

Review

The effects of tryptophan depletion on mood and psychiatric symptoms

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Abstract

Background: The number of studies using tryptophan depletion (TD) challenge has increased markedly in the past few years. Recently, a number of negative results have been published, implicating that the effect of TD on mood may be less consistent than previously thought. **Methods:** The literature on the mood effects of TD in psychiatric patients and healthy volunteers was reviewed. **Results:** TD has a mood-lowering effect in subgroups of recovered depressed patients, patients with seasonal affective disorder and vulnerable healthy subjects. The mood effect in former patients is of a different quality, however, than the effect in healthy subjects. Some recent negative studies in depression might be explained by insufficient lowering of plasma tryptophan levels. Preliminary evidence exists for an effect of TD on bulimia nervosa, autism, aggression and substance dependence. **Conclusions:** The effects of TD on mood may be more consistent than suggested by a number of recent negative studies. Response to TD in recovered depressed patients is associated with prior treatment. However, even in SSRI-treated patients the relapse rates are not higher than 50–60%, which needs to be explained. The clinical usefulness of the response to TD in recovered patients (prediction of relapse after treatment discontinuation) and in symptomatic patients (prediction of treatment refractoriness) deserves more research attention. Further suggestions for future research include the cognitive effects of TD in recovered depressed patients and the effect of dietary habits on response to TD. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Tryptophan depletion; Mood; Psychiatric symptoms; Depression; Relapse; Cognition

1. Introduction

Tryptophan depletion (TD) is an experimental procedure to temporarily lower tryptophan availability. Following the demonstration that TD had an

impact on mood of normal males (Young et al., 1985), a small but steady stream of studies has been published, utilizing this procedure in patients with mood disorders and in healthy volunteers. In the past few years, however, a marked increase has occurred in both the number of studies and the populations investigated. The purpose of this article is to review these studies, and to explain some apparently contradictory findings. The methodology of TD will be

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Table 1
Overview of the results of tryptophan depletion studies in psychiatric patients and healthy volunteers^a

	Population, design	Treatment	Free plasma TRP in TD condition			Results/comments:
			Baseline	After TD	Change	
Depression: symptomatic						
Delgado et al., 1994	MDE, in-/outpatients <i>n</i> = 43.	Heterogeneous.	8.7±3.4	Not reported	- 83%	Little change in mood during test day. Next day: transient improvement for 16, transient worsening for 10 patients. Latter group treatment refractory.
Price et al., 1997	Depressed in- and outpatients. <i>n</i> = 38.	On placebo prior to drug trial (> 2 weeks)	2.2±0.3	0.9±0.3	- 59%	No effect of TD on mood. Cortisol response to i.v. TRP greater during TD than during placebo.
Price et al., 1998	MDD, in- and outpatients. <i>n</i> = 22.	On placebo prior to drug trial (> 2 weeks)	1.8±0.6	0.5±0.6	- 70%	No effect of TD on mood. Cortisol response to i.v. mCPP greater during TD than placebo.
Depression: remitted						
Delgado et al., 1990	MDE, in-/outpatients. <i>n</i> = 21. 16 MDD, 5 BPD	4 Desipramine, 6 fluvoxamine, 3 phenelzine 8 other/combination	10.3±8.8	1.0±1.5	- 91%	11/21 relapsed 7 h after TD, additional 3 relapsed next day. Mean HDRS increased from 8.4 to 20.4.
Delgado et al., 1991	MDE, pooled data, <i>n</i> = 115 69 medication-free, depressed 46 medicated, in remission.	11 Desipramine 10 fluoxetine 6 fluvoxamine, 6 MAOI 13 other/combination	<i>Diet + AA mixture (n = 75):</i> 2.1±0.8 0.3±0.3		- 85.7%	Delayed effect in about half of drug-free patients. About half (24/46) of medicated patients relapsed, probable relation with treatment (SSRI and MAOI higher risk). Pooled data, overlaps with Delgado et al. (1990, 1994).
			<i>AA mixture alone (n = 40):</i> 2.0±0.4 0.8±0.8		- 60%	
Smith et al., 1997a	MDE, fully remitted. Females <i>n</i> = 15. History of comorbid bulimia nervosa in 4 patients.	Medication-free for > 6 months. Prior medication not reported	<i>Total plasma TRP:</i> ^b Not reported Not reported		'About 75%'	Significant increase (+ 7.3) in HDRS scores. Five patients full recurrence, 5 patients partial recurrence of symptoms.
Leyton et al., 1997a	MDE, fully remitted. <i>n</i> = 14. 9 MDD, 3 SAD, 2 BPD	Unmedicated. Prior treatment not reported.	Not reported Not reported		- 88.1%	No effect on mood (HDRS, POMS, VAS ratings).
Bremner et al., 1997	MDD, improved with SSRI. <i>n</i> = 21.	19 Fluoxetine, 2 paroxetine. In treatment since 1–335 weeks.	<i>Relapse group (n = 7):</i> 1.6±0.5 0.4±0.2		- 77.9%	Difference in TRP levels between relapse/no relapse not statistically significant. Relapse associated with decreased metabolism in middle frontal gyrus, thalamus and orbito-frontal cortex.
			<i>No relapse group (n = 14):</i> 1.9±0.5 0.8±1.0		- 57.5%	
Cassidy et al., 1997	MDD, fully remitted. <i>n</i> = 5	ECT (improved depression score by 87%)	<i>Total plasma TRP:</i> ^b 45±12 6±2		- 85%	No effect on depression scores (changed from 4.2 to 3.6) 8 h after TD: small increase HDRS (not clinically significant: 1.7⇒3.2). Effect on sleep architecture: reversal of REM-suppressing effects of SSRIs.
Moore et al., 1998	MDE, medicated. Full remission since 2–9 months. <i>n</i> = 10. Males.	6 Fluoxetine, 3 paroxetine, 1 sertraline (since 2.5–13 months) dosage 20–60 mg/day	5±1 2±1		- 52%	
Aberg-Wistedt et al., 1998	MDE, <i>n</i> = 20. Between-Ss design. 12 TD/8 placebo.	Citalopram > 1 month. Dosage not reported.	<i>Total plasma TRP:</i> ^b 65±14 36±14		- 44.6%	Small mood effect in 4 patients, larger effect in 1. Baseline cortisol higher in responders. Modified AA mixture.

Neumeister et al., 1998a,b	MDD or BPD. $n = 22$. 11 patients TD, 11 placebo	One night sleep deprivation. Medication-free.	8.1±3.0	1.2±1.0	– 85%	No effect of TD on mood during test day. However, TD postponed the relapse after one night of recovery sleep.
Delgado et al., 1999.	MDD ($n = 28$), BPD ($n = 2$) In remission.	15 patients fluoxetine 15 patients desipramine	10.6±3.9	2.4±1.5	– 77%	8/15 patients treated with fluoxetine relapsed, 1/15 patient treated with desipramine relapsed.
Bipolar disorder (manic)						
Benkelfat et al., 1995	BPD, in remission. Men. $n = 10$.	Lithium carbonate, 930±386 mg/day	<i>Total plasma TRP:</i> ^b		– 85%	No effect of TD on mood.
Cappiello et al., 1997	BPD (manic), recently recovered. $n = 7$.	Lithium, Lorazepam. 5 patients neuroleptics	Not reported	Not reported	Not reported	TD increased manic symptoms for 3 days. 2 patients fulfilled criteria for manic relapse (and 1 patient after placebo).
Seasonal Affective Disorder						
Lam et al., 1996	SAD, in remission. $n = 10$. HDRS score < 8.	Light therapy; medication-free > 2 weeks	1.1±0.1	Not reported	– 72%	8/10 showed significant depressive and anxiety symptoms after TD.
Neumeister et al., 1997a,b	SAD, symptomatic. $n = 11$.	Medication-free	5.6±1.4	0.7±0.6	– 85.8%	No effect on HDRS (stable at approximately 15).
Neumeister et al., 1997a,b	SAD, in remission since 2 weeks. $n = 12$.	Light therapy; medication-free > 10 months	<i>Estimated:</i> ^c 7.7	2.3	– 70.6%	<i>Estimated:</i> ^c HDRS increase: 3⇒7 (⇒ 10 on next day).
Neumeister et al., 1998a,b	SAD, fully remitted. $n = 11$. Age 39±12 years	Medication-free since at least 4 months.	7.6±1.6	0.9±0.6	– 88.2%	Significant increase in depression scores. 8 of 11 patients relapsed after TD.
Neumeister et al., 1998a,b	SAD (MDE/BPD), remitted. TD/AMPT/placebo.	Light therapy; medication-free > 6 months.	<i>Estimated:</i> ^c 7.0	0.9	– 87.1%	Significant increase in HDRS after TD and after AMPT. Only study to report a depressive relapse after placebo.
Obsessive–Compulsive Disorder						
Barr et al., 1994	OCD. $n = 15$. 10 pts. Lifetime, depression, now in remission.	SSRI since 5–104 weeks	9.3±3.9	1.5±1.5	– 84%	No effect of TD on OC symptoms. Small effect on HDRS, particularly in patients with lifetime depression.
Smeraldi et al., 1996	OCD. $n = 12$. 2 pts. lifetime depression, now in remission.	Medication-free since at least 2 weeks.	<i>Total plasma TRP:</i> ^b		– 72.5%	No effect of TD on OC symptoms or depressive symptoms (VAS ratings).
			63±15	17±11		
Bulimia Nervosa						
Weltzin et al., 1994	BN, female inpatients. $n = 13$. HDRS: 17±11.	No information	<i>Total TRP</i> ^b , <i>estimated:</i> ^c		– 64%	Small significant rise in anxiety and depression ratings after TD.
			47	12		
Weltzin et al., 1995	BN, female inpatients. $n = 10$ (8 comorbid depression).	Medication-free since 4 weeks	<i>Total TRP</i> ^b , <i>estimated:</i> ^c		– 80%	Small increase in irritability, labile mood and retarded affect. Marked increase in food intake.
			48	8		
Oldman et al., 1995	BN, female, $n = 8$. ‘Abstinent’. Six pts. history mood disorder.	No medication within previous year.	0.8	0.3	– 59.8%	No effects on mood, appetite or food intake. Modified AA mixture (52 g). Lower baseline TRP level in bulimics.
Smith et al., 1999a,b	BN, females, fully recovered. $n = 10$.	No medication for at least 6 months.	Not reported	Not reported	Not reported	TD caused lowering of mood, increase in body image concern and subjective loss of control of eating.

Table 1. Continued

	Population, design	Treatment	Free plasma TRP in TD condition			Results/comments:	
			Baseline	After TD	Change		
Healthy volunteers							
Young et al., 1985	Males. $n = 3 \times 12$. Between-Ss design: TD/T + /placebo.	None	1.9±0.2	0.8±0.2	– 60%	Small but significant rise in depression ratings (self-report) after TD.	
Smith et al., 1987	Males. $n = 8 \times 10$. Between-Ss design: TD/placebo//cognitive/environmental manipulations	None	1.6	0.3	– 79%	Small (15.5 → 19) but significant rise in depression ratings after TD. No effect of cognitive and environmental manipulations	
Danjou et al., 1990	Males. $n = 2 \times 9$. Between-Ss design: TD, placebo	None	<i>Estimated:</i> ^c 1.1	0.4	– 77%	No effect on mood ratings (self-report).	
Abbott et al., 1992	Males. $n = 2 \times 30$. Between-Ss design: TD/placebo	None	Not reported	Not reported	Not reported	No effect on mood ratings. Low baseline mood ratings. TD reversed effect (increase pain tolerance) of morphine.	
Oldman et al., 1994	Females. $n = 12$. Cross-over design: TD/placebo/water	None	<i>Estimated:</i> ^c 0.9±0.1	0.3±0.05	– 67%	No effect on POMS or VAS ratings. Low baseline scores Lower AA dosage (50 g)–less competition from LNAAs	
Weltzin et al., 1994	Females. $n = 9$.	None	<i>Total TRP</i> ^b , <i>estimated:</i> ^c 47	13	– 63%	Small significant rise in ratings of ‘depressed’ and ‘overreactive’ after TD.	
Benkelfat et al., 1994	Males. $n = 39$. W/wo family history (FH) of depression.	None	<i>FH + (n = 20):</i>	1.4±0.2	0.3±0.2	– 78.6%	Change in POMS depression only in FH + sample, but no change on BDI or HDRS.
			<i>FH – (n = 19):</i>	1.4±0.2	0.3±0.4	– 7.8%	
Weltzin et al., 1995	Females. $n = 10$.	None	<i>Total TRP</i> ^b , <i>estimated:</i> ^c 60	12	– 80%	No effect on mood or on food intake.	
Ellenbogen et al., 1996	Females. $n = 20$. Three sessions: 1 × placebo, 2 × TD (1-month interval)	None	1.3±0.09	0.2±0.02	– 85.6%	Significant effect on POMS scoring only during first TD session: poor temporal stability of mood effect.	
			<i>Second TD session:</i> 1.3±0.08	0.3±0.02	– 80.6%		
Smith et al., 1997a,b	6 Males, 6 females.	None	0.4±0.04	0.1±0.03	– 66%	No effect on POMS ‘sad’ or ‘anxious’. Slight ↓ effect on ‘happy’ in females. Effect mood induction: TD = placebo.	
Barr et al., 1997	Six healthy Ss (4 males). Pre/post 6 weeks fluoxetine.	Fluoxetine 20 mg/day	<i>Pre:</i>	9.8±2.7	1.1±3.9	– 89%	Slight ↓ effect on ‘happy’ ratings at first measurement No effects after 6 weeks of fluoxetine ‘treatment’.
			<i>Post:</i>	7.7±1.8	1.0±0.1	– 87%	
Salomon et al., 1997	4 Males, 4 females 2 depletions: TD + AMPT	None	2.0±0.2	0.6±0.9	– 71.8%	No effect on any rating.	
Bhatti et al., 1998	Males. $n = 10$.	None	3.3±0.6	0.7±0.03	– 78.8%	No effect on POMS depression, but some changes on other subscales in <i>both conditions</i> . REM latency decrease.	
			<i>Placebo:</i>	4.8±1.1	2.6±0.7		– 47.0%

^a Notes: some of the ‘other conditions’ (see text) are not listed in this table, because most of these concern only one study. Abbreviations: TRP, tryptophan; TD, tryptophan depletion; MDE, major depressive episode; MDD, major depressive disorder; BPD, bipolar disorder; HDRS, Hamilton Depression Rating Scale; AA, amino acid; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor; SAD, seasonal affective disorder; POMS, profile of mood states; VAS, visual analogue scale; ECT, electroconvulsive therapy; AMPT, α-methylparatyrosine (catecholamine depletion); BDI, Beck Depression Inventory; OCD, obsessive–compulsive disorder; BN, bulimia nervosa; LNAA, large neutral amino acid.

^b Free plasma TRP not reported.

^c Values estimated from figure.

discussed only briefly, since it has recently been reviewed elsewhere (Reilly et al., 1997). Articles were searched up to July 1999 using the Medline and PsycLit databases. Search terms were: 'serotonin or tryptophan' and 'depletion' in the title, or 'tryptophan depletion' appearing anywhere in title, abstract or keywords. Articles were selected that used acute dietary tryptophan depletion in human subjects. The search was complemented by searches of personal collections and the reference lists of articles.

2. The procedure of tryptophan depletion

L-Tryptophan (TRP) is an essential amino acid, and the precursor of serotonin. A rapid and substantial, but easily reversible lowering of plasma TRP can be induced by drinking an amino acid (AA) mixture that lacks TRP and contains a large number of large neutral amino acids (LNAA). The mixture stimulates protein synthesis, which requires TRP. Furthermore, the LNAAs compete with TRP for the same transport system into the brain (Biggio et al., 1974). TRP plasma levels reach their lowest level 5–7 h after ingestion of the AA mixture. Depending on the dosage and perhaps on time of administration, the minimum level is 9–55% of baseline values (see Table 1). Central effects (reduction of brain serotonin levels) have been demonstrated in animals (Biggio et al., 1974; Gessa et al., 1974; Moja et al., 1989) and humans (Nishizawa et al., 1997; Carpenter et al., 1998; Williams et al., 1999). Furthermore, a direct comparison between TD and depletion of the amino acid lysine revealed that the latter procedure failed to produce any significant effect (Klaassen et al., 1999). This suggests that TD affects brain serotonin metabolism and not brain protein metabolism in general.

3. Methodological remarks

Almost all reviewed studies used a double-blind crossover design, in which subjects are tested twice with a 1-week interval, once with a TRP-deficient AA mixture, once with placebo. Sometimes, subjects keep a diet (tryptophan-low or placebo) on the day

before the procedure. The composition of the placebo mixture has varied, particularly since TRP was banned from the US market in 1989 because of a suspected association with eosinophilia–myalgia syndrome (Williamson et al., 1998). Before that time—and still in other countries—the placebo mixture was identical to the experimental mixture, with TRP added to it. Alternative placebos are a 25% strength preparation of the AA mixture (Krahn et al., 1996) and lactose, whereby both the active and placebo mixtures were given in capsules (Wolfe et al., 1995). The different placebo mixtures vary in their effects on TRP levels: the 25% strength preparation often causes small to moderate reductions of plasma TRP, while the original procedure usually caused a marked rise of plasma TRP. However, LNAAs also increase, and the ratio TRP/LNAA has been noted to decrease after placebo (55% reduction) (Weltzin et al., 1994). This is important because of the competition of TRP with LNAAs at the blood–brain barrier. However, the ratio TRP/LNAA is not routinely reported. Some studies only provide total plasma TRP, in spite of the fact that free TRP appears to be a better correlate of brain serotonin function (Biggio et al., 1974; Moja et al., 1989).

4. Tryptophan depletion in mood disorders

4.1. Depression

In the first TD study in depression, 14 of 21 patients receiving antidepressants experienced a brief relapse following TD, whereas a placebo mixture produced no effects (Delgado et al., 1990). Eleven patients relapsed by the end of the test day; the other three had relapsed the next morning. TD caused general depressive symptoms, but often also the specific thought contents that had been present before treatment. Subsequent research strongly suggested treatment specificity: patients treated with monoamine oxidase inhibitors (MAOIs) or selective serotonin re-uptake-inhibitors (SSRIs) were more likely to relapse than those treated with noradrenergic tricyclics (73 vs. 18%) (Delgado et al., 1991). This was confirmed in a recent study in which responders to fluoxetine were more vulnerable to TD than were responders to desipramine (Delgado et al.,

1999). Contrary to the results of remitted patients, symptomatic depressed patients did not experience a mood change during the depletion day (Delgado et al., 1994). However, 23% had a clinically significant worsening of depression scores the next day, whereas 37% had a transient improvement. The former group subsequently proved to be refractory to treatment (Delgado et al., 1994). This bimodal effect was not observed in two recent studies (Price et al., 1997, 1998), but these included a pharmacological intervention at the point of maximal depletion.

A PET scan study found decreased metabolism in the middle frontal gyrus, thalamus and orbitofrontal cortex in seven patients with a TD-induced depressive relapse compared with 14 patients who were unaffected by TD (Bremner et al., 1997). This decreased metabolism correlated with increase in depression scores. Furthermore, increased baseline metabolism was observed in patients vulnerable to TD-induced relapse, which may be the result of an adaptive mechanism (Bremner et al., 1997). Corroborating data were recently reported (Smith et al., 1999a).

The mood-lowering effect of TD has been replicated by independent investigators in SSRI-treated patients (Smith et al., 1999a,b). Women with a history of recurrent depressive episodes, but who were medication-free for at least 6 months, were also affected by TD (Smith et al., 1997a,b). However, in another study of medication-free remitted depressed patients, TD did not affect mood (Leyton et al., 1997a). It has been suggested (Leyton et al., 1997b) that the positive findings may be related to a high number of patients with a history of suicidal ideation. However, TD had no effect on guilt or suicidal thoughts in that study.

Further evidence for treatment-specificity comes from negative findings in responders to ECT (Cassidy et al., 1997), and in responders to sleep deprivation (Neumeister et al., 1998a). However, in the latter study TD postponed the relapse after one night of recovery sleep (to the second to fourth night).

4.2. Negative findings in major depression

The findings in major depression seem robust, with typically a little more than half of the SSRI- or MAOI-treated patients relapsing. Recently, however,

some unexpected negative findings were reported. One study found no effect (Moore et al., 1998), two studies found only a low percentage of patients responding (Bremner et al., 1997; Aberg-Wistedt et al., 1998). Moore et al. (1998) attribute their unexpected finding to sample differences and timing. TD was begun in midafternoon, whereas other studies typically start in the morning. This may have been relevant, considering the diurnal variation of plasma AA concentrations (Eriksson et al., 1989). Furthermore, in comparison with earlier studies, their patients had been longer in treatment and were less depressed, suggesting that the effect may be limited to *recently* recovered, *medicated* patients (Moore et al., 1998). However, clinically significant symptom increases have been observed in euthymic patients who had been off medications for at least 6 months (Smith et al., 1997a,b). As recently pointed out (Van der Does, 2000), insufficient depletion should also be considered as an explanation for negative findings. It may be possible that a threshold exists in the relation between TRP values and mood scores (Van der Does, 2000). In the three above-mentioned (partly) negative studies, TD reduced plasma TRP levels by 45–58%, which is lower than the typically reported 75–90% (see Table 1). In one of these studies (Aberg-Wistedt et al., 1998), this may have been due to the use of a modified AA mixture.

4.3. Other mood disorders

In a sample of seven recently recovered patients with *bipolar disorder*, TD was associated with increased manic symptoms for 3 days (Cappiello et al., 1997). Two patients met categorical criteria for a relapse. However, one patient fulfilled these criteria following the placebo depletion. In two other studies, euthymic patients who were being treated with lithium were unaffected by TD (Benkelfat et al., 1995; Cassidy et al., 1998). Patients in these studies had been in remission longer. Furthermore, patients in the Cappiello et al. study were on more complex medication regimes (see Table 1). Many of the studies reviewed above used mixed samples of patients with major depression or bipolar disorder (depressed phase, treated with anti-depressants) (see Table 1). As far as can be determined, the findings

do not indicate that bipolar depressed patients are more or less vulnerable to TD than unipolar patients.

In *seasonal affective disorder (SAD)*, TD was associated with a worsening of mood in unmedicated, euthymic patients who had responded to light therapy (Lam et al., 1996; Neumeister et al., 1997a, 1998b,c). No effect was found in currently depressed SAD patients (Neumeister et al., 1997b). These results parallel those obtained in major depression, which is not unexpected since melatonin is synthesized from serotonin (Delgado et al., 1991).

5. Tryptophan depletion in genetically vulnerable samples

TD had an effect on depression ratings in young males with a family history of mood disorders, but no effect in males without a family history of psychiatric disorder (Benkelfat et al., 1994). However, this was only measurable with the Profile of Mood States (POMS), and not with the Hamilton and Beck depression inventories, indicating that the mood reductions were small and not comparable to the effects observed in depressed patients. Unexpectedly, the same research group found no effect of TD in young women who had extensive, multi-generational family histories of mood disorders (Ellenbogen et al., 1999). These different findings cannot be explained by differences in the extent of depletion. Rather, it appears that a high exclusion and drop-out rate in the negative study may have resulted in the selection of a sample from which all those who had an actual genetic susceptibility to depression had been eliminated (Ellenbogen et al., 1999).

6. Tryptophan depletion in other psychiatric conditions

Considering the efficacy of SSRIs in conditions other than major depression, TD has recently been used to investigate the involvement of serotonergic mechanisms in these disorders. In *obsessive-compulsive disorder*, TD had no effect on OCD symptoms, but it did have a mood effect in patients with prior depressive symptoms (Barr et al., 1994). Another study found no effect on OCD symptoms or

mood (Smeraldi et al., 1996). The prevalence of patients with lifetime depression was much lower in the latter study (17 vs. 67%). Furthermore, this study investigated unmedicated patients, whereas the positive study used SRI-treatment responders.

In inpatients with *bulimia nervosa*, TD had a small effect on mood (Weltzin et al., 1994, 1995) and a marked effect on food intake (Weltzin et al., 1995). In recovered, medication-free women, TD caused a significant lowering of mood, an increase in body image concern and a subjective loss of control of eating (Smith et al., 1999b). The greatest changes in depression scores were observed in subjects with a history of depression, and some of the eating disorder symptoms correlated with changes in depression scores. Consequently, the bulimia symptoms may be secondary to depressive relapse. In an earlier study, no effects were found on mood, appetite or food intake in partially recovered patients (Oldman et al., 1995). However, in this study half the usual amount of AA mixture was used, resulting in a reduction of free plasma TRP of only 59.8%.

The evidence in *panic disorder* is mixed. None of eight medication-free patients had a panic attack or an increase in depression scores after TD (Goddard et al., 1994). In healthy subjects, TD did not alter the panicogenic effects of CCK-4 (Koszycki et al., 1996), nor did it increase the rate of panic attacks following 35% CO₂ provocation (Klaassen et al., 1998). Positive findings in these studies were larger increases in ACTH/cortisol and prolactin secretion (Koszycki et al., 1996) and slightly increased nervousness (Klaassen et al., 1998). Increased nervousness was also observed in response to a combination of TD and yohimbine challenge in normal subjects (Goddard et al., 1995). Finally, a preliminary report suggests that in panic patients, 5% CO₂ after TD leads to higher levels of anxiety than after placebo (Miller et al., 1996). However, this was not confirmed in a small uncontrolled study (Kent et al., 1996). The latter study did find that panic disorder patients increased respiration during TD while controls did not.

It has been hypothesized that TD might improve *schizophrenia* symptoms, given the facts that many neuroleptics are high-affinity antagonists of serotonin receptors, and that an earlier study had shown very small but significant positive effects of a 4-day

TRP-deficient diet in schizophrenia (Rosse et al., 1992). However, TD *worsened* negative symptoms in 16 inpatients with schizophrenia (Sharma et al., 1997), but the effect was small, and occurred on the day after TD.

A significant worsening of behavioral symptoms was observed in medication-free adult patients with *autistic disorder* (McDougle et al., 1996). TD also induced symptoms, particularly irritability, in seven of 16 women with *pre-menstrual syndrome* (Menkes et al., 1994).

TD increased aggressive responding in high-trait *aggressive* individuals (Cleare and Bond, 1995; Pihl et al., 1995; Moeller et al., 1996; Bjork et al., 1999). However, conflicting evidence also exists (Smith et al., 1986; Salomon et al., 1994; LeMarquand et al., 1998).

TD reduced craving and the effects of cocaine in patients with *cocaine dependence* (Aronson et al., 1995; Satel et al., 1995). Case reports were published on depression associated with *Parkinson's disease* (McCance-Katz et al., 1992) and *body dysmorphic disorder* (Barr et al., 1992). Finally, no effect was observed on tics or OCD symptoms in medication-free patients with *Gilles de la Tourette's syndrome* and OCD or OCD features (Rasmussen et al., 1997).

7. Mood effects of tryptophan depletion in healthy subjects

Some findings reviewed in this section are actually the results of normal control groups in studies on psychopathology. In a pioneering study in young healthy males (Young et al., 1985), depression ratings (self-report) increased from approximately 13 to 18 in the TD group (compared to a stable 14–15 in two groups receiving a TRP-supplemented or a balanced mixture). The authors conclude that TD resulted in a mild depressive state. This finding (including the magnitude of the effect) was replicated by the same group (Smith et al., 1987). Interestingly, this study addressed the question whether manipulation of cognitions (expectancy) and environment (pleasant or unpleasant) would influence the effect. The results were unequivocal in that the results were caused by the biological manipulation, and not by the cognitive or environmental

manipulation. The small mood effect was subsequently replicated in two studies (Weltzin et al., 1994; Ellenbogen et al., 1996), but not in five others (Danjou et al., 1990; Abbott et al., 1992; Oldman et al., 1994; Weltzin et al., 1995; Smith et al., 1997b). No behavioral effects were observed of TD in combination with α -methyl-*para*-tyrosine (which affects norepinephrine and dopamine) (Salomon et al., 1997). In one of the negative studies, however, TD countered the effect of morphine on pain tolerance (Abbott et al., 1992).

A very small effect (negative effect on 'happy' ratings) was found in six healthy subjects (Barr et al., 1997). These subjects subsequently took fluoxetine 20 mg/day for 6 weeks, in order to assess whether this would "confer on healthy subjects the vulnerability to the depressant effects of TD similar to that which has been observed in psychiatric patients receiving SRI treatment" (ibid., p. 950). Fluoxetine had no effect on POMS ratings or quality of life. After fluoxetine, TD had no effects. Ellenbogen et al. (1996) also repeated TD in normal subjects. The first TD session induced significant depression-like changes on several POMS subscales. However, this effect was completely disappeared during the second TD session 1 month later, despite comparable reductions of TRP levels (85.6 vs. 80.6%). They then investigated a subgroup of 13 subjects who had a reduction of at least 80% on both occasions. The results were reportedly unchanged: a mood effect at the first TD session, but not at the second. However, in the selective sample ($n = 13$), the mean change in POMS depression scores at the first session was 6.1, compared with 3.9 in the total sample ($n = 22$). The change score of the remaining nine subjects is not reported, but can be calculated as only 0.7. In other words, more than 80% reduction of plasma TRP led to a change score of 6.1, whereas the remaining subjects had virtually no change, despite a reduction of TRP levels of probably above 50%, providing some indirect support for the threshold hypothesis of mood effects of TD (Van der Does, 2000).

Finally, TD had an effect on sleep architecture (decreased REM latency) in the absence of mood effects (Bhatti et al., 1998). The same effect was observed in the placebo condition, which had also resulted in a substantial (47%) reduction of free plasma TRP. In another study in which the placebo

condition did not result in a decrease of serum tryptophan (Voderholzer et al., 1998), the following effects were confined to subjects in the tryptophan depletion condition: decreased non-REM stage 2 sleep, increase of wake percent and increase of REM density.

In summary, the results in healthy volunteers—including family members of patients with mood disorders—convincingly demonstrate that depressive episodes following TD do not occur in these samples. Some individuals experience small effects. The exact characteristics of these individuals are unclear, but some studies suggest that they may be more vulnerable to depression (higher baseline depression scores, positive family history, female gender).

8. Discussion

8.1. In recovered depressed patients, the characteristics of responders and non-responders to TD are unclear

TD has a negative effect on mood in a subgroup of recovered patients with major depression or SAD. In patients with major depression, the probability of relapse is clearly associated with type of treatment. Patients treated with SSRIs or MAOIs have a greater probability than those treated with TCAs, and patients responding to sleep deprivation or ECT do not relapse. However, not all studies using SSRI-treated patients have shown the effect. Furthermore, the fact that about half of the SSRI-treated patients are not affected by TD deserves more attention. Future research or a re-analysis of pooled data may elucidate the relative contribution of the following variables: gender, illness and treatment duration, time since remission, degree of remission, history of suicidal ideation, family loading of mood disorder and extent of plasma TRP reduction (including a possible threshold effect (Van der Does, 2000)).

8.2. The delayed effects of TD in symptomatic patients are understudied and may be clinically useful

One study showed that TD has a delayed bimodal effect in untreated depressed patients (Delgado et al.,

1994). The direction of this effect was indicative of treatment refractoriness, suggesting that the procedure may have clinical significance. However, this study is often cited as having found no effect of TD in symptomatic patients. The predictive power of TD for the effect of different types of treatment deserves more research attention.

8.3. Psychological factors can be ruled out as variables influencing response to TD

This may seem as a bold conclusion given the fact that psychological and environmental variables were systematically manipulated in only one study that concerned healthy volunteers (Smith et al., 1987). However, in more than 60 studies, involving well over 600 subjects, the placebo procedure has been documented to produce a (small) increase of symptoms in only two patients. It seems therefore worthwhile to consider *abandoning the placebo condition (at least, in previously researched populations)*, in favour of designs in which several strengths of the AA mixture are compared. For instance, studies could systematically compare procedures aimed at 90% reduction of plasma TRP with procedures aimed at 40 or 50% reduction. In some studies this has occurred unintentionally, because of the varying effects of different control procedures. The advantage of such designs is that it could directly address the threshold hypothesis (Van der Does, 2000), and that it could investigate the possibility that other neurobiological effects, e.g., changes in sleep architecture (Bhatti et al., 1998; Moore et al., 1998) occur at levels at which symptomatic changes do not yet occur. A potential pitfall, however, is the fact that a number of studies have found that two full-strength depletion sessions on separate occasions had poor temporal stability (Ellenbogen et al., 1996; Ellenbogen et al., 1999).

8.4. Qualitative description of the effect of TD deserves more attention

According to several authors, the quality of the effect of TD is a transient return of the mood and the thought contents that were present prior to treatment. For instance, Delgado et al. (1990) published several vignettes, illustrating the resemblance of the symp-

toms produced by TD and those of the prior depressive episode. In general, however, the change scores do not strike as indicative of a full-blown clinical relapse for most of the patients (see Table 1). Of course, some symptoms, e.g., sleep or weight changes, cannot occur in a 5–7-h time frame. But still, it would be useful to document the resemblance of TD-induced symptoms to those of prior depressive episodes by phenomenological descriptions in a prospective design.

9. Further suggestions for future research

The composition of the TRP-free AA mixture is very similar across studies, but the placebo drink is not. In view of the different effects of various placebo procedures, and the uncertainty regarding which factor is the best indicator of central serotonergic function, it is recommended that future publications report the following three parameters: total and free level of plasma TRP, and the ratio TRP/LNAAs. The latter parameter is important because of the competition of TRP with LNAAs at the blood–brain barrier.

The general diet of the study groups has not been systematically assessed in TD studies. Strict dieting, which is more common among the female population, may be a factor why healthy females appear to be more vulnerable to TD than males (although there are exceptions, e.g., Ellenbogen et al., 1999). In a study where TRP levels were assessed in healthy volunteers after a 3-week low calorie diet, the women had lower plasma TRP levels than the men despite a similar percent weight loss. Only in women was dieting associated with enhanced prolactin response after intravenous TRP, a measure of serotonin function (Anderson et al., 1990).

Conceptualizing the effects of TD as a temporary reversal of the effects of antidepressants in some patients, it could be investigated whether response to TD is a useful predictor of which patients need to remain on antidepressants. In other words, the clinical usefulness of TD as a predictor of response to treatment discontinuation is an important topic for research.

Analogous to the above-mentioned changes in sleep architecture, the more subtle or pre-clinical

effects of TD in psychiatric conditions, such as cognitive changes, could also be further investigated. Serotonin influences mood as well as cognitive functions. In normal subjects, TD has a negative impact on memory (Park et al., 1994; Riedel et al., 1999) but a positive effect on attention (Rowley et al., 1997; Schmitt et al., 2000), which may be due to a removal of inhibitory effects at the cortical level (Schmitt et al., 2000). Since a clinical state of depression has only negative effects on cognitive functions, it would be interesting to see how TD affects attention in recovered depressed patients. This may further our understanding about the complex interplay between cognitive and affective symptoms of depression.

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