



Phenytoin in Bipolar Depression: An Old Chapter, but Not Yet Properly Evaluated

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Abstract

Objectives: To review and analyze the repurposing of phenytoin as a treatment for bipolar disorders. Phenytoin is an 80-years-old drug and its putative clinical value is neglected for psychiatric disorders. Only few studies have been published in this field, and most studies are pilot trials. However, since the beginning of the use of phenytoin in the neurological clinic, a number of observations suggests its clinical relevance in a variety of indications, related to depression, anxiety and psychosis. As the pharmacotherapeutic arsenal for bipolar disorders is still suboptimal, we will discuss in this article the data related to the potential value of phenytoin in the treatment of bipolar disorders.

Methods: Literature search and PubMed search.

Results: Although there have been a number of observations and positive pilot studies, evaluating the value of phenytoin in bipolar disorders, none of the studies are clearly convincing, as each study recruited only a handful of patients and thus were underpowered.

Conclusions: The preclinical profile of phenytoin supports bipolar disorders as putative indications for phenytoin, amongst others due to its mechanism of action as a broad acting sodium channel blocker and an anti-inflammatory compound. Phenytoin might be of use in bipolar disorders, most probably in the treatment of the manic phases, perhaps less so in the depressed phases.

The key question whether phenytoin might contribute to the treatment of bipolar patients has thus not been adequately answered. There seem to be sufficient data to support a full powered study. In such a study, the primary endpoint most probably needs to focus on the manic phases, both from the perspective of symptomatic treatment as well as prophylactic treatment.

Keywords

Bipolar, Therapy, Diphantoin, Phenytoin, Anticonvulsants

Introduction

Treatment of bipolar disorders remain a challenge. In this indication three different classes of drugs are used, all characterized as ‘mood stabilizer’s: lithium, anticonvulsants and atypical antipsychotic drugs. A number of the newer anticonvulsants however, have been tested in relative small clinical trials and failed to demonstrate clinical relevant efficacy [1,2]. Most guidelines support the prescription for acute and long-term management of mood stabilizers such as lithium or valproate, and atypical antipsychotics, such as olanzapine, risperidone, aripiprazole and quetiapine [3]. There are some indicators for both bipolar subtypes, that prescription behavior is changing, lithium prescriptions seem to decrease in certain western countries, while the use of lamotrigine

and quetiapine is rising [4]. It was recently pointed out that there are significant cultural differences in this field: while the Europeans consider mania mainly as a mood episode and prefer lithium as first-line treatment, the Americans feel psychotic symptoms dominate and thus prescribe antipsychotic agents [5]. Although Americans

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like atypical antipsychotics better for mania than the Europeans, some feel this is not because they prioritize psychosis; it's just that Americans think antipsychotics are mood stabilizers in the nonpsychotic indications as well. However, there is a clear consensus that we need a broader therapeutic armamentarium for the treatment of bipolar disorders.

Phenytoin in Psychiatric Indications

Phenytoin has been described as a remarkable multi-purpose drug. Some decades ago, a Wall street icon and billionaire Jack Dreyfuss (August 28, 1913 - March 27, 2009), suffering from depression, was successfully treated with phenytoin. Because depression was off-label use, and rarely prescribed in depression, he started a foundation to promote phenytoin in depression and a number of other psychiatric disorders, including OCD and Gilles de la Tourette [6]. He was said to have invested 100.000.000 dollar via his foundation to popularize the use of phenytoin beyond the classical indication of epilepsy, but in vain, although he is said to have sent two books about phenytoin to every physician in the USA and met with President Nixon to lobby for recommending phenytoin for a variety of indications. Perhaps his actions had opposite effects. And his non-rational approach alienated physicians to further look into the potentiality of phenytoin in psychiatric disorders. He probably should have initiated a full powered and well-designed trial, especially since phenytoin is off patent and no pharmaceutical industries are interested anymore in investing in such a drug. Phenytoin has been evaluated in a number of psychiatric indications, but sadly enough only via academic driven small pilot trials: agitated depression [7], post-traumatic stress disorder [8,9], OCD [10], Gilles de la Tourette syndrome [11], schizophrenia and psychotic episodes [12-14], dysphoria [15,16], anxiety [17,18], addiction [19,20], impulsive-aggressive behavior [21-24], autism [25], binge-eating [26].

Phenytoin: Preclinical Properties

Interestingly, we could not identify any preclinical study evaluating different dosages of phenytoin in the rat forced swimming model. This is quite remarkable given all the attention given to this indication by Dreyfuss. There are however a number of interesting preclinical findings, related to the pharmacological effects of phenytoin in a number of different paradigms relevant for psychiatric indications.

Phenytoin can reverse long term stress damage in rats [27]. It has neuroprotective properties in a number of paradigms based on ischemia and trauma [28-31]. It also reduces fear [32]. PCP (phencyclidine) induce a cognitive deficit in rats can be reduced by phenytoin

[33]. It reduces glutamate release and excitatory neurotransmission, and protects against N-Methyl-D-Aspartate (NMDA) glutamate receptor hypofunction [34-36]. Phenytoin also protects cells in various paradigms of neuroinflammation [37-40]. This is of interest, as Bipolar disorders seem to be associated with increased inflammation, which is seen as an important pathogenetic factor [41-43]. Furthermore, lithium is said to have anti-inflammatory properties [44]. Hamadi, et al. already pointed out this neuroinflammatory pathogenesis needs to be taken into account in modern treatments of bipolar disorder, and they emphasized that During mania, IL-2, IL-4 and IL-6 were increased pro-inflammatory cytokines, and IL-6 was found to be increased during depression [45]. Phenytoin is known to inhibit pro-inflammatory cytokines such as IL-6, although there are some conflicting data in this field [46,47]. To date, the exact influence of phenytoin on our innate immune system is still unexplored.

Animal paradigms for bipolar disorder are virtually non-existent; phenytoin was effective in a new putative (non-validated) model for this indication [48]. Kindling models are in general regarded as relevant models for bipolar disorders, and phenytoin in such a model indeed has prophylactic properties [49].

Phenytoin in Depression

It was the focus of to bring phenytoin more into the center of attention for the treatment of depression. Although he invested much time and energy in this topic, not many clinical trials have been conducted since, evaluating the safety and efficacy of phenytoin in depression.

One clinical study compared phenytoin to fluoxetine [50]. This was a controlled double blind pilot study in 28 patients who completed at least 3 weeks of treatment; plasma levels were adequate, and there was no difference between both treatment groups in overall rate of response. In a different small pilot trial phenytoin however did not augment the clinical efficacy of SSRIs in depression, in patients refractory for SSRIs [51]. Interestingly, fluoxetine could augment the anticonvulsant activity of phenytoin [52].

Phenytoin in Bipolar Disorders

Kalinowski and Putnam described in 1934 a case-series of 60 patients suffering from a variety of psychiatric disorders, mainly schizophrenia (41), manic depressive psychosis (9) and depression [53]. Dose was raised step by step up to 600 mg/daily. Patients suffering from schizophrenia with catatonic excitement reacted best, as well as the 9 manic depressive patients, from whom 5 patients had complete remissions of the manic episodes. The authors concluded that phenytoin had a positive

influence on states of excitement in various psychoses. After stopping therapy, the symptoms reappeared, and disappeared on reinstating therapy. The therapeutic antimanic effects started to emerge within a few days on therapy.

Blair, et al. [54] reported that phenytoin not only acted as an effective anticonvulsive drug, but they described positive mood effects, patients became more cheerful and less quarrelsome and complaining, as a result of the treatment [54]. Some years later [55] in 1967 Klein and Greenberg treated 15 patients suffering from a variety of psychiatric disorders, among which agitated depression and schizophrenia and found no effect of a daily dose of 300 mg [56].

In 1989 a small series of 5 carbamazepine resistant bipolar patients were treated with phenytoin, without results [57].

In a small placebo-controlled trial, published in 2000, 39 patients were entered based on the DSM-IV criteria for bipolar I disorder, manic type, or schizoaffective disorder, manic type (by consensus of two independent specialist psychiatrists). Mishory, et al. [58] Of the 39 patients entering the study 25 patients completed 5 weeks. Patients admitted to the study were started on haloperidol at doses determined individually. Phenytoin or placebo was started at 300 mg/day and the daily dose was increased to 400 mg after 4 days. Most patients (2/3) had schizoaffective disorder, manic type, and 1/3 had bipolar disorder, manic type. Completing 5 weeks were six bipolar manic patients taking phenytoin, four bipolar manic patients taking placebo, seven schizoaffective manic patients taking phenytoin, and eight schizoaffective manic patients taking placebo. Mean plasma levels at week 5 were 21.4 µg/ml. Although the design was suboptimal due to the presence of haloperidol and the small number of patients, the ratings on BPRS and CGI suggested a benefit of phenytoin in the bipolar manic patients.

Based on these positive data, the same group initiated a prophylactic placebo-controlled cross-over study in patients with DSM-IV criteria for BP disorder I or schizoaffective disorder [59]. Rapid cyclers were excluded. Ongoing prophylactic treatment with lithium, carbamazepine, valproate or neuroleptics was not changed. Phenytoin or placebo (as randomized) was added slowly (100 mg/week). Clinical scales used were the Brief Psychiatric Rating Scale (BPRS) (10), Young Mania Scale (YMS) (11), Hamilton Depression Scale (HMS) (12) and Global Clinical Impression (GCI). 23 patients who completed 6 months without relapse were crossed over during a month of weekly visits with one drug (phenytoin or placebo) being reduced by 100 mg/week and the other increased by 100 mg/week. At month 6 mean phenyto-

in dose was 380 ± 80 mg, and mean placebo-equivalent dose was 410 ± 60 mg. Mean plasma levels at month 6 was 10.7 ± 4.2 µg/ml. The primary outcome measure was the time to event: an affective relapse. There was a significant prophylactic effect of phenytoin ($p = 0.02$).

The results of the 2000 study were later discussed by Bersudsky, et al. [58], and the data on the bipolar subgroup were highlighted in a separate graphic representation. He also discussed previously generated data in the 2003 study, and concluded that this study: 'suggests prophylactic effects of add-on phenytoin in bipolar illness' [60]. He pointed out that the patient group was relatively resistant to treatment with a number of other mood stabilizers, making the added benefit of phenytoin more impressive. Phenytoin could also inhibit manic scores in corticosteroid induced mood swings.

In the internet one can find a number of testimonies of physicians and patients, supporting the use of phenytoin in depression and bipolar disorders. Academicians, such as Dr. R H Belmaker from the Ben Gurion University of the Negev (Israel) states: 'some bipolar patients respond amazingly well to phenytoin'. The challenge would be to identify those patients, and carefully dissect the clinical contribution of phenytoin in bipolar I and II patients and define the optimal clinical context for this compound.

Conclusion

The preclinical profile of phenytoin supports bipolar disorders as putative indications for phenytoin, amongst others due to its mechanism of action as a broad acting sodium channel blocker and an anti-inflammatory compound.

Phenytoin might be of use in bipolar disorders, most probably in the treatment of the manic phases, perhaps less so in the depressed phases. Although there have been a number of observations and positive pilot studies, evaluating the value of phenytoin in bipolar disorders, none of the studies are convincing, as each study recruited only a handful of patients and thus were underpowered.

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Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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