Psychiatry Research 279 (2019) 155–171

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

A systematic review of blood-based serotonergic biomarkers in Bulimia Nervosa

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ARTICLE INFO

Keywords:
Plasma
Serum
Serotonin
Biological marker

ABSTRACT

Bulimia Nervosa (BN) is a serious eating disorder, which affects 0.8–2.9% of the young population. The etiology is unknown and biomarkers would support in understanding the pathophysiology of BN, and in identifying BN patients that may benefit from medical treatment. This systematic review aims to answer whether (a) BN deviate from healthy controls in terms of serotonin (5-HT) biomarkers in blood, and whether (b) blood-based 5-HT biomarkers could be used to tailor psychopharmacological treatment in BN. A literature search using PubMed, PsycINFO and Embase was done using the following search terms: "Bulimia Nervosa" AND "serotonin" AND "blood" OR "plasma" OR "serum". 32 studies were included in this systematic review. Several biomarkers and challenge tests were identified and all studies described an association with BN and dysregulation of the 5-HT system compared to healthy controls. Several studies pointed to an association also to borderline symptoms in BN. BN deviate from healthy controls in terms of 5-HT biomarkers in blood supporting an abnormal 5-HT system in BN. 5-HT biomarkers and associated methods could be used to tailor treatment in BN although as yet, most tests described are unpractical for bedside use.

Abbreviation

AFFIN	affinity for the serotonin transporter receptor
AN	Anorexia Nervosa
AN-bp	Anorexia Nervosa binge eating-purging type
AN-res	Anorexia Nervosa restrictive type
APD	Avoidant Personality Behavior
ATD	Acute Tryptophan depletion
β-HBA	Beta-Hydroxybutyrate
BDHI	Buss Durkee Hostility Inventory
BDI	Bech Depression Inventory
BED	Binge Eating Disorder
BIS	Barratt Impulsiveness Scale
BITE	Bulimic Investigatory Test, Edinburgh
BN	Bulimia Nervosa
BN-pur	Bulimia Nervosa purging type
BN-rec	Bulimia Nervosa recovered
BN-rem	Bulimia Nervosa remitted
BN-MDD	Bulimia Nervosa with Major Depressive disorder
BN-SSRI	Bulimia Nervosa treated with Selective Serotonin Reuptake Inhibitor
BPD	Borderline Personality Disorder
BPS	Binge-purge syndrome
CAPS	Clinician Administered PTSD Scale
CES-D	Center for Epidemiologic Studies Depression Scale
CHO	breakfast rich in carbohydrates
CIDI	Composite International Diagnostic Interview
CO	Cross Over
CORT	Cortisol
CSF	Cerebrospinal Fluid
CTI	Childhood Trauma Interview
d-FEN	dex-fenfluramine
d,l-FEN	racemic mixture of dex- and levofenfluramine
DAPP-BQ	Dimensional Assessment of Personality Pathology
DB	Double Blind
DENS	Density of binding to the serotonin transporter receptor
DES	Dissociative Experiences Scale
DIS-4	Diagnostic Interview Schedule for DSM-IV
DSED	Diagnostic Schedule for Eating Disorders
DSM	Diagnostic Statistical Manual
EAT 26	Eating Attitudes test 26
EASI-III	Emotionality Activity Sociability Impulsivity Temperament

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https://doi.org/10.1016/j.psychres.2018.12.167
Received 26 August 2018; Received in revised form 20 December 2018; Accepted 30 December 2018
Available online 31 December 2018

	Survey III
ED	Eating Disorder
EDE	Eating Disorder Examination
EDI	Eating Disorder Inventory
EDNOS	Eating Disorder Not Other Specified
FEN	Fenfluramine
GAF	Global Assessment of Functioning
GH	Growth Hormone
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
HC	Healthy Controls
5-HT	Serotonin
5-HTP	Hydroxytryptophan
HVA	Homovanillic Acid
LNAA	Large Neutral Amino Acids
LSD	Lysergic Acid Diethylamide
mCPP	m-Chlorophenylpiperazine
MAO	Monoamine Oxydase
MDD	Major Depressive Disorder
MPS	Multidimensional Perfectionism Scale
NA	not applicable
NE	Norepinephrine
NEO-PI-R	Neuroticism-Extraversion-Openness Personality Inventory, Revised
OCD	Obsessive Compulsive Disorder
PDQ-R	Personality Diagnostic Questionnaire-Revised Version
POMS	Profile of Mood States
PRL	Prolactin
PRO	breakfast rich in proteins
RDC	Research Diagnostic Criteria
SADS-L	Schedule for Affective Disorders and Schizophrenia – Lifetime
SCID-II	Structured Clinical Interview for DSM-IV-TR
SSI	Starvation Symptoms Inventory
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State Trait Anxiety Inventory
TAI	Trait Anger Inventory
TRP	Tryptophan
VAS	Visual Analog Scale
YBOCS	Yale-Brown Obsessive Compulsive Scale

1. Introduction

Bulimia Nervosa (BN) is characterized by repeated episodes of binge eating (i.e. excessive food intake paired with a sense of loss of control), and associated with compensatory behaviors for example self-induced vomiting, laxative use, excessive exercise, and/or food restriction. The prevalence of BN is estimated to between 0.8 to 2.9% (Stice et al., 2013; Smink et al., 2014), and it is more frequent in women with men being affected in only 1% (Steinhausen and Jensen 2015) to 10% of cases (Fichter, 2008). About 50% of patients with BN are free of symptoms after more than 5 years, while about 20% continue to fulfill all the criteria of the disorder (Keel et al., 1999). Similar to Anorexia Nervosa (AN), BN also carries an elevated mortality, albeit not as extreme as AN (Berg et al., 2013; Smink et al., 2013; Smyth et al., 2007; Yilmaz et al., 2014).

In spite of that the condition of BN has been well-known for many years, and cognitive schemas that describe the psychopathology has proven effective in understanding the nature of the disorder, the etiology is still unknown (Arcelus et al., 2011; Attia and Walsh, 2007; Bulik et al., 2006). A number of risk factors have been proposed for the development of BN, from genetic to psychosocial risk factors, but these studies have also underscored how limited our knowledge is on the etiology of BN (Bulik et al., 2006; Jacobi et al., 2004). The serotonergic (5-HT) system has been proposed to be involved in the etiology of BN (Treasure and Campbell, 1994), and the Selective Serotonin Reuptake Inhibitor (SSRI) fluoxetine is approved for treatment of BN (Aigner et al., 2011). Although the 5-HT system is involved in the pathophysiology of other disorders such as depression (Dell'Osso et al., 2016; Cowen and Browning 2015), harm-avoidance in different disorders (Koller et al., 2008; Mandelli et al., 2009), anxiety (Helton and Lohoff 2015), and anorexia nervosa (Kaye et al., 2013), at least for eating disorders it may be differentially implicated, for AN more normal in restricting type than in bulimic (Bailer et al., 2007), and delineating how the 5-HT system is impacted in BN may help find clues to treatment.

Several studies have shown a strong heritability in BN and estimates vary between 0.55 and 0.62 (Bulik et al., 1998; Bulik et al., 2010). Variance in core BN symptoms (especially vomiting) has also been shown to be due to additive genetic factors (Mazzeo et al., 2010). Hypothesis-driven genetic research, correlating phenotypes with genes, have proposed the involvement of the 5-HT system in BN. This is due to its involvement in a broad range of relevant biological, physiological and behavioral functions, for example body weight regulation and eating behavior (Blundell, 1992; Blundell et al., 1995; Brewerton and Jimerson, 1996; Halford and Blundell, 2000b; Kaye, 1997). In addition, 5-HT may contribute to the psychopathological characteristics of several eating disorders (ED) such as perfectionism, obsessionality and impulsivity (Carver and Miller, 2006; Hinney et al., 1997; Kaye, 1997). Moreover, numerous studies have also implicated hyper 5-HT activity as a trait marker in EDs (Brewerton and Jimerson, 1996; Kaye et al., 2005, 1998, 1991) which as well may predispose for the development of these disorders.

Studies on the gene 5-HTTLPR polymorphism have strengthened the hypothesis of an involvement of the 5-HT system in BN. In 5-HTTLPR polymorphism, the short (s) allele in the promoter region of the 5-HT transporter gene (5-HTTLPR) has been associated with low transcription of the 5-HT transporter protein, and, clinically associated with impulsivity, affective disorder, and BN (Steiger et al., 2005a, 2008). A recent systematic review including seven studies and 1750 patients of which 64.5% were female, investigated the interaction between 5-HTTLPR and an environmental or psychological factor, with an ED-related outcome variable. The review revealed that using a multiplicative model, the low function (s) allele of 5-HTTLPR interacted with traumatic life events and the experience of both sexual and physical abuse (but not only one) to increased likelihood of an ED and bulimic symptoms, respectively. Using an additive model, there was also an interaction between sexual or physical abuse considered independently and 5-HTTLPR, but no interaction with traumatic life events. No other gene vs. environment interactions were significant (Rozenblat et al., 2017). Albeit convincing, a recent large genome-wide association study has not been able to support previous findings (Solmi et al., 2016), a finding also supported by a recent meta-analysis (Lee and Lin 2010) and other studies where the association seem more related to nutritional impairment and harm-avoidance (Monteleone et al., 2006). Targeted studies on other 5-HT genes have investigated amongst others the 5-HT receptor 1Dβ gene (HTR1B) and found preliminary evidence suggesting a role in susceptibility to development of BN subtypes (Hernandez et al., 2016). In spite of the conflicting findings on 5-HTTLPR gene polymorphism, this does not rule out a 5-HT disturbance in BN.

Taken together, although BN most likely has a multifactorial etiology that involves complex interactions between genes and environment, biologically, the 5-HT system may be a major contributor. Using 5-HT biomarkers to explore the disease mechanisms would greatly improve our understanding of the pathophysiology of the disease. In addition, there is a great need for tailored personalized treatment and here, 5-HT biomarkers have a great potential to help identify those patients with BN that may benefit from 5-HT medicines such as SSRI.

Ideally, a biomarker should reflect an essential and conceivably unique characteristic of the disease. In general, there are three different

types of biomarkers: trait, state, and rate biomarkers. A measure of disease trait is a marker such as a genetic mutation that predicts the likelihood of developing a disease. A measure of disease trait may also indicate susceptibility to disease, for instance cholesterol levels and heart disease risk. A measure of disease state is, in essence, a diagnostic biomarker, and indicate the presence of an active disorder. A rate biomarker reflects the pace at which the disease is evolving. Biomarkers are usually characterized according to sensitivity and specificity and other measures that describe how accurately a biomarker detects a specific aspect of the disorder or the diagnosis.

The purpose of this systematic review was to identify studies on 5-HT biomarkers in blood, (plasma and serum) and qualitatively present the results of these studies to be able to answer the following questions: a) does BN deviate from healthy controls (HCs) in terms of 5-HT biomarkers in blood, and as an inference of the results, b) could any of the blood-based 5-HT biomarkers identified in this systematic review be used to tailor psychopharmacological treatment in BN?

2. Method

2.1. Registration

This study has been registered in PROSPERO, the International Prospective Register of Systematic Reviews (Registration number CRD42018094063).

2.2. Data sources and search strategy

A systematic literature search using the PubMed (Medline), PsycINFO and Embase databases (July 17, 2017) was done. A systematic review was undertaken in the spring of 2018.

The following search terms, including MeSH terms or subject headings were used:

-Bulimia Nervosa
-Serotonin
-Blood OR plasma OR serum

2.3. Eligibility criteria

Participants diagnosed with or treated for BN of any ethnicity and sex were included. Measurements of biomarkers related to the 5-HT system must be performed in blood (plasma or serum). Biomarkers could be related to prognosis, diagnosis and treatment. A comparison with a HC group was mandatory. The following criteria were used to exclude articles: Review articles, case reports, non-English language articles, non-human studies, genetics, non blood-based studies, medical imaging-studies without blood-based 5-HT markers. Interventional studies were not in target for this systematic review. However, if challenge probes were used e.g. in experimental studies to explore the response after activation of the 5-HT system, then these publications were included.

A PRISMA diagram was generated to summarize the flow of studies through the stages of the review (Fig. 1).

Since the aim was to qualitatively describe the evidence for an involvement of the 5-HT system in Bulimia Nervosa, and intervention studies were not in target of this systematic review, we did not rate “risk of bias”.

2.4. Data management, extraction and statistical calculations

Search results from all electronic databases were aggregated using EndNote X7 software. De-duplication was carried out using both EndNote X7 search for duplicates, and after manual review. First, titles/abstracts were screened by the authors AS, MW, KCH. Thereafter, the full-text of included publications were reviewed by authors AS, MW, JMS and KCH to determine if they met the inclusion/exclusion criteria. Thus, four eyes review was performed at each step and any disagreements between reviewers was resolved by consensus or in consultation with a senior reviewer (JMS) if needed. AS, KCH, JSH and JMS extracted data from the articles.

Data from the individual studies were extracted into Tables 1-7. Effect sizes (Cohen's d) and the effect-size correlation ("r"), were either calculated comparing the HC and patient groups using the means and standard deviation, or from the F-value of Analyses of Variance.

2.5. Additional information

JMS wrote the manuscript. JSH provided important revisions on science and content to the manuscript. All authors read and approved the manuscript.

3. Results

There were 32 identified unique publications on 5-HT biomarkers in blood and they were divided into the following categories (some studies were in two categories) and summarized in tables:

- Challenge tests, 15 studies (Tables 1 and 2).
- Tryptophan depletion studies, 4 studies (Table 3).
- Platelet monoamine oxidase activity (MAO) studies, 5 studies (Table 4).
- LSD binding, 1 study (Table 5).
- Platelet paroxetine binding, 9 studies (Table 5).
- 5-HT uptake in platelets, 2 studies (Table 6).
- Other studies, 1 study (Table 7).

4. Discussion

4.1. Centrally acting 5-HT probes

4.1.1. m-chlorophenylpiperazine

Several previous studies have demonstrated that m-chlorophenylpiperazine (mCPP) have both antagonistic and agonistic activity at 5-HT2 and 5-HT1 receptor sites with additional binding at 5-HT3 receptors (Murphy et al., 1991; Zajdel et al., 2007). Furthermore, mCPP has been shown to stimulate serotonin transporter (SERT)-mediated release of endogenous 5-HT from neurons (Pettibone and Williams, 1984), and inhibit reuptake of 5-HT and noradrenaline (Garattini et al., 1976). mCPP has been extensively used as a probe to study 5-HT function in psychiatry, and mCPP have been shown to increase body temperature, blood pressure and heart rate, cause anxiety, euphoria, nausea, dizziness, headaches, sweating and reduced sleep, usually in a dose-dependent fashion (Murphy et al., 1991). A blunted response in this context would imply that the 5-HT system is less responsive or inhibited. Weighing in the receptor affinity, which is the highest for 5-HT2A-C, and that the PRL response can be blocked by ritanserine (Di Renzo et al. 1989), a 5-HT2C receptor agonist, an increase in PRL after mCPP challenge would mostly indicate a stimulation of 5-HT2C post-synaptic receptors, and a blunted PRL reponse after mCPP, reduced post-synaptic 5-HT2C responsiveness (Franklin et al., 1995).

In nine studies (Table 1), mCPP challenge test was used and prolactin measured as a response reflecting 5-HT activity (Balsa et al., 1998). A blunted prolactin response was found in six of the studies in BN compared to HC (Table 1) (Brewerton et al., 1992; Levitan et al., 1997; Steiger et al., 2001a,b,c, 2003).

In one of these studies, patients with impulsiveness had a more blunted prolactin response (Steiger et al., 2003), and in another, healthy controls with a history of trauma (called “abused” in the publication) also had a blunted prolactin response to mCPP (Steiger et al., 2001a). In yet another study, BN with a history of self-destructiveness

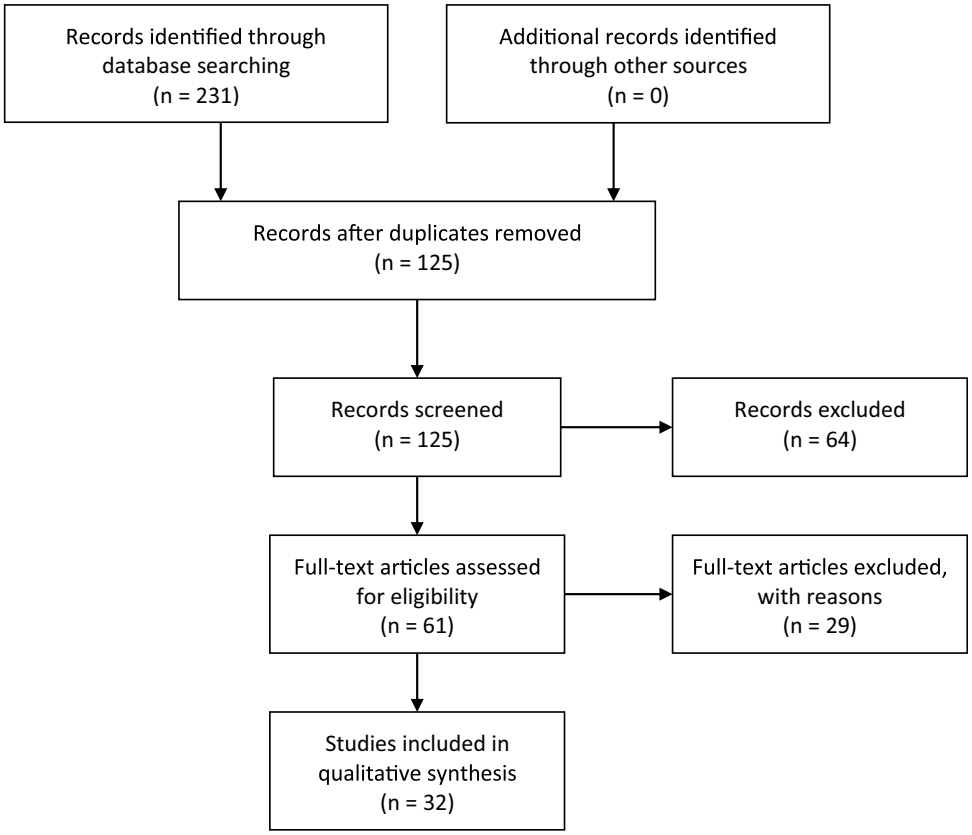

Fig. 1. PRISMA flow diagram.

had the most remarkable blunting in prolactin response (Steiger et al., 2001b).

A blunted prolactin response to mCPP was also found in one study in BN with the GG genotype of the 5-HT2A receptor gene promotor polymorphism (1438 G/A), a group which also had higher impulsiveness, but not in the A or AG genotypes (Bruce et al., 2005), and in BN with avoidant personality (Bruce et al., 2004), but not in the BN group lacking avoidant personality.

In a study on BN, who were recovered from the disorder, the prolactin response following mCPP challenge was normal (Kaye et al., 1998). Overall, this indicates a reduced responsiveness in the 5-HT system at the postsynaptic level, a response being influenced of current BN disease state and personality characteristics.

4.1.2. Fenfluramine

d,l-fenfluramine and D-fenfluramine drug challenge tests are among the most widely used biomarker probes of the 5-HT system. *d,l*-fenfluramine, an indirect 5-HT agonist, increases the release and inhibits the reuptake of 5-HT at the 5-HT neural synapse (Quattrone et al., 1979, 1983, Rothman et al., 2003). Oral administration induces 5-HT-mediated prolactin secretion, thereby providing a measure of net central 5-HT responsivity (Quattrone et al., 1979, 1983). D-fenfluramine also induces 5-HT release, which, by means of activating 5-HT2 receptors, increases prolactin and cortisol secretion. Compared to its 5-HT releasing effect, fenfluramine is also 10 times less potent as a norepinephrine releasing agent, and this effect is primarily mediated via its active metabolite norfenfluramine, which also acts on 5-HT2B and 5HT2C with high affinity, and with moderate affinity to 5HT2A receptors (Rothman et al., 2003). In most studies done in patients with depression, a blunted prolactin and cortisol responses to D-fenfluramine have been reported (Newman et al., 1998). In depressed patients with suicidal or impulsive aggressive behavior, an even greater 5-HT dysregulation of prolactin has been found after D-fenfluramine challenge (Correa et al., 2000).

In four studies (Table 2), fenfluramine (two with *d,l*-fenfluramine and two with D-fenfluramine) was used to investigate the 5-HT biomarker response in BN. In all studies, lower baseline prolactin was observed in BN compared to controls. Furthermore, a blunted prolactin response was found in BN after fenfluramine challenge, however in one study only in high bingeing BN (Jimerson et al., 1997; Monteleone et al., 1998, 2000; Wolfe et al., 2000). In three studies, the prolactin response was found to correlate negatively to frequency of bingeing (Jimerson et al., 1997; Monteleone et al., 1998, 2000). In one study, a normal prolactin response was found in a group of recovered BN patients (Wolfe et al., 2000).

In view of its both presynaptic and to a lesser extent, post-synaptic effects on the 5-HT system of fenfluramine, the results in BN points to a blunted or dysregulated 5-HT system in BN.

4.1.3. 5-HT precursors

L-tryptophan (L-TRP) is the amino acid precursor to L-5-hydroxytryptophan (L-5-HTP), which is converted to 5-HT in the brain (Fernstrom, 1983). Both L-5-HTP and L-TRP crosses the blood-brain barrier upon administration in contrast to administered 5-HT. A study using L-5-HTP found a blunted prolactin and growth hormone response in BN patients (Goldbloom et al., 1996), and another study found a blunted prolactin response to L-TRP in BN patients that also suffered from major depressive disorder (Brewerton et al., 1992) (Table 2).

4.1.4. Tryptophan depletion

Numerous studies have found that ingestion of tryptophan deficient mixture (ATD) both lowers human plasma tryptophan and also lowers the ratio of plasma tryptophan to the sum of the other large neutral amino acids (LNAA) in plasma, all that compete with tryptophan for entry into the brain. After ATD, there is a correlation between plasma tryptophan/LNAA to the level of the 5-HT metabolite, 5-

Table 1
Overview of studies using centrally acting 5-HT probes; challenge with m-chlorophenylpiperazine[a]

Study	Aim	Participants (adult females)	Diagnostic system	Study design	Intervention or test probe	Outcomes	Effect size[b]	Results
Brewerton et al. (1992)	Assess 5-HT function in BN.	BN, $n=26$, whereof BN-MDD $n=10$, HC, $n=16$. Medication free for 4 weeks. No other comorbidity than MDD.	DSM-III-R	CO, DB, random order study design.	m-CPP or placebo	Plasma PRL, CORT, estradiol. Questionnaires: SADS-L, BDI and HAM-D.	$r=0.45$ $d=1.0$[c]	BN: lower PRL at baseline and after m-CPP, the latter regardless of MDD or not. PRL inversely correlated with baseline CORT.
Bruce et al. (2005)	5-HT2A receptor gene promoter polymorphism 1438G/A vs. impulsiveness and 5-HT function in BN.	BN: BNA+, $n=21$ BNGG, $n=12$ HC: HCA+, $n=19$ HCGG, $n=9$. Comorbidities included MDD, PTSD, other anxiety dis. Medication free for 6 weeks.	DSM-IV	CO Tested during follicular phase of menstrual cycle	m-CPP	Plasma PRL Questionnaires: EAT-26, DIS-4, BIS-11	BNGG vs. BNA: $d=0.83$[c] BNGG vs. HCGG: $d=1.0$[c]	BNGG: Blunted PRL response and higher impulsiveness. No other differences between groups in PRL. No influence of other disorders
Bruce et al. (2004)	Impact of co-morbid APD on behavioral inhibition and 5-HT in BN.	BN+APD, $n=13$ BN-APD, $n=23$ HC, $n=23$. Comorbidities included MDD, PTSD, other anxiety dis. Medication free 6 weeks.	DSM-IV	Group comparisons. Tested during follicular phase of menstrual cycle	m-CPP	Plasma PRL Questionnaires: EAT-26, DIS-4, SCID-II, DAPP-BQ, Go/No-Go task.	$d=0.48$[c]	BN+APD: Blunted PRL. BN-APD: Modestly blunted PRL. Axis II, borderline and OCD more common in BN than HC. Effects not due to covariates affective instability or self-harm.
Levitan et al. (1997)	Assess 5-HT function in BN.	BN, $n=16$ HC, $n=14$ Medication free for 8 weeks. Some BN also had MDD.	DSM-III-R	Randomized DB Tested during follicular phase of menstrual cycle	m-CPP or placebo	Plasma PRL and CORT. Questionnaires: BDI, HAM-21 EDE, VAS.	$d=1.3$[c]	BN: Lower baseline PRL, blunted PRL and CORT following mCPP.
Steiger et al. (2003)	Assess 5-HT function in BN.	BN-pur, $n=45$ BN-non-pur, $n=6$ 'subclin.' BN-pur, $n=5$ HC, $n=29$. Medication free for 6 weeks. Influence of mood and impulsivity used in the study analyses.	DSM-IV	Group comparisons. Tested during follicular phase of menstrual cycle	m-CPP	Plasma PRL. Questionnaires: BIS, DAPP-BQ, CES-D and Affective Instability subscale.	$r=0.23$ $d=0.48$[d]	All BN: blunted PRL. BN with both compulsive and impulsive traits had higher baseline PRL.
Steiger et al. (2001a)	Assess 5-HT function in BN and relationship with childhood abuse.	BN, $n=35$ Abused BN=22, Non-abused BN=8. HC, $n=25$. Medication free 6 weeks. Comorbidities included MDD, PTSD, borderline.	DSM-IV	Group comparisons. Tested during follicular phase of menstrual cycle.	m-CPP	Plasma PRL and CORT Questionnaires: DIS-4, SCID-II, CES-D and DES, CTI	Abused BN: $r=0.34$ $d=0.73$[c] Non-abused BN: $r=0.97$ $d=8.2$[ce] both compared to HC.	Blunted PRL in abused and non-abused BN and abused HC compared to non-abused HC. Low CORT in abused HC and all BN. Influence of mood, or MDD not assessed.
Steiger et al. (2001b)	Assess 5-HT function in BN, vs. self-destructiveness.	BN-pur, $n=31$ BN non-pur, $n=6$ 'subclinical' BN-pur, $n=3$ HC, $n=21$. Medication free for 6 weeks. Comorbidities included depressiveness and Axis II.	DSM-IV	Group comparisons. Tested during follicular phase of menstrual cycle.	m-CPP	Plasma PRL and CORT Questionnaires: BIS, CES-D, BPD, SCID-II, DAPP-BQ.	$r=0.25$ $d=0.52$[d]	BN: blunting of PRL and CORT. Most remarkable in BN with a history of self-destructiveness. PRL not correlated with depressiveness.
Steiger et al. (2001c)	Assess 5-HT function in BN, and association with bulimic, impulsive, affective symptoms.	BN, $n=26$ BN-pur, $n=22$ BN-non-pur, $n=2$	DSM-IV	Group comparisons. Tested during follicular phase of menstrual cycle.	m-CPP	Plasma PRL Questionnaires: BIS, CES-D and DAPP-BQ	$r=0.26$ $d=0.55$[c]	BN: blunted PRL. PRL not correlated with

(*continued on next page*)

Table 1 (*continued*)

Study	Aim	Participants (adult females)	Diagnostic system	Study design	Intervention or test probe	Outcomes	Effect size[b]	Results
		'subclinical' BN-pur, $n = 2$ HC $n = 22$. Medication free for 6 weeks. Influence of comorbid depression and Axis II assessed.						depressiveness or affective instability.
Kaye et al. (1998)	Assess 5-HT function after long-term recovery from BN.	BN-rec > 1year, $n = 30$ HC, $n = 31$. Medication free. BN group had higher frequency of comorbidities.	DSM-III-R	DB. Tested during follicular phase of menstrual cycle.	m-CPP or placebo	Plasma CORT, PRL, estradiol, progesterone, TRP, LNAA, β-HBA. Questionnaires: SADS-L, HAM-D, BDI, SS-TAI, Y-BOCS-ED, EDI and MPS.	NA	BN-rec: Normal hormonal response, anxious and disorganized behavior after m-CPP. Addition: Increased CSF baseline 5-HIAA. No influence of lifetime MDD, or any Axis I disorder.

[a] A list of abbreviations is provided on title page.
[b] Effect size is calculated as Cohen's *d*. *r* is the effect size correlation.
[c] *r* and *d* calculated from mean peak delta-PRL of HC vs. BN if not otherwise stated.
[d] *r* and *d* calculated from Area Under the Curve for PRL of HC vs. BN if not otherwise stated.
[e] This effect size value was not included in figure 2 due to the small number of patients and large SD.

hydroxyindoleacetic acid (5-HIAA), in the cerebrospinal fluid (CSF) (Moreno et al., 2010). Nishizawa et al. (1997) used PET, with α-[11C] methyl-L-tryptophan as a tracer, to study the rate of 5-HT synthesis after ATD in healthy volunteers and found that the decline in 5-HT synthesis was greater than 85% in all brain regions studied, and that it was greater in women than in men. The lowering of 5-HT synthesis after ATD had been confirmed in several studies that demonstrated a lowering of 5-HIAA in the CSF of volunteers undergoing ATD (Carpenter et al., 1998; Moreno et al., 2010; Salomon et al., 2003).

There were three studies in BN and one in recovered BN patients (Table 3) investigating the biochemical and clinical effects of depleting tryptophan i.e. providing an amino acid mixture lacking the 5-HT precursor tryptophan and comparing it with a balanced mixture (Bruce et al., 2009; Kaye et al., 2000; Smith et al., 1999; Weltzin et al., 1995). All studies confirmed the lowering of plasma levels of tryptophan and in three studies also plasma LLNA (Bruce et al., 2009; Kaye et al., 2000; Weltzin et al., 1995). Tryptophan depletion influenced mood, mood lability or mood irritability in all four studies, and desire to binge in two studies in BN patients (Kaye et al., 2000; Smith et al., 1999), an effect found to be influenced by concurrent SSRI treatment in one study (Bruce et al., 2009). Marked effects of tryptophan depletion on mood was observed in both BN and HC in a study by Bruce et al. (Bruce et al., 2009), while causing only mild irritability in HC in the study by Kaye et al., (2000).

4.2. Peripherally acting 5-HT probes

4.2.1. Monoamine oxidase

MAO is an enzyme involved in degradation of different biogenic amines, and is present in the brain in two isoforms, MAO-A and MAO-B, which share 70% homology in amino acid sequence (Chen and Shih, 1998), but differ in their substrate specificities, immunological properties and tissue distribution (Bortolato and Shih, 2011). MAO has been proven to have an important role in the regulation of mood, emotions and behavior (Edmondson et al., 2009). MAO has also been proposed to be involved in the pathophysiology of various mental and neurodegenerative disorders. MAO-B is also detectable in blood platelets and there is support that low platelet MAO activity reflects low 5-HT turnover in the brain, potentially due to a common genetic control (Oreland et al., 1983). There is also a positive correlation between platelet MAO activity and the concentration of the 5-HT metabolite, 5-HIAA in the CSF in chronic pain patients (von Knorring et al., 1986) and in healthy subjects (Oreland et al., 1981).

Platelet MAO-B activity has been suggested to reflect behaviors such as sensation- and novelty-seeking, extraversion, low harm avoidance, impulsive and risky behavior, psychopathy- and aggression-related personality traits (Harrow et al., 2004; Oreland, 2004; Stalenheim, 2004).

Platelet MAO activity was found to be significantly lower in two studies of BN compared to HC (Carrasco et al., 2000; Hallman et al., 1990), and in a third study BN had the lowest mean values and smallest standard deviation compared to HC and, thereby, significantly different, albeit not specifically mentioned (Diaz-Marsa et al., 2011) (Table 4). In a fourth study, BN was included in the group of ED patients without a separate analysis; here, the ED group is described as tending to have lower MAO activity than HC (Podar et al., 2007). A fifth study found no difference in platelet MAO activity between BN and HC (Verkes et al., 1996) (Table 4).

In the study by Diaz-Marsa et al. (2011) of several different diagnostic groups of ED, MAO activity was reduced in ED patients with borderline personality disorder features, and there was a significant inverse relation between MAO activity and BPD. In addition, presence of bingeing/purging was also related to a lower MAO activity.

MAO activity in BN was also found to differ from HC, especially, when there were signs of impulsivity and suicidality (Carrasco et al., 2000) (Table 4).

Table 2
Overview of studies using centrally acting 5-HT probes; challenge with *d,l*-fenfluramine, *d*-fenfluramine, or 5-HT precursors[a]

Study	Aim	Participants (adult females)	Diagnostic system	Study design	Intervention or test probe	Outcomes	Effect size[b]	Results
Jimerson et al. (1997)	Compare 5-HT function in BN and HC.	BN, $n=15$ HC, $n=14$. Medication free for 6 weeks. No Axis I or medical complications for past 6 months.	DSM-III-R	Cross-sectional, fixed sequence, placebo-first, single-blind. Tested during follicular phase of menstrual cycle.	*d,l*-FEN or placebo	Plasma FEN, nor-FEN, PRL, CORT, estradiol, progesterone, thyroid hormones, β-hydroxybutyrate, TRP, LLNA, HVA. Questionnaires: HAM-D, EAT, STAI, subject-rated symptoms.	$r=0.37$ $d=0.79$[d]	BN: Lower baseline PRL and thyroid hormones. Blunted PRL after *d*-FEN. Frequency of binge eating episodes correlated inversely with PRL.
Monteleone et al. (1998)	Assess 5-HT function in BN.	BN , $n=14$ (low binge, $n=7$; high binge $n=7$) HC, $n=14$. Medication free for 4 weeks. No other Axis I, II or medical complications	DSM-IV	DB. Tested during follicular phase of menstrual cycle.	*d*-FEN or placebo	Plasma PRL, estradiol, CORT. Questionnaires: EDI, BITE, HDRS, Y-BOCS, BDHI.	BN tot: $r=0.82$ $d=2.8$[d] BN high binge: $r=0.89$ $d=3.9$[d] BN low binge: ns[d]	BN: Lower baseline estradiol and PRL. BN high binge: blunted PRL after *d*-FEN. Frequency of binge eating episodes correlated inversely with PRL.
Monteleone et al. (2000)	Assess 5-HT function in BN.	AN, $n=15$ BN, $n=18$ (low binge $n=9$; high binge $n=9$) BED, $n=10$ HC, $n=15$. Medication free for 6 weeks. No medical complications. Two AN patients also OCD.	DSM-IV	DB. Tested during follicular phase of menstrual cycle.	*d*-FEN or placebo	Plasma PRL, estradiol, CORT. Questionnaires: EDI, BITE, HDRS, YBC-EDS, BDHI.	BN high binge: $r=0.95$ $d=6.4$[d] BN: $r=0.89$, $d=4$[d] BN low binge: ns[d]	BN and AN: Lower baseline estradiol and PRL. AN: lower baseline CORT. BN high binge: Blunted PRL after *d*-FEN. BN low binge and BED: Normal PRL after *d*-FEN.
Wolfe et al. (2000)	Assess 5-HT function in remitted BN.	BN, $n=19$ BN-rem < 3 months, $n=21$ HC, $n=21$. Medication free for 8 weeks. No comorbidity.	DMS-III-R	Single-blind, placebo-first, fixed order. Tested during follicular phase of menstrual cycle.	*d,l*-FEN or placebo	Plasma PRL, total FEN and TRP, LNAA, estradiol, progesterone, thyroid hormones, CORT. Questionnaires: EAT, BDI, SSI and HAM-D	$r=0.01$ $d=0.2$[c]	BN: Lower baseline PRL and thyroxin. PRL blunted after *d*-FEN. BN-rec: Lower baseline CORT and thyroxine. PRL response as in HC.
Goldbloom et al. (1996)	Assess 5-HT function in BN by stimulating 5-HT synthesis.	BN, $n=8$ HC, $n=8$. Medication free for 4 weeks. Two BN had MDD.	DSM-III-R	Group comparison.	Intravenous L-5-HTP with prior peripheral decarboxylase inhibitor.	Serum PRL, CORT, GH and plasma 5-HTP and 5-HT. Questionnaires: DIS, EAT, EDI, HAM-D.	$r=0.85$ $d=3$[c]	BN: Elevated post-infusion plasma 5-HTP, blunted PRL and GH response. No influence of MDD.
Brewerton et al. (1992)	Assess 5-HT function in BN by stimulating 5-HT synthesis.	BN, $n=23$, whereof BN-MDD $n=8$, HC, $n=16$. Medication free for 4 weeks. No other comorbidity.	DSM-III-R	CO, DB, random order study design.	L-TRP or placebo	Plasma PRL, CORT, estradiol. Questionnaires: SADS-L, BDI and HAM-D.	$r=0.58$ $d=1.44$[c]	BN with MDD: Blunted PRL responses BN vs HC ns. MDD did influence results.

[a] A list of abbreviations is provided on title page.
[b] Effect size is calculated as Cohen's *d*. *r* is the effect size correlation.
[c] r and *d* calculated from mean peak delta-PRL of HC vs. BN if not otherwise stated.
[d] *r* and *d* calculated from Area Under the Curve for PRL of HC vs. BN if not otherwise stated.

Table 3
Overview of studies using centrally acting 5-HT probes; tryptophan depletion[a]

Study	Aim	Participants (adult females)	Diagnostic system	Study design	Intervention or test probe	Outcomes	Effect size[b]	Results
Bruce et al. (2009)	ATD in BN and effects on mood and eating-related urges.	BN medication free, $n=26$, BN-SSRI, $n=12$ HC, $n=25$. No other medications for 4 weeks. AN and psychosis excluded.	DSM-IV	DB, randomized CO. Tested during follicular phase of menstrual cycle.	ATD or balanced mixture	Plasma TRP and LNAA. Questionnaires: POMS	POMS: $d=0.36$ Urge to binge: $d=0.39$	All groups: Reductions in mood. BN-SSRI: Increased urge to binge. Largest effects in urge to binge seen in medicated BN, who were also more depressed. No influence of Axis I disorders. No differences in lifetime mood or anxiety disorders between any of the groups.
Kaye et al. (2000)	ATD in BN and effects on mood and eating-related urges.	BN, $n=22$ HC, $n=16$ Medication free for 4 weeks. BN: higher scores on depression.	DSM-IV	DB. Challenge test design. Tested during follicular phase of menstrual cycle.	ATD or balanced mixture	Plasma TRP and LNAA Questionnaire: BDI	Mood liability: BN after ATD: $r=0.47$ $d=1.1$	HC: mild irritability. BN: increased depression, mood lability, sadness and urge to binge/purge. No influence of lifetime axis I disorders. Not associated with BDI scores.
Smith et al. (1999)	ATD in BN and effects on mood and eating-related urges in recovered BN.	BN-rec, $n=10$ HC, $n=12$. Medication free for 6 months. All had previous MDD.	DSM-III-R	DB, CO. Tested during follicular phase of menstrual cycle.	ATD or balanced mixture	Plasma TRP. Questionnaire: HAM-D Observer and self-rated measures of mood, eating disorder symptoms, cognition.	Change in mood (Ham-D): $r=0.67$ $d=1.8$ "Loss of control": $d=1.5$	BN-rec: increased HAM-D score, lowering of mood, increased body image concern, subjective loss of control of eating. The effect was larger in BN subjects with history of "BN independent episode of MDD"
Weltzin et al. (1995)	ATD in BN and effects on mood and eating-related urges.	BN, $n=10$ HC, $n=10$ Medication free for 4 weeks. 8 BN had MDD.	Structured clinical interview	DB. Tested during follicular phase of menstrual cycle.	ATD or balanced mixture	Plasma TRP and LNAA. Self-report and observer-rated instruments for broad range of symptoms.	Irritability (peak change): $r=0.39$ $d=0.86$	BN: increase in caloric intake, mood irritability and labile mood. No relation to MDD.

[a] A list of abbreviations is provided on title page.
[b] Effect size is calculated as Cohen's *d*. *r* is the effect size correlation. Values are calculated from BN before and after ATD if not otherwise stated.

Table 4
Overview of studies using peripherally acting 5-HT probes; platelet monoamine oxidase activity[a]

Study	Aim	Participants (adult females)	Diagnostic system	Study design	Intervention or test probe	Outcomes	Effect size[b]	Results
Carrasco et al. (2000)	MAO activity in ED	BN, $n=30$ AN-bp, $n=17$ HC, $n=30$ Medication free for 4 weeks. No comorbid disorder.	DSM-IV	Group comparisons. Adjusted for menstrual phase and smoking.	Platelet MAO activity	Platelet MAO. Questionnaires: EDI, BITE, HAM-A, HAM-D, BIS, Rosembaum self-control scale, VAS specifically designed, SCID-II.	$r=0.51$ $d=1.2$[c]	BN: lower MAO activity. No differences between BN and AN-bp. MAO activity inversely correlated with impulsivity and BPD.
Diaz-Marsa et al. (2011)	MAO activity in ED and relation to borderline psychopathology	BN, $n=30$ AN-res, $n=25$ AN-bp, $n=14$ AN not otherwise specified, $n=3$ HC, $n=28$. Medication free. No comorbid disorder except BPD.	DSM-IV	Case-Control study.	Platelet MAO activity	Platelet MAO. Questionnaires: SCID-II, EDI, BITE, Zanarini Rating Scale -BPD, BIS.	BN: $r=0.6$ $d=1.5$ bp all vs. non-bp: $r=0.31$ $d=0.7$	ED: lower MAO activity than HC. ED with BDP: lower MAO activity than ED without BDP. ED with bp and BDP: lower MAO activity than ED with bp without BDP and than HC. MAO activity inversely correlated with number and severity of BPD clinical features.
Hallman et al. (1990)	MAO activity, platelet 5-HT update rate and efflux	BN, $n=16$ HC, $n=12$. No information on medication. No severe MDD.	DSM-III	Group comparisons	Platelet MAO activity, platelet 5-HT uptake rate and platelet 5-HT release.	Platelet MAO activity, 5-HT uptake rate, and release. Personality traits	BN vs. HC: $r=0.43$ $d=0.98$	BN: lower MAO activity. Rates of 5-HT uptake and efflux comparable.
Podar et al. (2007)	MAO activity in BN over 9 months	AN, $n=11$ BN, $n=43$ HC, $n=138$. MDD (60%). Antidepressant medication (74%).	ICD-10	Longitudinal study Group comparisons	Platelet MAO activity ($n=54$), and follow-up samples on a subset ($n=34$ at 3 months; $n=26$ at 6 months).	Platelet MAO activity. Questionnaires: EDI-2 and NEO-PI-R.	All patiens vs. HC: $r=0.16$, $d=0.33$	AN and BN: lower MAO activity. Influence of MDD not assessed.
Verkes et al. (1996)	MAO in BN with or without BPD and in women with suicidal behavior.	BN, $n=15$ With recurrent suicidal behavior, $n=15$ HC, $n=15$. Medication free (analgesics and bzd [13%] allowed). Axis I disorders excluded.	DSM-III-R	Randomized CO, DB. Tested during follicular phase of menstrual cycle.	Platelet MAO activity following exposure to fluoxetine or placebo.	Platelet MAO activity. Questionnaires: PDQ-R, TAI, EASI-III and BDI	NA	MAO activity in BN not different from HC.

[a] A list of abbreviations is provided on title page.
[b] Effect size is calculated as Cohen's *d*. *r* is the effect size correlation. Values are calculated from BN vs. HC if not otherwise stated.

Table 5
Overview of studies using peripherally acting 5-HT probes; platelet [^{3}H]paroxetine or [^{3}H]LSD binding[a]

Study	Aim	Participants (adult females)	Diagnostic system	Study design	Intervention or test probe	Outcomes	Effect size[b]	Results
Ekman et al. (2006)	Paroxetine binding in BN.	BN, $n=20$ HC, $n=14$. Medication free. No Axis I disorders.	DSM-IV	Group comparison. Tested during follicular phase of menstrual cycle.	Platelet [^{3}H] paroxetine binding	Paroxetine binding density and affinity.	DENS: $r=0.57$ $d=1.4$	BN: reduced paroxetine binding density and increased ligand affinity.
Ramacciotti et al. (2003)	Paroxetine binding in BN.	AN, $n=11$ BN, $n=15$ HC, $n=26$. 42% MDD, no other Axis I disorder or somatic, and all were medication free.	DSM-IV	Group Comparisons.	Platelet [^{3}H] paroxetine binding	Paroxetine binding density. Questionnaires: DSED and HRSD.	DENS: BN: $r=0.94$ $d=5.7$ AFFIN: NA	All ED: reduced paroxetine binding density. No variation with binge-eating, purging, impulsive behaviors, or symptoms of depression.
Steiger et al. (2000)	Paroxetine binding in BN with or without BPD.	BN, $n=27$ BN-BPD, $n=11$ HC, $n=25$ (16 for PARB). 15% BN had just started SSRI. No other comorbid disorders.	DSM-IV	Group comparisons. Tested during follicular phase of menstrual cycle.	Platelet [^{3}H] paroxetine binding	Paroxetine binding density. Questionnaires: EAT-26, DES, BIS, DAPP-BQ, CTI.	DENS: BN (all): $r=0.59$ $d=1.47$	BN: Lower paroxetine-binding density independent of comorbid BPD. Affinity not different. No influence of affective instability.
Steiger et al. (2001a)	Paroxetine binding in BN and relationship with childhood abuse.	BN, $n=35$ HC, $n=25$. Medication free for 6 weeks. BN: 50% MDD, 29% BDD.	DSM-IV	Group comparisons. Tested during follicular phase of menstrual cycle.	Platelet [^{3}H] paroxetine binding	Paroxetine binding density. Questionnaires: DIS4 and SCID-II, CES-D and DES, CTI.	$r=0.5$ $d=1.15$	BN lower paroxetine binding. No effect from childhood abuse. Influence of MDD or mood not assessed.
Steiger et al. (2006)	Paroxetine binding in BN probands and first-degree relatives.	BN-purging, $n=18$ BN EDNOS, $n=15$ HC, $n=19$ Mothers to ED,$n=31$ HC, $n=18$ Sisters to ED, $n=7$ HC $n=7$. 16 BN on 5-HT medication.	DSM-IV	Group Comparisons. Assessed menstrual status.	Platelet [^{3}H] paroxetine binding	Paroxetine binding density. Questionnaires: BIS, DAPP-BQ, CES-D. DIS4 in most, then SCID-I and CAPS.	DENS: BN all probands: $r=0.65$ $d=1.7$ BN mothers vs. HC mothers: $r=0.62$ $d=1.6$	BN and their mothers and sisters: lower paroxetine binding. Effect of comorbidity weighed in on paroxetine binding. No effect of medication or MDD on paroxetine binding.
Steiger et al. (2003)	Assess 5-HT function in BN by paroxetine binding in BN, and relationship with bulimic, impulsive, affective spt.	BN-purging, $n=45$ BN-non-pur, $n=6$ 'subclinical' BN-pur, $n=5$ HC, $n=29$. Medication free for 6 weeks. Influence of mood and impulsivity used in the study analyses.	DSM-IV	Group comparisons. Tested during follicular phase of menstrual cycle.	Platelet [^{3}H] paroxetine binding after mCCP challenge. No placebo.	Paroxetine binding density and affinity. Questionnaires: BIS, DAPP-BQ, CES-D and Affective Instability subscale.	DENS: All BN $r=0.50$ $d=1.15$	BN: reduced paroxetine binding density and affinity. Influence of MDD not assessed.
Steiger et al. (2001c)	Paroxetine binding in BN, and association with impulsive, affective symptoms	BN-pur, $n=22$ BN non-pur, $n=2$ 'subclinical' BN pur, $n=2$ HC, $n=22$. Medication free for 6 weeks. Influence of comorbid depression and Axis II assessed.	DSM-IV	Group comparisons. Tested during follicular phase of menstrual cycle.	Platelet [^{3}H] paroxetine binding after mCCP challenge. No placebo.	Paroxetine binding density and affinity. Questionnaires: BIS, CES-D and DAPP-BQ.	DENS: All BN: $r=0.43$ $d=0.96$	BN: reduced paroxetine binding density. Inverse assoc. with impulsivity and paroxetine binding. No effect of MDD.
Steiger et al. (2005a)	Influence of 5-HTTLPR polymorphism on behavioral or affective dysregulation and paroxetine binding.	BN-pur, $n=37$ BN non-purge, $n=3$ AN-bp, $n=4$ EDNOS, $n=15$. 5-HT medication allowed	DSM-IV	Group comparisons (BPS vs non-BPS). Blinded. Tested during	Platelet [^{3}H] paroxetine binding. Genotyping	Paroxetine binding density and affinity. Questionnaires: Impulsiveness Scale version 11, CES-D, DAPP, SCID-II and interview for BPD.	DENS: All patients: $r=0.28$ $d=0.59$ Medication free,	Carriers of s allele of 5-HTTLPR had more affective instability, behavioral impulsivity, interpersonal insecurity, comorbid BPD, and lower paroxetine binding density.

(*continued on next page*)

Table 5 (*continued*)

Study	Aim	Participants (adult females)	Diagnostic system	Study design	Intervention or test probe	Outcomes	Effect size[b]	Results
		but adjusted. Influence of comorbidity explored.		follicular phase of menstrual cycle.			s-allele vs. no s-allele: $r = 0.34$ $d = 0.72$	Relation to MDD not specifically assessed.
Steiger et al. (2005b)	Paroxetine binding in BN and remitted BN	BN, $n = 22$ BN-rem, $n = 11$ HC, $n = 22$. Medication free for 6 weeks. Comorbidities compared.	DSM-IV	Group comparisons.	Platelet [^{3}H] paroxetine binding.	Paroxetine binding density and affinity. Questionnaires: BIS, DAPP-BQ, CES-D and a computerized version of DIS4. Blood samples.	DENS: BN: $r = 0.64$ $d = 1.7$ BN-rem: $r = 0.45$ $d = 1.0$	BN and BN-rem: reduced paroxetine binding density. No influence of comorbidity.
Spigset et al. (1999)	To investigate the platelet 5-HT2A receptor in AN and BN.	AN, $n = 10$ BN, $n = 23$ HC, $n = 33$. BN: 9% SSRI. BN: 30% MDD. No other Axis I or Axis II.	DSM-IV	Treatment naïve vs. 1-year post treatment. Group comparisons.	[^{3}H]LSD binding	LSD binding density and affinity. Questionnaire: GAF scale.	DENS for BN: $r = 0.46$ $d = 1.0$ Median given for AFFIN. *d*-not calculated.	BN (and AN): enhanced 5-HT2A receptor density and LSD binding affinity. No difference between BN with or without depression, neither vs. HC.

[a] A list of abbreviations is provided on title page.

[b] Effect size is calculated as Cohen's *d*. *r* is the effect size correlation. Values are calculated from BN vs. HC if not otherwise stated. Affinity effect size not given if lower effect size than Density.

4.2.2. Paroxetine and LSD binding studies

Platelet [^{3}H]paroxetine binding is a marker for the 5-HT uptake site in the human brain (Backstrom et al., 1989). Although this is a peripheral measure, there is good evidence that it indirectly measures the activity of the central SERT protein (Mellerup et al., 1983) as assessed by density of receptors (B-max), and by binding affinity of the drug at the receptor site (Kd). Paroxetine has a very high affinity for SERT, and is also highly specific with more than 200 times selectivity over other receptors (Sanchez et al., 2014).

There were nine studies identified in the literature (Table 5) that investigated the effect on platelet paroxetine binding sites in BN, whereof one study included genetic data. In comparison with HC, patients with BN had reduced number of paroxetine binding sites in all nine studies (Ekman et al., 2006; Ramacciotti et al., 2003; Steiger et al., 2000, 2001a,c, 2003, 2005a,b, 2006), In one study, paroxetine binding sites were reduced also in remitted BN patients (Steiger et al., 2005b), and in one study also in first degree relatives to patients with BN (Steiger et al., 2006). In three studies, reduced paroxetine binding sites were found to be associated with, or predicted, lowered mood and self concept before and after binge (Steiger et al., 2003). In one study, paroxetine binding density was decreased in BN carriers of the s-allele of the 5-HTTLPR gene (Steiger et al., 2005a).

In another study (Table 5), ^{3}H-LSD binding density and affinity on platelets were investigated and found increased, indicating enhanced 5-HT2A receptor binding sites and affinity in BN (Spigset et al., 1999). To conclude, activity of the central SERT is clearly decreased in BN.

4.2.3. Platelet 5-HT

In one study, platelet 5-HT uptake was analyzed and found to be increased in BN compared to HC (Goldbloom et al., 1990) (Table 6). Another study found no difference in plasma 5-HT content compared to HC (Verkes et al., 1996), while linear regression revealed a significant positive relation between platelet 5-HT and the symptom ``anger" and DSM-III cluster B personality disorder, respectively, in BN (Table 6).

4.2.4. Amino acid levels in blood

In one study (Table 7), the fasting tryptophan/LNAA ratio was found slightly higher in BN compared to HC (Pijl et al., 1995), however, other studies found no differences in tryptophan and/or LLNA blood baseline levels (Bruce et al., 2009; Jimerson et al., 1997; Kaye et al., 2000; Wolfe et al., 2000) (Tables 2 and 3). The same applied to HC and recovered BN (Kaye et al., 1998; Smith et al., 1999) (Tables 1 and 3). After tryptophan depletion, amino acid levels were comparable between HC and BN or recovered BN (Bruce et al., 2009; Kaye et al., 2000; Smith et al., 1999) (Table 3). After L-5-HTP infusion, plasma levels of 5-HTP were higher in BN compared to HC (Goldbloom et al., 1996) (Table 6). Overall, this indicates that LLNA and tryptophan concentrations seem to be at normal levels, at least in plasma in BN.

4.3. Short summary of included studies

Fig. 2 illustrates the findings summarized here. By using the m-CCP and fenfluramine challenge tests as well as L-5-HTP and L-TRP administration tests, a blunted prolactin response was observed in BN. This indicates a predominating 5-HT2C down- or dysregulation postsynaptically and/or a reduced release of 5-HT presynaptically. Weighing in the increased affinity of ^{3}H-LSD, which binds to 5-HT2A receptors, this may reflect that the 5-HT2A receptors are not affected in BN, or that a compensatory upregulation due to a lack of 5-HT in the synapse is present. The LSD study has not been replicated while the studies using mCPP and fenfluramine have been repeated, why the finding using ^{3}H-LSD should be interpreted with caution. Furthermore, the prolactin response was normal in recovered patients indicating state dependency. In addition, prolactin level was related to personality characteristics and correlated negatively with bingeing. One study found this to be strongly influenced by GG homozygocity in the 5-HT2A

Table 6
Overview of studies using peripherally acting 5-HT probes; platelet 5-HT[a].

Study	Aim	Participants (adult females)	Diagnostic system	Study design	Intervention or test probe	Outcomes	Effect size[b]	Results
Goldbloom et al. (1990))	5-HT uptake in BN.	BN, $n = 22$ HC, $n = 20$. Medication free for 4 weeks. BN: 14% MDD.	DSM-III-R	Group comparisons. Tested during follicular phase of menstrual cycle.	Platelet 5-HT uptake	Platelet 5-HT uptake. Questionnaires: EAT-26, EDI and HRSD.	$r = 0.91$ $d = 4.5$	BN: higher platelet 5-HT uptake. No correlation with depression score, weight and frequency of bingeing/vomiting.
Verkes et al. (1996)	Platelet 5-HT in BN with or without BPD and in women with suicidal behavior.	BN, $n = 15$ Women with recurrent suicidal behavior, $n = 15$ HC, $n = 15$. Medication free (analgesics and bzd [13%] allowed). Axis I disorders excluded.	DSM-III-R	Randomized CO, DB. Tested during follicular phase of menstrual cycle.	Platelet 5-HT content following exposure to fluoxetine or placebo.	Platelet 5-HT content. Questionnaires: PDQ-R, TAI, EASI-III and BDI.	NA	BN not different from HC. In BN, anger and cluster B personality disorder influence platelet 5-HT content.

[a] A list of abbreviations is provided on title page.
[b] Effect size is calculated as Cohen's *d*. *r* is the effect size correlation. Values are calculated from 5-HT uptake in platelets in BN vs. HC.

receptor gene promoter polymorphism 1438 G/A (Bruce et al., 2005) suggesting a phenotypic modification by a specific genotype.

The platelet paroxetine binding studies, which shows a decreased SERT binding, indicates a reduced SERT availability or function, an effect also found in first-degree relatives to BN patients and in BN carriers of the s-allele of the 5-HTTLPR gene. The effect was not found in remitted BN which suggest both a potential genetic modifying effect and a reversibility of a dysregulated or blunted SERT activity. Moreover, the studies of platelet MAO activity indicates reduced presynaptic 5-HT turnover in BN.

Tryptophan and LLNA metabolism appears unaffected in BN. However, tryptophan depletion induced more evident irritability and effects on mood in BN and recovered BN compared to HC. This points to state-independent increased sensitivity of the serotonergic system, possibly at the presynaptic level.

Effect sizes of each finding were included to allow for a comparison of the results using different 5-HT biomarkers. It must be interpreted with caution, since comparisons between studies using different biomarkers may not reveal a true picture of a real difference in biological changes between the different parts of the 5-HT system, since the samples in general were small, and the effect sizes are more suited for comparisons between effects in properly designed Randomized Controlled Studies. The highest effect sizes were found using fenfluramine, paroxetine and studying 5-HT uptake in platelets. Should this be translated to real effects that are fully comparable, a presynaptic 5-HT dysregulation may be more exaggerated than changes of other parts of the 5-HT system.

Taken together, the findings point to that the 5-HT system is blunted or showing a reduced activity at both a presynaptic and postsynaptic level, together with a reduced SERT binding in BN, while an increased binding to post-synaptic 5-HT2A is present. The latter findings (SERT and 5-HT2A) may hypothetically be compensatory changes to a reduced overall 5-HT function. This dysregulation may be even more exaggerated in BN patients with signs of borderline personality.

4.4. 5-HT and behaviors associated with BN

The association between disturbances of the 5-HT system and appetite dysregulation is well established (Blundell, 1984,1992; Blundell et al., 2001, 1995; Halford and Blundell, 2000a,b; Halford et al., 2011), and in addition, relevant also in anxious and obsessional behaviors and extremes of impulse control (Fineberg et al., 2010; Fontenelle et al., 2011). In addition, several studies have found evidence of disturbances of the monoamine function both in acutely ill patients with ED, and after recovery from AN and BN (Kaye, 2008).

According to one definition, emotional regulation may be viewed from a multidimensional perspective that emphasizes adaptively responding to emotional distress versus efforts to rigidly control or suppress emotional arousal (Lavender et al., 2015). Emotional dysregulation is common in BN and plays an important role in the development and maintenance of the disorder (Markey and Vander Wal, 2007). Since the 5-HT system is one of the major neurochemical systems in the brain involved in emotional processing and regulation (Aznar and Klein, 2013; Macoveanu, 2014; Outhred et al., 2013; Shikanai et al., 2013), it may be assumed that a disturbance in the 5-HT system in BN will influence the emotional dysregulation characteristic of BN.

In all studies reviewed, there is a change in the 5-HT system in BN pointing to a reduced activation. In addition, presence of borderline or "impulsive" personality traits/disorder in BN subsets reflect a greater 5-HT dysfunction in such patients (Steiger et al., 2001c; Verkes et al., 1996), albeit one study found a more general reduction in the 5-HT system independent of signs of BPD (Steiger et al., 2000).

Steiger et al indicate that the disturbance in the 5-HT system is heritable (or an endophenotype), and carried by BN patients and their first-degree relatives, even when asymptomatic (Steiger et al., 2006). Further support for this notion comes from studies of clinical correlates

Table 7
Overview of studies using peripherally acting 5-HT probes; fluoxetine with test meal[a]

Study	Aim	Participants (adult females)	Diagnostic system	Study design	Intervention or test probe	Outcomes	Effect size[b]	Results
Pijl et al. (1995)	Investigate amino acid concentration in BN vs. HC	BN, $n=15$ HC, $n=19$. Medication free. No axis I disorders.	DSM-III-R	DB, CO, 2x2 factorial design.	Either fluoxetine or placebo for 4 days. Combined with carbohydrate or protein rich breakfast. Tested during follicular phase of menstrual cycle.	Serum glucose, insulin, tyrosine, TRP, phenylalanine, isoleucine, leucine and valine. Questionnaire: EDI	$r=0.66$ $d=1.77$	BN: Increased fasting tTRP/LNAA ratio, insulin, and glucose. Increased TRP/LNAA ratio in BN after breakfast (120 min). CHO increased TRP/LNAA ratio, while PRO decreased TRP/LNAA ratio in BN.

[a] A list of abbreviations is provided on title page.
[b] Effect size is calculated as Cohen's *d*. *r* is the effect size correlation.

List of abbreviations used in the tables

AFFIN, affinity for the serotonin transporter receptor; A*N*, Anorexia Nervosa; AN-bp, Anorexia Nervosa binge eating-purging type; AN-res, Anorexia Nervosa restrictive type; AP*D*, Avoidant Personality Behavior; AT*D*, Acute Tryptophan depletion; β-HBA, Beta-Hydroxybutyrate; BDHI, Buss Durkee Hostility Inventory; BDI, Bech Depression Inventory; BED, Binge Eating Disorder; BIS, Barratt Impulsiveness Scale; BITE, Bulimic Investigatory Test, Edinburgh ; B*N*, Bulimia Nervosa; BN-pu*r*, Bulimia Nervosa purging type; BN-rec, Bulimia Nervosa recovered; BN-rem, Bulimia Nervosa remitted; BN-MDD, Bulimia Nervosa with Major Depressive disorder; BN-SSRI, Bulimia Nervosa treated with Selective Serotonin Reuptake Inhibitor; BPD, Borderline Personality Disorder; BPS, Binge-purge syndrome; CAPS, Clinician Administered PTSD Scale; CES-D, Center for Epidemiologic Studies Depression Scale ; CHO, breakfast rich in carbohydrates; CIDI, Composite International Diagnostic Interview ; CO, Cross Over; CORT, Cortisol; CSF, Cerebrospinal Fluid; CTI, Childhood Trauma Interview; *d*-FEN, dex-Fenfluramine; *d,l*-FEN, racemic mixture of dex- and levofenfluramine; DAPP-BQ, Dimensional Assessment of Personality Pathology; DB, Double Blind; DENS, Density of binding to the serotonin transporter receptor; DES, Dissociative Experiences Scale; DIS-4, Diagnostic Interview Schedule for DSM-IV; DSED, Diagnostic Schedule for Eating Disorders; DSM, Diagnostic Statistical Manual; EAT 26, Eating Attitudes test 26; EASI-III, Emotionality Activity Sociability Impulsivity Temperament Survey III ; ED, Eating Disorder; EDE, Eating Disorder Examination; EDI, Eating Disorder Inventory; EDNOS, Eating Disorder Not Other Specified; FEN, Fenfluramine; GAF, Global Assessment of Functioning; GH, Growth Hormone; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; HC, Healthy Controls; 5-HT, Serotonin ; HTP, Hydroxytryptophan; HVA, Homovanillic Acid; LNAA, Large Neutral Amino Acids; LSD, Lysergic Acid Diethylamide; mCPP, m-Chlorophenylpiperazine; MAO, Monoamine Oxydase; MDD, Major Depressive Disorder; MPS, Multidimensional Perfectionism Scale; NA, not applicable; NE, Norepinephrine; NEO-PI-*R*, Neuroticism-Extraversion-Openness Personality Inventory, Revised; OC*D*, Obsessive Compulsive Disorder; PDQ-R, Personality Diagnostic Questionnaire-Revised Version ; POMS, Profile of Mood States; PRL, Prolactin; PRO, breakfast rich in proteins; RDC, Research Diagnostic Criteria; SADS-L, Schedule for Affective Disorders and Schizophrenia – Lifetime; SCID-II, Structured Clinical Interview for DSM-IV-TR; SSI, Starvation Symptoms Inventory; SSRI, Selective Serotonin Reuptake Inhibitor; STAI, State Trait Anxiety Inventory; TAI, Trait Anger Inventory; TRP, Tryptophan; VAS, Visual Analog Scale; YBOCS, Yale-Brown Obsessive Compulsive Scale

of the 5-HTTLPR polymorphism in BN, which underscores that 5-HTTLPR polymorphism may be a factor determining proneness to impulsivity, affective dysregulation, and reduced central 5-HT reuptake (Steiger et al., 2005a).

Other scientists (Kaye et al., 2000; Treasure and Campbell, 1994) also hypothesise that disturbance of the 5-HT system is a trait contributing to the pathogenesis of BN. Our interpretation of the responses in recovered BN individuals is that some findings of the 5-HT dysregulation is state dependent, especially the 5-HT2C related findings, (Kaye et al., 1998; Wolfe et al., 2000) while for pre-synaptic 5-HT function and the SERT, it may potentially be trait related (Smith et al., 1999; Steiger et al., 2005b). This implyes that 5-HT dysregulation in BN is both state and trait related.

4.5. Potential use as personalized biomarker tool

The second purpose of this systematic review was to evaluate the use of 5-HT biomarkers as guiding tools for personalized medicine. Since most, if not all, of the included tests are easy to use in a clinical specialist outpatient setting, they would qualify in terms of practicability of use for bedside specialist utilization. However, the laboratory analytical part do make some, if not most of the tests, too difficult to qualify for practical bedside utilization. Should the analytical part be made bedside friendly then most of the tests could be used for tailoring treatment, answering to the question as to whether it would be worthwhile to expose patient with BN to different types of 5-HT medicines in an effort to reduce symptoms. The only swift test of the ones reviewed may be the ATD, since it does not require any laboratory analyses afterwards. The mere induced sensitivity would help decide on exposure to 5-HT medicines. And should there be a biochemical laboratory present at the same institution, the paroxetine binding test would further support in treatment decisions.

We did not find any studies where the blood-based 5-HT biomarkers identified in this systematic review where used to make decisions on treatment. Furthermore, we did an exploratory search in PUBMED and could not find any such studies. Should future studies be done to investigate the relation between e.g. a paroxetine binding affinity in BN and the clinical benefit of SSRI in BN, then we would be a step closer to tailored treatment in BN. In fact, recent updates on treatment of BN indicate that both SSRIs and Serotonin-Norephinephrine Reuptake Inhibitors are well tolerated and effectively reduce the bulimic crisis and purging episodes in patients with ED (Capasso et al., 2009), why having biomarkers to select patients for these medicines would be useful.

In terms of specificity and selectivity of the reviewed tests and biomarkers, the identified biomarkers in this systematic review includes a range of both general e.g. ATD and highly specific biomarkers e.g. paroxetine binding for SERT. Overall, the identified biomarkers could help determine if the reduced activity is pre- or post-synaptic, or involving SERT, but several questions remain unanswered such as the relation between a biomarker result and the effect of 5-HT treatment addressing this 5-HT biomarker e.g. decreased paroxeting binding and the effect of SSRI treatment, and the implication of the results from using more general 5-HT system activators, and the inference of the peripheral biomarkers on treatment decision. Furthermore, what these biomarker findings tell of the pathophysiology of the disease beyond that they support a dysregulation of the 5-HT system in BN, is unclear. Using a combination may help decide whether to use SSRI, 5-HT2a or 5-HT1 acting agents, but, as yet, these types of studies has not been done.

4.6. Limitations

There are several potential biases and weaknesses in the reviewed studies, the major being that there is no information on negative studies. This means that potentially negative findings are not known and the representativeness of the published studies cannot completely be evaluated. Furthermore, the design of several studies is open, not placebo controlled, which means that the validity of these particular studies may be less strong. In addition, several studies are small.

As mentioned above, the biomarkers for the 5-HT system identified in this systematic review cover a range of selectivity and specificity from general to highly selective and specific. None of these biomarkers can be used for diagnostic purposes, nor are most of the biomarkers complete with regard to gaining a deeper insight into mechanisms of disease. However, they are helpful to describe changes to the 5-HT system, which may be part of the pathophysiology in BN, and future research may tell whether they have a potential as biomarkers to tailor treatment.

A potential limitation may have been the use of different diagnostic systems for inclusion of patients into the studies. However, the vast majority used either the DSM-III-R or DSM-IV, which have been shown to identify the same patients (Sunday et al., 2001), and the remaining three studies used either DSM-III (Hallman et al., 1990), a structured interview without further specification (Weltzin et al., 1995) or ICD-10 (Podar et al., 2007). The study using ICD-10 was done in a specialist research setting why a high accuracy of diagnosis of BN may be assumed. Excluding all these three studies, or only two, would not change any of the conclusions made.

Regarding influence of comorbid depression on the results, 11 of the 32 included studies had excluded Axis I disorders and in the remaining 21 publications, there was no effect of MDD in 14, an effect in 2 studies (Brewerton et al., 1992) where L-TRP was affected by current MDD, and (Smith et al., 1999) where a larger effect of ATD was seen in BN with a history of independent MDD. Furthermore, it was not assessed in the remaining 5 studies. Influence of comorbid depression on the results thereby seem to be low.

Another potential confounder may be concomitant medication. However, in the majority of studies (82,5%), patients were medication free for several weeks before exposure to the challenge test or the 5-HT biomarker analysis, and in an additional 6% of studies, patients had either just started medication (which for at least the first 7 days seem to have no effect on 5-HT biomarkers (Kasahara et al., 1996)) or only had per request need medication with no 5-HT effect. In an additional 6% of studies, medication was either adjusted for statistically, or only given to very few individuals (less than 10%). In the remaining 2 studies, the effects of medication on 5-HT biomarkers was either investigated (Bruce et al., 2009) and found exaggerated for BN with SSRI (and in the same direction as non-SSRI medicated BN) or compensated for in the statistical analyses (Steiger et al. 2005a,b). Thereby, we believe the effects of medication on the results overall may be disregarded in the included studies.

Finally, it would have been beneficial to have more information on potential covariates e.g. duration of disease, severity, and previous treatment attempts reflecting refractoriness, in the included studies. Furthermore, only adult females were included in the reviewed studies. Albeit BN being uncommon in men, having balanced groups and including potential covariates, would have helped to put the findings in a more natural context.

5. Conclusion

This systematic review finds support that there is a dysregulation in the 5-HT system in BN as evidenced by the results from 5-HT biomarker studies in blood. In studies where personality measures were included, an exaggerated response were found linked to impulsivity and borderline personality features. The main weakness is potential publication bias, exploratory study designs and small sample sizes. From a biomarker point of view, none of the biomarkers used are diagnostic and few were highly selective for certain 5-HT receptors. In a specialized setting, some of the 5-HT tests/biomarkers e.g. ATD and paroxetine binding, could be used as bed-side tests to inform about

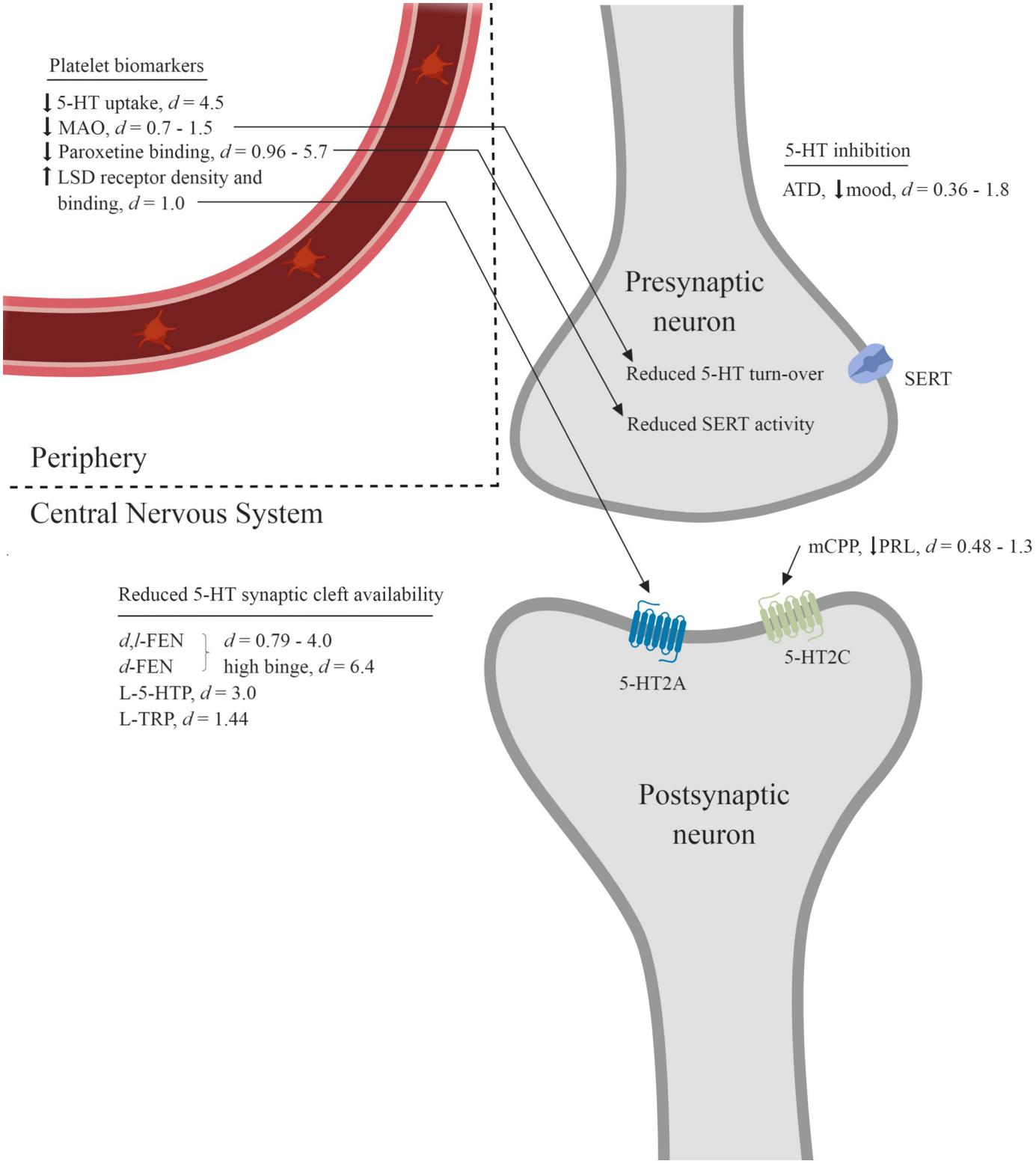

Fig. 2. Illustration of blood biomarker findings of the 5-HT system in BN. The investigated biomarkers appear peripherally or in the central nervous system. Several of the platelet biomarkers reflect neuronal functions, including 5-HT turn-over (MAO activity), SERT activity (paroxetine binding) and 5-HT2A receptor activity (LSD binding). Effect size (Cohen's *d*) calculated for the reviewed studies is stated only for BN patient groups. Please refer to the list of abbreviations.

serotonergic dysregulation to enabel treatment decisions, however, not in general practice. Thereby tailoring treatment is currently only possible at a more general level, e.g supporting the use of post-synaptic 5-HT receptor agonists, and partly also the use of SSRI to enhance 5-HT neurotransmission. In general, current 5-HT biomarker studies in blood remain useful to better understand the pathophysiology of EDs.

Declaration of interest

None

Acknowledgements

We would like to acknowledge the support from the Mental Health Center Ballerup, Capitol Region Denmark.

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