Controlled Double-Blind Trial of Phenytoin vs. Fluoxetine in Major Depressive Disorder

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Background: Phenytoin was the first nonsedative anticonvulsant introduced and is still the anticonvulsant most widely used worldwide in neurology. Given the efficacy of the anticonvulsant lamotrigine in the depressed phase of bipolar disorder, a critical theoretical question is whether other anticonvulsants used in treating bipolar disorder might be similarly effective. We therefore undertook a controlled trial of phenytoin versus fluoxetine in major depressive disorder.

Method: Data were collected from July 2001 to July 2003. Thirty-three subjects entered the study. All patients met DSM-IV criteria for major depressive disorder and scored a minimum of 18 on the 24-item Hamilton Rating Scale for Depression (HAM-D) at baseline. After a 3-day washout of any previous medications, patients were randomly assigned to fluoxetine or phenytoin in identical capsules. Each capsule contained phenytoin 100 mg or fluoxetine 7 mg plus cornstarch. Patients started with 1 tablet daily and increased every other day until they were taking 1 tablet 3 times daily with meals. Blood phenytoin levels were taken after 1 week, 3 weeks, and 6 weeks, and dosage was adjusted to achieve blood levels of 10 to 20 μg/mL, to a maximum dose of 4 capsules per day or a minimum dose of 2 capsules per day. Fluoxetine patients were assigned dummy blood phenytoin levels by the control psychiatrist such that the treating physician would raise the number of capsules to at least 3 per day (20 mg of fluoxetine).

Results: Thirty-three patients entered the study, and 28 (N = 14 in each treatment group) completed at least 3 weeks and were included in the data analysis. Patients who dropped out after week 3 (3 patients) were included in the study as last value carried forward. There was no difference between treatment groups in overall rate of response or speed of response.

Conclusion: The absence of a placebo arm in our study allows for the possibility that neither treatment was more effective than placebo. However, the exclusion of past fluoxetine nonresponders and the minimum HAM-D score at baseline of 18 make this possibility unlikely.

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Phenytoin was the first nonsedative anticonvulsant introduced and is still the most widely used anticonvulsant worldwide in neurology. Interestingly, in the 1940s and 1950s, numerous reports were published on improvement of depressive symptoms and irritable symptoms in adults and children with epilepsy who were treated with phenytoin. Some controlled studies of phenytoin in depression-related syndromes were published.[1–4] However, no modern study has been done of the efficacy of phenytoin in DSM-IV–diagnosed major depressive disorder. Given the apparent efficacy of other mood stabilizers in depression, the possible efficacy of phenytoin would be of significant theoretical importance. Moreover, the treatment of epilepsy is characterized by a trial-and-error polypharmacy approach. Despite the fact that many antiepileptic compounds have similar modes of action on voltage-activated sodium channels and γ-aminobutyric acid (GABA), it is clinically well accepted that efficacy can be improved by finding the right drug for the right patient and/or adding a second drug when the first is not entirely effective even if both drugs have similar mechanisms of action.

Recently, lamotrigine has attracted considerable interest as an anticonvulsant treatment of bipolar disorder with possible specific activity in the treatment and prophylaxis of the disorder's depressive phase. Calabrese et al.[5] reported acute efficacy of lamotrigine in depressed bipolar patients. Bowden et al.[6] reported prophylactic efficacy of lamotrigine for depressive episodes of bipolar disorder over 18 months in over 200 patients versus placebo.

Lamotrigine's efficacy in the depressed phase of bipolar disorder raises the critical theoretical question as to whether it is different in this matter from other anticonvulsants used in treating bipolar disorder or indeed from the classic mood stabilizer lithium. Lithium was studied as an antidepressant in numerous small studies in the 1970s. In most studies, it was shown to be effective.[7–13] While many of the studies would not meet modern U.S. Food and Drug

Administration methodological criteria, for instance because of small sample size or crossover design, it would seem unwise to ignore them, given their consistent message of efficacy. In Europe, several large studies found powerful prophylactic effects of lithium in unipolar depression as well.[14–16] One key study[13] found antidepressant efficacy for lithium in acute depression, although its efficacy was smaller than that of the comparator, imipramine. In animal models, lithium is usually found to be active as an antidepressant, although not necessarily as powerful as monoamine reuptake inhibitors.[17] Taken together, these data would seem to support the concept that lithium has effects in depression despite methodological criticism of specific studies.

Carbamazepine, the first anticonvulsant mood stabilizer, was first tried in bipolar disorder because of reports by neurologists of mood improvement in depressed epileptic patients taking carbamazepine. Only small studies exist of carbamazepine in bipolar or unipolar depression, but these are generally positive.[18–20] Supporting the concept that carbamazepine too has antidepressant properties are the reports that carbamazepine, like lithium, can augment the effects of monoamine reuptake inhibitors in patients who have failed to fully respond to those monoamine reuptake inhibitors.[21] Valproate, a mood stabilizer widely used in the United States today, for which large controlled studies have been conducted with the patented divalproex sodium, has also been studied in depression.[22–26] These studies were preceded by early reports of the beneficial effects of divalproex sodium on mood in epileptic children and adults with depression or irritability.

Given all of the above-described findings, the possibility that phenytoin may be useful in depression may be of value to some patients who have not responded to other antidepressants. We therefore undertook a controlled trial of phenytoin versus fluoxetine in major depressive disorder. Ethical considerations made a trial of placebo versus phenytoin problematic.

METHOD

The protocol was approved by the Ethical Review Board of Ben Gurion University to comply with the recommendations of the Declaration of Helsinki. Data were collected from July 2001 to July 2003. Patients were recruited from clinician referrals to the Beersheva Mental Health Center Depression Clinic, Beersheva, Israel; no advertisement was done. All patients met DSM-IV criteria for major depressive disorder. Minimum Hamilton Rating Scale for Depression[27] (24-item HAM-D) score at baseline was 18. Patients entered the study after baseline physical exam, blood chemistry and hematology, and electrocardiogram were performed and written informed consent was obtained. Patients with significant risk of suicide, need for hospitalization, or unstable medical illnesses were excluded. Patients currently (in the past month) receiving antidepressant treatment were excluded. First-episode patients were excluded. Patients who had not responded to any antidepressant treatment in the past, e.g., had received electroconvulsive therapy or were depressed without remission for more than 1 year continuously despite treatment in past episodes, were excluded. Most patients were referred because of side effects from SSRIs other than fluoxetine in past episodes of depression.

After a 3-day washout of any current benzodiazepine medications, patients were randomly assigned to fluoxetine or phenytoin in identical capsules. Each capsule contained phenytoin 100 mg or fluoxetine 7 mg plus cornstarch. Patients started with 1 tablet daily and increased every other day until they were taking 1 tablet 3 times daily with meals. Blood phenytoin levels were taken after 1 week, 3 weeks, and 6 weeks, and dosage was adjusted to achieve blood levels of 10 to 20 μg/mL, to a maximum dose of 4 capsules per day or a minimum dose of 2 capsules per day. Fluoxetine patients were assigned dummy blood phenytoin levels by the control psychiatrist (R.H.B.) such that the treating physician would raise the number of capsules to at least 3 per day (20 mg of fluoxetine). Fluoxetine is considered to be equally effective in doses from 20 to 30 mg daily.[28] The treating psychiatrist who performed the rating scales was blind to whether the patient was taking phenytoin or fluoxetine. Upon entry of a patient into the study, the treating psychiatrist received from the control psychiatrist a bottle of tablets of phenytoin or fluoxetine, according to prearranged random order. Patients were allowed up to 10 mg diazepam daily in addition to study medication.

Patients were evaluated at baseline and weekly thereafter with the 24-item HAM-D by an experienced psychiatrist. The trial lasted 6 weeks. Significance was set at $p < .05$.

Special attention was given to instruction of patients in dental hygiene to minimize the risk of gingival hyperplasia. Studies in epilepsy show that this side effect is surprisingly uncommon, despite wide publicity. No cases of gingival hyperplasia were seen in our previous study of phenytoin prophylaxis in bipolar disorder.[29] Patients with any significant side effects were dropped from the study.

RESULTS

Thirty-three patients entered the study, and 28 completed at least 3 weeks and were included in the data analysis. Demographics for these patients are shown in Table 1. Twenty-five patients completed the entire 6 weeks. Patients who dropped out after week 3 (3 patients) were included in the study as last value carried forward. Table 2 shows mean HAM-D total scores for each treatment group from study baseline through endpoint. There was no difference in overall rate of response or speed of

Table 1. Demographic Data of Subjects With Major Depressive Disorder Treated With Phenytoin or Fluoxetine for 6 Weeks

	Phenytoin		Fluoxetine	
Characteristic	Women (N = 8)	Men (N = 6)	Women (N = 12)	Men (N = 2)
Age, mean ± SD, y	45.9 ± 12.2	49.8 ± 4.6	49.6 ± 8.1	38.5 ± 7.8
Age at onset of illness, mean ± SD, y	38.0 ± 13.8	45.8 ± 6.1	40.5 ± 8.5	37.5 ± 9.2
No. of previous affective episodes, mean ± SD	2.6 ± 1.2	3.0 ± 1.0	2.8 ± 1.7	2.0 ± 1.4

Table 2. Response of Subjects With Major Depressive Disorder to Fluoxetine vs. Phenytoin as Measured by the HAM-D[a]

	HAM-D Score (mean ± SD)	
Timepoint	Fluoxetine (N = 14)	Phenytoin (N = 14)
Baseline	29.0 ± 5.4	30.9 ± 5.5
Week 1	23.3 ± 7.2	22.8 ± 10.1
Week 2	20.1 ± 10.5	20.6 ± 11.2
Week 3	17.6 ± 10.1	18.6 ± 9.7
Week 4	13.3 ± 8.2	15.4 ± 8.5
Week 5	11.6 ± 7.2	12.3 ± 6.9
Week 6	10.4 ± 7.4	12.8 ± 6.2

[a]Two-way analysis of variance with Greenhouse-Geisser correction for degrees of freedom shows effect of treatment in both groups with significant improvement on the HAM-D during the 6-week study ($F = 39.1$, $df = 2.8,73.3$; $p < .001$). There are no differences in overall rate of response or speed of response of phenytoin vs. fluoxetine ($F = 0.24$, $df = 2.8,73.3$; $p = .87$ for interaction and $F = 0.22$, $df = 1,26$; $p = .64$ for group effect).

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

response to phenytoin versus fluoxetine. Twelve of 14 fluoxetine patients and 12 of 14 phenytoin patients improved more than 50% on the HAM-D.

Eight patients dropped out: 5 before week 3 (2 fluoxetine and 3 phenytoin) and 3 after week 3 (1 fluoxetine and 2 phenytoin). Of the 3 fluoxetine dropouts, 1 withdrew due to panic attacks, 1 due to improvement and refusal to continue, and 1 due to agitation. Of the 5 phenytoin dropouts, 1 withdrew due to somnolence, 1 due to facial rash, 1 due to depression worsening, 1 due to gastrointestinal side effects, and 1 due to chest pain not diagnosed as myocardial infarction after workup.

Blood phenytoin levels ± SEM were 10.8 ± 1.8 μg/mL at week 1, 13.1 ± 2.8 μg/mL at week 3, and 10.9 ± 2.0 μg/mL at week 6. Dummy blood phenytoin levels were similar.

Table 3 shows a HAM-D item analysis of the responses to fluoxetine and phenytoin. There was not a single significant difference in any item, and there were no clinically relevant trends toward a different pattern of response between the 2 drugs.

CONCLUSION

The ethical and methodological advantages and disadvantages of a placebo arm in a study of disorders with known effective treatment have been extensively discussed.[30] The absence of a placebo arm in our study allows for the possibility that neither treatment was more effective than placebo, although the exclusion of nonresponders in past episodes and the minimum HAM-D score at baseline of 18 make that possibility unlikely. However, the chance that the response in both groups merely reflects an equal placebo response cannot be ruled out.

There were some patients who seemed to have a marked response to phenytoin in a way that did not characterize their previous responses to antidepressants. One 32-year-old married woman had been suffering from recurrent major depressive disorder for 6 years. She had had 4 major depressive episodes and a family history of depression (her mother had been treated with various antidepressants for several decades due to severe recurrent major depressive disorder). The patient, in past episodes, had mildly improved with treatment including venlafaxine up to 225 mg/day, fluoxetine 60 mg/day, mirtazapine 45 mg/day, paroxetine 40 mg/day, and reboxetine 8 mg/day, separately and in various combinations, each given for at least a month. During her most recent episode, she had depressed mood with marked retardation, late insomnia, and diurnal variation (with a score of 30 on the 24-item HAM-D). Her symptoms disappeared dramatically within a week after phenytoin 300 mg daily was started, with a score of 1 on the HAM-D and blood phenytoin level of 29.9 μg/mL. Despite this toxic level of phenytoin, she had no side effects. At week 3 she deteriorated, with a score of 21 on the HAM-D and a phenytoin level of 40 μg/mL, and complained of fatigue, drowsiness, and depressed mood. After 2 days of phenytoin washout she improved and finished the study at week 6 with a score of 13 on the HAM-D and a blood phenytoin level of 19.6 μg/mL. She seemed to be tolerant of high blood phenytoin levels and was also a dramatic responder. This response may be similar to the case of Jack Dreyfus, who wrote an anecdotal autobiographic account of his own dramatic response to phenytoin and his lack of side effects.[31] In general, side effects of phenytoin have been favorably reassessed within the last decade.[32]

Average phenytoin levels that were above 10 μg/mL were in the therapeutic range for epilepsy treatment and were reasonable for a dose of 300 mg daily. If the dose and blood levels had been higher, it is possible that the therapeutic response would have been increased, but side effects might also have been greater.

Not all anticonvulsants have been found to be effective treatments for depression. In particular, those anticonvulsants acting on the GABA receptor complex, such as phenobarbital and benzodiazepines, are sedative and anxiolytic but not antidepressant. Of those anticonvulsants

Table 3. Analysis of Baseline HAM-D Item Scores and Improvement After 6 Weeks of Phenytoin or Fluoxetine in Subjects With Major Depressive Disorder

	Baseline Score		Improvement[a]		
Item	Phenytoin (N = 14)	Fluoxetine (N = 14)	Phenytoin (N = 14)	Fluoxetine (N = 14)	p
1 Depressed mood	2.1 ± 0.4	2.1 ± 0.4	1.14 ± 0.90	1.50 ± 0.76	.21
2 Feelings of guilt	1.6 ± 0.7	1.4 ± 0.7	1.36 ± 0.75	1.21 ± 0.76	.64
3 Suicide	0.8 ± 0.7	0.9 ± 0.8	0.64 ± 0.65	0.86 ± 0.87	.55
4 Insomnia, early	1.1 ± 0.9	1.5 ± 0.8	0.79 ± 0.86	1.21 ± 0.76	.19
5 Insomnia, middle	1.1 ± 0.9	0.8 ± 0.9	1.00 ± 0.96	0.64 ± 0.95	.35
6 Insomnia, late	1.2 ± 1.0	0.7 ± 0.9	0.93 ± 0.95	0.43 ± 0.87	.16
7 Work and activities	2.1 ± 0.3	2.0 ± 0.6	1.07 ± 0.49	1.36 ± 0.87	.27
8 Retardation	1.8 ± 0.6	1.6 ± 0.8	1.36 ± 0.77	1.21 ± 1.09	.73
9 Agitation	0.3 ± 0.6	0.4 ± 0.7	0.00 ± 0.55	0.29 ± 0.63	.25
10 Anxiety, psychic	1.5 ± 0 9	1.9 ± 0.4	0.93 ± 0.69	1.14 ± 0.69	.42
11 Anxiety, somatic	1.7 ± 0.8	1.9 ± 0.4	0.64 ± 0.51	1.07 ± 0.76	.10
12 Somatic symptoms, gastrointestinal	1.6 ± 0.7	1.6 ± 0.7	0.64 ± 0.65	0.79 ± 0.73	.59
13 Somatic symptoms, general	1.9 ± 0.4	1.9 ± 0.4	0.50 ± 0.65	0.79 ± 0.93	.29
14 Genital symptoms	2.0 ± 0.0	1.6 ± 0.8	0.57 ± 0.87	0.43 ± 0.96	.94
15 Hypochondriasis	0.6 ± 0.7	0.4 ± 0.6	0.43 ± 0.50	0.14 ± 0.29	.18
16 Actual weight change	1.4 ± 0.9	1.2 ± 0.9	1.36 ± 0.95	1.21 ± 0.90	.60
17 Insight	0.1 ± 0.4	0.0 ± 0.0	0.07 ± 0.28	0.00 ± 0.00	.32
18 Diurnal variation	1.3 ± 0.9	0.9 ± 0.9	0.93 ± 0.95	0.57 ± 0.88	.34
19 Depersonalization and derealization	0.3 ± 0.9	0.1 ± 0.6	0.29 ± 0.86	0.00 ± 0.00	.15
20 Paranoid symptoms	0.1 ± 0.6	0.1 ± 0.3	0.00 ± 0.00	0.07 ± 0.28	.32
21 Obsessional and compulsive symptoms	0.2 ± 0.4	0.2 ± 0.4	0.14 ± 0.38	0.14 ± 0.38	1.00
22 Helplessness	2.0 ± 0.4	1.9 ± 0.7	1.07 ± 0.64	1.07 ± 0.86	.83
23 Hopelessness	2.2 ± 0.4	1.9 ± 0.6	1.43 ± 0.66	1.43 ± 0.88	1.00
24 Worthlessness	2.1 ± 0.5	2.0 ± 0.6	1.21 ± 0.73	1.36 ± 0.77	.72

[a]Baseline score minus score at end of treatment.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

acting on voltage-activated sodium channels, many have not been substantially studied in depression.

Clearly, pharmaceutical company funding for clinical trials or advertising for phenytoin is minimal, and this must be taken into account in evaluating literature on phenytoin versus other drugs. It is difficult to create a level playing field between drugs with and without pharmaceutical company backing in the race for scientific attention. Phenytoin might be a reasonable option, third or fourth line, in depressed patients who have not responded to monoamine reuptake inhibitors or mood stabilizers.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), diazepam (Valium and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), phenytoin (Dilantin and others), venlafaxine (Effexor).

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