b>                 |                          |   |   |  |
| Trazodone                    | Carbamazepine            | Otani et al. <sup>14</sup> (1996)             | (N = 3)   | Trazodone and its active metabolite ↑  |
| Mianserin                    | Carbamazepine            | Leinonen et al. <sup>1</sup> (1991)           | (N = 4)   | Mianserin ↓ (~30%)   |
| Bupropion                    | Carbamazepine, valproate | Ketter et al. <sup>15</sup> (1995)            |   | Carbamazepine: bupropion ↓, hydroxybupropion ↑<br>Valproate: bupropion no change<br>hydroxybupropion ↑ |

\*Symbols: ↑ = increase in serum level, ↓ = decrease in serum level.

**Table 2. Therapeutic Effect of the Combination of Amitriptyline and Carbamazepine in a Pivotal Study With 10 Patients\***

| Patient | Age (y) | Gender | Medication (mg) |               | Success |
|---------|---------|--------|-----------------|---------------|---------|
|         |         |        | Carbamazepine   | Amitriptyline |         |
| 1       | 34      | F      | 100             | 35            | ++      |
| 2       | 60      | M      | 150             | 25            | (+)     |
| 3       | 42      | F      | 400             | 65            | ++      |
| 4       | 44      | F      | 150             | 30            | ++      |
| 5       | 60      | M      | 100             | 30            | +       |
| 6       | 63      | M      | 300             | 35            | ++      |
| 7       | 51      | M      | 100             | 25            | +       |
| 8       | 40      | M      | 150             | 25            | +       |
| 9       | 59      | M      | 200             | 30            | +       |
| 10      | 47      | F      | 400             | 30            | ++      |

\*The therapeutic success is noted with symbols: ++ = very good effect (reduction of HAM-D score [21 items] > 50% after 4 weeks of treatment), + = good/moderate effect (HAM-D reduction between 30% and 50%), (+) = only slight effect.

depression itself, and another is the reduction of side effects, which may also enhance the overall compliance of the patients. A further advantage is that anticonvulsants as well as antidepressants may be given in a single dose at night, which simplifies the drug administration in general, reduces the recognition of unwanted side effects by the patients, and makes use of other side effects to improve sleep. Although severe drug-drug interactions are unlikely to occur at these dosages, serum level controls of anti-

convulsants and TCAs may be useful. In the case of a combination of tricyclics and carbamazepine, the serum tricyclic level can be decreased; therefore, an enhancement of tricyclics may be required. When combining TCAs with valproate, the possible increase in serum level of the tricyclics should be carefully observed. SSRIs may increase the serum levels of carbamazepine—and valproate—to a certain extent, whereas the combination of MAOIs and carbamazepine induces no major or very small interferences. With regard to the idea of a multimodal targeting of depression and a possible more-than-additive antidepressant effect, it appears that serum levels of anticonvulsants as well as antidepressants may be below the normal therapeutic levels when these drugs are combined. The experiences from the above-mentioned pivotal study support this evidence.

Summarizing these findings, anticonvulsants used to augment antidepressant medication under specific conditions, e.g., therapy resistance of depressive syndromes or appearance of major side effects with “normal” doses of monotherapy, are of great theoretical and practical interest.

*Drug names:* amitriptyline (Elavil and others), bupropion (Wellbutrin), carbamazepine (Tegretol and others), clonazepam (Clozaril), desipramine (Norpramin and others), diltiazem (Cardizem), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (To-

franil and others), nortriptyline (Pamelor and others), phenelzine (Nardil), phenobarbital (Luminal and others), phenytoin (Dilantin and others), tranylcypromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil), verapamil (Calan and others).

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#### DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated as antidepressants: carbamazepine, valproate.