

Vitamin B₃ for Depression: Case Report and Review of the Literature

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Abstract *While on parental leave during November 2009, my clinical shift was spearheaded by one of my colleagues who recommended fairly significant doses of inositol hexaniacinate to treat a patient's depression. In January 2010, the patient returned for a visit on my clinical shift, and much to my surprise her long-standing depression had resolved. As a result, I conducted a search for articles describing the use of vitamin B₃ for depression. Six articles were found to meet the inclusion criteria and were included in this review. There is evidence that niacin and niacinamide (in combination with tryptophan) might be effective for the treatment of depression. Hypothetical reasons for niacin's effectiveness include its vasodilatory properties, while the mechanisms responsible for the effectiveness of niacinamide involve its ability to inhibit tryptophan pyrrolase and possibly protect neurons from damage. The side effect profiles of niacin and the niacinamide-tryptophan combination are also discussed. Even though the mechanisms of action for niacin and niacinamide have not been substantiated from well conducted controlled clinical trials, these forms of vitamin B₃ appear to have beneficial effects upon depression. It is imperative that properly designed controlled trials are developed in order to determine the true therapeutic effects and adverse effect profile of both preparations of vitamin B₃ for depression.*

Introduction

The most commonly cited uses of vitamin B₃ (niacin/nicotinic acid and niacinamide/nicotinamide) are for the treatment of pellagra. Pellagra is a disease caused by a cellular deficiency of the nicotinamide coenzymes due to inadequate dietary supply of tryptophan and vitamin B₃. Diarrhea, dermatitis and dementia characterize this deficiency disease. Although it is not usually fatal, when the 3 Ds are present death can occur. The adult intake of vitamin B₃ necessary to prevent pellagra is around 20 mg per day. The body can manufacture approximately 1 mg of niacin equivalents from 60 mg of tryptophan obtained mostly from di-

etary protein. This in vivo conversion makes it rather difficult to develop frank pellagra in affluent, industrialized countries where food supply is seldom scarce unless there are mitigating factors like disease (anorexia nervosa, hypothyroidism, and alcoholism),¹⁻⁶ medication-induced nutrient depletion (the use of anticonvulsants),^{7,8} or from a lack of food intake (homelessness and undernutrition).^{9,10}

While it is not common practice to use vitamin B₃ for medical reasons unless pellagra has been identified, orthomolecular practitioners have been using vitamin B₃ therapeutically for more than 50 years to treat numerous neuropsychiatric conditions. One of the first publications documenting the need for

vitamin B₃ occurred in the early 1940s when the late Dr. William Kaufman of Connecticut detailed its use as a treatment for a syndrome that he termed, “aniacinamidosis.”¹¹ Kaufman’s description of aniacinamidosis is practically indistinguishable from the modern clinical presentations of anxiety and mood disorders (Table 1, below). The treatment of this syndrome could not be ameliorated by dietary modifications, but required between 150–350 mg of niacinamide each day to reverse its clinical manifestations.¹¹

One decade later, Dr. Abram Hoffer of Regina, Saskatchewan, along with his team of investigators, conducted a total of six double-blind, randomized controlled clinical trials involving schizophrenic patients from 1953–1960. These trials demonstrated that vitamin B₃ doubled the recovery rate of acute schizophrenic patients, and also reduced patients’ reliance upon the health care system.¹² These studies did not, however, show a favorable response among chronic schizophrenic patients who were ill longer

than one year. When Hoffer reviewed this problem more substantially, he discovered that the treatment duration was not long enough to have produced adequate results. Chronic patients required vitamin treatment for five or more years in order to derive observable benefits.^{13–15}

From the 1950s until Hoffer’s death in 2009, he elucidated numerous additional therapeutic uses of vitamin B₃ for the treatment of various neuropsychiatric conditions. Some of Hoffer’s reports included those involving children with learning and behavioral issues,^{16,17} dementia of both the Alzheimer’s and non-Alzheimer’s type,^{18–20} Huntington’s disease,^{21–23} and the starvation-stress syndrome (similar to post-traumatic stress disorder).²⁴ While Hoffer was prolific in his writings about the therapeutic uses of vitamin B₃ and other nutrients, he did not author (to my knowledge) a single report documenting the merits of vitamin B₃ for the treatment of depression. He merely alluded to it when discussing the psychiatric

Table 1. Psychiatric Manifestations of Aniacinamidosis

- Has not felt “like himself” for weeks or years
- Feels tense; can’t relax
- Is impatient and irritable
- Frequently has unwarranted anxieties
- Worries about unimportant things and can’t seem to shake worries
- Has the feeling of impending trouble
- Not sure of his knowledge or abilities
- Has uncertainties about what the future will hold for him
- Has lost his former interest in work, family, and friends
- Adjusts poorly to ordinary life situations
- Lacks initiative
- Not cooperative
- Routine duties become particularly burdensome
- Delays making decisions
- Shuns and fears unfamiliar people, ideas, situations
- Frequently wishes to be alone, to get away from everyone
- Is unhappy, frequently without apparent cause
- Frequently thinks that something is seriously wrong with him
- Can’t sleep right

and somatic complications of having a dependency on vitamin B₃. He did, however, report on the relationship between chronic allergies and depression, and the need for allergy treatment as an effective antidepressant strategy.^{25,26}

Like Hoffer, I have not considered vitamin B₃ to be an effective antidepressant and have typically prescribed other treatments, such as omega-3 essential fatty acids, 5-hydroxytryptophan, tyrosine, Rhodiola, and St. John's wort extract to augment mood. While on parental leave during November 2009, my clinical shift was spearheaded by one of my colleagues who recommended fairly significant doses of no-flush niacin to treat a patient's depression. In January 2010, the patient returned for a visit on my clinical shift, and much to my surprise her long-standing depression had resolved.

Case Presentation

The patient was a 47-year-old female that presented to the Robert Schad Naturopathic Clinic on October 21, 2009. She had a 27 year history of both anxiety and depression. When she was 20 years old she moved away from her home due to the stress imposed by her mother's bipolar disorder. As a result, the patient became depressed, which was further complicated by the challenges of taking care of her teenage sister. The patient referred to this as her "subclinical" depression that had lasted her entire adult life. Her father had mental health issues of his own, for he had depression and was a heavy social drinker. The patient reported suicidal thoughts on and off since being depressed. She also tried numerous antidepressant medications and found them to be ineffective while also having the unfortunate side effect of increasing suicidality. She was currently taking 0.5 mg of lorazepam daily and 7.5 mg of zopiclone at bedtime to help with sleep. Her affect was depressed and flat. Her diagnosis was consistent with dysthymic disorder. On October 28, she returned for a second visit and was prescribed 3,000 mg of no-flush niacin (inositol hexaniacinate/hexanicotinate), 300 mg of gamma-amino butyric acid (GABA), and a probiotic to improve overall health.

On November 24, the patient returned for a third visit. With the 3,000 mg of no-flush niacin, she felt better overall, more calm, more balanced, and reported no anxiety attacks as well. Her affect was normal and she even smiled during the intake. The no-flush niacin was increased to 6,000 mg in divided doses daily. On January 5, 2010, she returned for a fourth visit and was on my clinical rotation. She reported an absence of depression. There was even a marked improvement in her premenstrual depression that apparently plagued her as well. As of the latest entry in her chart, dated March 22, 2010, her depression (dysthymic disorder) was noted to be in clinical remission presumed to be the result of the no-flush niacin. While it cannot be ascertained if the GABA and probiotic helped in reducing this patient's depression, the patient did attribute her mood improvement to the no-flush niacin.

Review of the Literature

While this case is not very compelling, it did make me consider the possible antidepressant effects that vitamin B₃ might possess. As a result, I conducted a search for articles describing the use of vitamin B₃ for depression. To be included in my final review the articles had to (1) report on the use of vitamin B₃ for depression either alone or in combination with other medicines; and (2) describe the method of vitamin B₃ administration. A total of eight potential eligible articles were screened. One article was excluded because it was not possible for me to obtain.²⁷ A second article was excluded²⁸ because it merely summarized a more descriptive article that was included in the final review.²⁹ Six articles were found to meet the inclusion criteria and were included in this review.²⁹⁻³⁴ **Table 2**, (pp 6-8) displays the characteristics of the studies included in this review.

Discussion

The results of this review indicate that vitamin B₃ may have a therapeutic effect on depression. The quality of the evidence at this point, however, is only hypothesis generating, and randomized trials are required to determine the clinical implications of this

novel treatment.

There are several important limitations to consider in the interpretation of this review. I was unable to find any randomized or high quality controlled trials assessing vitamin B₃ by itself or in combination with other medications for the treatment of depression. I cannot determine to what extent publication bias has on the results of this review. I am unable to draw clinical inferences on the results of the included studies as they were of low quality and have a low level of external generalizability. Despite these limitations, I attempted to conduct an exhaustive search and included all reports of relevance.

Given these limitations, it is still important to comment on the biochemical and physiological mechanisms that might account for some of the positive results reported in Table 2. For the studies in which niacin was used alone³⁰ and in combination with phenobarbital,³² the mechanism believed to produce its antidepressant benefits was cerebral vasodilatation. Niacin causes peripheral vasodilatation and cutaneous flushing by inducing the production of prostaglandin D₂ (PGD₂) in the skin, leading to a marked increase of its metabolite, 9 α , 11 β -PGF₂, in the plasma.³⁵ When niacin is administered orally in amounts of 500 mg or topically via a 6-inch patch of 10⁻¹ M aqueous methylnicotinate on the forearm, PGD₂ is markedly released in the skin and its metabolite appears in high amounts in the plasma.^{35,36} It is not known if PGD₂ causes vasodilatation of the intracranial arteries, but niacin's ability to abort acute migraine headaches suggests that this might be what is occurring.³⁷ Old reports cited by Bicknell and Prescott,³⁸ demonstrate that niacin does indeed cause vasodilatation of the cerebral and spinal vessels, and that intravenous administration increases the rate of intracranial blood flow in human beings for 20-60 minutes without any significant change in blood pressure. Other published data pertaining to niacin's effects on cerebral vasodilatation has been equivocal. In one study, subjects having various diseases (e.g., pernicious anemia, congestive heart failure, hysteria, diabetes, and hyper-

tensive vascular disease) were administered intravenous niacin (300-800 mg in 200-300 ml of saline over 20-25 minutes) and numerous measurements were obtained, such as arterial pressures, blood oxygen contents, glucose, cerebral oxygen utilization, cerebral glucose utilization, and cerebrovascular resistance.³⁹ The results of this study failed to find any effect upon cerebral vasodilatation by the intravenous administration of niacin. In an animal study using anesthetized cats, intravenous injection of niacin (0.5 ml/kg) caused a short-term increase in both cerebral blood flow and in arterial blood pressure in venous vessels of the head, but this was followed by a lowering of these parameters.⁴⁰ In a study assessing cerebral blood flow in baboons under anesthesia using single photon emission computed tomography (SPECT) of the brain, a combination of niacin and pentifylline increased cerebral blood flow compared to the control baseline ($p < 0.01$).⁴¹ In another study of similar design, the cerebral blood flow was increased above that of the control when a combination of pentifylline and niacin were administered to baboons.⁴² The increase in cerebral perfusion that resulted from the pentifylline-niacin combination was 2.31 ± 0.19 versus 1.79 ± 0.13 for the control. Based on the results of these reports, it appears that intravenously-administered niacin might increase cerebral blood flow, but more studies are warranted. Unfortunately, there have no reports examining the effects of orally-administered niacin upon cerebral blood flow in human or animal subjects.

If intravenous and oral niacin do increase cerebral blood flow, this therapeutic benefit might be important since there are studies that have documented reduced cerebral blood flow in depressed patients and improved cerebral blood flow following treatment. Presumably, increasing brain perfusion would benefit depression. In a study of patients with late-life depression (55 years of age or older), reduced cerebral blood flow was increased in certain brain areas following a mean of 13.7 weeks of pharmacotherapy.⁴³ Specifically, reduced cerebral blood flow

increased (improved) in the left dorsolateral prefrontal cortex to precentral areas and in the right parieto-occipital regions. In another study, patients with refractory depressive disorder had alterations in regional perfusion in specific brain areas (decreased activity of the bilateral prefrontal areas) that differed from patients having non-refractory depressive disorder.⁴⁴ A more compelling study evaluated cerebrovascular reactivity (CVR) following a dilatory stimulus (acetazolamide) in a healthy control group and a depressed group of patients.⁴⁵ CVR reflects the compensatory dilatory capacity of cerebral arterioles to a dilatory stimulus, and is a vital mechanism that enables constant cerebral blood flow. The group of acutely depressed patients had a more significant reduction in their CVR values compared to healthy controls. On follow-up 21 months later when the depressed patients had received treatment and were in remission, their CVR had significantly improved, whereas the CVR values of the control group remained unchanged. Another study demonstrated that 81.48% of patients with depressive disorders had reduced cerebral blood perfusion as measured by SPECT.⁴⁶ In a study evaluating CVR in 16 patients with unipolar depression, their CVR was reduced during the depressive phase of their illness, and increased in most of the depressed patients when in remission.⁴⁷ Based on the data cited here, it appears that depression is marked by reduced cerebral blood flow and that improvement is characterized by increased (or normalized) cerebral blood flow. These findings suggest that niacin might hypothetically have the capacity to increase cerebral blood flow and therefore assist in ameliorating depression.

Another biochemical mechanism that might account for the antidepressant benefits of vitamin B₃ involves the use of niacinamide in combination with tryptophan.^{29,33,34} Niacinamide functions as an inhibitor of the liver enzyme, tryptophan pyrrolase, which prevents the metabolism of tryptophan by the kynurenine pathway.²⁹ When tryptophan is administered in combination with niacinamide, more tryptophan enters into

the brain.⁴⁸ This would have the therapeutic benefit of increasing the production of 5-hydroxytryptophan, and subsequently increasing the production of the serotonin neurotransmitter. This makes the niacinamide-tryptophan combination a therapeutically attractive intervention for the treatment of depression. Niacinamide also provides protection against neuronal and vascular injury.⁴⁹ While the mechanisms that account for these unique therapeutic properties are very complex and require further delineation, niacinamide might provide some antidepressant benefit by reducing neuronal damage because it protects against anoxia and nitric oxide cytodeneration.⁴⁹ Niacinamide also alters tryptophan metabolism to increase serotonin synthesis while limiting the formation of “kynurenines.” Kynurenine production or the induction of indoleamine 2,3-dioxygenase (a.k.a., tryptophan pyrrolase) has been linked to mental depression as well as apoptotic, neurotoxic, and prooxidative effects, and upregulation of inducible nitric oxide synthase, phospholipase A₂, arachidonic acid, prostaglandins, 5-lipoxygenase, and the leukotriene cascade.⁵⁰ In patients with major depression or in animal models of depression, significant increases in the production of pro-inflammatory cytokines have been reported, leading to an overproduction of glucocorticoids, free radicals and oxidants, which adversely affects glial cell functions and damages neurons in the brain.⁵¹ Other data has shown depression to be associated with neuroinflammation⁵² and cell-mediated immune activation.⁵³ Precisely how niacinamide would interface and/or limit neuroinflammation and neuronal injury requires more study, but published data suggests that it might be very useful. Whether or not niacinamide's neurotrophic mechanisms have any direct antidepressant benefits also requires further study. I cannot, therefore, rule-out the possibility that niacinamide alone possesses antidepressant effects.

With respect to dosing, it makes sense to use niacin alone or in combination with antidepressant medications. Since cutane-

Table 2. Summary of Articles Demonstrating Vitamin B₃'s Effectiveness for the Treatment of Depression

Ref	Condition	n	Protocol	Outcome	Type of Study
30	Various types of depression	15	All patients were given niacin as an adjunct to psychotherapy. Intravenous niacin (300-400 mg) was given to 10 patients, followed by oral niacin. Five other patients were given niacin orally and never did receive an initial intravenous dose. All patients received gradually increasing doses of niacin before meals until they reached 900 mg daily, but one patient reached 2,500 mg daily. All patients were maintained on their maximum daily dose for 7-10 days, and then the dose was gradually tapered. The average duration of niacin treatment varied from 2-6 weeks.	14 of the 15 patients exhibited subjective and objective improvement following the use of niacin in conjunction with psychotherapy.	Case Series
31	Various types of depression	16	Eleven patients were given 450-600 mg of niacin daily for the first week, then 900 mg daily for 2 weeks in divided doses. Treatment was then terminated abruptly. Five patients were given identical-looking placebo pills and no niacin in the same manner to the patients that were given niacin. Nightly sedatives were also prescribed to patients when necessary.	No benefit was observed	Case Series
32	Patients with a mixture of depressive and anxiety symptoms	100	Patients were given a combination of niacin and phenobarbital in tablet form or elixir. Each tablet or 5cc of the elixir contained 100 mg of niacin and 8 mg of phenobarbital. All patients received increasing daily dosages of the combination until 900 mg of niacin and 72 mg of phenobarbital was reached	47.2% of patients reported definite improvement; 34.0% reported some improvement; 13.2% reported no improvement; and 5.4% discontinued treatment.	Case Series

Table 2. Summary of Articles Demonstrating Vitamin B₃'s Effectiveness for the Treatment of Depression

Ref	Condition	n	Protocol	Outcome	Type of Study
			on day 15. From day 16 to day 21, daily doses of the combination were reduced to 450 mg of niacin and 36 mg of phenobarbital. Presumably, the combination was discontinued after day 21.		
33	Unipolar depression	27	Patients randomly assigned to 2 groups: group 1 received 2 electroconvulsive therapy (ECT) treatments unilaterally weekly with a minimum of 8; group 2 received 3 g of L-tryptophan and 1 g of niacinamide daily. Thirteen patients in group 1 completed the trial, while 12 patients in group 2 completed the trial. The Beck self-rating scale for depression was used the day before the trial began, and then on days 3, 7, 10, 14, 17, 21, 24, and 28. The mean baseline Beck score for group 1 was 25.6, and the mean baseline Beck score for group 2 was 24.4.	Group 2 improved more than group 1 on day 10 (Beck scores: group 1, 16.8 and group 2, 15.2). By day 21, the results achieved statistical significance (Beck scores: group 1, 8.8 and group 2, 3.7; $p < 0.05$). Scores for each group on day 28 were almost identical.	Human pilot open-label trial
29	Newly admitted depressed patients with primary affective disorder	11	Patients received tryptophan-niacinamide combination for four weeks. Patients were given 2 g L-tryptophan and 0.5 g niacinamide during week 1, and then gradually increased to 6 g L-tryptophan and 1.5 g of niacinamide at the start of week 3. All patients received diazepam if needed for insomnia or agitation. The mental status of patients was scored before treatment, and on days 7, 14, 21, and 28, on a modified Hamilton Depression Rating Scale, and a Clinical Global Impression Scale of Severity of Depression (CGI). In addition, the Beck Depression Inventory was completed at the same intervals.	There were statistically significant improvements (i.e., reductions) in the mean scores of all patients among all the inventories used ($p < 0.01$). The mean Hamilton score went from a 33.7 on day 0 to a 20.5 on day 28. The Beck score went from a 33.1 on day 0 to 20.9 on day 28. The CGI went from a 7.2 on day 0 to a 4.5 on day 28. On the basis of percentage improvement on the Hamilton scale, there were 3 marked-responders (50% or more), 4 moderate-responders (25-49%), and 4 non-responders (< 25%).	Human pilot open-label trial

Table 2. Summary of Articles Demonstrating Vitamin B₃'s Effectiveness for the Treatment of Depression

Ref	Condition	n	Protocol	Outcome	Type of Study
34	Newly admitted severely depressed patients	25	All medications were administered under double-blind conditions for a period of 4 weeks. Eight patients received the tryptophan-niacinamide combination for 4 weeks. They were given 2 g L-tryptophan and 0.5 g niacinamide during week 1, and then gradually increased to 6 g L-tryptophan and 1.5 g of niacinamide at the start of week 3. Eight patients were given a single dose at bedtime of 75 mg of imipramine for week 1, which was increased to 225 mg at the start of week 3. Nine patients were given the tryptophan-niacinamide-imipramine combination using the same daily dosages described above. Throughout the study, the tryptophan-niacinamide group received imipramine placebo and the imipramine group received tryptophan placebo and niacinamide. All patients received diazepam if needed for insomnia or agitation. The mental status of patients was scored before treatment, and on days 7, 14, 21, and 28, on a modified Hamilton Depression Rating Scale, and a CGI of Severity of Depression. In addition, the Beck Depression Inventory was completed on the specified days.	Superior results occurred among patients in the imipramine group and in the tryptophan-niacinamide-imipramine group. However, if bipolar patients were excluded from the analysis (n=7), there were no differences in the therapeutic efficacy of the 3 treatments in unipolar patients.	Controlled study

ous flushing is an important aspect to the putative therapeutic benefits of niacin, the daily dose should be low enough so that flushing is not significantly lessened. The daily dose should also be kept low since 900 mg was the dose most often used (except in one patient whose daily dose was 2,500 mg) in the cited studies. I speculate that there might be a relationship between the cutaneous flushing (peripheral vasodilatation) induced by niacin and cerebral vasodilatation. When niacin is administered at 1,000 mg (or more) three times daily, the cutaneous flushing is dramatically reduced after the first few days of use by depleting PGD2 and other metabolites in the skin. Therefore, lower daily doses of niacin would presumably be more therapeutic than daily doses that deplete PGD2 and other metabolites in the skin. I recommend that patient's take 100-300 mg of niacin about 15-20 minutes before meals three times daily. A patient's tolerance (or intolerance) to niacin's cutaneous effects might require dose adjustments. Preparations that produce no flushing, such as inositol hexaniacinate or niacinamide, or those that significantly lessen the flushing, such as timed-, sustained-, or slow-release preparations, would presumably be less effective than niacin at increasing cerebral blood flow. A 28-42 day trial seems appropriate since this approximates the duration of niacin treatment that was reported to be beneficial in the cited studies. If niacin does indeed benefit a patient, it might be necessary to prolong treatment for 4-6 months or several years depending on a patient's stability and functional capacities. Side effects such as headache, nausea, and/or vomiting are possible and patients should be informed that they are usually temporary. Transaminases are unlikely to increase from daily doses of niacin below 1,000 mg. A baseline measurement should be obtained and transaminase levels should be monitored every six months until treatment is discontinued.

When treating depression with niacinamide, it should be used in combination with tryptophan. In studies that used this

combination, the niacinamide-tryptophan was administered twice daily and away from food. Taking this combination in the morning and prior to bed is an effective dosing strategy. The initial dose of this combination should be 500 mg of niacinamide and 1,000 mg of tryptophan twice daily, which should be doubled over several weeks of use. The daily dose of tryptophan does not need to exceed 4,000 mg and the daily dose of niacinamide does not need to exceed 1,500 mg to obtain an effective antidepressant effect. Doses of tryptophan above 4,000 mg are unlikely to provide additional benefit for unipolar depression, but for bipolar depression the daily dose of tryptophan should exceed 4,000 mg to be effective.³⁴ Older adult patients do not need as much niacinamide as do younger adult patients since they have less tryptophan pyrrolase activity.²⁹ For older patients the daily amount of niacinamide does not need to exceed 1,000 mg, but for younger adult patients the daily amount might need to exceed 1,500 mg to enable the accumulation of free plasma tryptophan in the blood and consequently increase cerebral serotonin.²⁹ Trying this combination for 28 days seems appropriate since this approximates the duration of treatment that was reported in the cited studies. Consideration to increase treatment duration should be discussed with patients that have a positive treatment response, for it can take 4-6 months of treatment or even years before there is clinically significant improvement in a patient's stability and functional capacities. Side effects from this combination are usually not severe, but patients can experience mild rigidity, mild tremor, dry mouth, constipation, nausea, vomiting, dizziness, fainting, anorexia, heartburn, and increased thirst. A rare side effect is serotonin syndrome (due to the tryptophan), which can be severe. Transaminases are unlikely to increase from daily doses of niacinamide at or below 1500 mg. I do recommend baseline transaminase measurements and then monitoring the levels every six months until treatment is discontinued.

Conclusion

Even though vitamin B₃'s mechanisms of action have not been substantiated from rigorous controlled clinical trials, it does appear to have beneficial effects upon depression. Oral niacin is believed to increase cerebral blood flow and decrease depression. Intravenous niacin has some supportive data demonstrating that it might increase cerebral blood flow, but data on oral niacin and cerebral hemodynamics is lacking. Niacinamide in combination with tryptophan has more robust data demonstrating an effective antidepressant response among patients with unipolar depression. The niacinamide-tryptophan combination increases serotonin levels within the brain, but niacinamide by itself might possess antidepressant effects. It is imperative that properly designed and well conducted controlled trials are developed in order to determine the true therapeutic effects and adverse effect profile of niacin and niacinamide for depression.

Acknowledgements

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