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L-Tryptophan as an antidepressive agent in the management of treatment-resistant unipolar depression in borderline personality disorder: Three case reports

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ABSTRACT

A narrative of three case reports is used to illustrate the use of L-tryptophan as an adjuvant and stand-alone antidepressive agent in treatment-resistant unipolar depression with comorbidity of borderline personality disorder and a history of self-mutilation and suicide attempts. Rationale, results and some general observations as to effectiveness, tolerability and safety of this therapy are presented.

1. Introduction

Only a minority of depressed patients achieve remission with standard medications [1]. If co-morbid with borderline personality disorder (BPD), the mortality of unipolar depression may be increased [2]. Management of these patients may be further complicated by the side effects of medications [3]. These issues together present significant clinical dilemmas.

Emerging studies suggest novel dietary approaches are worth pursuing in supporting mental health [4]. A nutrient that has received attention for its antidepressive properties is L-tryptophan.

2. Existing research on L-tryptophan

L-tryptophan is an essential amino acid and the precursor of serotonin and melatonin [5] and has a "long history of successful use" ([6], Table 4.8) as an augmentation agent in treatment-resistant depression. The typical Western diet contains approximately 0.5 g of L-tryptophan per day but due to peripheral metabolism and competition with other long-chain neutral amino acids only 2–3% of this enters the brain for conversion, via 5-hydroxytryptophan, into serotonin [7].

The effects of L-tryptophan may be studied as part of the diet. For instance a tryptophan-rich drink improved the stamina of normal women performing a battery of cognitive and emotional tests [8], as well as increasing emotionally positive interpretations of the tests and reducing negative bias. Similarly, Kroes et al. [9] showed that a L-tryptophan rich drink lifted the mood of healthy women and affected the function (seen on MRI) of brain regions known to be associated with mood regulation.

L-tryptophan has also shown efficacy as an isolated substance in the treatment of depressed patients. Hale et al. [10] presented case studies where L-tryptophan was successfully and safely added to clomipramine and lithium. There has been a single randomised controlled trial of L-tryptophan augmentation, conducted by Levitan et al. who found that the addition of tryptophan to fluoxetine was associated with a greater improvement within the first week of treatment but not thereafter. It also lessened the fluoxetine-induced decrements in slow wave sleep. There were no cases of serious toxicity of the combination; it was very well tolerated overall ([11], p. 343).

3. Choice of L-tryptophan over 5-hydroxytryptophan (5-HTP) in the present study; efficacy

The author has focused in the present series upon L-tryptophan rather than 5-HTP, the next step along the pathway to serotonin synthesis, because of its presence in dietary protein and therefore its perception by patients as "natural". Although 5-HTP crosses the blood brain barrier more readily, it has a similar efficacy and side effects profile with possibly a greater likelihood of nausea [12].

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Considering both L-tryptophan and 5-hydroxytryptophan as monotherapy for unipolar depression or chronic dysthymia, Shaw et al. [12], in a review for the Cochrane Collaboration, made the following observations regarding the pooled results from the two studies they deemed capable suitable for inclusion: "Results of this meta-analysis are inconclusive due to the small number of sufficiently rigorous studies available on which to base conclusions. It is therefore difficult to recommend or discourage the use of 5-HTP and tryptophan in treatment of unipolar depression. More evidence is clearly needed to assess efficacy. Although the order of magnitude of effectiveness of 5-HTP and tryptophan was found in this study to be similar to Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs), the body of evidence evaluating the efficacy and safety of SSRIs and TCAs is more rigorous and comprehensive... Also, the relative potency of SSRIs and TCAs is possibly much greater, even though order of effectiveness is comparable. In settings where depression is mild, and the use of traditional antidepressants is unacceptable to the patient, tryptophan and 5-HTP may be considered as treatment alternatives" ([12], p. 5 of PDF version).

4. Borderline personality disorder – symptoms, standard management and links with depression

Borderline personality disorder is a serious clinical problem facing clinicians. Regarding standard treatment for BPD, Beatson and Rao [13], in a review of evidence-based therapies, state "Individual psychotherapy is the primary treatment for BPD" whilst also noting the need for "symptom targeted pharmacotherapy..." (p. 127), for instance, where the patient becomes depressed.

Conversely, a contributor to treatment-resistant depression is the presence of personality disorder. [14]. The present author's practice case-mix certainly attests to this common comorbidity.

Abnormal sleep is an important feature of both depression and BPD. It is known that sleep abnormalities are present in many cases of treatment-resistant depression [15]. Furthermore, disturbed sleep may itself be part of borderline personality disorder and most studies examining this question have shown this even when co-existing depression has been controlled for [16].

Suicidal gestures are a major complication in the management of individuals with BPD, and impulsivity is thought to be at the core of such acts in this population [17]. Considering that impulsivity is itself worsened by sleep deprivation, it is clear that a therapy improving sleep is therefore likely to assist both depression and suicidality. In an attempt to rectify sleeplessness in this population, however, clinicians frequently find that benzodiazepine abuse may further complicate management. Therefore, treatments with the effect of ameliorating insomnia may be seen as highly desirable.

Considering this clustering of borderline personality disorder, depression and insomnia, the question therefore arises as to whether borderline personality disorder may involve abnormal tryptophan metabolism. There has been some interest in this question and Amad et al. in a 2014 review [18] noted that six out of seven genetic studies examined have indeed associated borderline personality disorder with a genetic abnormality in tryptophan metabolism.

5. Rationale for the present study

Although there is some evidence for the efficacy of L-tryptophan for unipolar depression, especially in treatment-resistant cases, there is to the author's knowledge nothing in the literature regarding use of L-tryptophan in treatment-resistant depressed patients with BPD, yet as shown above, the rationale for it is evident. In treating three BPD patients who had treatment-resistant depression and who wanted a "natural" therapy, the author made use of L-tryptophan with them and the results are presented for consideration. Each patient gave written informed consent for the use of their material.

6. Summary of clinical data – table

Patient	Gender	Age	Symptoms	Current Treatment	Past treatment	l-tryptophan dose	Adverse effects	Domains of improvement
1	F	44	Moderate to severe depression, hallucinosis, cutting, suicidal ideation	Long term psychodynamic psychotherapy, desvenlafaxine, lithium	SSRI, SNRI, TCA, MAOI, antipsychotics, valproate, lithium	1 g TDS	Nil	Sleep, energy, volition, self criticism, sense of feeling "whole" and "contained", suicidality
2	M	39	Moderate to severe depression, cutting, suicidal ideation	Long term psychodynamic psychotherapy. Nil medications.	First and second generation antipsychotics, SSRIs, and TCAs	0.5 g BD	Nil	Sleep, motivation and activity aimed at seeking employment, cognition, enjoyment, emotional awareness, suicidality
3	F	26	Moderate to severe depression, delusions, cutting, suicide attempts	Doxepin, Aripiprazole, psychotherapy	SSRI, SNRI	1 g BD	Daytime somnolence improved by light exposure.	Sleep, affect

7. Clinical data

Patient 1 is a 44-year-old single female student who has been a disability pensioner for many years. Despite long term psychodynamic psychotherapy with the author she has never been free of chronic dysthymia. No appreciable difference has been made to her mood by SSRIs, an SNRI, a TCA, a classical MAOI, atypical antipsychotics, valproate and lithium. She agreed to trial tryptophan as an adjunct to her current therapy with desvenlafaxine and lithium, which had had almost no effect. Initial tryptophan dose was 0.5 g BD and she instantly felt "more worthy" of participating in her course of tertiary study. This and other parameters benefitted upon increase to 1 g TDS. On 1 g TDS, sleep improved "dramatically": it became less broken- from waking every hour, she now wakes every 3 h. Energy and volition are improved, as well as an ability to get off the couch and go for outings she'd been putting off. Mood is unchanged yet she describes being less guilty and angry. She describes more enjoyment in her university course. Self esteem is still dominated by self-loathing yet at times she is able to describe feeling more "whole" and "contained". She feels more able to present herself publicly. Cognition she feels improved after the increase from 0.5 g to 1 g TDS. She had not enacted deliberate self harm or attempted suicide for some years but with

tryptophan she feels more confident that, should she feel suicidal, she could withstand this feeling and not act out.

Patient 2 is a 39-year-old male single disability support pensioner in long-term psychodynamic psychotherapy with the author. His chronic dysthymia, suicidal preoccupation, frequent paranoia, and deliberate self-harm (most recently one year prior) had not responded to first and second generation antipsychotics, SSRIs, and TCAs. He felt angry about the side effects he had experienced from those drugs. He noticed an improvement in mood when he improved his diet and wanted to augment that by using a natural remedy. Tryptophan 0.5 g BD, irregularly, was used without an antidepressant. Whilst sleep is still "abysmal" at times, it instantly improved significantly, going from often not sleeping at all, to being able, on many nights, to achieve 6 h per night. He has also noticed less initial insomnia, and experienced his first period without nightmares for many months. He still rated energy levels at 4–6/10, but reported being more active through the day, with better motivation to work on his preparations for employment. He noted that his "brain is functioning better" especially in the morning. He described his enjoyment of music as improving. On tryptophan, he described his mood as "debilitating" at times yet he came to feel "more in touch with my anger". He still considers killing himself, but now feels his suicide risk is not as high as previously. He is pleased that L-tryptophan is a food, unlike other antidepressants:"...on a lot of the meds ... I get a dirty feeling, [and I feel] dissatisfaction with me in that state... Tryptophan doesn't do that. It's a food... Being aware of that makes a difference... It's a part of a protein".

Patient 3 is a 26-year-old single female student with a history of moderate to severe psychotic depression with borderline personality disorder, repeated deliberate self-harm for years up until only weeks prior, and suicide attempts. She was being treated by the author with doxepin (SSRIs having been ineffective) and aripiprazole, and was in psychotherapy with another practitioner. Tryptophan was started at a dose of 0.5 g nocté initially, and increased to 1 g BD after no initial effect; attempts to use it by day were initially abandoned due to daytime sedation, which resolved with increased sun exposure. On 1 g BD, sleep improved somewhat- she subjectively estimated it as improving from 5/10 to 7.25/10 in quality. Energy, appetite, mood and cognition and suicidality have not changed – the latter is still intermittently high. On examination she appears brighter in affect and more optimistic. She continues to feel condemning towards herself and retains her fixed beliefs about bodily decomposition and her inherent evil.

8. Dosing rationale

The author has found in a range of patients that a 1 g dose of L-tryptophan has an appreciably superior effect to 0.5 g. Each patient is instructed to start at 0.5 g, whereupon the effect is noted, and then the patient is instructed to increase it to 1 g for comparison. This usually gives a further response. Another dosage increase is then attempted to 2 g but this manoeuvre in these three patients conferred no additional benefit. This concurs with the author's usual experience. It is interesting therefore to compare the recommendation of Taylor et al. ([6], Table 4.8) of 2–3 g TDS.

9. Cost of L-tryptophan

In Australia, the retail cost for a pensioner to receive a month of fluoxetine is $6.10, and for a non-pensioner $18.65. By comparison, one brand of L-tryptophan powder costs $39 for 30 × 0.5 g, and L-tryptophan 500 mg capsules cost $42.95 for 60.

Each of the three patients, all pensioners, found the L-tryptophan difficult to afford and occasionally reduced their dosage to make their supply last longer.

10. Results and discussion

Of the three case reports presented, sleep was improved markedly in two cases, slightly in one. In all cases was subjective sleep quality improved. Energy improved in two cases and motivation and ability to function socially were improved in all three. Mood was minimally improved in two cases. Suicidality was slightly improved in two cases.

Daytime somnolence in one patient resolved with greater light exposure, presumably via switching off daytime melatonin synthesis. There were no other reported side effects. Each patient found that the effect began minutes after the first dose, would last for some twelve hours, and this was sustained over a period of many weeks for as long as the tryptophan was being taken. Each patient also experienced the necessity to take the L-tryptophan on an empty stomach for any effect to be achieved.

Mood improvement was modest in two cases and was not achieved in the case of the most severe depression. In the two improved cases, both patients had experienced an improvement in sleep, and both felt that they could better withstand any future suicidal impulses. The patients noticed a dose-response effect, with 1–2 g/d being more effective than 0.5 g daily. This dosing is at the low end of that documented in reviews by Young [7] and Taylor et al. [6].

Possible drawbacks of tryptophan treatment need to be considered. In a review of complementary antidepressant augmentation agents, Ravindran notes that serotonin syndrome resulting from augmentation of antidepressants with L-tryptophan is "rare" [19]. Considering the possibility of serotonin syndrome in Australia, since 1970 the Australian Therapeutic Goods Administration (TGA) has reported no cases of confusion with tryptophan, one case of tremor, one case of muscle twitching, and no hypertonia [20].

Eosinophilia-myalgia syndrome (EMS) is a subacute condition involving neuropathy, skin induration, myalgia and peripheral eosinophilia. In 1989, approximately 40 people died from the condition, and it has been almost conclusively linked to a contaminated batch of L-tryptophan. In reviewing this outbreak and its consequences, Allen et al. [21] noted in 2011 that there had been only one case of EMS since the ban on tryptophan's use was lifted in 2005. In Australia, since 1970, the TGA has reported 5 cases of either eosinophilia or myalgia with tryptophan [20].

11. Strengths and limitations of the study

The strength is that it is entirely naturalistic. These three patients had responded poorly to previous treatments, and their chronic suicidality necessitated better therapeutic options. Limitations of the study include the use of qualitative data only, small sample size and publication bias since only patients who have responded are discussed. Positive transference may have played a part – the two patients whose responses were better were, unlike the other patient, both in psychotherapy with the author. The study does not have the power to disentangle such possible effects.

12. Conclusion

Management of treatment-resistant unipolar depression in patients with borderline personality disorder is difficult. Emerging studies suggest novel dietary approaches are worth pursuing in supporting mental health in general. In this series of three patients, L-tryptophan was found to be a well tolerated and useful adjunct and standalone antidepressive agent in treatment-resistant unipolar depressed borderline personality disorder patients, with positive effects on sleep, suicidality and social engagement. In addition, the clinical data suggests that patients may be receptive

to adjuvant nutritional treatments. The data suggests that further exploration and documentation of L-tryptophan as antidepressant agent is warranted.

Conflicts of interest

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