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FEATURE REVIEW

Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies

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Dysfunction in the monoamine systems of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) may causally be related to major depressive disorder (MDD). Monoamine depletion studies investigate the direct effects of monoamines on mood. Acute tryptophan depletion (ATD) or para-chlorophenylalanine (PCPA) deplete 5-HT, acute phenylalanine/tyrosine depletion (APTD) or alpha-methyl-para-tyrosine (AMPT) deplete NE/DA. Available depletion studies found conflicting results in heterogeneous populations: healthy controls, patients with previous MDD in remission and patients suffering from MDD. The decrease in mood after 5-HT and NE/DA depletion in humans is reviewed and quantified. Systematic search of MEDLINE and EMBASE (1966–October 2006) and cross-references was carried out. Randomized studies applying ATD, PCPA, APTD or AMPT vs control depletion were included. Pooling of results by meta-analyses was stratified for studied population and design of the study (within or between subjects). Seventy-three ATD, 2 PCPA, 10 APTD and 8 AMPT studies were identified of which 45 ATD and 8 APTD studies could be meta-analyzed. 5-HT or NE/DA depletion did not decrease mood in healthy controls. 5-HT or NE/DA depletion slightly lowered mood in healthy controls with a family history of MDD. In drug-free patients with MDD in remission, a moderate mood decrease was found for ATD, without an effect of APTD. ATD induced relapse in patients with MDD in remission who used serotonergic antidepressants. In conclusion, monoamine depletion studies demonstrate decreased mood in subjects with a family history of MDD and in drug-free patients with MDD in remission, but do not decrease mood in healthy humans. Although depletion studies usefully investigate the etiological link of 5-HT and NE with MDD, they fail to demonstrate a causal relation. They presumably clarify a vulnerability trait to become depressed. Directions for further investigation of this vulnerability trait are proposed.
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Introduction

Major depressive disorder (MDD) is characterized by a lowered mood. MDD is a disabling disease which affects 20% of the world's population.[1] MDD is often treated with antidepressants (ADs), mostly selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrin reuptake inhibitors (SNRIs), norepineprine reuptake inhbitors (NERIs) or tricyclic antidepressants (TCAs).[2–5]

The working mechanism of AD is believed to be either by (1) increased neurotransmission by increased synaptic levels of serotonin, norepinephrine (NE) and dopamine (DA) (monoamines) or (2) specific agonistic effects on serotonin or NE (sub-)receptors. The increased levels of monoamines were discovered in the late fifties, when the TCAs and Monoamine-oxidase A inhibitors (MAO-I) appeared to effectively treat MDD. This discovery led to the monoamine hypothesis: MDD might etiologically be explained by a deficiency in monoamine neurotransmitters: serotonin (5-HT), NE or (to a lesser degree) DA. The monoamine systems in the brain have complex interactions. Therefore, the current, less pertinent view is that the monoamine hypothesis only partially explains MDD and the response to AD.[6–10]

Depletion of the available 5-HT, NE and/or DA is used as a model to test the involvement of monoaminergic systems in MDD. Two reviews recently described and reviewed the techniques of monoamine precursor depletion and enzyme-blocking methods.[11,12]

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In brief, 5-HT depletion can be achieved by rapidly lowering the levels of the essential amino-acid tryptophan, which cannot be synthesized by the body and must be ingested to enable formation of 5-HT. To achieve depletion, a tryptophan free amino-acid mixture is administered (acute tryptophan depletion (ATD)).[13] Depletion of NE and DA uses the same concept (acute depletion of the essential amino acids phenylalanine/tyrosine (APTD)).[14] As an alternative to induce a state of depletion, enzyme-blocking agents decrease the production of the monoamines. Parachlorophenylalanine (PCPA) blocks 5-HT synthesis,[15,16] and alpha-methyl-para-tyrosine (AMPT) NE and DA synthesis.[17] Since 1975 an increasing number of depletion studies have been conducted. Monoamine depletion showed differential effects in different study populations: healthy controls, healthy controls with a family-history of MDD, patients with MDD in remission using AD or after cessation of AD, and patients who had a current episode of MDD.

Previous reviews summarized the methodology of depletion tests.[18] Others reviewed the findings of specific depletion tests across different psychiatric illnesses,[11,18–20] or the prediction of response to depletion.[21,22] Booij *et al*.[21] presented a study that pooled results across studies individual subject data of six ATD studies ('mega-analysis') in order to investigate the mediating role of clinical, demographic and biochemical characteristics in the mood response to ATD in remitted subjects who previously had MDD. However, a clear summary of the mood effects of monoamine depletion across different populations is lacking. Except from the study of Booij *et al.*, we are unaware of any attempt of pooling studies. Pooling is important because the small-sized depletion studies might not have detected small differences by a lack of power. Finally – as in drug research – pooling will quantify the weight of positive vs negative studies.

Therefore, we aimed to review the evidence for mood lowering properties of monoamine depletion studies as a model for MDD. Our main question was: does the depletion of monoamine (5-HT and NE/DA) systems lower mood in humans? A secondary question was: is the lowering of mood different across different populations? This paper reports our systematic review with a stratified meta-analysis of the mood effects of monoamine depletion studies.

Methods and materials

Design of the study

We included all available randomized prospective monoamine depletion studies (tryptophan and phenylalanine/tyrosine) and enzyme blocking studies (PCPA or AMPT) in humans. Included studies measured a change in mood after depletion. Two study designs were included. First, randomized *within-subjects* studies, where each subject was exposed to a true depletion vs a sham intervention at a second occasion. This way, each subject served as his/her own control. Second, randomized *between-subjects* studies, where two groups of subjects were compared, with the intervention applied to one group and a control intervention to the other group. We excluded animal studies and studies which selected patients with apparent co-morbidity (e.g. substance abuse or dependence, studies with only smokers, psychotic disorders, anxiety disorders). Additionally, we excluded studies in depression subtypes with a supposed different etiology (e.g. seasonal affective disorder, bipolar disorder). We also excluded studies that combined depletion with other interventions (e.g. sleep deprivation) or studies that did not report mood effects. Finally, we excluded studies recruiting a patient group with both unipolar and bipolar depression when >25% of subjects had bipolar depression and when no separate data for the unipolar group were provided.

Literature searches and selection

We searched PubMed from 1966 to 1 October 2006 and EMBASE from 1980 to 1 October 2006 using a comprehensive search strategy (Table 1). We retrieved additional references identified in previous reviews[11,12,18–20,23–25] and cross-references from

Table 1 Search terms

No.	Search terms used
1	Depressive disorder[MeSH] OR depression[MeSH] OR (depressive[TW] AND symptoms[TW]) OR mood[TW]
2	Indoleamine$ OR serotonin[MeSH] OR 5-hydroxytryptamine[TW] OR 5-HT[TW]
3	((Tryptophan[MeSH] OR Tryptophan[TW]) AND depletion[All Fields]) OR (fenclonine[MeSH] OR PCPA[TW] OR parachlorophenylalanine[TW])
4	#1 AND #2 AND #3
5	Catecholamines[MeSH] OR norepinephrine[MeSH] OR epinephrine[MeSH] OR Dopamine[MeSH]
6	((Tyrosine[MeSH] OR Tyrosine[TW]) AND depletion[All Fields]) OR (alpha-methyltyrosine[MeSH] OR AMPT[TW] OR alpha-methyl-para-tyrosine[TW])
7	#1 AND #5 AND #6
8	(#4 OR #7) NOT (Animal[MeSH] NOT Human[MeSH])

Abbreviations: MeSH = Medical Subject Heading, TW = textword.
Note: PubMed search terms are provided; these terms were slightly modified for EMBASE-searches.

identified studies. Two reviewers (HGR and NSM) independently selected articles based on the *a priori* inclusion and exclusion criteria as stated above. In case of doubt an article was retrieved and the full content was considered. In 85.4% the reviewers agreed on selection instantly. The initial kappa for agreement was 0.61 (95% confidence interval (CI): 0.52–0.71). Agreement was mainly influenced by a differential inclusion of research letters, studies in depression subtypes with a supposed different etiology and studies without apparent mood-scores in the abstract. Discrepancies in included studies were discussed between both reviewers until full consensus was reached.

Data extraction and assessment of the studies
Two authors (HGR and NSM) abstracted the retrieved studies as follows: population studied, study design (within-subjects or between subjects), applied mood scale(s), number of subjects (and – if applicable – number of subjects for each sequence of intervention and control depletion), male/female ratio, the intervention and its control condition (including dosage and duration). Furthermore, we extracted plasma levels of tryptophan, tyrosine or relevant levels of monoamine-metabolites before and after intervention and control condition and other relevant data that could influence the outcome of the study (e.g. different consistency of control drink, unclearly reported data, combined interventions). Primary outcome variables were changes in mood-scale scores before and after intervention and control, and the number of relapses in the intervention and control group. If more than one mood-scale was used, we primarily used the Profile of Mood States (POMS).[26] Otherwise, we used the Multiple Affect Adjective Checklist (MAACL),[27] Visual Analogue (Mood) Scales (VA[M]S),[28] Hamilton-depression rating-scale (HAMD),[29] and Montgomery-Åsberg Depression Rating Scale (MADRS).[30] However, in studies in patients with previous MDD in remission we primarily chose the HAMD or MADRS followed by the POMS, because most of these studies used depression rating scales to measure effects of depletion. If subscales were used, we took the subscale representing depressed mood.

We validated the abstracted studies (criteria available on request). We based criteria on previous reviews and the Cochrane handbook.[11,12,18,31] We assessed studies as poor, moderate or good *in the context of this meta-analysis*. We particularly assessed quality as good when studies applied a randomized double-blind design, when the achieved depletion was judged to be sufficient, and when mood-scale ratings were provided.[11,18] If more than one of these items was rated inadequate, we assessed the study as moderate. If studies had one of these items missing and at least one other aspect of the study was not well reported, we also assessed the study as moderate. If crucial data (e.g. scores and SDs) were missing the study was assessed as poor.

Data synthesis
We qualitatively summarized all included studies in Tables 2–5 (ATD, PCPA, APTD and AMPT respectively), irrespective whether the studies were pooled in the meta-analysis. We acknowledged three clinically heterogeneous study populations *a priori*: (A) healthy controls (A1 negative/A2 positive family history of MDD); (B) patients with a previous MDD currently in remission (B1 currently not using AD/B2 currently using AD); and (C) patients with a current episode of MDD (with or without AD). These populations were considered and analyzed separately.

Statistical pooling
Mostly, continuous scores for changes in mood rating scales were reported. Some studies in patients with MDD in remission presented relapse rates. In order to pool continuous effect estimates from different scales, we applied a standardization (providing Hedges' *g*). The effect estimates (one per study) with the corresponding standard error (SE) were entered in the inverse-variance statistics for pooling in Review Manager 4.2.[125,126] Appendix gives the formulas used to determine Hedge's *g*, the difference in relapse rates and corresponding SEs for different study designs.

Different study designs were not combined in pooling. Especially the within-subject design needs attention in meta-analysis. In this design, differences between the experimental and control condition are statistically paired. As paired data improve power, calculations with data from a within subjects (or cross-over) design in a weighted mean differences model would not be justified.[126]

Heterogeneity, effect modification, sensitivity-analysis and assessment of publication bias
We first performed the meta-analyses with fixed effects models. We assumed more homogeneous results after our *a priori* attempt to reduce clinical heterogeneity by stratification. However, if effect-estimates and 95% CI for the individual studies showed graphical poor overlap or consistency, we interpreted this an indication of statistical heterogeneity. We used the χ^2 test and I^2 in addition. I^2 represents a χ^2 statistic relative to its degree of freedom. An I^2 value $>50\%$ is indicative of heterogeneity.[127] We applied a conservative random effects model[128] when we suspected statistical heterogeneity.

We investigated effect modification by gender, and the influence of a positive family history of MDD in healthy controls. Furthermore, we investigated whether different mood scales caused differences in outcomes. Therefore, we stratified analyses for these variables, and presented stratified Hedges' *g*, with 95% CI. Differences between strata were tested by subtracting the χ^2 heterogeneity statistic per stratum from the total χ^2 heterogeneity statistic. This residual (Q_{res}) has a χ^2 distribution, with the total number of strata-1 degrees of freedom.

We imputed $R=0.5$ to calculate missing pooled SDs within each intervention/control and for the changes

Table 2 Included studies ATD

Author (year)[a]	*Design*	*N*	*Adeq. of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
(A) Healthy controls						
Abbott (1992)[32]	Rand., DB, Betw. SS	2[a]30 M	Not clearly reported	POMS-depression: ATD: BL: 2.50 (±0.58 SE), post-test: 1.73 (±0.71). CONT: BL: 2.50 (±0.58), post-test: 1.98 (±0.58)	Study primarily investigates effect of ATD on analgesia	Moderate
Allen (2006)[33]	Rand., DB, Within SS, FH−	10 M+F	Good	VAS: no exact scores reported, no sign. difference in mood found	Study investigates effects of ATD on cognition (verbal fluency and working memory) and prefrontal activity by fMRI	Moderate
Amin (2006)[34]	Rand., DB, Within SS	19 F	Good[e]	POMS and HAMD: no exact scores reported, no sign. Difference in mood found on total POMS or HAMD	Study investigates effect of ATD on cognition (memory, visuospatial learning) and the protective effects of estrogen therapy (ET) in peri-/post-menopausal women. Only pre-ET-data used	Moderate
Barr (1997)[35]	Rand., DB, Within SS, FH−	6 M+F	Good	VAS-happy: ATD: BL: 51.2 (±9.1), post-test: 42.7 (±13.8). CONT: 51.7 (±25.9), post-test: 62.7 (±12.2); POMS not reported	Study investigates effect of fluoxetine treatment on ATD in healthy controls, only pre-fluoxetine data used	Good
Benkelfat (1994)[36]	Rand., DB, Within SS, FH−	19 M	Good	POMS-depressed: ATD: BL: 57.2 (±2.0 SE), post-test: 58.9 (±2.0), change: 1.7 (±1.4). CONT: BL: 56.3 (±2.6), post-test: 60.0 (±2.1), change: 4.3 (±2.3). No one reached 10 point decline in POMS-D	POMS changed in FH+ sample, not in FH− sample in same study (data provided separately)	Good
Bhatti (1998)[37]	Rand., DB, Within SS, FH−	10 M	Good	POMS-depressed: ATD: BL: 0.9 (±1.3), post-test: 0.7 (±3.3), CONT: BL: 0.9 (±1.3), post-test: 0.4 (±1.0)	Control-drink is 25% intervention drink, ATD and CONT differ >48 h. Study investigates effects of ATD on sleep EEG	Moderate
Craen (2002)[38]	Rand.?, DB?, Within SS, 85% FH−	20 M	Good	POMS-depressed: No exact scores reported, no sign. Difference in mood found	Study investigates difference in impulsivity after ATD between controls with FH+ and FH− for alcoholism	Poor
Danjou (1990)[39]	Rand., DB, Betw. SS,	2[a]10 M	Good[e]	VAS and adaptation of MAACL, exact scores not reported, no sign. Difference in mood found	Study focuses on psychomotor and neuroendocriene effects of ATD	Moderate
Debener (2002)[40]	Rand., DB, Within SS, FH−	18 F	Not tested	Mood 'questionnaires' did not reveal differences in affect for ATD	Study investigates the effect of ATD on auditory evoked potentials with EEG	Poor
Ellenbogen (1996)[41]	Rand., DB, Within SS, FH−	21 F	Good	POMS-depressed[e]: ATD: change −4 (±1.6 SE), CONT: change: 0.8 (±1.55); VAMS	Study also examines stability of ATD response which appears to be poor	Good
Evers (2005)[42,43]	Rand., DB, Within SS, FH−	12 M	Good	VAS sadness: ATD: BL: 1.8 (±1.6), post-test: 2.0 (±1.6). CONT: BL: 1.0 (±0.7), post-test: 1.8 (±1.6)	Study investigates effect of ATD on amygdale reactivity to fearful faces with fMRI	Moderate
Evers (2006a)[44,45]	Rand., DB, Within SS	13 M	Good	POMS: No exact scores reported, no sign. difference in mood found	Study investigates effects of ATD on cognition (performance monitoring and response inhibition and memory) and prefrontal/hippocampal activity by fMRI	Moderate
Evers (2006b)[46]	Rand., DB, Within SS, FH−	15 F	Good	POMS: No exact scores reported, no sign. difference in mood found	Study investigates effects of ATD on a combined cognitive and emotional task by fMRI	Moderate
Gallagher (2003)[47]	Rand., DB, Within SS	15 M	Good	VAMS-contentedness-scale: scores not completely reported. ATD: post-test: 83.4 (±7.5), CONT: post-test: 86.5 (±7.8) No sign. Changes in mood	Study focuses on executive neurocognitive functions	Moderate

Table 2 Continued

Author (year)[a]	*Design*	*N*	*Adeq. of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
Harrison (2002)[48]	Rand., DB, Within SS, FH−	13 F	Good	POMS-depressed: ATD: BL: 2.07 (±0.63 SE), post-test: 0.76 (±0.63) CONT: BL: 1.61 (±0.52), post-test: 1.15 (±0.56)	Study also reports absence of effects of ATD and APTD on interleukin-6 activation	Good
Harrison (2004)[49]	Rand., DB, Within SS, FH−	13 F	Good	VAMS: exact scores not reported, no sign. Differences in mood found	Study also investigates memory and cognitive effects of ATD and APTD	Moderate
Hayward (2005)[50]	Rand., DB, Betw. SS, 20 FH−	2[a]12 M+F	Good	HAMD: ATD: BL: 0.17 (±0.11 SE), post-test: 0.67 (±0.19), CONT: BL: 0.33 (±0.19), post-test: 0.41 (±0.19). BDI: ATD: BL: 1.5 (±0.56 SE), post-test: 0.58 (±0.33), CONT: BL: 2.13 (±0.57), post-test: 2.25 (±0.80). POMS and VAS: exact scores not reported. No significant effect on any scale found	Study also investigates cognitive processing in formerly depressed vs healthy controls during ATD	Moderate
Hughes (2000)[51]	Rand., DB, Within SS, FH−	20 M	Good	Undefined scale: no significant changes in mood found	Study investigates effects of ATD on auditory evoked potentials on EEG	Poor
Hughes (2003)[52]	Rand., DB, Within SS, FH−	20 M	Good	VAS-sadness: ATD: BL: 90.7 (±3.5 SE), post-test: +6.7 (±4.7), CONT: BL: 94.8 (±2.6), post-test: −1.6 (±1.9). No significant main effects on any VAMS scale	Study investigates effects of ATD on verbal and visuospatial learning and memory, attention and executive function	Good
Kähkönen (2005)[53]	Rand., DB, Within SS	14 M+F	Good	VAS-depression: ATD: change 41.5 (±20.7), CONT: change 21.5 (±17.6)	Study investigates effects of ATD on auditory response, MEG and EEG signals	Moderate
Klaassen (1999a)[54]	Rand., DB, Within SS	13 M+F	Good	POMS-depressed: ATD: BL: 0.6 (±1.3), post-test: 1.5 (±3.3), CONT: BL: 0.5 (±1.0), post-test: 0.2 (±0.6). VAS-depressed: ATD: BL: 2.7 (±6.6), post-test: 8.2 (±18.2), CONT: BL: 3.2 (±6.3), post-test: 4.5 (±13.0)	Study investigates specificity of ATD vs LYS-depletion on mood-effects and memory	Good
Klaassen (1999b),[55] **Klaassen (2002)**[56]	Rand., DB, Within SS, FH+ & FH−	11 FH− M+F	Good	POMS-depressed: scores not completely reported. ATD-CONT differences: FH− 0.0 (±0.45)	No baseline POMS-scores provided ('nonsignificant differences'). Study compared FH+ group with FH−. The FH+ ves responded to tryptophan depletion with a significant lowering of POMS scores, but FH− ves did not. Also memory effects measured	Moderate
Koszycki (1996)[57]	Rand., DB, Betw. SS, FH−	2[a]20 M	Good	VAMS-depressed: ATD: BL: 1.5 (±1.0 SE), post-test: 0.8 (±0.6). CONT: BL: 3.4 (±1.8), post-test: 4.5 (±1.4)	Study investigates effect of administration of cholecystine-tetrapeptide after ATD on occurrence of panic-attacks	Good
Leyton (1999),[58] **Leyton (2000)**[59]	Rand., DB, Betw. SS, FH−	15 ATD 14 CONT F	Good	POMS[e]: ATD: change: −3.28 (±1.4 SE). CONT: change −1.04 (±1.2 SE). VAMS-depressed: ATD: BL: 1.0 (±0.9), post-test: 0.8 (±0.8), change: −0.3 (±0.8). CONT: BL: 0.4 (±0.5), post-test: 0.4 (±0.4), change: 0.1 (±0.4)	POMS; no exact scores reported. Third arm with APTD included	Moderate
McAllister-Williams (2002)[60]	Rand., DB, Within SS, FH−	14 M	Good	POMS: No exact scores reported, no sign. Difference in mood found	Study investigates effects of ATD on event related brain potentials on EEG during an episodic memory task	Moderate

Table 2 Continued

Author (year)[a]	*Design*	*N*	*Adeq. of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
Miller (2000)[61]	Rand., DB, Within SS, FH−	19 M+F	Good	POMS[e]: ATD: BL: 1.8, post-test: 0.3. CONT: BL: 2.9, post-test: 0.7 VAS-sad[e]: ATD: BL: 8.0, post-test: 10.1. CONT: BL: 12.2, post-test: 10.9. No SDs reported, no sign. Differences in mood found	No clear presentation of mood-scores; study compares ATD+ CO2−challenge in healthy controls vs patients with panic disorder	Poor
Moreno (1999),[62] Moreno (2000)[63]	Rand., DB, Within SS, FH−	12 M+F	Good	HAMD-25, POMS and IDS scores not clearly reported. ATD did not cause significant increases in depressive symptoms in healthy control subjects	Study compared ATD effects in healthy controls vs. patients with MDD in remission. Instead of placebo a 25% strength depletion drink was used as a control	Poor
Murphy (2002)[64]	Rand., DB, Within SS	11 F	Good	Scores reported separately for groups with ATD first and CONT first. VAMS-sadness: ATD first: ATD: change: −1.4 (±5.5), CONT: change: −0.2 (±0.5). CONT first: ATD: change: 0.8 (±26.6), CONT: change: −12.5 (±26.1) Weighted averaged score (with highest SDs) used for meta-analysis	Study investigates cognitive and emotional processing after ATD	Good
Neumeister (2002)[65]	Rand., DB, Within SS, FH−	24 F	Good	HAMD-21: s/s subtype ($n=4$): ATD: change 8.5 (±2.9). CONT: 0.3 (±0.5) s/l subtype ($n=10$): ATD: change 4.6 (±2.9). CONT: 0.5 (±0.9) l/l subtype[e] ($n=10$): ATD: change −0.1 (±1.3). CONT: 0.0 (±1.1)	Study investigates effect of biallelic serotonin transporter promoter (5-HTTPR) genotype and effect of ATD	Good
Neumeister (2004)[66]	Rand., DB, Within SS, FH−	19 M+F	Good	HAMD-24[e]: ATD: BL: 0.5 (±0.1), post-test: 3.4 (±0.6). CONT: BL: 0.5 (±0.1), post-test: 2.6 (±0.5)	Study mainly investigates regional cerebral blood-flow changes during ATD with PET-scans	Good
Neumeister (2006)[67]	Rand., DB, Within SS, FH−	26 M+F	Good	HAMD[e]: s/s subtype ($n=7$): ATD: BL: 0.4 (±0.4 SE), post-test: 3.6 (±1.4). CONT: BL: 0.8 (±0.4), post-test: 2.4 (±0.8). s/l subtype ($n=12$): ATD: BL: 0.4 (±0.4), post-test: 5.2 (±1.1). CONT: BL: 0.4 (±0.4), post-test: 2.5 (±0.6). l/l subtype ($n=7$): ATD: BL: 0.4 (±0.4), post-test: 2.4 (±1.3). CONT: BL: 0.2 (±0.4), post-test: 1.2 (±0.8)	Study investigates effect of triallelic serotonin transporter promoter (5-HTTPR) genotype and effect of ATD on mood and regional cerebral metabolism with PET	Good
Oldman (1994)[68]	Rand., DB, Within SS	12 F	Good	POMS-depressed: ATD: BL: 1.1 (±0.52 SE), post-test: 0.9 (±0.58). CONT: BL: 1.9 (±0.92), post-test: 2.3 (±0.89). VAS-sad: ATD: BL: 15.0 (±4.99 SE), post-test: 9.2 (±4.5). CONT: BL: 11.7 (±4.73), post-test: 8.3 (±3.87)	In this study a second placebo-arm (plain water) is used; comparisons here are for balanced drink as CONT. Effects of ATD on appetite investigated also	Good
Park (1994)[69]	Rand., DB, Within SS	12 M	Good	VAMS-sad: ATD: BL: 6.7 (±5.7 SE), post-test: 6.6 (±8.1). CONT: BL: 3.2 (±3.0), post-test: 5.6 (±6.8)	Study investigates cognitive performance after ATD	Good
Praschak-Rieder (2005)[70]	Rand., DB, Within SS, FH−	14 M+F	Good	No exact VAS-ratings provided in study; none of the 14 subjects experienced a transient deterioration in mood [...] levels	Study primarily investigates effects of ATD on serotonin transporter density/affinity during ATD	Moderate

Table 2 Continued

Author (year)[a]	*Design*	*N*	*Adeq. of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
Ravindran (1999),[71] **Knott (1999)**[72]	Rand., DB, Betw. SS, FH−	2[a]13 M	Good	POMS-change: ATD −1.29 (±0.94) vs CONT +1.41 (±0.55). Significant changes in mood, but this occurred in five of the 13 subjects only, while in others in the ATD-group no decrease of mood was observed	No clear presentation of data on mood-scores; probably SDs reported. Study also investigates effect of fenfluramine administration after ATD and effect of ATD on immune measures and EEG	Moderate
Richell (2005)[73]	Rand., DB, Betw. SS	15 + 13 M + F	Good	No baseline data on POMS or VAS reported, only measures during the noise-stress paradigm reported after ATD, no sign. Differences in mood found	Study especially investigates difference in response to noice-stress by ATD vs CONT	Poor
Rubia (2005)[74]	Rand., DB, Within SS, FH−	9 M + F	Good	No VAS-scores reported, no sign. Changes of mood observed by ATD	Study investigates functional brain activity by fMRI with a response inhibition-task	Poor
Rubinsztein (2001)[75]	Rand., DB, Betw. SS, 80% FH−	2[a]15 M + F	Good	POMS-depressed: no exact scores reported. Scores were similar between test and placebo groups, also on VAMS, no sign. Differences in mood found	Study investigates effects of ATD on cognitive test concerning attention	Poor
Schmeck (2002)[76]	Rand., DB, Betw. SS, FH−	12 M + F	Good	Eigenschaftswörterliste: no exact scores reported. High aggressive women were sign. More depressed after ATD than other groups. High aggressive men did not show an effect of ATD on mood. The mood of non-aggressive men and women did not change after ATD	Study looked at different reaction to ATD in high and low-aggressive males and females	Poor
Schmitt (2000)[77]	Rand., DB, Within SS, FH−	17 M + F	Good	POMS-depression: ATD: BL: 0.92 (±0.11 SE), post-test: 0.93 (±0.12). CONT: BL: 0.95 (±0.11), post-test: 0.96 (±0.13)	Study investigates cognitive performance after ATD	Good
Shansis (2000)[78]	Rand., DB, Within SS, 7/12 FH−	12 M	Good	POMS-depressed & VAS: no exact scores reported. Mood changes on control day not sign. Different than on ATD day for any of the six dimensions in the POMS and VAS	Previous mood-disorder in one subject (not excluded). Study investigates effects of ATD on attention and memory	Poor
Smith (1987)[79]	Rand., DB, Within SS	80 M	Good	MAACL[e]: ATD: BL: 10.9, post-test: 18.2. CONT: BL: 9.5, post-test: 8.2. No SDs reported. Significant lowering of mood scores by ATD	Study investigates ATD in negative and positive environment. Both conditions show a significant change on mood scores	Moderate
Smith (1997b)[80]	Rand., DB, Within SS, FH−	11 M + F	Good	VAS-sadness: no exact scores reported. No significant main effects were seen. VAS-happy for females ($n = 6$) reported separately[e]: ATD: BL: 69.7 (±5.6 SE), post-test: 61.6 (±6.4). CONT: BL: 71.4 (±5.3), post-test: 66.1 (±6.1). For males ($n = 5$)[e]: ATD: BL: 72.2, post-test: 67.8. CONT: BL: 77.2, post-test: 70.6. No SEs reported	Study also investigates effect of ATD when sad-mood is induced. Data for females VAS-happy used in meta-analysis	Moderate
Stewart (2002)[81]	Rand., DB, Within SS, FH−	27 M + F	Good	POMS-depression: ATD: BL: 1.7 (±2.6), post-test: 1.1 (±2.3), change: −0.6 (±2.1). CONT: BL: 3.4 (±6.0), post-test: 2.4 (±4.8), change: −1.0 (±4.6)	Study also investigates effect modification by high vs low neuroticism scores during ATD (on mood and psychometric performance)	Good
Talbot (2006a)[82]	Rand., DB, Betw. SS, FH−	17 + 15 M + F	Good	VAMS: No exact scores reported, no sign. Difference in mood found	Study investigates effects of ATD on decision making and learning	Moderate

Table 2 Continued

Author (year)[a]	*Design*	*N*	*Adeq. of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
Talbot (2006b)[83]	Rand., DB, Within SS, FH−	16 M	Good	VAMS: ATD: change −0.5 (±6.1). CONT: change −5.7 (±8.1) BDI: ATD: change −0.0 (±1.4). CONT: change 0.4 (±1.5)	Study investigates effect of ATD on Regional Cerebral Blood Flow by SPECT	Good
Voderholzer (1998)[84]	Rand., DB, Within SS, FH−	12 M + F	Good	HAMD-6: ATD: BL: 0.83 (±1.8), post-test: 0.42 (±1.2). CONT: BL: 0.17 (±0.4), post-test: 0.42 (±0.7).	Study investigates effects of ATD on sleep EEG	Good
Weltzin (1994)[85f]	Rand., DB, Within SS	9 F	Good	Only peak-changes for ATD and CONT are provided for an unclearly defined mood-scale: ATD: 0.78. CONT 0.0. SDs not reported. SD of difference estimated conservatively from $p < 0.05$: ±1.01	Study investigates effect of ATD on mood in bulimic patients ($n = 13$) and healthy controls ($n = 9$)	Moderate
Weltzin (1995)[86f]	Rand., DB, Within SS	10 F	Good	Only peak-changes between ATD and CONT are provided for an unclearly defined mood-scale: 0.0 (±1.3), this value used in meta-analysis	Study investigates effect of ATD on mood and short-term eating behaviour in bulimic patients ($n = 10$) and healthy controls ($n = 10$).	Moderate
Yatham (2001)[87]	Rand., DB, Within SS, FH−	10 F	Good	HAMD-20, POMS: No exact scores reported, no sign. Difference in mood found	Study investigates effects of ATD on 5-HT_2 receptors with PET	Moderate
Young (1985)[13]	Rand., DB, Betw. SS	3[a]12 M	Good	No clear MAACL-scores or SDs reported per group for ATD vs CONT. Sign. Decrease of mood after ATD	Study investigates effects of ATD on proofreading task with or without distraction	Poor
(A2) Healthy controls with + ve family history for MDD						
Benkelfat (1994)[36]	Rand., DB, Within SS, FH+	20 M	Good	POMS-depressed: ATD: BL: 55.2 (±1.7 SE), post-test: 51.2 (±1.6), change: −4.0 (±1.6). CONT: BL: 54.0 (±1.6), post-test: 57.3 (±1.1), change: 3.3 (±1.6). Six (30%) of people showed a decline of 10 points or greater on POMS-D	POMS changed in FH+ sample, not in FH− sample in same study	Good
Ellenbogen (1999)[88]	Rand., DB, Within SS, FH+	13 F	Good	POMS-depressed[e]: 1st ATD: change: −0.3 (±1.7 SE). CONT: change: −1.1 (±1.5). VAMS: no exact scores reported. No significant change in mood on any of the POMS or VAMS items	Possible selection-bias by exclusion of many former patients mentioned: extremely FH+ sample, but never depressed Study found poor temporal stability of ATD in repeated testing	Good
Klaassen (1999b),[55] **Klaassen (2002)**[56]	Rand., DB, Within SS, FH+ & FH−	16 FH+ M + F	Good	POMS-depressed: scores not completely reported. ATD-CONT differences: FH+ 1.94 (±3.17)	See above in section 'healthy controls'	Moderate
Neumeister (2002)[65]	Rand., DB, Within SS, FH+	21 F	Good	HAMD-21: s/s subtype ($n = 5$): ATD: change 9.2 (±2.1). CONT: 0.8 (±0.5) s/l subtype ($n = 7$): ATD: change 10.0 (±4.5). CONT: 0.1 (±0.4) l/l subtype[e] ($n = 9$): ATD: change 0.4 (±1.2). CONT: −0.2 (±1.3)	Study investigates effect of biallelic serotonin transporter promoter (5-HTTPR) genotype and effect of ATD	Good
Stewart (2002)[81]	Rand., DB, Within SS, FH−	5 M + F	Good	POMS-depression: ATD: BL: 5.2 (±10.0), post-test: 5.6 (±10.4), change: 0.4 (±0.5). CONT: BL: 6.4 (±12.7), post-test: 4.2 (±7.4), change: −2.2 (±5.5)	See above in section 'healthy controls'	Good

Table 2 Continued

Author (year)[a]	*Design*	*N*	*Adeq. of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
(B1) Patients with MDD previously, but currently in remission (without medication)						
Cassidy (1997)[89]	Rand., DB, Within SS 1–4 days after ECT	5 M+F Rx-free <3 months	Good	MADRS: ATD: BL: 4.2 (±3.5), post-test: 3.6 (±3.2). CONT: BL: 4.8 (±2.9), post-test: 4.0 (±3.5)	Study investigates recurrence of MDD after ATD in patients successfully treated with ECT	Good
Delgado (1991)[90]	Rand., DB, Within SS⩾2 weeks after 'stability'	69 M+F Rx-free ?? months	Good	HAMD-25: exact scores not reported; no sign. difference by ATD. 30% experienced an improvement of mood the day after ATD. Depressive relapse: No exact data provided	In original studies Bipolar patients included; unclear whether these were excluded in this pooled analysis	Poor
Haynes (2004)[91]	Rand., DB, Within SS 1-2 weeks response	13 M+F Post-CBT	Good	POMS-depression: ATD: BL: 6.4 (±7.4), post-test (8 h): 4.9 (±6.4). CONT: BL: 5.5 (±7.7), post-test: 5.0 (±7.8). HAMD-19: ATD: BL: 4.7 (±3.7), post-test: 4.9 (±3.9). CONT: BL: 3.3 (±2.5), post-test: 3.5 (±4.3)	Study investigates recurrence of MDD after ATD in patients successfully treated with CBT, and effects on REM-sleep	Moderate
Hayward (2005)[50]	Rand., DB, Betw. SS, 11 FH−⩾6 months remission	2[a]12 M+F Rx-free⩾ 3 months	Good	HAMD: ATD: BL: 1.0 (±0.41 SE), post-test: 1.38 (±0.36), CONT: BL: 0.42 (±0.23), post-test: 0.50 (±0.19). BDI: ATD: BL: 2.25 (±0.76 SE), post-test: 1.75 (±0.68), CONT: BL: 2.17 (±0.63), post-test: 1.63 (±0.53). POMS and VAS: exact scores not reported. No significant effect on any scale found	Study also investigates cognitive processing in formerly depressed vs healthy controls during ATD	Moderate
Moreno (1999),[62] Moreno (2000)[63]	Rand., DB, Within SS⩾3 months remission (average 29 months)	12 M+F Rx-free⩾ 3 months	Good	HAMD-25, POMS and IDS scores not clearly reported. ATD caused nonsignificant increases in depressive symptoms in history-positive subjects Post-test: mean peak HAMD scores ATD: 14 (±6), 'CONT': 10 (±7)	Study compared healthy controls with patients with MDD in remission. Instead of placebo a 25% strength depletion drink was used as a control	Poor
Neumeister (2004)[66]	Rand., DB, Within SS⩾3 months remission	27 M+F Rx-free⩾ 3 months	Good	HAMD-24[e]: ATD: BL: 1.2 (±0.2), post-test: 11.5 (±10.3). CONT: BL: 0.7 (±0.2), post-test: 2.1 (±0.3). 16/27 (59%) patients experienced transient return of MDD during ATD vs 0/27 during CONT	See above in section 'healthy controls'	Good
Neumeister (2006)[67]	Rand., DB, Within SS⩾3 months remission	27 M+F Rx-free⩾ 3 months	Good	HAMD[e]: s/s subtype ($n=7$): ATD: BL: 0.4 (±0.4 SE), post-test: 7.0 (±1.4). CONT: BL: 0.6 (±0.4), post-test: 2.6 (±0.8). s/l subtype ($n=12$): ATD: BL: 0.8 (±0.4), post-test: 11.4 (±1.0). CONT: BL: 0.8 (±0.4), post-test: 2.4 (±0.6). l/l subtype ($n=8$): ATD: BL: 2.0 (±0.3), post-test: 14.6 (±1.2). CONT: BL: 0.9 (±0.4), post-test: 1.7 (±0.6)	Study investigates effect of triallelic serotonin transporter promoter (5-HTTPR) genotype and effect of ATD on mood and regional cerebral metabolism with PET	Good
O'Reardon (2004)[92]	Rand., DB, Within SS 5 months remission	10 M+F Post-CBT	Good	HAMD-24[e]: ATD: change: 4.97 (±1.0 SE). CONT: change: 3.22 (±1.0) 0/10 patients relapsed in either condition	Currently not using antidepressant medication, responders to CBT treatment	Good

Table 2 Continued

Author (year)[a]	*Design*	*N*	*Adeq. of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
Smith (1997a)[93]	Rand., DB, Within SS⩾6 months remission	15 F Rx-free⩾ 6 months	Good	HAMD-12: ATD: change (7 h): 7.3. CONT: change: 0.1. SD of difference ATD-CONT calculated from 95% CI: 7.2 (±4.9) 5/15 patients experienced relapse during ATD, 0/15 during CONT	Currently not using antidepressant medication (recovered MDD)	Moderate
(B2) Patients with MDD previously, but currently in remission (currently using medication)						
Aberg-Wistedt (1998)[94]	Rand., DB, Betw. SS After response	12 + 8 M + F CIT	Insufficient	MADRS: exact scores not reported. Five of the 12 patients with ATD showed a Worsening of depressive symptoms in ATD: 5/12 (MADRS 12–71%). CONT: 0/8	Study also investigates relation with relapse due to ATD and other variables (plasma cortisol, platelet-serotonin)	Moderate
Booij (2005a)[95]	Rand., DB, Within SS After⩾partial remission	20 M + F SSRI SNRI	Good	MADRS: ATD: BL: 4.6 (±0.9 SE), post-test: 7.9 (±1.8). CONT: BL: 3.7 (±0.9), post-test: 3.7 (±0.9). Relapse of MDD: ATD: 7/20; CONT: 0/20 assumed	Inclusion of subjects with HDRS < 15 (partial remission). A 25% strength tryptophan deficient mixture was used as CONT	Good
Booij (2006)[96]	Rand., DB, Within SS After⩾partial remission	19 M + F SSRI SNRI	Good	HAMD-17 scores sign. lower after ATD: SI+ (n = 8): ATD: BL: 2.5 (±0.8 SE), post-test: 7.6 (±2.0). CONT: Not given SI− (n = 11): ATD: BL: 2.9 (±0.7), post-test: 3.4 (±0.6). CONT: Not given MADRS scores sign. Lower after ATD: SI+: ATD: BL: 5.0 (±1.2 SE), post-test: 12.00 (±2.4). CONT: Not given SI−: ATD: BL: 5.4 (±1.3 SE), post-test: 9.3 (±1.7). CONT: Not given	Inclusion of subjects with HDRS < 15 (partial remission). A 25% strength tryptophan deficient mixture was used as CONT. No data for ATD mood-ratings after CONT provided. Study also investigates effect of ATD on Heart Rate Variability (HRV) and impulsivity and the interaction by +ve/-ve history of suicidal ideation (SI+/SI−)	Moderate
Bremner (1997)[97]	Rand., DB, Within SS Average remission 45 weeks	21 M + F FLX PAR	Good	Relapse of MDD: ATD: 7/21; CONT: 1/21. HAMD-scores are split between relapse and non-relapse group. With relapse (n = 7): ATD: BL: 6.86 (±4.98), post-test: 15.57 (±6.92). CONT: BL: 7.00 (±5.45), post-test: 6.71 (±6.07). Without-relapse (n = 14): ATD: BL: 4.79 (±3.45), post-test: 6.36 (±4.25), CONT: BL: 6.21 (±4.69), post-test: 9.21 (±5.99)	19/21 of patients used FLX. Study investigates brain metabolism with PET during ATD and associations with MDD relapse	Good
Delgado (1991)[90]	Rand., DB, Within SS⩾2 weeks after 'stability'	46 M + F various	Good	HAMD-25: exact scores not reported. Depressive relapse: ATD: 24/46, CONT: 0/46	Heterogeneous population currently using various AD. BUP or DES-treatment lower chance of relapse In original studies Bipolar patients included; unclear whether these were excluded in this pooled analysis	Moderate
Delgado (1999)[98]	Rand., DB, Within SS⩾2 weeks response	30 M + F FLX DES	Good	HAMD-25: FLX-treated patients: ATD: BL: 7.7, post-test 17.1. CONT: not reported Relapse: ATD 8/15, CONT 0/15. DES-treated patients: ATD: BL: 8.6, post-test 10.7. CONT: not reported. Relapse: ATD 1/15, CONT 0/15	Two bipolar patients included. Study replicates previous finding that DES-treated remitters do not suffer a relapse if improved on DES, but did after FLX-induced remission	Moderate
Evans (2002)[99]	Rand., DB, Within SS After⩾partial remission	8 M + F BUP	Good[e]	POMS-depressed: ATD: BL: 5.25 (±1.62 SE), post-test: 3.12 (±1.37). CONT: BL: 5.25 (±1.62), post-test: 3.50 (±1.80) HAMD-19: ATD: BL: 4.38 (±1.21 SE), post-test: 5.00 (±1.02). CONT: BL: 4.38 (±1.21), post-test: 4.12 (±0.81)	Study also investigates effects of ATD on sleep-EEG. One Bipolar II patient included. Five patients in partial remission (HAMD 7–9)	Good

Table 2 Continued

Author (year)[a]	*Design*	*N*	*Adeq. of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
Landolt (2003)[100]	Rand., DB, Within SS, PHZ After remission	5 M + F PHZ	Good	POMS-depression: no BL measures were given separately for ATD and CONT: BL: 0.4 (± 0.4 SE). ATD: post-test: 2.0 (±1.5). CONT: post-test: 1.0 (±0.4). Post-test measures taken next morning after ATD or CONT at 1600 hours	Study primarily investigates effect of ATD on recurrence of REM-sleep while using PHZ	Moderate
Moore (1998)[101]	Rand., DB, Within SS⩾2 months remission	10 M FLX SER PAR	Good	POMS-depressed: ATD: BL: 3.0 (±1.3 SE), post-test: 2.7 (±1.4), CONT: BL: 3.0 (±1.3), post-test: 3.3 (±1.6). HAMD-25 ratings not exactly reported but did not change significantly	Study also investigates effects of ATD on REM-sleep. A 25% strength tryptophan deficient mixture was used as CONT. Subjects in remission >2 months	Good
Morris (1999)[102]	Rand., DB, Within SS Full remission	8 M SSRI AMI TRAZ PHZ TCP Li	Good	Modified HAMD-12, BDI. No exact scores given. HAMD increase >5 points (relapse): ATD: 7/8, CONT: 0/8	Study investigates brain metabolism with PET during ATD and associations with MDD relapse. Six of 8 participants received ⩾6 months antidepressants. No indication which drugs were currently used	Moderate
O'Reardon (2004)[92]	Rand., DB, Within SS 5 months remission	9 M + F FLX PAR	Good	HAMD-24[e]: ATD: change: 8.22 (±1.2), CONT: change: 2.56 (±1.2). 3/9 patients relapsed during ATD vs 0/9 during control	Currently using antidepressant medication, responders to SSRI treatment	Good
Praschak-Rieder (2004)[103]	Rand., DB, Within SS 2 months remission	8 M CIT	Good	HAMD-21: ATD: BL: 3.88 (±2.6), post-test: 12.3 (±5.4). CONT: no scores reported. Relapse: ATD: 6/8 patients, CONT: no numbers reported 0/8 assumed for analysis	Study primarily investigates effects of ATD on regional 5-HT_{1A} binding potential with PET	Poor
Smith (1999)[104]	Rand., DB, Within SS⩾6 months remission	8 M various	Good	HAMD: no exact scores reported Relapse: ATD: 6/8 patients, CONT: 1/8	Study primarily investigates effects of ATD on regional brain activity with PET. Subjects in remission >6 months. 2 patients did not use antidepressants, 6 used various types (SSRI, TCA, MAO-I)	Moderate
Spillmann (2001)[105]	Rand., DB, Within SS⩾3 months remission	10 M + F FLX SER VLX PAR	Good	HAMD-6: ATD: BL: 1.1 (±1.2) post-test (7 h): 4.7 (±3.4), change: 3.6 (±3.1); CONT: BL: 1.4 (±1.7) post-test: 1.0 (±1.4), change: -0.4 (±1.2). Increase in scores on the HAMD-6 was significantly higher for ATD than for CONT	In remission after SSRI, currently using antidepressant medication. 5 initial participants dropped out	Good
(C) Patients currently with MDD (with or without antidepressants)						
Booij (2005b)[106]	Rand., DB, Within SS	14 M + F VLX MIR TCA Li	Good	HAMD: ATD: BL: 12.9 (±1.5 SE), post-test: 13.1 (±1.9). CONT: BL: 11.4 (±1.4), post-test: 13.6 (±1.3). MADRS: ATD: BL: 22.7 (±3.7), post-test: 23.1 (±4.7). CONT: BL: 19.6 (±3.3), post-test: 22.9 (±2.0).	A 25% strength tryptophan deficient mixture was used as CONT. *Improvement* of mood-ratings 24hr after full ATD in VLX/MIR treated patients, but not in patients treated otherwise	Good
Delgado (1994)[107]	Rand., DB, Within SS	43 M + F⩾2 weeks Rx-free	Good	HAMD-25: No exact mood-scores provided One day after ATD 16/43 patients experienced improvement of mood, 10/46 decrease in mood relative to CONT	*Improvement* of mood-ratings 24hr after full ATD associated with treatment response after antidepressant treatment	Poor

Table 2 Continued

Author (year)[a]	*Design*	*N*	*Adeq. of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
Price (1997)[108]	Rand., DB, Within SS	22 M + F Rx-free	Good	VAS, HAMD-25: No exact scores provided; scores unaffected by ATD	Study investigates the (biochemical) effects of *m*-chlorophenylpiperazine (mCCP; serotonin-agonist) on HAMD, cortisol, prolactin and growth-hormone during ATD	Poor
Price (1998)[109]	Rand., DB, Within SS	36 M + F ⩾ 3 weeks Rx-free	Good	HAMD-25: ATD: BL: 28 (±7), post-test 28 (±7). CONT: 27 (±9), post-test 26 (±9)	Study included 4 patients with BD. Study investigates the (biochemical) effects of rapid tryptophan infusion on HAMD, cortisol, prolactin and growth-hormone after ATD	Good

Abbreviations: AD = antidepressants; AMI = amitriptyline; AMPT = Alpha-methyl-para-tyrosine; ATD = acute tryptophan depletion; BD = bipolar disorder; BDI = Beck depression inventory; Betw. SS = between-subjects parallel groups design; BL = baseline; BUP = buproprion; CBT = cognitive behaviour therapy; CIT = citalopram; CONT = control; DB = double-blind; DES = desipramine; ECT = electro-convulsive therapy; EEG = electro-encephalography; FLX = fluoxetine; HAMA = Hamilton Anxiety Scale; HAMD = Hamilton Depression Scale; IMI = imipramine; LYS = lysine; Li = lithium; MAACL = Multiple Affect Adjective CheckList; MADRS = Montgomery Åsberg Depression Rating Scale; MAO-I = monoamine oxidase inhibitor; MDD = major depressive disorder; MEG = magneto-encephalography; MIR = mirtazapine; NOR = nortriptyline; PAR = paroxetine; PHZ = phenelzine; POMS = Profile of Mood States; Rand. = randomized; SD = standard deviation; SE = standard error; TCA = tricyclic antidepressants; TCP = tranylcypromine; TRAZ = trazodone; VA(M)S = Visual Analogue (Mood) Scale; VLX = venlafaxine; Within SS = within-subjects cross over design.

[a]Studies included in the meta-analysis in bold.

[b]Plasma tryptophan declined by at least 50%.

[c]SD given unless indicated otherwise (e.g. SE).

[d]Judgement in the context of applicability for this meta-analysis.

[e]Estimated from figure.

[f]Unclear whether partially the same population is reported (Weltzin *et al*., 1994[85] and 1995[86]).

Table 3 Included studies with Para-chlorophenylalanine (PCPA)

Author (year)	*Design*	*N*	*Adequacy of depletion*	*Results mood scores (scale, scores (±SD))*	*Remarks*	*Judgement*[a]
Shopsin (1975)[15]	Within SS, MDD in remission by IMI	1	Not measurable; poor	PCPA given in small doses for relatively short periods caused a reversal of the antidepressant effect of IMI. HAMD, no exact mood scores reported	Note: $n=1$, 1 patient with BD and 3 patients treated with AMPT not included here	Poor
Shopsin (1976)[110]	Within SS, MDD in remission by TCP	3	Not reported; poor	All patients experienced a relapse. HAMD, no exact mood scores reported	2 patients with BD not included here	Poor

Abreviation: PCPA = para-chlorophenylalanine.
For other symbols and abbreviations see footnote in Table 2.

in mood-scores between interventions (Appendix). We checked the impact of this imputation on the calculated effect estimates. Therefore, we increased R to 0.8 (less conservative) and decreased R to 0.2 (more conservative) to compare the new effect estimates with the original findings for $R=0.5$.

We assessed publication bias graphically with a funnel-plot, plotting Hedges' g vs the precision of the study (the inverse of the standard error of Hedges' g). Additionally, we tested publication bias with Galbraith's radial plot, which regresses the standard normal deviate (Hedges' g divided by its standard error) against the precision. For a set of studies not distorted by selection bias the intercept of the regression model will be close to zero.[129]

Results

Identified studies

Our systematic searches identified 392 articles. In total, we selected 90 studies. Three studies applied both ATD and APTD and a control.[48,49,58,59] Therefore, 73 studies with ATD, two with PCPA, 10 with APTD and eight with AMPT as monoamine depletion method were identified (summarized in Tables 2–5 respectively). Several studies investigated contrasts in different populations.[36,50,55,56,65,66,67,81,90,92,103] A list of excluded studies is available on request. Most studies had a within-subjects design ($n=74$). The majority of studies investigated healthy controls ($n=64$).

Qualitative summary

The majority of the 90 studies also investigated other effects of monoamine depletion: 24 studies measured effects on cognitive functions,[13,33,34,44–47,49,50,52,56,60,64,69,75,77,78,82,95,112–117] 11 measured effects on other behavioral measures (pain, impulsivity, panic attacks, appetite, noise-stress, aggression),[32,38,57,61,68,73,76,86,96,111,120] eight measured effects on neuroendocrine parameters,[39,48,71,108,109,112,118,121] 11 measured electric encephalogram (EEG) alterations and/or sleep effects,[37,40,51,53,60,72,84,91,99–101] 14 measured changes in brain function with positron emission tomography (PET),[66,67,70,87,97,103,104,123] single photon emission computed tomography (SPECT),[83] or magnetic resonance imaging (MRI).[33,42–46,74] Two studies stratified mood response to ATD by genetic polymorphism of the 5-HT transporter promoter region.[65,67]

We judged the overall methodological quality of the identified studies as good, with appropriate application of the ATD, APTD or AMPT depletion. Two studies with PCPA reported case series only and were rated 'poor'.[15,110] In eight studies no data on the adequacy of the achieved depletion was reported.[15,32,40,110,111,118,119,123] In two studies insufficient depletion was attained.[94,115] In 10 studies no clear SDs or SEs were given for the observed mood effects.[13,61,71,72,79,85,98,118,119,123,124] Six studies included patients (<25% of total) with Bipolar I or II disorder.[15,98,99,108,117,124] In total, this were 14 patients. The reason that several apparently high-quality studies were rated as moderate in this review was due to the lack of presentation of the mood effects, which in those studies was not the primary outcome.

In 34 of 90 studies the POMS was used, in two studies the MAACL, in 34 studies a visual analogue scale, in 29 studies a version of the HAMD, and in five of the 90 studies the MADRS. In five studies only other or undefined mood-scales were used.[40,51,76,85,86] Especially for the POMS and the VAS the direction of a decrease of mood in subjects was not always clearly reported.[52,68,77,85] In our meta-analysis no differential effect of the applied mood-scale was observed ($Q_{res}=3.89$, df = 2, $P>0.05$; data not shown).

Quantitative summary (pooling)

Fifty-eight percent (52/90) of the studies supplied enough data to be included in the meta-analysis. Meta-analysis was possible for ATD and APTD studies only. Table 6 gives an overview of the number of identified studies for each pre-defined population and eligibility for meta-analysis. Due to remaining heterogeneity we used random effects models for all meta-analyses.

ATD

In Figure 1 the pooled results of ATD in healthy controls in studies with a within subjects design are

Table 4 Included studies acute phenylalanine/tyrosine depletion (APTD)

Author (year)[a]	*Design*	*N*	*Adequacy of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
(A1) Healthy controls						
Coupland (2001)[111]	Rand., DB, Within SS	5 M	Not reported	POMS-depressed: APTD: change: −0.2 (±2.7) CONT: change: 0.2 (±2.6)	Study investigates effect of pentagastrine to induce anxiety after APTD	Moderate
Harmer (2001)[112]	Rand., DB, Within SS	12 M+F	Good	VAS-depressed: APTD: change: 2.03 (±4.98). CONT: change: −4.20 (±15.23)	Study investigates effect of APTD on prolactin, neuropsychological and subjective measures	Good
Harrison (2002)[48]	Rand., DB, Within SS, FH−	13 F	Good	POMS-depressed: APTD: BL: 0.92 (±0.56 SE), post-test: 1.15 (±0.55) CONT: BL: 1.61 (±0.52), post-test: 1.15 (±0.56)	Study also reports absence of effects of ATD and APTD on interleukin-6 activation	Good
Harrison (2004)[49]	Rand., DB, Within SS, FH−	13 F	Good	VAMS, no significant changes observed; exact scores not reported	Study also investigates memory and cognitive effects of ATD and APTD	Moderate
Leyton (1999), (2000)[58,59]	Rand., DB, Betw. SS, FH−	12 APTD 14 CONT F	Good	POMS[e]: APTD: change: −2.39 (±2.1 SE). CONT: change −1.04 (±1.2). VAMS-depressed: APTD: BL: 1.3 (±1.6 SD), post-test: 1.7 (±2.7), change: 0.4 (±1.6). CONT: BL: 0.4 (±0.5), post-test: 0.4 (±0.4), change: 0.1 (±0.4)	POMS; no exact scores reported. Third arm with ATD included	Moderate
Lythe (2005)[113]	Rand., DB, Within SS	12 M+F	Good	VAMS, no significant changes observed; exact scores not reported	Study investigates effect of APTD on neuropsychological and subjective measures	Moderate
McLean (2004)[114]	Rand., DB, Betw. SS	19+20 M+F	Good[e]	VAMS-contentedness: APTD: BL: 10.2 (±0.7 SE), post-test: 11.5 (±0.5). CONT: BL: 11.8 (±0.5), post-test: 11.8 (±0.5)	Study investigates effect of APTD on neuropsychological and subjective measures	Good
(A2) Healthy controls with +ve family history for MDD						
Grevet (2002)[115]	Rand., DB, Within SS, 6/10 FH+	10 M+F	Insufficient	POMS-depressed: APTD: BL: 23.40 (±7.21), post-test: 23.50 (±6.48). CONT: BL: 21.30 (±8.05), post-test: 25.20 (±4.73). VAMS-contentedness: APTD: BL: 2.78 (±1.43), post-test: 3.24 (±1.49). CONT: BL: 3.12 (±1.26), post-test: 2.79 (±1.29)	Study investigates effect of APTD on neuropsychological and subjective measures	Moderate
(B1) Patients with MDD previously, but currently in remission (without medication)						
McTavish (2005)[116]	Rand., DB, Within SS⩾6 months remission, average 41 months	15 F Rx-free⩾6 months	Good Only (TYR+ PHE)/NAA ratio provided	HAMD-6[e]: APTD: BL: 1.7 (±0.7 SE), post-test: 2.4 (±0.9). CONT: BL: 1.0 (±0.4), post-test: 2.7 (±1.1). VAS-depressed not significantly changed by APTD vs CONT; no exact scores provided	Study investigates effects of ATPD on subjective and a spatial recognition memory-task	Good
Roiser (2005)[117]	Rand., DB, Within SS⩾6 months remission	17 M+F Rx-free⩾6 months	Insufficient TYR depletion; (TYR+ PHE)/ NAA ratio decreases 80%)	HAMD-19: APTD: BL: 2.1 (±2.0), post-test: 2.2 (±2.0). CONT: BL: 1.4 (±1.3), post-test: 1.1 (±1.1). VAS-contentedness: APTD: BL: 12.4 (±1.5), post-test: 12.8 (±1.5). CONT: BL: 12.3 (±1.8), post-test: 12.8 (±1.8)	BD-II patients included (n=?). Study investigates effects of ATPD on subjective and neurocognitive measures	Good
(B2) Patients with MDD previously, but currently in remission (currently using medication)						
—						
(C) Patients currently with MDD (with or without antidepressants)						
—						

Abbreviations: APTD = acute phenylalanine/tyrosine depletion; NAA = neutral amino acids; PHE = phenylalanine; TYR = tyrosine.
[b]Tyrosine levels declined by at least 60%.
For other symbols and abbreviations see footnote in Table 2.

Table 5 Included studies Alpha-methyl-para-tyrosine (AMPT)

Author (years)[a]	*Design*	*N*	*Adequacy of depletion*[b]	*Results mood scores (scale, scores (±SD*[c]*))*	*Remarks*	*Judgement*[d]
(A1) Healthy controls						
Krahn (1999)[118]	Rand., DB, Within SS, FH−	10 M+F	Not reported	HAMD scores increased significant (change: 3 SD not reported) in AMPT compared to CONT (no more data provided) POMS no significant changes (no more data provided)	Study investigates effects of AMPT on melatonin secretion. Promethazine 25 mg as CONT	Poor
McCann (1993)[119]	Rand., DB, Betw. SS	40 M	Not determined; unspecified sign. prolactin rise in AMPT group	VAS-sadness[e]; AMPT: BL: 3.2, post-test: 13.1. CONT: BL: 11.2, post-test: 16.9. (no SDs provided) (only resting condition provided here) no sign. Difference AMPT and placebo in rested condition	Subjects were randomized to 1. AMPT+rest, 2. AMPT+SleepDepr., 3. CONT+SleepDepr., 4. CONT+rest	Moderate
McCann (1995)[120]	Rand., DB, Betw. SS	41 M	Not determined; prolactin rise of 188% in AMPT group	POMS- sadness, VAS-sadness; no exact scores provided; figure for calmness shown. AMPT caused maximal ratings of tension, which was reversed by addition of+L-dopa/carbidopa. Nonsignificant increase in sadness reported in AMPT-group (regardless L-dopa/carbidopa).	Subjects were randomized to 1. AMPT+PLAC, 2. AMPT+L-dopa/carbidopa, 3. CONT+L-dopa/carbidopa, 4. CONT+PLAC, in order to investigate the specificity of AMPT-changes by effects on catecholamines	Moderate
Zimmermann (1996)[121]	Rand., DB, Within SS, FH−	10 M+F	Sufficient MHPG decrease in M+F	HAMD, POMS: No significant differences. No exact scores reported	Study investigates effects of AMPT on prolactin and melatonin secretion, including gender-effects. Promethazine 50 mg as CONT	Moderate
(A2) Healthy controls with +ve family history for MDD						
—						
(B1) Patients with MDD previously, but currently in remission (without medication)						
Berman (1999)[122]	Rand., DB, Within SS⩾4 months remission, Average 18 months	15 M+F Rx free⩾ months	Good	HAMD-23; AMPT: BL: 3.1 (±3.2), Peak: 23.9 (±12.0). CONT: BL: 2.8 (±3.4), peak: 9.0 (±9.7). IDS; AMPT: BL: 8.2 (±7.2). Peak: 23.6 (±14.8). CONT: BL: 6.1 (±6.6), peak: 10.0 (±8.1). Relapse in 10/14 AMPT-patients and in 1/13 CONT.	No separate data for $n=12$ who underwent both tests. Given scores are peak scores. Post-test scores not reported	Moderate
(B2) Patients with MDD previously, but currently in remission (currently using medication)						
Bremner (2003)[123]	Rand., DB, Within SS After remission	18 M+F DES NOR	Not reported	HDRS[e]; no exact scores and SDs reported AMPT: With AMPT relapse: BL: 7.4, post-test: 24.8. Without relapse: BL: 11.5, post-test: 12.5 CONT: With AMPT relapse: BL: 8.5, post-test: 8.5. Without relapse: BL: 6.4, post-test: 13.2 Relapses: AMPT: 11/18, CONT: not provided, 0/18 assumed.	Study primarily investigates brain metabolic correlates of AMPT induced depressive relapses with PET	Moderate
Delgado (1993)[17]	Rand., DB, Within SS 'Various' length of remission	14 M+F DES MAZ FLX SER	Good[e]	HDRS-25; No exact scores reported. Significant effects of AMPT vs CONT in DES and MAZ treated patients, not in FLX or SER treated patients.	Patients were currently using noradrenergic or serotonergic antidepressant medication.	Moderate

Table 5 Continued

Author (years)[a]	*Design*	*N*	*Adequacy of depletion*[b]	*Results mood scores (scale, scores (±SD[c]))*	*Remarks*	*Judgement*[d]
(C) Patients currently with MDD (with or without antidepressants)						
Miller (1996)[124]	Rand., DB, Within SS	17 M+F	Good	HAMD-25[e]; AMPT: BL: 29, post-test: 28.5. CONT: BL: 30.5, post-test: 29.5. SDs not reported. VAS: exact data not provided; sign decrease in subscales 'tired' and 'energetic' for AMPT vs CONT	Patients were not using antidepressant medication. 2/17 patients had bipolar depression, 6/17 had comorbid anxiety, dysthymic or eating disorders	Moderate

Abbreviations: AMPT = alpha-methyl-para-tyrosine; IDS = Inventory of Depressive Symptoms; MAZ = mazindol; PLAC = additional placebo; SleepDepr. = sleep deprivation.
[b]Decline in catecholamine metabolites homovanillic acid (HVA) by at least 60% or 3-methoxy-4-hydroxyphenylglycol (MHPG) by at least 40%.
For other symbols and abbreviations see footnote in Table 2.

Table 6 Identified studies for different types of depletion and design and eligibility for meta-analysis

	Identified (in meta-analysis)	
	Within subjects	*Between subjects*
Acute tryptophan depletion		
(A) Healthy controls		
FH−	41 (22)	10 (5)
FH+	5 (5)	0
(B) Patients with MDD in remission		
Without AD	8 (6)	1
With AD	13 (12)	1
(C) Patients with current MDD		
Without AD	3 (1)	0
With AD	1 (1)	0
Para-chlorophenylalanine		
(B) Patients with MDD in remission		
With AD	2	0
Acute phenylalanine/tyrosine depletion		
(A) Healthy controls		
FH−	5 (3)	2 (2)
FH+	1 (1)	0
(B) Patients with MMD in remission		
Without AD	2 (2)	0
Alpha-methyl-para-tyrosine		
(A) Healthy controls		
FH−	2	2
(B) Patients with MDD in remission		
Without AD	1	0
With AD	2	0
(C) Patients with current MDD		
Without AD	1	0

Abbreviations: AD = antidepressant; FH = family history; MDD = major depressive disorder.

presented. Overall Hedges'*g* (95% CI) was −0.27 (−0.45 to −0.09). We stratified results by family history for MDD (negative, positive or not reported in the studies). Pooled Hedges' *g* for healthy controls with a negative family history (−0.19 (−0.43 to 0.05)) was significantly different ($Q_{res} = 6.59$, df = 1, $P = 0.01$) compared to controls with a positive family history (−0.56 (−1.00 to −0.13)). The pooled result in studies that did not report the family history status resembled the studies with a negative family history (−0.28 (−0.57 to 0.00) $Q_{res} = 1.36$, df = 1, $P = 0.24$). In between subjects studies similar results were found. Pooled Hedges' *g* was −0.63 (−1.95 to 0.70) for controls with a negative family history and −0.06 (−0.57 to 0.45) in one study that did not report family history status ($Q_{res} = 0.14$, df = 1, $P = 0.71$). The large Hedges' *g* in controls with a negative family history was largely determined by one study.[71] Leaving this study out reduced Hedges' *g* to 0.16 (−0.43 to 0.76) (data not shown).

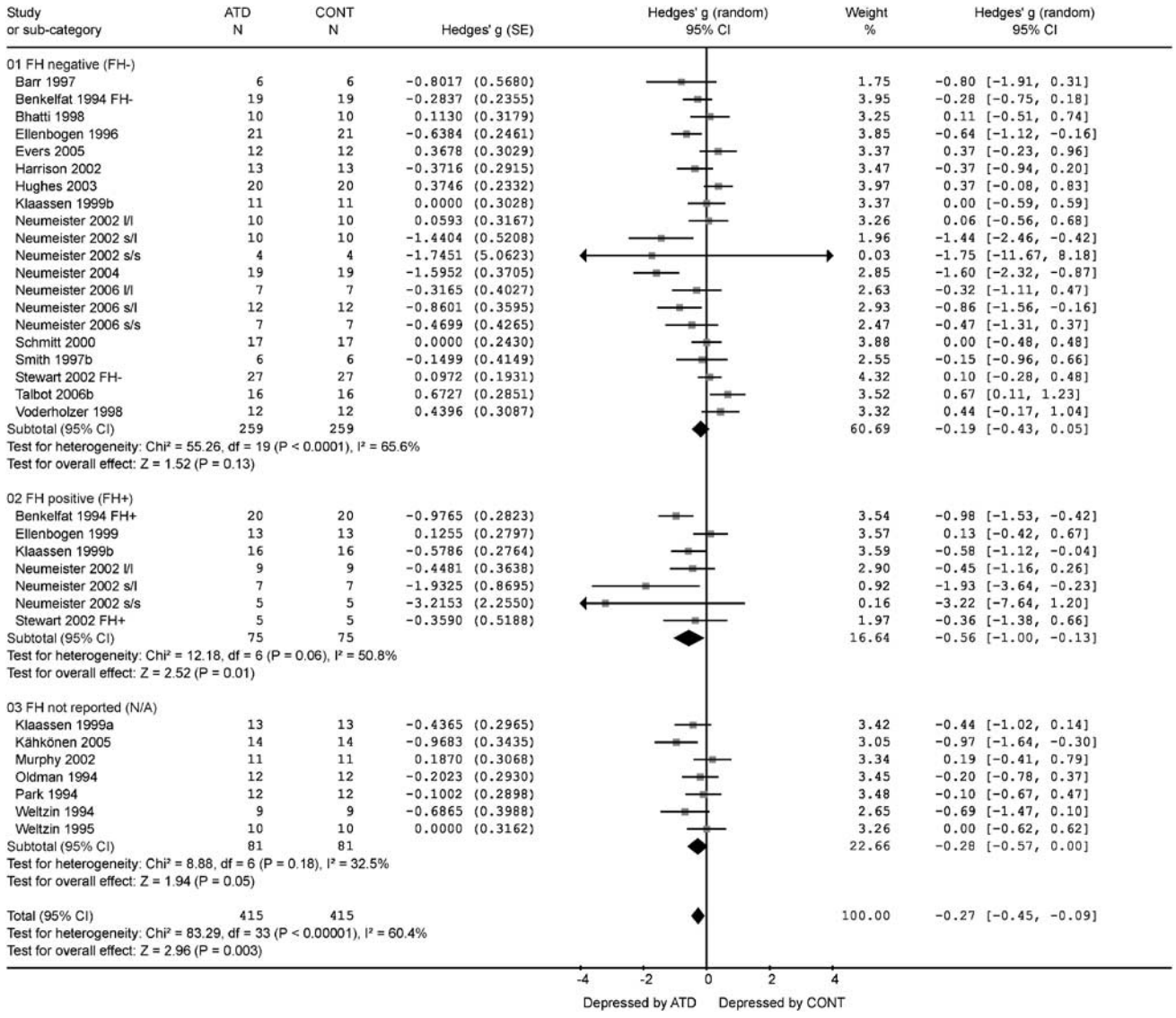
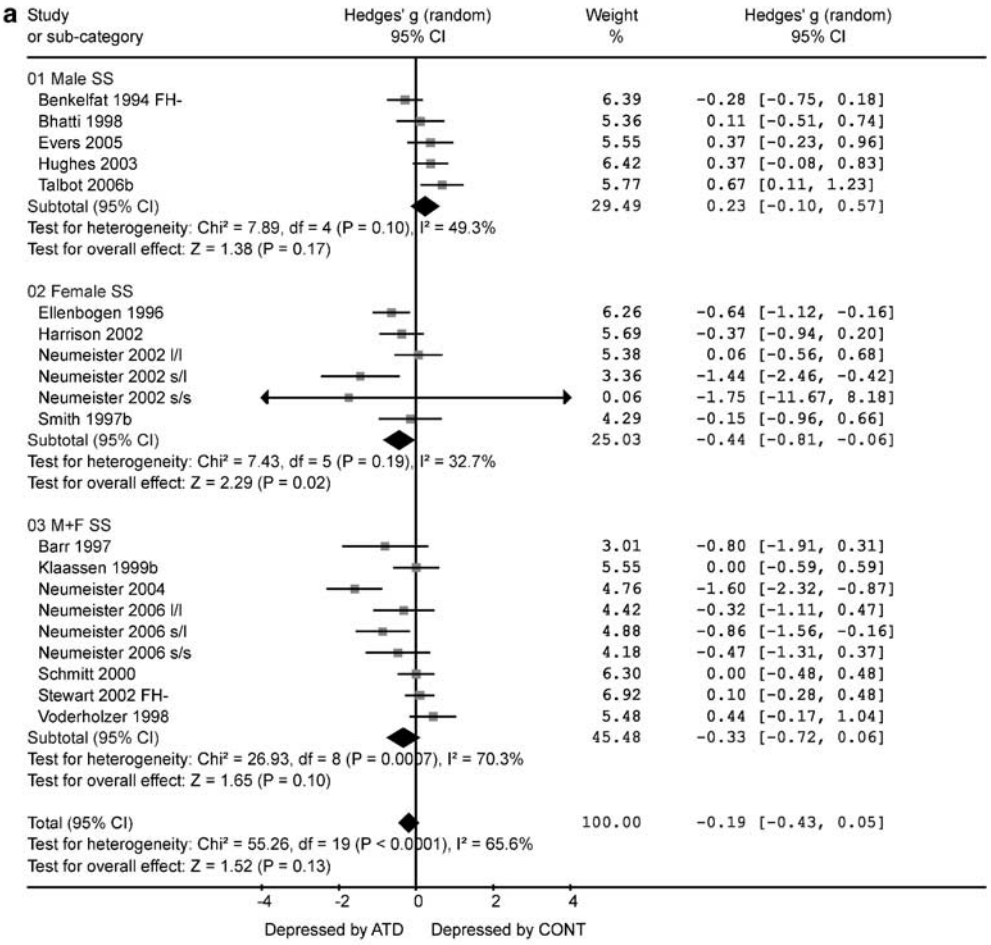


Figure 1 ATD in healthy controls studied in a within subjects design, stratified by status of family history for depression (negative or positive for major depressive disorder). References to studies as indicated, different subgroups per study handled as separate studies with appropriate pooling weights. FH− = family history negative, FH + = family history positive, N/A = not reported.

Figure 2a and b show the modification of Hedges' *g* by gender for healthy controls (within subjects design) with a negative or positive family history. The difference in Hedges' *g* between males and females was most prominent in healthy controls with a negative family history (0.23 (−0.10 to 0.57) vs −0.44 (−0.81 to −0.06) respectively; $Q_{res} = 11.92$, df = 1, $P < 0.001$). In controls with a positive family history, males experienced a larger decrease in mood after ATD in only one study (Hedges' *g* −0.98 (−1.53 to −0.42) $Q_{res} = 11.92$, df = 1, $P < 0.001$). In contrast, females with a positive family history only had a slightly larger Hedges' *g* (−0.56 (−1.43 to 0.31)) than females with a negative family history ($Q_{res} = 0.62$, df = 1, $P = 0.43$).

Figure 3a and b present the pooled Hedges' *g* for patients with MDD in remission without or with current AD (within subjects design). In the remitted patients without current AD, we stratified results by length of time without AD. Only two studies with 3–6 months without AD[66,67] largely differed in Hedges' *g* (−4.35 (−7.39 to −1.31) compared to one study directly after successful electroconvulsive therapy (Hedges' *g* 0.04 (−0.85 to 0.94),[89] and three studies with at least 6 months without AD (pooled Hedges' *g* −0.60 (−1.38 to 0.18) ($Q_{res} = 29.34$, df = 2, $P < 0.0001$).[91–93] Leaving one possible outlier[66] out diminished the overall pooled Hedges' *g* for remitted patients without AD from −1.90 (−3.02 to −0.78) to −1.06 (−1.83 to −0.29), but



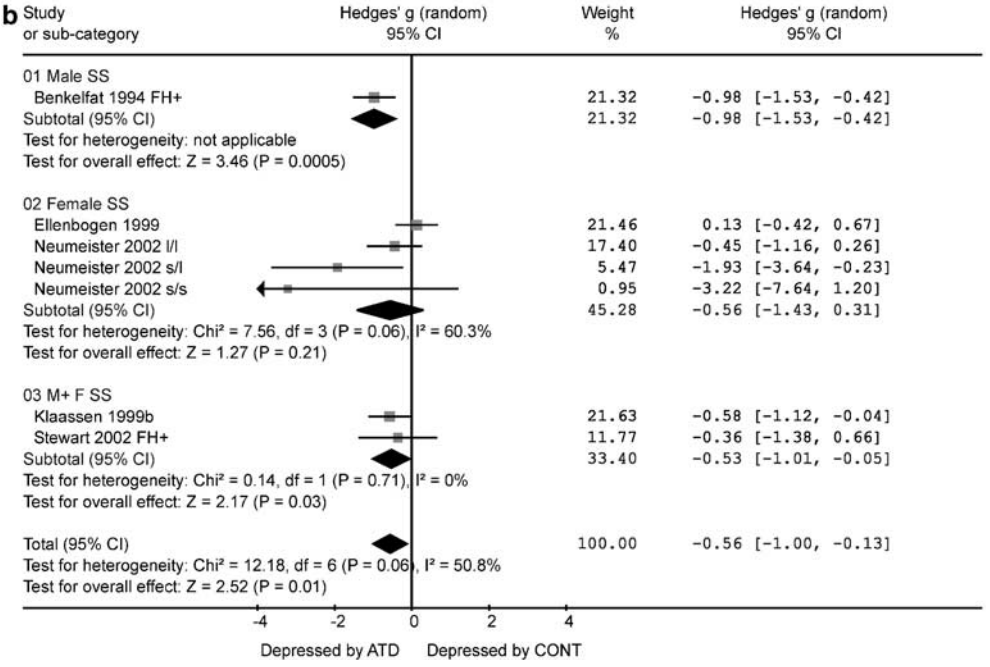


Figure 2 (**a**) Family history negative for MDD and (**b**) family history positive for MDD). ATD in healthy controls studied in a within subjects design, stratified by status of family history for depression and gender included in the studies. References to studies as indicated, different subgroups per study handled as separate studies with appropriate pooling weights. FH− = family history negative, FH + = family history positive, MDD = major depressive disorder.

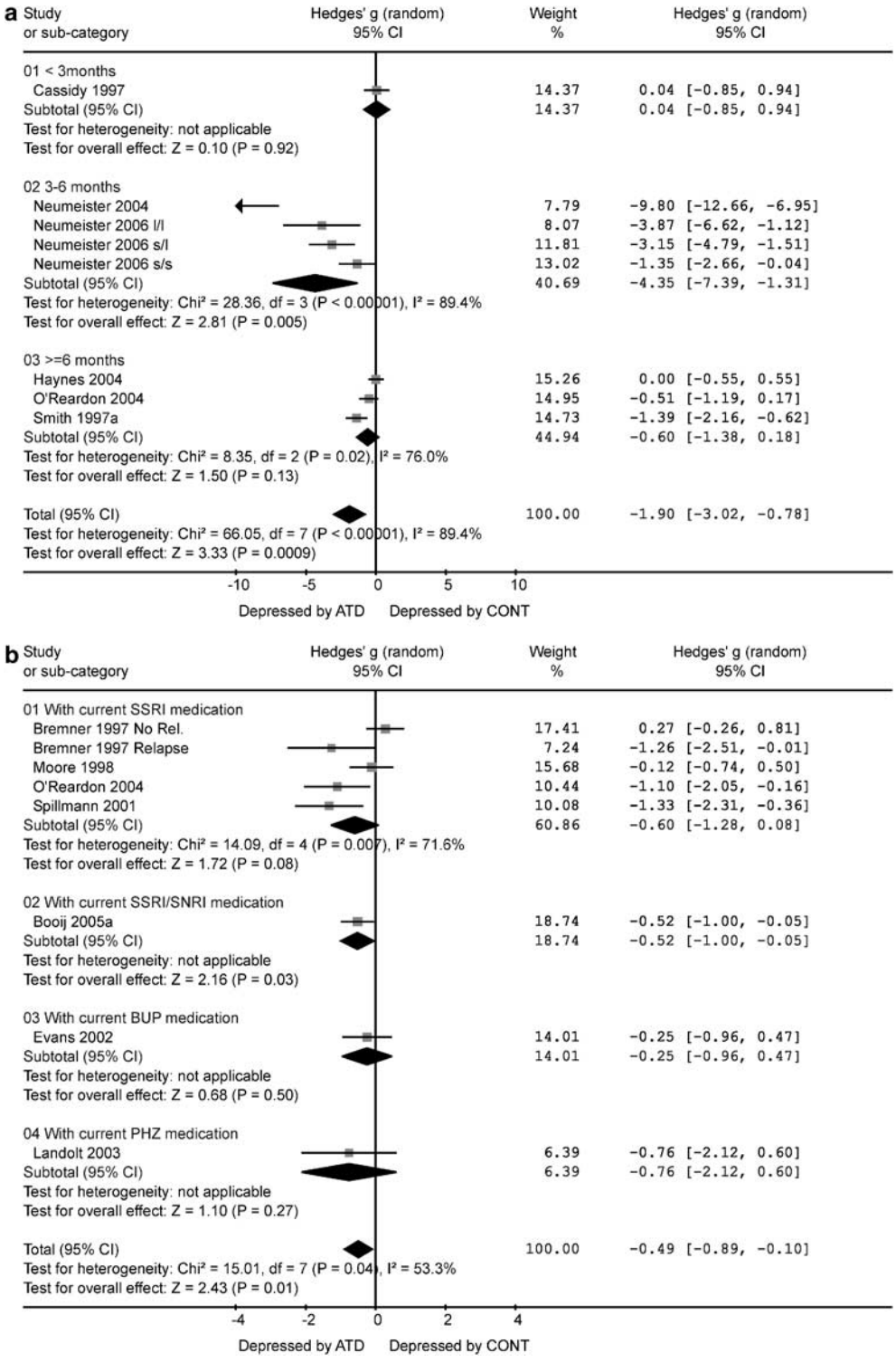


Figure 3 (**a**) Without current medication and (**b**) with current medication. ATD in former depressed patients in remission, studied in a within subjects design without or with current medication. (**a**) Stratified by length of time without medication. (**b**) Stratified by type of medication used by patients. References to studies as indicated, different subgroups per study handled as separate studies with appropriate pooling weights. BUP = bupropion; SNRI = serotonin norepinephrin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; PHZ = phenelzine.

the observed effect modification by length of time without AD remained highly significant ($P < 0.001$; data not shown).

In remitted patients previously depressed and currently using AD, ATD caused a decrease in mood (pooled Hedges' g −0.49 (−0.89 to −0.10). Hedges' g

varied slightly depending on type of AD ($Q_{res} = 0.92$, df = 3, $P = 0.82$). Surprisingly, the pooled Hedges' g for SSRIs showed a moderate point estimate, which did not reach significance (−0.60 (−1.28 to 0.08). Especially for bupropion treatment Hedges' g was small and not significant (−0.25 (−0.96 to 0.47). No ATD studies with other ADs without a 5-HT mechanism of action were available for this comparison.

We stratified the results of ATD studies by length of remission, which revealed significant effect modification. In remitted patients using AD decreased mood after ATD was especially seen in the first 5 months after the achievement of remission (pooled Hedges' g −0.55 (−0.90 to −0.21) $Q_{res} = 47.18$, df = 2, $P < 0.0001$).[92,95,99–101,105] In contrast, remitted patients without AD showed more decrease in mood after ⩾2 months of remission (Hedges' g −1.65 (−2.60 to −0.69) $Q_{res} = 13.81$, df = 2, $P = 0.001$)[67,92,93] (figure available on request).

Relapse rates in remitted patients with AD were increased after ATD compared to control depletion (pooled difference in relapse rate 47% (28–66%); Figure 4). This increase in relapse rate was especially seen in patients using SSRIs (47% (27–67%)) or an SNRI (35% (14–56%)). The NE acting drug desipramine showed no significant difference in relapse rate (7% (−6 to 19%)) after ATD. This effect modification by drug was statistically significant ($Q_{res} = 18.02$, df = 2, $P < 0.001$).

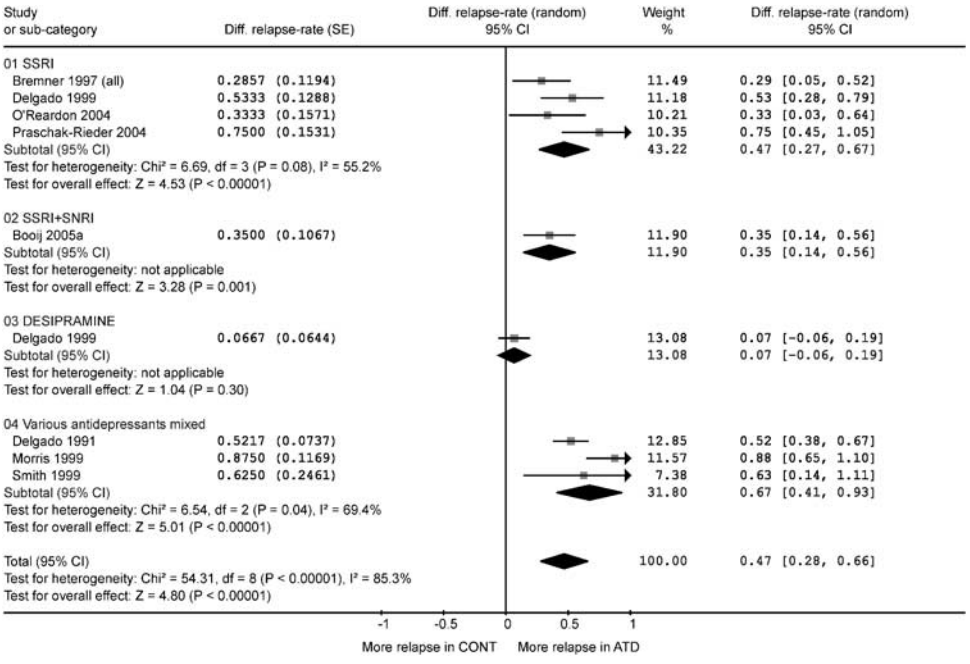


Figure 4 ATD in former depressed patients in remission, differences of relapse rates vs control depletion studied in a within subjects design in remitted patients stratified by current medication use. References to studies as indicated. SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin Reuptake inhibitor.

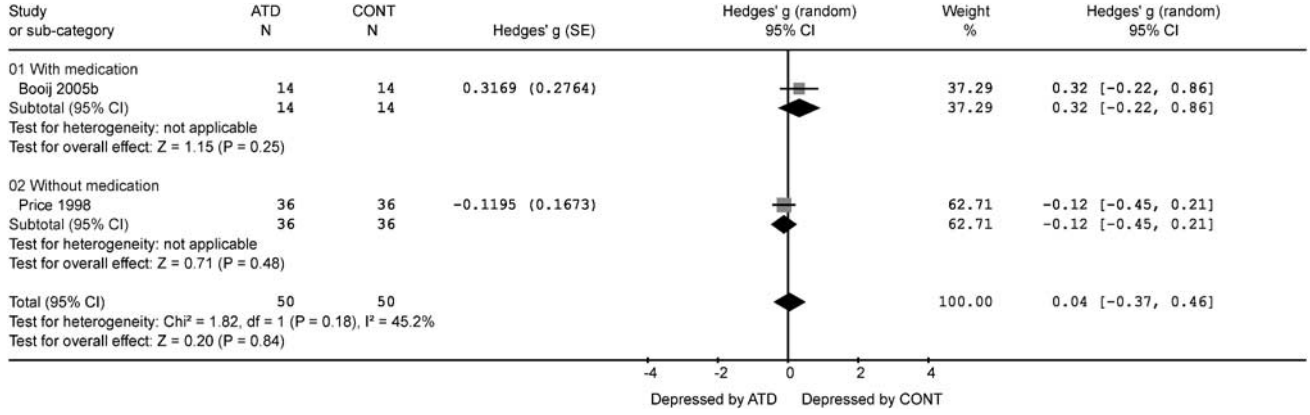


Figure 5 ATD in depressed patients stratified by use of concurrent medication (within subjects design). References to studies as indicated.

In patients who were depressed at the time of ATD we found two studies for meta-analysis. These studies included patients who used,[106] or did not use[109] AD (Figure 5). The effects of ATD were opposed: Hedges' *g* was 0.32 (−0.22 to 0.86) for patients using different types of ADs, and −0.12 (−0.45 to 0.21) for patients without AD. Two studies in depressed patients without AD were not suitable for meta-analysis. ATD did not decrease mood during depletion in these studies.[107,108] Contra-intuitively, in one study mood *increased* the day after depletion in 16/43 patients,[107] a result which was also found by one study in the meta-analysis.[106]

APTD

Figures 6a and b show results from APTD studies in healthy controls (within and between subjects). APTD did not decrease mood: pooled Hedges' *g* were 0.10 (−0.23 to 0.43) in within subjects, and 0.12 (−0.43 to 0.68) in between subjects studies. However, in one study with healthy controls with a positive family history for MDD, a moderate but nonsignificant effect on mood was found (Hedges' *g* −0.49 (−1.17 to 0.19)).[115] In patients with MDD in remission without AD (Figure 7), no effect of APTD was observed in two studies (pooled Hedges' *g* −0.02 (−0.50 to 0.47).[116,117] No studies in patients with current MDD were identified.

Sensitivity analysis and publication bias

We examined our assumptions for intercorrelation of before–after mood ratings per condition in ATD studies in healthy controls without a family history of MDD. At the same examination, we also examined the assumed intercorrelation between two test conditions (ATD vs CONT). As expected, increasing the assumed *R* to 0.8 (less conservative) increased the pooled Hedges' *g* from −0.19 (−0.43 to 0.05) to −0.31 (−0.64 to 0.02). Reducing *R* to 0.2 (more conservative) decreased the pooled Hedges' *g* to −0.14 (−0.34 to 0.06). The calculated *R*'s were higher than 0.5 in 80% of the studies that reported all relevant data. Therefore, we judged the imputed value of 0.5 for *R* as acceptable.

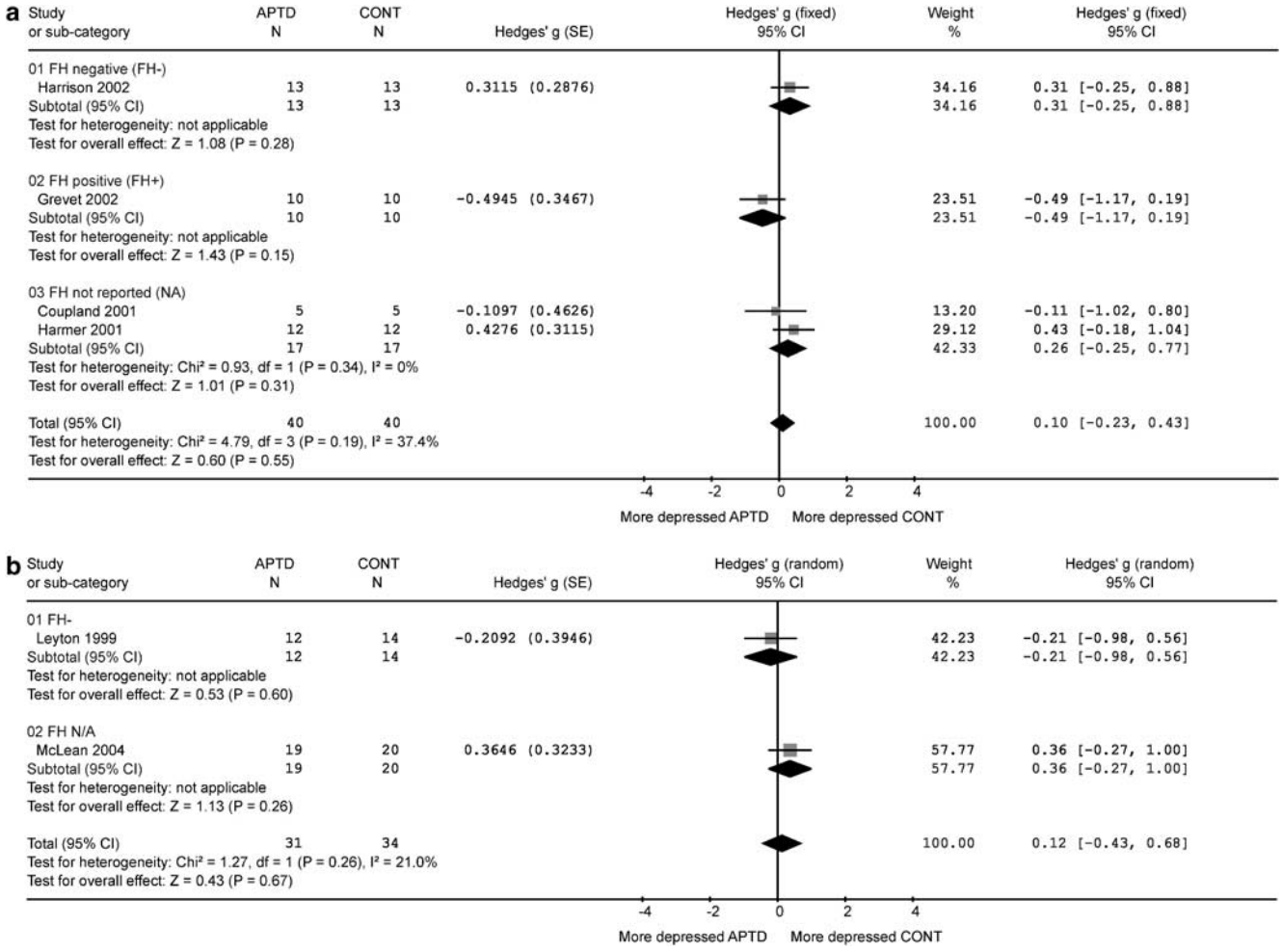


Figure 6 (**a**) Within subjects design and (**b**) between subjects design. Acute phenylalanine/tyrosine depletion (APTD) in healthy controls ((**a**) within subjects design; (**b**) between subjects design), stratified by status of family history for depression. References to studies as indicated. FH− = family history negative, FH + = family history positive, N/A = not reported.

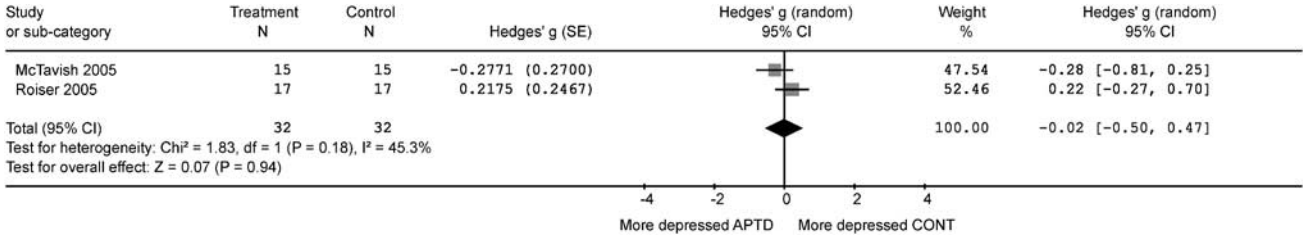


Figure 7 Acute phenylalanine/tyrosine depletion (APTD) in former depressed patients in remission without medication, studied in a within subjects design. References to studies as indicated.

Inspection of the funnel-plot of the within subjects ATD studies in healthy controls without a family history of MDD revealed asymmetry (figure available on request). More studies with a decrease in mood after ATD vs control depletion were published. In a Galbraith plot of studies, the intercept in the regression equation was −2.08 (SE 0.90; $P=0.030$). Therefore, we concluded that publication bias probably distorted our findings. We did not inspect funnel-plots in other populations of our review due to the limited number of studies.

Discussion

In this systematic review we performed the first meta-analysis of the mood effects in ATD and APTD studies. The depletion of monoamine systems (both 5-HT and NE/DA) does not decrease mood in healthy controls. However, in healthy controls with a family history of MDD the results suggest that mood is slightly decreased, both by ATD and APTD. Additionally, healthy female subjects are more affected by ATD than healthy male subjects, especially in controls without a family history of MDD. In patients who were previously depressed but in remission without AD, ATD moderately decreases mood, whereas APTD does not significantly decrease mood. ATD has comparable mood lowering effects in patients with MDD in remission who are still using ADs. The site of action of these ADs (5-HT or NE/DA) predicts the occurrence of a lowering of mood or a short relapse in MDD after depletion of the corresponding monoamine. Our findings are in line with the summaries in previous reviews.[11,18–20,24]

The most consistent finding from this review is the decrease of mood and relapse into a depressed state after ATD and APTD in remitted MDD patients who use AD. In remitted patients without AD relapses are less prominent. Because after remission medication is often continued, the difference in mood responses after depletion might be related to the duration of the achieved remission. Previous reviews discussed the relationship between the duration of the remission and the effect of monoamine depletion, with opposite conclusions. Bell *et al.*[130] concluded that effects of ATD were more pronounced early in recovery. Contrarily, Booij *et al.*[21] concluded that duration of remission was not associated with mood response to ATD.

Booij *et al.*[21] investigated predictors of relapse in a pooled analysis of the individual patient data of some of the studies included in this review. This is often referred to as a 'mega-analysis'. They found that recurrent depressive episodes ($\geqslant 2$), female gender, and a history of suicidal thoughts/attempts predicted relapse. Duration of remission did not contribute to this prediction when confounding was considered. We found a modest relationship between relapse and the duration of the remission after ATD. We defined the duration of remission as the reported average duration, or – if not stated – the minimum duration of remission used as inclusion criterion for the studies. We found that especially in the first 5 months after remission, ATD caused lowering of mood in remitted patients still using AD. However, the problem with our and Bell's comparison is the intraindividual spread in duration within the studies. This spread is not considered at the same level of detail as in a 'mega-analysis'. In addition, confounding can only be considered in 'mega-analysis'. Therefore – although their study did not include all available studies – we think that Booij *et al.* provide the best available indication of risk factors for mood lowering effects by ATD.

Do depletion studies elucidate the pathogenesis of MDD?

The absence of robust mood effects in healthy controls indicates that mood is not a direct correlate of 5-HT or NE levels in the brain. The only healthy controls who are modestly affected by monoamine depletion studies are healthy controls with a positive family history for MDD. This might be indicative of a biological vulnerability, which is revealed by depletion studies. Of interest are the findings of recent studies that combined ATD with neuroimaging or genetic sampling,[33,42–46,65,66,67,70,74,83,87,97,103,104,123] reviewed by Fusar-Poli *et al.*[25] The intelligent approach of combining depletion with imaging or genotyping appears very promising. A summary of the complex results of these studies goes beyond the scope of our review. However, these neuroimaging and genotyping studies also suggest that monoamine depletion discloses rather a 'trait' vulnerability than a pure 'state' dependent change due to depletion.

Additionally, a depressive relapse after monoamine depletion in remitted patients who use AD, occurs only if the target of the depletion (5-HT, NE) coincides

with the working mechanism of the AD used. This emphasizes that AD indeed specifically affect their supposed target systems. However, we may only conclude that an undepleted 5-HT system is required for serotonergic AD. The same holds for the NE system and norepinephrinergic AD. Delgado proposed an alternative explanation for the decrease in mood after monoamine depletion in patients: depletion of, for example, 5-HT may give the same effect as abrupt discontinuation of SSRIs.[131] Rapid discontinuation is also associated with mood effects, which are considered to be different from a depressive relapse.[132]

What certainly cannot be concluded is that MDD is *caused* by low levels of 5-HT and/or NE/DA. This simplification, which is often used to promote the use of AD specifically affecting 5-HT or NE or both systems, represents a Catch-22 argument, and ignores the notion that serotonergic and norepinephrinergic AD presumably act by a final common pathway. In this pathway postsynaptic changes at the cellular level are supposed to be responsible for the remission of MDD.[133] Cellular changes include up or down-regulated receptors, increased neuronal interconnections and sprouting and changes in levels of neuropeptides (e.g. corticotrophin releasing hormone). The clinical question of how to distinguish a patient who will respond to an AD with, for example, NE effects has not been solved. Descriptive variables at the symptom level have not yet sufficiently predicted the response to any selective agent. Therefore, a pragmatic approach to affect this final common pathway might be to prescribe ADs which target both 5-HT and NE. However, the effectiveness of this approach is still equivocal.[134–136]

In patients who are depressed at the time of monoamine depletion, no further decrease in mood is observed. A ceiling effect could be responsible for this finding. But, a more straightforward conclusion is that there is no simple relation between 5-HT or NE deficiency and mood or MDD. Nevertheless, this finding is complicated by the finding of some authors[106,107] that mood is lowered or elevated the day after ATD. A delayed decrease of mood was indicative for treatment refractoriness,[107] a finding that was not yet replicated by others.[106,108,109] The number of comparable studies to date is limited. Therefore, we think no clear conclusions or explanations can be made, except that even in MDD patients mood is not a correlate of 5-HT or NE levels in the brain.

We agree with the conclusion *of* Booij *et al*.[11,21] and Bell *et al*.[130] that a relapse of depressive symptoms in remitted patients after depletion probably reflects a biological vulnerability of the 5-HT system in remitted patients. This vulnerability increases their risk to become depressed. This increased risk was further demonstrated in two prospective studies, which used the response to ATD in remitted patients to predict later relapse/recurrence.[63,137] However, also these results need replication. Moreover, the cause of an increased vulnerability remains uncertain. Probably the cause is a combination of genetic, environmental and other determinants (e.g. 'scarring' the brain after multiple depressive episodes).[130]

In conclusion, monoamine depletion by ATD and APTD does not elucidate a causal factor in the pathogenesis of MDD. However, ATD and APTD remain useful models to safely and directly manipulate 5-HT, NE and DA function in living humans, and to study the behavioral consequences of this manipulation, especially in subgroups of humans with an apparent vulnerability.[11,12,24]

Still, several methodological issues need to be addressed. First, because of the competition of amino acids to pass the blood–brain barrier, ATD might unwillingly result in an intracerebral increase of tyrosine/phenylalanine.[24,138] Vice-versa, APTD might increase intracerebral tryptophan availability. Levels of other amino-acids than those depleted are not provided in the studies. Second, ATD provides a specific net lowering of 5-HT. Contrarily, depletion of tyrosine and phenylalanine lowers both NE and DA, which are synthesized in the same cascade (with DA thereafter transformed into NE by DA beta-hydroxylase). Also AMPT interferes early in this cascade. Although evidence from animal studies points to more DA depletion by APTD and more NE depletion by AMPT,[139] it is impossible to truly distinguish between net NE and DA depletion. Third, test re-test reliability for monoamine depletion paradigms was only tested for ATD and was rather limited, which limits the robustness of the method.[41,88] Fourth, also in healthy controls subtle cognitive effects of monoamine depletion in the brain occur: deficits in learning and memory consolidation and *improvement* in focused attention and executive function.[140] These effects show similarity with symptoms of MDD. The question remains whether these effects might represent mild first symptoms of MDD or the starting symptoms of a cascade of altered brain functions leading to MDD. Fifth, in line with the fourth issue, MDD does not develop within one day. Therefore, the changes by experimental monoamine depletion by ATD and APTD may be too short to really induce a complex biological and psychological deregulation which is recognized as MDD. Patients suffering from gastrointestinal carcinoid tumors – 5-HT producing tumors with expected prolonged states of secondary tryptophan depletion – are generally not depressed but do show improved focused attention.[141] However, carcinoid findings were not yet related to tryptophan levels over time. Sixth, the single depletion of one monoamine system by ATD or APTD/AMPT may be too simplistic, especially because of the complex interaction of monoamine systems. Five dual depletion studies were not included in this review.[49,142–145] In healthy controls contrasting results were found. Hughes *et al*.[143] found some decrease of mood on 3 VAMS-subscales, which was also found in another open study.[144] However, no effects were found in two other studies.[49,145] In unmedicated patients with MDD no significant increase of MDD was found after dual depletion.[142] It would be interesting to investigate the

effects of simultaneous depletion of 5-HT and NE/DA in other populations.

Limitations of the studies and the review

Several limitations should be mentioned. First, female gender is a risk-factor for MDD, and was also found to be a predictor of relapse after ATD in remitted patients. Based on several studies, gender differences in 5-HT metabolism are probable, and hormonal factors may play a role in 5-HT function.[21] In our results we examined the effect of gender in healthy controls. The difference between male and female subjects was most prominent in healthy controls without a family history of MDD. In the included studies hormonal status (pre- or postmenopausal state) was not distinguished in the results nor used as inclusion criterion. Second, many small differences between the studies existed: different composition of depletion and control drinks, different presentation of tryptophan/tyrosine/phenylalanine or their ratios to other neutral amino acids, different presentation of free vs total tryptophan/tyrosine/phenylalanine values, different measurements, different scales. Differences between studies undoubtedly introduced heterogeneity between the studies, which may bias the results of this review. Therefore, we recommend an international consensus protocol. Third, limited presentation of the data forced us to make assumptions, that may have influenced our findings. However, the assumptions appeared to have little influence on the results in a sensitivity analysis. Future studies need to address clear presentation of their data, preferably including a description of the directions of the effects, SDs, in cross-over designs the numbers of subjects having the control or sham first, and preferably include an SD of the pooled difference between the depletion and the control condition. For example, only 10 studies adequately reported the number of patients treated in each sequence in the within subjects design.[33,44,46,64,77,88,100,116,117,122] Fourth, six studies included Bipolar Patients. Three of these studies were also included in the meta-analysis.[98,99,117] This involved 6 patients of the total of 265 patients (2.2%) in the concerning meta analytical comparisons. Therefore, we consider the possibility of bias by the inclusion of this etiologically different disorder unlikely. Fifth, the rate of agreement in the selection of studies still may rise questions about the clarity of our selection criteria. However, discrepancies in agreement could easily be solved between the two reviewers. Therefore, we do not think our sensitive searches missed relevant studies. Finally, an indication of publication bias was found. If publication bias truly exists, the studies which found no effect or an *increase* in mood after ATD would not have been published. Indeed, the mood effects of studies that could not be included in the meta-analysis were mostly very small and nonsignificant. Furthermore, the exact information in studies required for meta-analysis forced us to exclude many studies. It seems natural that a non-significant result will not be given this level of detailed attention (change-scores with SDs), especially when mood effects are not the primary outcome in these studies. Without this publication bias the pooled effect of ATD in healthy controls would probably have been lower. Because our conclusion already is that there is no apparent mood effect of ATD in healthy controls, we conclude that the observed publication bias will not severely distort the general conclusion. Therefore, despite these limitations, we consider the results of our review after our strict methods as valid.

Conclusion and future studies

We conclude that although ATD and APTD are important in the investigation of the monoamine systems, monoamine depletion does not directly decrease mood. Although previously the monoamine systems were considered to be responsible for the development of MDD, the available evidence to date does not support a direct causal relationship with MDD. There is no simple direct correlation of 5-HT or NE levels in the brain and mood. The depletion of 5-HT by ATD and NE/DA by APTD most clearly decreases mood in vulnerable patients who are in remission from their MDD, while still using AD. Furthermore, depletion affects mood in unmedicated patients in remission or healthy controls with a family history positive for MDD. Therefore, the monoamine systems are probably important systems in the *vulnerability* to become depressed. The changes in brain metabolism in remitted patients who relapse after ATD or AMPT suggest that 5-HT and NE systems give input to a final common pathway, which needs further research to be clarified.

We suggest some lines for future research. First, three or four-armed depletion studies comparing ATD, APTD (and – if possible – their combination) vs sham depletion to investigate the differential effects of the 5-HT and NE systems on mood in remitted patients or controls with positive family history for MDD. Second, a further exploration of the relation between known genetic polymorphisms of the 5-HT, NE and DA systems (e.g. 5-HTTPR) and biological cerebral responses to depletion paradigms, as measured by PET/fMRI (e.g. like Neumeister *et al*.[65,67]). Third, the relations between monoamine depletion indicating biological vulnerability and psychological vulnerability for MDD (see Booij *et al*.[11]) Fourth, replication, further validation and standardization of the properties of ATD and other depletion paradigms as a diagnostic test for recurrences in remitted patients (see Moreno *et al*.[63] and Neumeister *et al*.[137]). New studies will increase our knowledge of the 5-HT and NE systems, which are important targets in the current treatments of MDD. This knowledge will finally improve the treatment for MDD.

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Conflict of interests

None.

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Appendix

Differences between intervention and control measurements

In depletion studies changes in mood scores typically represented mean mood-scores both before (pre) and after (post) the depletion/challenge (experimental intervention) and the placebo/sham/control-intervention. Because the mood scores were not necessarily identical at the start of the experiment and the control, we first calculated the mean change in mood-score (*pooled difference*) for the experimental and control condition separately per study. Some studies also provided the standard deviation (SD) of the pooled differences. When the standard deviation was not reported, we calculated the standard deviation of the pooled difference for paired data:

$$SD_{change} = \sqrt{SD_{pre}^2 + SD_{post}^2 - (2R\,SD_{pre}\,SD_{post})} \quad (A1)$$

In this formula, the correlation coefficient R was calculable in four studies only[36,59,81,105] and ranged between 0.42 and 1.00 for the experimental and between 0.34 and 0.95 for the control condition. To be able to calculate the standard deviation of the change between pre- and post-test mood scores for the rest of the studies we imputed a correlation coefficient R of 0.5. This value was considered to be a conservative assumption.

Statistics for studies with a within subjects design
The difference in the changes of mood scores between intervention and control were expressed as difference of change scores:

$$\text{Difference}_{\text{changes}} = \text{Change}_{\text{CONT}} - \text{Change}_{\text{INT}} \quad \text{(A2)}$$

For this difference the SD of the difference was calculated by again applying formula (A1), with an assumed R of 0.5.

To acknowledge the different mood scales to measure change in mood, the difference in changes between experimental and control condition were standardized by calculating Hedges' adjusted g, which is similar to Cohen's d, but includes an adjustment for small sample bias:[126]

$$\text{Hedges'}g = \frac{\text{Change}_{\text{INT}} - \text{Change}_{\text{CONT}}}{\text{SD}_{\text{Difference changes}}} \times \left(1 - \frac{3}{4(n_{\text{AB}} + n_{\text{BA}}) - 9}\right) \quad \text{(A3)}$$

In this formula n_{AB} and n_{BA} represent the number of subjects randomized to intervention or control as first test in the study. If the numbers for n_{AB} and n_{BA} were not reported, we assumed that the sample was split half for the two sequences. For Hedges' g an SE was calculated as follows:[146,147]

$$\text{SE} = \sqrt{\left(\frac{n_{\text{AB}} + n_{\text{BA}}}{4n_{\text{AB}} * n_{\text{BA}}} + \frac{\text{Hedges'}g^2}{2(n_{AB} + n_{BA} - 3.94)}\right)} \quad \text{(A4)}$$

Statistics for studies with a between subjects design
For between subject studies comparable statistics were used to calculate the mean change in mood-scores. Because the between-subjects design is a parallel group design, Hedges' g was calculated with formula (A3) in which for n_{AB} and n_{BA} n_{INT} and n_{CONT} were substituted. The formula for the SE was slightly different to acknowledge the absence of paired data:

$$\text{SE} = \sqrt{\left(\frac{n_{\text{INT}} + n_{\text{CONT}}}{n_{\text{INT}} * n_{\text{CONT}}} + \frac{\text{Hedges'}g^2}{2(n_{\text{INT}} + n_{\text{CONT}} - 3.94)}\right)} \quad \text{(A5)}$$

Statistics for relapse rates
For relapse rates of MDD after depletion provided in a within subjects design the difference in relapse rates was calculated as

$$\text{Difference}_{\text{Relapse-rate}} = \frac{n_{\text{Relapse\_INT}}}{N} - \frac{n_{\text{Relapse\_CONT}}}{N} \quad \text{(A6)}$$

in which N is the total number of patients included. The standard error then is

$$\text{SE}_{\text{Difference\_relapse-rate}} = \frac{1}{N}\sqrt{b + c - \frac{(b-c)^2}{N}}, \quad \text{(A7)}$$

in which b represents the number of patients with a relapse after the intervention but not the control condition and c the number of patients with a relapse after the control but not the intervention.[148] If the numbers of 'pairs' were not extractable from the paper, a conservative approach was used assuming the minimal number of patients relapsing both after the intervention and the control condition (maximal c), resulting in the largest SE.