A Transdiagnostic Perspective on the Measurement, Assessment, and Treatment of Cognitive Impairment in Neuropsychiatric Disorders

Zsófia Borbála Dombi

St Cross College

University of Oxford

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Abstract

Cognitive impairment is a core feature of numerous neuropsychiatric disorders yet remains under-addressed in routine clinical care. This PhD thesis adopts a transdiagnostic perspective to explore the measurement, assessment, and treatment of cognitive impairment across diagnostic boundaries. First, brain-derived neurotrophic factor (BDNF) and metabolic syndrome were evaluated for their potential as biomarkers in clinical settings. While both showed associations with cognitive function, neither proved specific or reliable enough for routine use due to measurement limitations and high dependence on external factors. Second, the development and real-world application of the Transdiagnostic Global Impression – Psychopathology scale (TGI-P), a brief tool assessing ten transdiagnostic symptom domains, including cognition was described. In a small inpatient sample, TGI-P scores correlated well with established scales such as the PANSS, particularly for positive and manic symptoms. Cognitive and depressive symptoms were less strongly correlated but still measurable, suggesting the scale's promise for integrating measurement-based care in psychiatry. Third, the cognitive effects of cariprazine, a third-generation antipsychotic was evaluated. A systematic review and meta-analysis indicated the potential of cariprazine as a transdiagnostic treatment for cognitive symptoms. This was further supported by findings from a 12-week observational study in patients with Huntington's and Parkinson's disease, where cariprazine showed promising effects on cognitive and affective symptoms. Overall, this thesis highlights the importance and challenges of addressing cognitive impairment independent from clinical diagnosis. While robust biomarkers are still lacking, practical tools like the TGI-P and emerging treatments like cariprazine may support better recognition and management of cognitive impairment in clinical practice.

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ABBREVIATION	MEANING
AC	acute
ACE	Addenbrooke's Cognitive Examinations
AD	Alzheimer's disease
ADHD	attention deficit hyperactivity disorder
AES	Apathy Evaluation Scale
ASD	autism spectrum disorder
AIWG	antipsychotic-induced weight gain
AP	antipsychotic medication
APA	American Psychiatric Association
ATRQ	Adult Treatment Rating Questionnaire
AVLT	Rey auditory and verbal learning test
BACS	Brief Assessment of Cognition in Schizophrenia
BAI	Beck Anxiety Inventory
BD	bipolar disorder
BDI	Beck Depression Inventory
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BP	blood pressure
BPD	borderline personality disorder
CANTAB	Cambridge Neuropsychological Tests Automated Battery
CBCL	Child Behaviour Checklist
CDT	Clock-Drawing Test
CGI-BP	Clinical Global Impression Bipolar Disorder
CGI-I	Clinical Global Impression Improvement
CGI-S	Clinical Global Impression Severity
CGI-SCH	Clinical Global Impression Schizophrenia
CH-SCHZ	chronic schizophrenia
CI	confidence interval
CLOZ	clozapine
COWAT	Controlled Oral Word Association Test
CPT	Continuous Performance Task
CR	cognitive remediation
CRP	C-reactive protein
CR-TRS	Clozapine-resistant treatment-refractory schizophrenia
CTT	Colour Trails Test
CSF-1	colony stimulating factor
CVLT	California Verbal Learning Test
D	depressive episode
d2-R	d2 Test of Attention Revised
DAST-10	Drug Abuse Screening Test
D-KEFS	Delis-Kaplan Executive Function System for executive functioning
DS	Digit Span forward and backward test
D-SCH	deficit schizophrenia

DSDT	Digit Span Distraction Test
DSM	Diagnostic and Statistical Manual of Mental Disorders
DVT	Digital Vigilance Test
ECNP	Annual Congress of the College of European Neuropsychopharmacology
ELISA	enzyme-linked immunosorbent assay
EPA	European Psychiatric Association
EQ-5D	EuroQol-5 Dimension
EU	euthymic state
FEDN	first-episode drug-naïve patients
FEP	first-episode patients
FGA	First-generation antipsychotics
FTT	Finger tapping test
GAD-7	Generalized Anxiety Disorder-7
GAF	Global Assessment of Functioning
GDS	Geriatric Depression Scale
HAM-D	Hamilton Rating Scale for Depression
HC	healthy controls
HD	Huntington's disease
HDL	high-density lipoprotein
HiTOP	Hierarchical Taxonomy of Psychopathology
HVLT	Hopkins Verbal Learning Test
ICC	Intraclass correlation coefficients
ICD	International Classification of Diseases
ID	Intellectual Disabilities
IDF	International Diabetes Federation
IED	intra/extra-dimensional set shift task
IGT	Iowa Gambling Task
IL-6	interleukin-6
IL-8	interleukin-8
ISMI	Internalized Stigma of Mental Illness Scale
JIS	Joint Interim Statement
KTT	Keep Track Task
LMT	Letter Memory Task
LS	least squares
LSMD	least squares mean difference
M	manic episode
MADRS	Montgomery-Åsberg Depression Rating Scale
MANOVA	Multivariate Analysis of Variance
MBC	measurement-based care
MCCB	Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery
MCI	mild cognitive impairment
MDD	major depressive disorder
MetS	metabolic syndrome
MMN	mismatch negativity
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment

NCEP-ATP III	National Cholesterol Education Program - Adult Treatment Panel III
ND-SCHZ	non-deficit schizophrenia
NF-L	neurofilament light-chain
NLT	Number-Letter Task
NPDs	neuropsychiatric disorders
NS	non-significant
OMC	only metabolically challenging antipsychotic
OMN	only metabolically neutral antipsychotic
PANSS	Positive and Negative Syndrome Scale
PANSS-AD	PANSS Anxiety / Depression factor score
PANSS-DT	PANSS Disorganized thoughts factor score
PANSS-N	PANSS Negative factor score
PANSS-P	PANSS Positive factor score
PANSS-UEH	PANSS Uncontrolled excitement / Hostility factor score
PASAT	Paced Auditory Serial Addition Test
pBDNF	brain-derived neurotrophic factor in the plasma
PD	Parkinson's disease
PHQ-9	Patient Health Questionnaire-9
PMT	Plus-Minus Task
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	post-traumatic stress disorder
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
RAPS	Rater Applied Performance Scale
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	randomized controlled trial
RDoC	Research Domain Criteria
REML	restricted maximum likelihood
RIS	risperidone
ROCFT	Rey–Osterrieth Complex Figure
SAFTEE	Systematic Assessment for Treatment Emergent Events
sBDNF	brain-derived neurotrophic factor in the serum
SCHZ	schizophrenia
SCT	Stroop Colour Test
SCWT	Stroop Colour-Write Test
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SE	standard error
SGA	second-generation antipsychotics
SGT	Semantic Generation Task
SMDs	standardized mean differences
SOCS	Stockings of Cambridge
SSP	Spatial Span
SSRI	selective serotonin reuptake inhibitors
SST	social skills training
SUD	substance use disorder
SUMD	Scale to Assess Unawareness of Mental Disorder

SWM	Spatial Working Memory
TAP	Test for Attentional Performance
TAVEC	The California Verbal Learning Test
TD	tardive dyskinesia
TGA	third-generation antipsychotics
TGI-P	Transdiagnostic Global Impression – Psychopathology
TICS	Telephone Interview for Cognitive Status
TMT	trail making test
TNF	Tumour Necrosis Factor
ToH	Hanoi Towers Test
ToL	Tower of London
TYP	typical antipsychotics
UD	unipolar depression
UHDRS	Unified Huntington's Disease Rating Scale
UKU SERS	UKU Side Effect Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale
USC	usual standard care
VFT	verbal fluency tests
VLMT	Verbal Learning and Memory Test
VWM	Visual Working Memory
WAIS	Wechsler Adult Intelligence Scale
WAIS-R	Wechsler Intelligence Scale for Adults–Revised
WCST	Wisconsin Card Sorting Test
WHODAS 2.0	World Health Organization Disability Assessment Schedule 2.0
WLT	Word Learning Task
WMS	Wechsler Memory Scale
YMRS	Young Mania Rating Scale

1
Background

1.1. Introduction

Neuropsychiatric disorders (NPDs) are a group of complex conditions that are characterized by neurological, psychological, as well as psychiatric symptoms (1). Examples of NPDs are schizophrenia (SCHZ), bipolar disorder (BD), major depressive disorder (MDD), Parkinson's disease (PD) and Huntington's disease (HD), just to name a few (2,3).

SCHZ and BD are major psychiatric disorders affecting around 1% of the general population (4,5). While the latter is characterized by the alternation of mood episodes and behavioural activation, SCHZ is defined by considerable distortions of thinking and perception driven mainly by positive, negative, and cognitive symptoms (6). An intermediate phenotype between the two disorders is schizoaffective disorder which is marked by the concurrent occurrence of both psychotic and affective symptoms manifesting either cross-sectionally or longitudinally (6). Therefore, the three disorders lie on a spectrum which can be referred to as the schizophrenia – bipolar spectrum (**Figure 1**).

Figure 1. The schizophrenia-bipolar spectrum

The figure illustrates how schizophrenia, schizoaffective disorder and bipolar disorder lie on a spectrum, with schizoaffective disorder being an intermediate between the two disorders in terms of symptom composition.

MDD is a mood disorder characterized by symptoms of low and depressed mood, loss of interest in activities, fatigue, thoughts of death or suicide, disturbed sleep or appetite, as well as impaired cognitive function (7). It affects approximately 15-20% of the population (8). Importantly, there are considerable gender differences in prevalence, with women being twice as likely to develop the disorder than men (7). To be diagnosed, symptoms must be present for at least two weeks (6).

PD and HD are both neurodegenerative disorders that primarily affect movement, behaviour, and cognitive function (9,10). The latter is known to be caused by the mutant Huntingtin protein, leading to widespread early neuronal dysfunction and death throughout the brain (10). While the aetiology of PD is still unknown, its pathology involves the formation of α-synuclein positive Lewy bodies targeting the nigrostriatal dopaminergic neurons (10). The mean age of onset for PD is 60-65 years (10). The prevalence of HD is around 10 in 100 000, while in PD it is influenced significantly by age, ranging from 0.3% in those aged 55-64 to 4.3% in those aged 85-94 years (11). In both diseases, psychiatric symptoms such depression, irritability, apathy, anxiety, and psychosis (hallucinations) often precede motor onset (12,13).

The diagnosis of NPDs is based on a set of specific criteria as outlined by the latest editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (6) or the International Classification of Diseases (ICD) (14). It is important to note however, that a diagnosis based on these classification systems does not necessarily mean a distinct set of symptoms that cannot be expressed in any other NPDs (15). Thus, in the past few years, the scientific dialogue has been shifting from the diagnostic view towards a more transdiagnostic understanding of mental and neurological disorders (16,17) to improve treatment decisions and reduce stigma (18).

1.2. Diagnostic vs. transdiagnostic approaches in neuropsychiatry

The diagnostic or categorical approach is primarily characterized by the identification of discrete mental and neurological disorders with clear boundaries (19). This implies that a) a patient either fits into a diagnostic category or not, b) there is no overlap between disorders, and c) disorders are independent from each other (19). Although the diagnostic approach and therefore the continuous hyper-specialization of NPDs has been defining the field in the past decades, there is growing concern regarding the utility of these distinct categories in everyday practice (20,21). Most of the concerns are coming from the fact that that there are high intra-diagnostic differences i.e. heterogeneity within, as well as inter-diagnostic symptom overlaps i.e. synergy and comorbidity between these disorders (20,21). To provide an example, anhedonia is a core component of both MDD as well as negative symptoms of SCHZ (21). Additionally, comorbidities are the rule, not the exception (17); about 40% of individuals with SCHZ have comorbid substance use disorder (22) and nearly half of the patients with MDD also experience some kind of anxiety disorder throughout their lives (23). In terms of heterogeneity within disorders, indeed, patients with the same diagnosis can have vastly different combinations and severity of symptoms (23). For instance, two individuals with a diagnosis of MDD could potentially have only one symptom in common from the nine listed in the DSM (17).

Therefore, while categorical classifications have long guided neuropsychiatric research and practice, their limitations have stimulated interest in complementary dimensional, or transdiagnostic, perspectives on mental ill-health (17,24). Examples of such novel frameworks are the Research Domain Criteria (RDoC) initiative of the US National Institute of Mental Health (25), the Hierarchical Taxonomy of Psychopathology (HiTOP) framework (26), the clinical staging framework, network theories, as well as research on the ‘p factor’

(27,28). The HiTOP views psychopathology as a collection of dimensions organized into increasingly broad, transdiagnostic spectra, therefore proposing an alternative to the traditional mental health classifications (26). The RDoC on the other hand aims to re-define psychiatric research by providing a multidimensional conceptualization of psychiatric disorders with neurobiological roots (25). The ‘p factor’, introduced by Caspi and colleagues in 2014, reflects a general dimension of psychopathology that contributes to the risk of multiple disorders (29). Collectively, these frameworks illustrate how dimensional approaches can enrich and extend categorical systems, offering a more nuanced understanding of shared mechanisms, heterogeneity, and comorbidity, while maintaining the clinical utility of established diagnostic categories. At the same time, limitations must be acknowledged: a systematic review by Fusar-Poli et al. highlighted methodological inconsistencies, low study quality, and limited replication in transdiagnostic research, with nearly one-fifth of studies not meeting true transdiagnostic criteria (30). The authors therefore caution that, despite their promise, transdiagnostic approaches have yet to deliver a paradigm shift in classification or clinical care and may currently represent refinements of existing concepts rather than fundamental innovations (30).

1.3. Cognitive impairment as a transdiagnostic symptom

One symptom domain that is continuously reported to be a transdiagnostic phenomenon is cognitive impairment (15,31). Cognitive impairment refers to deficits of various cognitive functions such as learning and memory, language, perceptual-motor function, executive function, attention and social cognition (32). In a systematic review and meta-analysis reviewing 12 major disorders, all disorders were associated with a broad underperformance across cognitive sub-domains (31), suggesting cognitive impairment to be a core feature of NPDs (33,34). This inspired the term ‘C factor’ which refers to cognitive dysfunction related

to the presence of psychopathology independent from diagnosis (31). Indeed, psychopathology and cognitive impairment seem to be unrelated dimensions that interact with each other; increased severity of psychiatric symptoms has been associated with worse cognition (15,31). Although cognitive impairment represents a core symptom of NPDs (1), the affected neurocognitive domains can slightly vary from disorder to disorder as summarized in **Table 1** (35–44).

Table 1. Cognitive domains & subdomains affected in neuropsychiatric disorders

COGNITIVE DOMAINS & SUBDOMAINS	SCHZ	BD	MDD	PD	HD
Learning & memory *Free recall, cued recall, recognition memory, semantic and autobiographical long-term memory, implicit learning*	X	X	X	X	X
Language *Object naming, word finding, fluency, grammar and syntax, receptive language*	X				X
Perceptual-motor function *Visual perception, visuo-constructional reasoning, perceptual-motor coordination*				X	X
Executive function *Planning, decision-making, working memory, responding to feedback, inhibition, flexibility*	X	X	X	X	X
Attention *Sustained attention, divided attention, selective attention, processing speed*	X	X	X	X	X
Social cognition *Recognition of emotions, theory of mind, insight*	X			X	X

BD, bipolar disorder; HD, Huntington's disease; MDD, major depressive disorder; PD, Parkinson's disease; SCHZ, schizophrenia

1.3.1. Cognitive impairment in disorders on the schizophrenia-bipolar spectrum

Cognitive impairment represents a core feature of disorders on the schizophrenia-bipolar spectrum (33,34). In BD, learning and memory, attention, and executive function is most affected (38,45–47). Importantly, the severity of the dysfunctions in BD is episode-dependent; cognitive functioning is worse during acute manic-depressive episode compared to euthymic states (38,45–47). In schizoaffective disorder, similarly to BD, attention, executive function,

as well as learning and memory is impaired (48). Interestingly however, deficits in cognition have been described as more severe in schizoaffective patients than in patients with BD (49,50). In SCHZ, on the other hand, learning and memory, language, executive function, attention as well as social cognition is described to be affected (36,37). These impairments are found to be stable throughout the disorder without considerable changes or improvements between psychotic episodes – a clear difference compared to BD (51,52).

1.3.2. Cognitive impairment in major depression

The affected cognitive domains in MDD are similar to BD; individuals with depression are reported to have problems in learning and memory, executive functioning, processing speed, attention, and concentration (53). Additionally, patients with MDD also exhibit cognitive biases, including excessive processing of negative stimuli and increased self-focus (54). These deficits contribute significantly to functional disability and reduced quality of life (53).

1.3.3. Cognitive impairment in Huntington's and Parkinson's disease

Although HD is primarily characterized by its motor symptoms, cognitive and behavioural changes are also common, in many cases even preceding the emergence of motor abnormalities (42). These are changes in speed of thinking, recognition of emotions, memory and attention deficits as well as impairments in executive functioning (42). In terms of PD, it is not uncommon to have subjective cognitive decline, mild cognitive impairment (MCI) or even dementia (55). The affected cognitive domains are learning and memory, perceptual-motor function, executive function, attention, and social cognition including theory of mind impairments (56).

1.4. Measurement of cognitive impairment

The utilisation of biomarkers represents a potential method for measuring cognitive impairment (57). A biomarker is a quantifiable characteristic that can be utilized for a variety of purposes like determining risk or supporting the diagnosis of a disorder (58,59). Biomarkers could provide information not only regarding the pathophysiology of a symptom domain but might also contribute to the development of novel treatments and interventions (60,61). There are several types of biomarkers from diagnostic through predictive to susceptibility, as discussed in **Table 2** (62,63). Most examples of utilized diagnostic biomarkers are currently coming from Alzheimer's disease (AD) (measuring amyloid and tau proteins (64)), as no clinically actionable biomarkers are available in other fields of psychiatry yet (63,65).

Table 2. Biomarker types and examples

BIOMARKER	DESCRIPTION	EXAMPLE
Diagnostic	Identifies or confirms the presence of a disorder or symptom of interest or detects a specific disorder subtype.	*P-tau181 in Alzheimer's disease (66)*
Monitoring	Can be measured repeatedly to evaluate the progression of a disorder or symptom domain.	*Plasma t-tau for monitoring the progression of cognitive impairment (67)*
Response	Alters in reaction to exposure to a medical product or an environmental agent.	*Decreased blood BDNF levels may be altered with treatment response in depressed patients (68,69)*
Predictive	Its presence or variation indicates that the individual is more likely to experience a certain outcome from exposure to a medical product or environmental factor.	*MMN may predict cognitive symptoms of schizophrenia (70,71)*
Prognostic	Determines the probability of a clinical event, disorder recurrence or progression.	*CSF-1, IL-8, NF-L may sign conversion to dementia from MCI (72)*
Safety	Signals the probability, presence, or severity of toxicity as an adverse event.	*Striatal function in schizophrenia may predict antipsychotic-induced weight gain (73)*
Susceptibility	Suggests the potential for developing a disorder or symptom domain at a time when there are no clinical signs of the disorder or symptom.	*Polygenic risk scores for PTSD may sign susceptibility (74,75)*

BDNF, brain-derived neurotrophic factor; CSF-1, colony stimulating factor 1; IL-8, Interleukin 8; MCI, mild cognitive impairment; MMN, mismatch negativity; NF-L, neurofilament light-chain, PTSD, post-traumatic stress disorder

Identifying reliable biomarkers for cognitive impairment remains a key objective in neuropsychiatry (76), as such markers could enable more objective and accessible

measurement in routine clinical settings. However, despite growing research efforts, diagnostic, monitoring, and prognostic biomarkers for NPDs remain underdeveloped, largely due to the significant symptomatic and biological heterogeneity across disorders. In response to these limitations, there has been increasing interest in transdiagnostic biomarkers; markers that are not bound to traditional diagnostic categories but instead relate to specific symptom domains across conditions. Given that cognitive impairment is a prevalent and functionally debilitating symptom across NPDs, it represents an ideal target for transdiagnostic biomarker research (76).

Transdiagnostic biomarkers for cognitive impairment may be identified by investigating shared underlying mechanisms across disorders, such as abnormalities in genetics, changes in neurotrophin levels or in peripheral blood markers (77). Among these, several blood-based biomarkers have been repeatedly studied in SCHZ, MDD and BD such as brain-derived neurotrophic factor (BDNF), Tumour Necrosis Factor alpha (TNF-alpha), interleukin 6 (IL-6), C-reactive protein (CRP) and cortisol (76). Of these, the present thesis focuses on BDNF due to its established role in synaptic plasticity and cognition. In addition, metabolic syndrome (MetS), a routinely assessed clinical feature, is explored as both a potential transdiagnostic biomarker and/or a modifiable risk factor linked to cognitive dysfunction.

1.4.1. Brain-derived neurotrophic factor

BDNF is a member of the neurotrophin family of nerve growth factors (78). Neurotrophins are proteins responsible for the regulation of neuronal generation, proliferation, differentiation and survival in both the peripheral and central nervous system (78). BDNF specifically has been indicated to enhance the growth and maintenance of various neuronal systems, ensure neuronal plasticity, modulate neurotransmitter activity and contribute to learning and memory throughout life in the central nervous system (79–82). It also facilitates neuronal plasticity via

the stimulation of dendritic growth, the formation of synapses as well as neurogenesis in brain areas related to memory such as the hippocampus (82,83). In the periphery however, BDNF has immunotropic, epitheliotropic and metabotropic properties as well (84).

Circulating levels of BDNF are proposed to reflect its concentrations in the brain (85–87) as it can cross the blood-brain barrier (88). Indeed, animal research corroborates this assumption, indicating a link between serum BDNF levels and BDNF expression in cortical brain regions (89). Furthermore, Lang et al. reported preliminary evidence suggesting that serum BDNF concentrations may reflect aspects of neuronal plasticity, as indicated by their association with cerebral N-acetyl aspartate levels, a well-established marker of neuronal integrity in the cortex (90). In contrast, a study found that while ketamine administration in rats induced a sustained increase in plasma BDNF, there were no corresponding changes in brain BDNF levels, concluding that peripheral BDNF is not a reliable biomarker of acute central BDNF changes (91). This was also the conclusion of a systematic review, where based on two human studies, no correlation was found between peripheral (plasma or serum) and brain BDNF levels (92). Despite the conflicting evidence, investigations linking peripheral BDNF to neuropsychiatric disorders have become prevalent (93,94).

When examining circulating BDNF levels however, it is essential to take into consideration the type of BDNF measured i.e. plasma (pBDNF) or serum (sBDNF), the circumstances of blood withdrawal, as well as other relevant factors to draw adequate conclusions (93,94). Indeed, there is conflicting evidence regarding whether plasma or serum provides a more accurate reflection of brain levels and therefore which one should be examined as a potential biomarker. For instance, Piccinni et al. reported that clinical improvement in untreated depressed patients was accompanied by normalization of pBDNF after one month of

treatment, whereas sBDNF remained consistently lower than in controls (95). Additionally, Fernandes et al., in a systematic review and meta-analysis in bipolar disorder, concluded that peripheral BDNF, particularly plasma, may serve as a biomarker of disease activity, though not of disease stage (60). In contrast, Bocchio-Chiavetto et al. found decreased sBDNF in major depression patients, while pBDNF levels were less consistently altered (96). Additionally, methodological factors further complicate interpretation. BDNF levels measured in serum are approximately 200 times higher than those in plasma, likely due to the release of BDNF from platelets during coagulation (97). Elfving et al. demonstrated that pre-analytical conditions critically affect pBDNF measurements, but not serum or whole blood, highlighting technical variability in plasma assays (98). In addition, Polyakova et al. assessed storage and handling effects, finding BDNF levels stable in both serum and ethylenediaminetetraacetic acid-plasma for up to six months, but recommending serum due to higher reliability (99). In animal models, Nakamura et al. suggested that plasma, rather than serum, may better reflect circulating BDNF in vivo following mesenchymal stem cell infusion after ischemic stroke, potentially indicating functional viability of transplanted cells (100). Collectively, these findings underscore that both biological and methodological factors influence peripheral BDNF measurements, and that serum and plasma may provide complementary, rather than interchangeable, information regarding central BDNF dynamics.

1.4.1.1. Blood BDNF levels in neuropsychiatric disorders

Aiming to understand the role of BDNF in NPDs, numerous studies examined plasma and serum concentrations compared to healthy controls (HCs). In general, most studies reported both sBDNF (101–113) and pBDNF (102,104,114–116) to be reduced in different SCHZ populations compared to HCs (**Table 3**), however with moderate quality of evidence (117–119). Findings in BD are similar; circulating BDNF levels (serum / serum protein) were found

to be reduced in both manic and depressed but not in euthymic BD patients compared to HCs (**Table 3**) (120–124). Meta-analyses have confirmed these reports (60,125–130). A summary of the results of different meta-analyses examining circulating BDNF levels in patients on the schizophrenia-bipolar spectrum compared to HCs is found in **Table 4**.

Table 3. Mean serum BDNF levels in patients on the schizophrenia-bipolar spectrum

Study	**Participant characteristics**			**BDNF characteristics**		
	Study population	N	Mean age (SD), years	Sample type	Mean concentrations (SD), ng/ml	Difference* p-value
Heitz et al. 2018	At-risk mental state	16	24.6 (5.3)	Serum & plasma	Serum: 19.1 (4.7) Plasma: 0.3 (0.3)	-
Buckley et al. 2007	FEDN	14	21.8 (8.8)	Plasma	0.02 (0.0)	↓ < 0.001
	HC	15	25.3 (5.7)		0.05 (0.0)	
Jindal et al. 2010	FEDN	41	22.4 (5.5)	Serum	9.7 (3.1)	↓ 0.038
	HC	41	22.3 (5.7)		11.7 (3.8)	
Man et al. 2018	FEDN	80	25.7 (8.9)	Serum	8.8 (3.1)	↓ < 0.001
	HC	80	34.9 (8.8)		12.1 (2.2)	
Rizos et al. 2011	FEDN	20	30.8 (10.6)	Serum	9.8 (4.6)	↓ 0.003
	HC	21	34.0 (4.7)		15.3 (6.3)	
Sotiropoulou et al. 2013	FEDN	50	29.8 (8.2)	Serum	12.6 (1.9)	↓ 0.002
	HC	50	31.4 (8.0)		14.5 (2.2)	
Wu et a. 2020	FEDN	354	26.9 (9.4)	Serum	9.1 (3.3)	↓ <0.001
	HC	152	28.3 (7.7)		12.1 (2.2)	
Pillai et al. 2010	FEDN	M: 15 F: 19	M: 34.8 (9.2) F: 29.6 (8.3)	Plasma	8.0 (-)	↓ 0.031
	HC	M: 13 F: 23	M: 39.4 (10.0) F: 37.2 (10.5)		10.0 (-)	
Heitz et al. 2018	FEP	6	29.4 (6.3)	Serum & plasma	Serum: 24.5 (2.4) Plasma: 0.5 (0.5)	-
Chen et al. 2014	SCHZ	151	30.8 (8.3)	Plasma	6.7 (7.0)	↓ <0.001
	HC	126	32.4 (7.5)		17.3 (9.1)	
Niitsu et al. 2011	SCHZ	63	35.9 (8.2)	Serum	15.3 (3.8)	N.S.
	HC	52	34.9 (7.3)		14.6 (4.4)	

Palomino et al. 2006	SCHZ	21	23.7 (-)	Plasma	7.6 (4.3)	-
	BD	14			7.9 (3.6)	
Zhang et al. 2012a	SCHZ	657	48.4 (13.7)	Serum	Val/Val: 9.6 (3.1) Met/Val: 9.5 (2.9) Met/Met: 9.8 (2.7)	↓ <0.001
	HC	445	44.9 (13.6)		Val/Val: 11.8 (2.6) Met/Val: 11.8 (2.7) Met/Met: 11.9 (2.1)	
Zhang et al. 2015	SCHZ	164	48.3 (6.4)	Serum	6.8 (2.4)	↓ <0.001
	HC	50	45.6 (5.1)		9.5 (4.4)	
Carlino et al. 2011	CH-SCHZ	40	48.0 (-)	Serum	25.5 (3.5)	↓ 0.018
	HC	40	44.5 (-)		28.9 (7.5)	
Heitz et al. 2018	CH-SCHZ	11	38.4 (6.6)	Serum & plasma	S: 28.1 (4.0) P: 1.3 (1.1)	-
Huo et al. 2021	CH-SCHZ (elderly)	48	63.8 (2.9)	Serum	8.8 (2.3)	↓ <0.001
	HC (elderly)	45	64.6 (3.2)		12.6 (5.1)	
Wei et al. 2020▪	CH-SCHZ	189	50.7 (8.8)	Serum	M: 7.0 (2.3) F: 5.7 (1.9)	↓ < 0.001
	HC***	60	47.7 (4.5)		M: 9.6 (5.1) F: 9.8 (3.6)	
Xiu et al. 2019▪	CH-SCHZ	232	51.1 (8.8)	Serum	6.9 (2.4)	↓ < 0.001
	HC***	60	47.7 (4.5)		9.7 (4.5)	
Zhang et al. 2012b	CH-SCHZ	251	52.1 (8.3)	Serum	9.9 (2.0)	↓ < 0.001
	HC	206	51.8 (9.2)		11.9 (2.3)	
Cunha et al. 2006	BD I - D	21	40.7 (9.3)	Serum protein	0.15 (-)	↓ 0.027
	BD I - MA	32	40.1 (12.6)		0.14 (-)	↓ 0.019
	BD I - EU	32	40.3 (12.0)		0.19 (-)	N.S.
	HC	32	40.7 (12.1)		0.20 (-)	-
Tramontina et al. 2009	BD I - MA	10	34.9 (13.9)	Serum protein	0.26 (0.1)	↓ 0.013
	HC	10	34.4 (4.0)		0.31 (0.1)	
Mora et al. 2019	BD I/II-MA	32	41.3 (12.9)	Serum	35.0 (10.6)	↓ < 0.0001
	BD I/II- EU	52	47.3 (11.9)		40.0 (9.9)	
	HC	49	48.3 (12.1)		45.9 (13.6)	
Oliveira et al. 2009	BD – Drug free	22	39.8 (12.9)	Serum protein	0.23 (0.1)	↓ < 0.001
	BD – Medicated	22	40.0 (8.9)		0.29 (0.2)	
	HC	22	39.7 (10.8)		0.40 (0.1)	

Rabie et al. 2014	BD I - D	25	32.1 (8.3)	Serum	23.3 (-)	↓ < 0.001
	BD I - MA	25	29.8 (6.7)		19.0 (-)	
	HC	15	30.5 (5.0)		42.2 (-)	

** direction and significance of difference: patients compared to controls: ↓ means decreased in patients vs controls, ↑ means increased in patients vs controls*
**** same control group*
■ *studies are highly similar, likely to be from the same dataset*
BD I, Bipolar I disorder; CH-SCHZ, chronic schizophrenia; D, depressive episode; EU, euthymic state; F, females; FEDN, first-episode drug-naïve; FEP, first-episode psychosis; HC, healthy controls; MA, manic episode; M, males; NS, non-significant; SCHZ, schizophrenia
References: (120)

Table 4. Meta-analyses of circulating BDNF levels in patients on the schizophrenia-bipolar spectrum compared to healthy controls

NPDs	N PATIENTS	N HCs	BDNF TYPE	ES	REFERENCE
SCHZ	1109	956	blood^{+}	-0.46**	Green et al. 2011 (117)
BD	1978	1560	blood^{+}	-0.28*	Munkholm et al. 2016 (126)
	363	273	blood^{+}	-0.60***	Lin 2009 (128)
BD: manic episode	548	565	blood^{+}	-0.81***	Fernandes et al. 2011 (127)
	89	100	plasma	-1.00***	Polyakova et al. 2015 (125)
	100	172	serum	-0.66***	
BD: depressive episode	548	565	blood^{+}	-0.97*	Fernandes et al. 2011 (127)
	46	50	plasma	-1.65**	Polyakova et al. 2015 (125)
	71	111	serum	-0.97**	
BD: euthymic state	426	457	blood^{+}	0.005	

*$^{+}$plasma and serum levels together; *p < 0.05, ** p < 0.01, *** p < 0.001*
BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; ES, effect size; HC, healthy control; NPDs, neuropsychiatric disorders; SCHZ, schizophrenia

At the time of investigation, no studies have been found that reported on circulating BNDF levels in schizoaffective patients. Reduction in sBDNF levels compared to HCs is also described in PD (131–133), HD (134), and MDD, especially in acute episode (125). Nonetheless, in another study, no difference between patients with HD and HCs were detected, and the authors concluded that peripheral BDNF is not an informative nor a reliable biomarker for HD (135).

1.4.1.2. BDNF as a potential biomarker for cognitive impairment

Playing a pivotal role in maintaining optimal function of neurons combined with the fact that it can be readily measured from blood in the periphery, several studies investigated the

associations between peripheral concentrations of BDNF and cognitive impairment. To give a few examples, animal studies reported that social isolation in mice resulted in decreased BDNF levels in several brain areas including the prefrontal cortex, hippocampus, and hypothalamus (136). In terms of the general population, a large trial of 4463 individuals over the age of 65 reported sBDNF levels of 1.5 standard deviation (SD) lower than the age- and sex-adjusted means to be associated with significant risk of MCI (137). Similarly, in a study with participants between ages 57-79, 1.0 SD decrease in pBDNF was found to increase the risk of having a low score on the Mini Mental State Examination (MMSE) by 63% but only in women (138). Nonetheless, no longitudinal association was found between sBDNF and cognition measured by the MMSE in a 10-year study with 912 individuals (139). Furthermore, circulating BDNF levels have been associated with hippocampal volume and spatial memory in older adults, with lower levels of BDNF correlating with smaller volume of the hippocampus and worse performance on neurocognitive tests (140). In contrast, McPhee et al. (2020) reported the overall relationship between cognition and BDNF to be small and nonsignificant with high heterogeneity in healthy adults (141).

Despite the mixed results, BDNF has gained considerable attention as a possible transdiagnostic biomarker for neurocognitive processes in several NPDs (142) such as AD (143), PD (131–133), HD (134), autism spectrum disorder (ASD) (144), or disorders on the schizophrenia-bipolar spectrum (60,126–130,145,146).

Indeed, a study examining patients with AD and MCI compared to HCs showed significant correlation between sBDNF levels and cognitive impairment as measured by the MMSE and found that both age and education significantly influence sBDNF independently from diagnosis (147). Additionally, Ng and colleagues compared pBDNF in individuals with MCI vs HC and reported significantly higher pBDNF in the clinical population (143). According to

their interpretation, the increased peripheral BDNF levels might be a compensatory mechanism in the early stages of MCI (143).

In terms of SCHZ, Ahmed et al. (2015) did not observe significant connection between cognitive impairment and circulating BDNF levels in a meta-analysis based on five SCHZ studies (148). In contrast, another systematic review and meta-analysis by Bora et al. (2019) involving 21 studies with SCHZ patients reported a positive correlation between cognitive impairment and reduced blood BDNF levels, especially in chronic samples (129). One systematic review and meta-analysis evaluated BDNF levels and cognition in BD patients, however only qualitatively and with the conclusion of having some evidence for an association but with high level of uncertainty (149).

Additionally, positive association between sBDNF and cognitive performance measured by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (133) and Montreal Cognitive Assessment (MoCA) (150) was reported in PD. In HD, negative correlation between sBDNF levels and symptoms severity (both motor and cognitive scores) as measured by the Unified Huntington's Disease Rating Scale (UHDRS) was found (134). Nonetheless, in another study by Zuccato et al., no difference between patients with HD and healthy controls were detected and the authors concluded that peripheral BDNF is not an informative nor a reliable biomarker for HD (135). In terms of MDD, reduced cerebrospinal fluid BDNF levels were found to be associated with cognitive impairment in late-life MDD (151). Therefore, to clarify the mixed evidence described here, BDNF will be explored as a potential transdiagnostic biomarker for cognitive impairment in the present thesis.

1.4.2. Metabolic syndrome

MetS is a complex phenomenon defined as the combination of various interrelated risk factors such as raised blood pressure and fasting glucose, reduced high-density lipoprotein (HDL) cholesterol, as well as abdominal obesity (152). The diagnostic criteria by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) for MetS are shown in **Table 5** (153).

Table 5. Diagnostic criteria by NCEP-ATP III for metabolic syndrome

CRITERIA	MEN	WOMEN
Waist circumference	≥ 102 cm	≥ 88 cm
Triglycerides*	≥ 150 mg/dL	≥ 150 mg/dL
HDL cholesterol*	< 40 mg/dL	< 50 mg/dL
Blood pressure*	≥ 130/85 mmHg	≥ 130/85 mmHg
Fasting glucose*	≥ 110 mg/dl	≥ 110 mg/dl
DIAGNOSIS REQUIREMENT	3 out of 5 criteria	
**or on treatment*		

1.4.2.1. Metabolic syndrome in neuropsychiatric disorders

There is a high comorbidity between MetS and NPDs such as SCHZ (between 32.5% and 45.9%) (154,155), BD (between 8 and 56%) (156), and MDD (30.5%) (157). Research on the prevalence of MetS in PD and HD however is scarce. Reported comorbidities might be due to a bidirectional relationship involving many overlapping mechanisms (158), including inflammation (159,160), changes in neurotransmitters (161–163) and altered BDNF levels (164,165).

1.4.2.2. Metabolic syndrome as a potential biomarker for cognitive impairment

There is growing body of evidence linking MetS and its components to cognitive impairment (77,166,167). Significant relationship was detected between cognitive dysfunction and MetS in two meta-analyses in patients with SCHZ (168,169). One showed that those affected by MetS have significantly greater cognitive impairment than those without (169). This might be

explained by the fact that MetS and components can cause structural abnormalities in the brain which can in turn result in cognitive problems (170). Therefore, MetS might also be able to act as a transdiagnostic biomarker and/or modifiable risk factor for cognitive impairment.

1.4.2.3. The relationship between metabolic syndrome, BDNF and cognitive impairment

Although several studies have shown a potential role of BDNF in the regulation of food intake (171) and glucose metabolism (172), findings regarding the relationship between circulating BDNF and MetS are mixed. While some studies reported reduced circulating BDNF concentrations in diabetic and obese populations (173–176), others observed the opposite: higher blood concentrations in subjects with obesity, diabetes and MetS (177–180), or no significant difference between men with or without MetS in sBDNF concentrations (181). Nonetheless, a meta-analysis of 5 case-control studies involving 543 subjects concluded that BDNF levels (both plasma and serum) in patients with MetS are reduced (182). In addition, data from the Baltimore Longitudinal Study of Aging involving around 500 middle-aged and elderly subjects showed pBDNF to be significantly associated with multiple risk factors for MetS such as diastolic blood pressure, total and LDL-cholesterol (in females only), and triglycerides (in males only) (183). Indeed, 4 out of 7 studies in a systematic review reported significantly lower BDNF levels in SCHZ patients with MetS than in those without (184). In contrast, a case-control study found higher sBDNF levels in male patients with SCHZ and MetS compared to those without MetS (185). Another study examining pBDNF and MetS in SCHZ patients treated with clozapine reported no significant difference in pBDNF levels in terms of MetS status (186).

Connecting the dots, Babaei and colleagues were interested in the impact of physical exercise (a 6-week aerobic training program) on sBDNF levels and cognition in middle-aged males with or without MetS (187). According to the results, baseline sBDNF was significantly higher in the MetS group and correlated with waist circumference (187). Interestingly, there was a significant change in sBDNF levels after physical training in both groups, however in the opposite directions; there was an increase in the non-MetS and decrease in the MetS group (187). In terms of cognition, neither short nor mid-term memory changed significantly in the MetS group after training, while a significant increase was detected in healthy individuals (187). The authors concluded that cognitive improvement due to aerobic training might be mediated via BDNF-linked mechanisms in healthy but not in MetS individuals and that in patients with MetS, high sBDNF levels might represent a compensatory response to the disease (187). In contrast, Katuri et al. examined 132 participants between ages 18-40 with and without obesity and found reduced sBDNF levels and a strong association between sBDNF and cognitive impairment as measured by MMSE in obese adults (188). Similarly, sBDNF levels and scores on the RBANS were reported to be significantly lower in patients with type 2 diabetes compared to HC (189).

1.4.2.4. The role of antipsychotics in metabolic syndrome and cognition

It must be noted however that MetS can also develop after prolonged antipsychotic use which has also been linked to cognitive impairment (190). Indeed, a meta-analysis examining MetS in patients with MDD reported that the use of antipsychotics was associated with significantly higher prevalence of MetS in patients (157). Additionally, the prevalence of MetS in psychiatric patients treated with atypical antipsychotic medications is closer to 60% (191–194), with women being three times more affected than men (195,196). In one study, the highest rates of MetS were detected in SCHZ patients treated with clozapine (52%), and the lowest with no medication (20%) (154).

One of the mechanisms through which antipsychotics increase the chance of developing MetS is antipsychotic-induced weight gain (AIWG) (197). Nonetheless, the risk of AIWG is different for each antipsychotic agent; most risk of AIWG is attributed to olanzapine and clozapine, while aripiprazole, cariprazine and lurasidone induces virtually no AIWG (198). It is also worth to note that the greatest degree of weight gain is detected in the first few months of the antipsychotic treatment (199). Being one of the most debilitating side effects of antipsychotic treatment, MetS often leads to medication non-adherence or even termination of treatment that ultimately poses a great risk for relapse (200). Therefore, the thesis also focuses on the role of MetS in cognitive impairment in order to clarify whether it can act as a transdiagnostic biomarker and/or modifiable risk factor.

1.5. Assessment of cognitive impairment

In most medical fields, clinicians rely on measurable biological markers or other objective physiological parameters to evaluate disorder status. For example, in cardiology, measurement of blood pressure is a clear and quantifiable indicator of a person's cardiac function. However, in the field of psychiatry, symptom assessment and disorder monitoring are quite different, given the above-described challenges of finding universally accepted, reliable and easily accessible biomarkers. As a result, clinicians (if aiming to quantify symptom severity and disorder progress) need to rely on the use of standardized and validated rating scales i.e., self-reports from patients and/or observations regarding symptom composition and severity (201,202). This reliance on subjective measures inherently introduces certain difficulties and biases regarding how psychiatric disorders are assessed, nonetheless using measurements in everyday clinical practice is still highly important in achieving better treatment outcomes (203).

1.5.1. The importance of measurement-based care

The continuous administration of validated rating scales in everyday clinical practice, termed as measurement-based care (MBC), provides quantifiable feedback for the clinicians in terms of the effectiveness of the therapeutic interventions (203). MBC involves the following components: a) regular administration of validated symptom rating scales prior to each clinical encounter; b) clinician analysis of the data; c) a shared review of the results between the patient and provider; and d) a collaborative approach to adjusting the treatment plan (204,205). In contrast, usual standard care (USC) in psychiatry follows a non-systematic approach, predominantly relying on the psychiatric interview (anamnesis-based data collection (206)), which includes the patient's medical history, subjective report of symptoms and the clinician's interpretation of this information (204,205).

Importantly, research has shown that the application of MBC is consistently linked to enhanced treatment outcomes (203,207,208). For instance, a study comparing 24 weeks of MBC versus USC in a randomized setting, found a higher proportion of patients achieving remission (73.8% vs. 28.8%) and response to treatment (86.9% vs. 62.7%) in the MBC group compared to the USC group (207). Indeed, findings of a meta-analysis by Zhu et al. indicate significantly greater remission rates, lower endpoint severity, and greater medication adherence in adults with depression where MBC was applied compared to those who received the USC (209). Therefore, it is not surprising that treatment guidelines strongly recommend clinicians to utilize measurement tools when monitoring disorder progress and treatment response (210,211). In addition, in certain countries, healthcare providers integrate the use of validated scales into their funding frameworks as well, thereby encouraging their everyday use (212,213). It is also important to note, that MBC is not a substitute for clinical judgment but rather a tool to enhance and objectively support the assessment and monitoring of a patient’s progress by experienced clinicians (214).

1.5.2. Psychiatric rating scales

The number of validated psychiatric rating scales available to clinicians is extensive and continues to grow, offering a diverse set of methods for assessing and monitoring various mental health conditions. For instance, the American Psychiatric Association (APA) identifies nearly twenty instruments relevant to the treatment of depression alone (215). Psychiatric rating scales can be categorized into four broad groups: those focusing on patients, either through diagnostic criteria or specific populations such as the Positive and Negative Syndrome Scale (PANSS) for SCHZ (216); those targeting symptoms, like the Patient Health Questionnaire-9 (PHQ-9) for symptoms of depression (217); those evaluating treatment outcomes e.g., the UKU Side Effect Rating Scale (UKU SERS) (218); and those assessing functioning and well-being such as the Global Assessment of Functioning (GAF) (219). A summary of these categories is provided in **Table 6**.

Table 6. A summary of psychiatric rating scale categories with description and examples

FOCUS	TYPE	DESCRIPTION	EXAMPLES	REFERENCE
Patient	Disorder-Specific Scales	Designed to assess symptoms specific to a particular psychiatric disorder.	PANSS, YMRS	(216,220)
	Population-Specific Scales	Tailored for specific populations, such as children, adolescents, or the elderly.	CBCL, GDS	(221,222)
Symptoms	Symptom-Specific Scales	Focusing on evaluating individual symptoms or symptom clusters.	PHQ-9, GAD-7	(217,223)
	Cognitive Tests	Assessing cognitive functioning, often in the context of specific psychiatric or neurodegenerative conditions.	MoCA, RBANS, BACS	(224,225)
Treatment	Treatment Response Scales	Evaluating the effectiveness of treatment interventions.	CGI-I, ATRQ	(226–228)
	Adverse Events Scales	Measuring treatment-related adverse effects and their severity.	UKU SERS, SAFTEE	(218,229)
Functioning & well-being	Global Functioning Scales	Assessing overall functioning and the impact of mental health conditions on daily life.	GAF, WHODAS 2.0	(219,230)
	Quality of Life Scales	Evaluating subjective and objective aspects of quality of life in individuals with mental health conditions.	EQ-5D, Q-LES-Q	(231,232)

	Stigma and Insight Scales	Quantifying levels of stigma, self-perception, or insight into mental health conditions.	ISMI, SUMD	(233,234)

Adult Treatment Rating Questionnaire, ATRQ; Child Behaviour Checklist, CBCL; Clinical Global Impression - Improvement, CGI-I; EuroQol-5 Dimension, EQ-5D; Geriatric Depression Scale, GDS; Generalized Anxiety Disorder-7, GAD-7; Global Assessment of Functioning, GAF; Montreal Cognitive Assessment, MoCA; Positive and Negative Syndrome Scale, PANSS; Patient Health Questionnaire-9, PHQ-9; Quality of Life Enjoyment and Satisfaction Questionnaire, Q-LES-Q; Repeatable Battery for the Assessment of Neuropsychological Status, RBANS; Scale to Assess Unawareness of Mental Disorder, SUMD; Systematic Assessment for Treatment Emergent Events, SAFTEE; Internalized Stigma of Mental Illness Scale, ISMI; UKU Side Effect Rating Scale, UKU SERS; World Health Organization Disability Assessment Schedule 2.0, WHODAS 2.0; Young Mania Rating Scale, YMRS

Additionally, psychiatric rating scales can be observer-rated or self-rated, introducing a further layer of complexity (235). While observer-rated scales are more time consuming they are not prone to patient bias (235,236). One of the most popular observer-rated scales are the Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) scales (227,228). These scales were initially developed as brief, simple, non-disease-specific measures to assess the clinician's perspective on a patient's global functioning before and after starting a medication (228). The CGI-S is scored from 1 (normal) to 7 (among the most severely ill), while the CGI-I is rated from 1 (very much improved) to 7 (very much worse) (228). In recent years, there is a rising demand for instruments that maintain the CGI's user-friendliness but offer enhanced inter-rater reliability, leading to the development of more disease-specific and transdiagnostic versions of the scale (203,237,238).

It is also important to note, that, although cognitive impairment may be considered one symptom domain among many others, its assessment differs significantly from the measurement of other symptoms such as depressive or positive symptoms (239). The key distinction lies in the fact that cognition can be quantified through performance-based tests (240), such as the Stroop Colour-Word Interference Test (SCT) (241) or the Clock-Drawing Test (CDT) (242).

1.5.3. The role of rating scales in clinical trials

Validated rating scales are also mandatory in clinical trials for new psychiatric medications, therefore playing an indispensable role in drug development (235). Nonetheless, if administered poorly, they can also contribute to the failure of clinical trials and ultimately, the termination of the development programme (243). To give an example, in a phase II clinical trial, all baseline Hamilton Rating Scale for Depression (HAM-D) interviews were audiotaped, and 25% were randomly selected for blinded evaluation using the Rater Applied Performance Scale (RAPS) (244). When interview quality was not accounted for, no significant difference was found between the treatment and placebo (mean difference = 0.5, P = 0.614) (244). However, when analysis was limited to interviews rated either as "good" or "excellent" on the RAPS, a significant effect favouring the drug emerged (mean difference = 6.8, P = 0.017) (244). Notably, only about 10% of the total sample met the criteria for "good" or "excellent" rating (244).

Additionally, clinical evaluators may intentionally or unintentionally exaggerate ratings prior to randomization to meet eligibility requirements for trial participation, a phenomenon termed as rater bias (243). In contrast, this is not the case with patient self-reports as patients are less likely to do so as they are unaware of the study's entry criteria (243). Indeed, DeBrota et al. found that in a trial requiring a minimum HAM-D score of 20, only 4 of 285 clinician-rated baseline scores fell below this threshold, compared to 110 patient self-reports, which followed a more normal distribution (243,245). In summary, the quality of the clinical interview depends on numerous factors such as the education, training, and clinical experience of clinicians (243). Nonetheless, studies indicate that on average, 24.9% of physicians have no prior experience with the primary outcome measure, and only 38% observe administering the scale before trial participation (243,244). Strikingly, in a study by Engelhardt et al. 45% of

interviews for HAM-D were completed in under 10 minutes, despite Hamilton's recommendation of a minimum 30-minute duration (246).

1.5.4. Real-world use of rating scales

The appropriate use of rating scales, however, is not only problematic in the context of clinical trials; applying MBC in everyday clinical practice is highly difficult (247). A survey conducted in the UK with more than 300 physicians reported that over 80% of the respondents do not routinely administer rating scales when monitoring treatment efficacy in patients with depression (248). The most frequently cited barriers to the use of rating scales included time constraints during clinical visits and insufficient training (248). Furthermore, many elaborated on the fact that disorder-specific rating scales are neither clinically useful nor practical in the fast-paced, high-volume clinical settings (248,249). This might be especially true for performance-based evaluations of cognitive impairment which need additional time and resources that are not necessarily feasible to provide in a routine clinical setting. Indeed, another survey with 500 consultant psychiatrists in the UK reported that clinical change was measured by only 19% of consultants (250).

In addition, in a study by Dowrick et al., general practitioners expressed scepticism about the utility of severity measures, emphasizing the importance of clinical judgment while voicing concerns about the reduction of the human element of visits (251). In contrast, patients generally viewed severity measures for depression positively, valuing them as structured tools that complemented clinical judgment and demonstrated thorough care (251). Similarly, another qualitative study with patients with early psychosis reported that the perspectives of patients on MBC was quite favourable as they perceived it as an instrument to engage patients in shared decision-making and communication (252). To address the challenges of implementing MBC, researchers recommend creating shorter versions of structured scales and

presenting research findings in clinically relevant formats (214,247). A summary of the benefits and barriers of utilizing MBC is found in **Table 7** (214).

Table 7. Benefits and barriers of utilizing measurement-based care

ASPECT OF CARE	BENEFITS	BARRIERS
Objective assessment	• Objective, quantifiable results • Reduction of subjective judgement errors	• Time-consuming process
Comprehensive monitoring	• Assessing broad symptom domains • Enabling longitudinal tracking for better decision-making	• Lack of protocol, resources and standardized training modules for scales
Patient-centredness	• Improved communication • Better therapeutic relationship • More personalized care	• Uncooperativeness, agitation or other barriers from patients towards measurements • Reduction of human-element
Improved outcomes	• Informed decision making • Increased remission rates • Lower risk of relapse • Improved medication adherence	• Perceived as additional burden • Requires additional paperwork and training
Research & resources	• Improved real-world data • Useful for quality assurance	• Limited resources

1.5.5. Assessment of cognitive impairment

The gold standard for assessing cognition in NPDs is the administration of an array of neuropsychological tests (239,253), while there is still continuous research towards finding reliable biomarkers that can aid to the diagnosis and measurement of this symptom domain (58,59). The currently used test batteries typically assess multiple cognitive domains from working memory through visuospatial abilities to attention, however there are considerable differences in terms of sensitivity and specificity, completion time, applicability to different disorders and how much training is needed for administration.

The most popular cognitive scales in NPDs are the Addenbrooke's Cognitive Examinations (ACE) (254), the Brief Assessment of Cognition in Schizophrenia (BACS) (255), the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (256), the MoCA (224), the MMSE (257), and the RBANS (224,225). Characteristics of these test batteries are summarised in **Table 8.** Clinicians can also opt for using individual cognitive tests such as the CDT (242), the SCT

(241) or the Digit Span forward and backward test (DS) (258), if interested in one specific sub-domain. Although these specific tests and test batteries can be used transdiagnostically, their usage is limited due to short visit durations and dependent on other psychiatric measurement batteries; in most of the cases, it is unrealistic to administer both symptom severity and cognitive test batteries at a regular visit. Therefore, the psychiatric scale arsenal currently lacks a tool that has the capacity to assess multiple symptom domains, including cognitive impairment, without increasing the visit time significantly.

Table 8. Characteristics of different cognitive test batteries

	ACE	BACS	MCCB	MoCA	MMSE	RBANS
COGNITIVE DOMAINS						
Learning & memory	X	X	X	X	X	X
Language	X	X	-	X	X	X
Perceptual-motor function	X	X	-	X	-	X
Executive function		X	X	X	X	-
Attention	X	X	X	X	X	X
Social cognition	-	-	X	-	-	-
TIME FOR COMPLETION						
Minutes	15	35	60	10	10-15	30
APPLICABILITY						
Bipolar disorder	X	X	X	X	X	X
Huntington's disease	X	-	-	X	X	X
Major depression	X	X	X	X	/	X
Parkinson's disease	X	-	-	X	/	/
Schizophrenia	X	X	X	X	/	X

X = applicable; / = applicable with limitations; - = not applicable or not used
ACE, Addenbrooke's Cognitive Examinations; BACS, Brief Assessment of Cognition in Schizophrenia; MCCB, MATRICS Consensus Cognitive Battery; MoCA, Montreal Cognitive Assessment; MMSE, Mini Mental State Examination; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status
References: (255,259–280)

1.6. Treatment of cognitive impairment

Due to its transdiagnostic nature and impact on everyday functioning and quality of life (281,282), cognitive impairment represents an important treatment target (15). To date, however, there is no approved medication for the treatment of cognitive dysfunctions in NPDs.

1.6.1. Antipsychotics

The impact of antipsychotic medication (AP) on cognition is highly variable and influenced by multiple factors, including the specific agent and dosage, duration of treatment, co-prescription of other medications (polypharmacy), and characteristics of the study population. In NPDs, some evidence suggests that second-generation (SGAs) or atypical antipsychotics, such as clozapine, olanzapine, risperidone, and quetiapine, may offer modest improvements in cognitive functioning (283). Indeed, risperidone has shown promise in enhancing aspects of executive function in euthymic patients with BD (284). However, findings across studies remain inconsistent. Several investigations have failed to detect significant cognitive differences between typical and atypical antipsychotics in SCHZ (285), and others have reported that higher doses or prolonged use of antipsychotics may exacerbate cognitive symptoms (286–288). Moreover, many SGAs are associated with metabolic side effects, including MetS, which has been independently linked to cognitive decline, as discussed earlier (289). More recently, third-generation antipsychotics (TGAs), characterized by dopamine partial agonism, have emerged as potential candidates for improving cognitive functioning in patients with NPDs (290).

One of the TGAs is cariprazine, a novel D_3-D_2 partial agonist with preferential binding to D_3 receptors (291). Cariprazine is currently approved for the treatment of only SCHZ in Europe, however in the US, it is also approved for BD with manic, depressive and mixed episodes and as add-on treatment for MDD. In a clinical trial, cariprazine was found to be effective in alleviating predominant negative symptoms of SCHZ (292) and post-hoc analyses indicate a potential efficacy in cognitive impairment as well in bipolar mania, bipolar depression, and SCHZ (293). In addition, cariprazine was found to have a positive effect on cognitive functions in patients with early stage of HD in an observational study (294). Importantly, cariprazine is considered to have a metabolically neutral safety profile (295).

1.6.2. Antidepressants

Research is mixed regarding the impact of antidepressants on cognitive functioning (296). Some found that selective serotonin reuptake inhibitors (SSRIs) can improve cognitive symptoms associated with depression, such as memory and attention deficits (297), while other reported gradual worsening (298). Tricyclic antidepressants however are more likely to induce cognitive deficits than SSRIs, mostly due to their cholinergic effect (299,300). Newer agents like vortioxetine have multimodal activity that targets both depressive symptoms and cognitive dysfunction and has been found to improve cognitive performance in patients with depression (301–303). SSRIs and other antidepressants might also help in managing mood symptoms that can exacerbate cognitive decline in PD and HD; however, evidence is limited and contradictory (304,305).

1.6.3. Cognitive enhancers

Cognitive enhancers such as donepezil, rivastigmine, galantamine and memantine are primarily used in the treatment of AD (306). These agents except memantine are cholinesterase inhibitors, while memantine is classified as an NMDA receptor antagonist (306). Studies suggest that anticholinergic medications in patients with SCHZ, BD, PD and HD might worsen cognitive impairment and increase the risk of dementia (307–311).

1.6.4. Mood stabilizers

Evidence regarding the impact of mood stabilizers on cognitive symptoms is mixed. In a meta-analysis of nine randomised controlled trials including 570 patients, mood stabilizers in adolescent bipolar disorder significantly improved emotional processing accuracy, while no significant effects were observed on attention, working memory, or overall cognitive functioning, including with lithium treatment (312). In contrast, in a study by Steen et al.,

serum levels of valproate, lamotrigine, and lithium in bipolar and schizophrenia spectrum patients were examined and according to the results, increasing valproate levels were associated with poorer memory, whereas higher lithium levels appeared to improve memory (313). Similarly, euthymic bipolar disorder patients on long-term valproate treatment showed greater deficits in executive function than those on lithium (314). Finally, based on a network meta-analysis Terao et al. concluded that lithium may be superior to aducanumab for the treatment of cognitive decline, and is more cost-effective (315).

1.6.5. Non-pharmacological treatments

There is evidence to suggest that non-pharmacological interventions such as cognitive remediation (CR) or physical exercise may be effective in improving cognitive impairment in SCHZ, MDD and BD. CR is a behavioural intervention that involves training on mental processes and tasks (316), and it has been shown promise in improving cognitive symptoms in individuals with SCHZ (317), MDD and BD (318). Additionally, physical exercise has been studied as a potential intervention for improving cognitive function in various disorders. Indeed, aerobic exercise has been shown to improve cognitive function in people with SCHZ, with moderate to large effects on several cognitive domains (319,320). Nonetheless, in HD, exercise interventions alone have shown negligible effects on cognition (321). Therefore, finding treatments (both pharmacological and non-pharmacological) is still an important goal in neuropsychiatry.

1.7. Aims & objectives

The aim of the thesis is to comprehensively investigate the *measurement, assessment,* and *treatment* of cognitive impairment as a transdiagnostic symptom domain in NPDs. This includes a special focus on BDNF and MetS as potential biomarkers and/or modifiable risk factors, the development of a novel transdiagnostic scale, and the investigation of cariprazine as a candidate treatment.

1.7.1. Measurement of cognitive impairment

The objective of this section is to investigate potential biomarkers and/or modifiable risk factors that could serve as objective and routine indicators of cognitive impairment in NPDs.

***Chapter 2*:** To evaluate circulating BDNF as a potential transdiagnostic biomarker for cognitive impairment in SCHZ, schizoaffective disorder, and BD patients via a systematic review and meta-analysis.

***Chapter 3*:** To assess MetS and its components as potential transdiagnostic biomarkers and/or modifiable risk factors for cognitive impairment in SCHZ, schizoaffective disorder, and BD patients via a systematic review and database analysis.

1.7.2. Assessment of cognitive impairment

The objective of this section is to develop and test a scale that enables efficient and practical assessment of transdiagnostic symptoms, including cognitive functions in everyday clinical settings.

Chapter 4: To develop a novel transdiagnostic scale for the measurement of overall psychopathology, including cognitive impairment in everyday clinical practice in patients with NPDs.

Chapter 5: To explore the application of the novel scale in real-world clinical settings, including its correlation with traditional cognitive measures, demonstrating its utility in applying measurement-based care.

1.7.3. Treatment of cognitive impairment

The objective of this section is to explore cariprazine, a TGA, as transdiagnostic treatment candidate for cognitive impairment.

Chapter 6: To conduct a systematic review and meta-analysis on the available evidence regarding the potential of cariprazine as a transdiagnostic treatment candidate for cognitive impairment, focusing on its effectiveness and tolerability in NPDs.

Chapter 7: To investigate the impact of cariprazine on cognitive impairment and metabolic syndrome and related parameters in patients on the more neurological end of the NPD spectrum via a 12-week observational study.

2

BDNF as a transdiagnostic biomarker for cognitive impairment in the schizophrenia-bipolar spectrum: A systematic review and meta-analysis

Most of the data in this chapter has been published in the *Frontiers in Psychiatry* "Brain Derived Neurotrophic Factor and Cognitive Dysfunction in the Schizophrenia-Bipolar Spectrum: A Systematic Review and Meta-Analysis" (322).

2.1. Introduction

Cognitive impairment is a pervasive, transdiagnostic symptom domain across multiple psychiatric disorders (31), including those on the schizophrenia – bipolar spectrum (33,34), as detailed in **Chapter 1** of this thesis. Identifying reliable biomarkers for cognition remains an important research goal in neuropsychiatry, as such markers could not only aid in the development of targeted treatments (23,76), but also facilitate more accessible and routine measurement in clinical practice. Although the gold standard for measuring cognitive impairment is the administration of an array of neuropsychological tests (239,253), these tools are often too time-consuming to be integrated easily into everyday clinical settings (248). Therefore, a simpler, blood-based proxy biomarker would be of significant value (58,59), offering clinicians a quick and objective measure of cognitive status without adding burden to their schedules.

The measurement of circulating BDNF (85–87) is a promising strategy for this role. As previously discussed, BDNF plays a key role in neural protection and synaptic plasticity

(323), and has been linked to cognitive impairment in various neuropsychiatric conditions (134,150), including disorders on the schizophrenia – bipolar spectrum (60,126–130). Although BDNF has gained considerable attention as a possible transdiagnostic biomarker for neurocognitive processes in NPDs (142), the evidence supporting its role in cognitive impairment, remains inconclusive (129,148,149,324).

2.1.1. Rationale

Numerous studies have explored the relationship between circulating BDNF levels and cognitive function in patients with disorders on the schizophrenia – bipolar spectrum, but the findings have been inconsistent (129,148,149). Ahmed et al. (2015) did not observe significant connection between cognitive impairment and circulating BDNF levels in a meta-analysis based on five schizophrenia studies (148). In contrast, another systematic review and meta-analysis by Bora et al. (2019) involving 21 studies with schizophrenia patients reported a positive correlation between cognitive impairment and reduced blood BDNF levels, especially in chronic samples (129). One systematic review and meta-analysis evaluated BDNF levels in patients with BD, however the relationship with cognitive impairment was assessed only qualitatively and with the conclusion of having some evidence for an association but with high level of uncertainty (149). Therefore, there is a lack of studies that specifically investigate the relationship between BDNF and cognition in the context of the schizophrenia – bipolar spectrum. Given the challenges with current cognitive assessments and the need for a biomarker that can be easily measured in clinical practice, this study addresses an important gap in the literature.

2.1.2. Aims & objectives

The present systematic review and meta-analysis aims to demonstrate whether plasma or serum BDNF levels can act as a transdiagnostic biomarker for cognitive impairment in patients with disorders on the schizophrenia – bipolar spectrum.

The objectives of the systematic review and meta-analysis are the following:

1. To provide an updated review of circulating BDNF levels in patients with disorders on the schizophrenia – bipolar spectrum compared to healthy controls.
2. To examine the severity of cognitive impairment in patients with disorders on the schizophrenia – bipolar spectrum compared to healthy controls.
3. To evaluate the relationship both qualitatively and quantitatively between circulating BDNF levels and cognitive impairment in patients with disorders on the schizophrenia – bipolar spectrum.

2.2 Methods

2.2.1. Search strategy

An electronic search was performed using the Embase and Medline databases for English language articles published in peer-reviewed journals between 1 January 2000 and 1 June 2021 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (325). The following search terms were utilized: (schizo* OR bipolar) AND (BDNF* OR “Brain Derived Neurotrophic Factor”) AND (“Neurocognit*” OR Cognit*). The bibliography of studies obtained via this search were also manually screened alongside with hand searches in order to identify any additional studies that might be relevant.

2.2.2. Inclusion & exclusion criteria

Studies were included if meeting the following criteria: (a) original research conducted with human subjects; (b) involves subjects with the following diagnoses according to either the DSM-IV/V or the ICD-10: schizophrenia, schizoaffective disorders, bipolar disorder; (c) includes at least one cognitive assessment test or scale; (d) reports enzyme-linked immunosorbent assay (ELISA) measurement of BDNF levels in blood serum or plasma; (e) includes at least one group of healthy participants. Studies were excluded if: (a) they examined only genetic BDNF data; (b) baseline blood BDNF levels were not adequately reported; (c) there was no appropriate comparison conducted between affected subjects and controls in terms of BDNF levels; and (d) cognitive scores were not adequately reported.

2.2.3. Recorded variables and data extraction

From each study, the following data were extracted: first author's name; year of publication; participant characteristics (study population, i.e. diagnosis and sub-diagnosis; sample size; mean age; sex); BDNF characteristics (BDNF sample type; collection time; mean concentrations; direction and significance of difference between BDNF levels in patients vs. controls); cognitive characteristics (domains and sub-domains; scales and tests; direction and significance of difference between patients vs. controls); relationship between BDNF and cognition. Study outcomes were tabulated. In case of duplicate publications, i.e. multiple publications from the same study, unique contributions were evaluated, and only non-overlapping data was included in the analyses.

2.2.4. Statistical analyses

Although the overarching hypothesis was that cognitive impairment represents a transdiagnostic dimension of psychopathology, ultimately, separate analyses for SCHZ and

BD were conducted. This decision was motivated by the substantial methodological heterogeneity already present across studies, including variation in BDNF assay type, patient populations, and cognitive measures. Pooling disorders in this context risked compounding heterogeneity to the extent that true associations would be undetectable. Analysing SCHZ and BD separately therefore provided a more rigorous and interpretable approach, while still allowing comparison across disorders. Moreover, although cognition is transdiagnostic at the symptom level, the biological correlates of cognition, including BDNF, may be differentially influenced by disorder-specific trajectories, treatments, and illness stages. Taken together, this strategy reflects a stepwise approach: by clarifying within-disorder associations, transdiagnostic patterns in future research can be evaluated more meaningfully.

2.2.4.1. Meta-analyses of mean BDNF levels in patients compared to controls

Mean standard deviations, effect sizes, and 95% confidence intervals were calculated in Microsoft Excel. Effect sizes were calculated for differences between baseline BDNF levels of SCHZ and BD patients as well as HCs in ng/ml using means and SDs [(mean BDNF levels in patients – mean BDNF levels in healthy controls) / ((SD patients + SD controls) / 2)]. The effect size measure, Hedge's g was computed since the studies included in the meta-analyses had relatively small sample sizes and Hedge's g is less biased in case when variance equality assumptions are not met.

Altogether, four meta-analyses were planned per patient population: separate analyses for serum and plasma BDNF levels using two different methods, standard univariate and multivariate meta-analytic approaches. Due to the fact that no studies examined schizoaffective patients and data was limited regarding serum BDNF levels in BD patients, six analyses were conducted as visualized in **Figure 2**.

First, three meta-analyses were performed using the 'meta' package in R studio, with standardized mean differences (SMDs) used as effect size measurements. While Z statistic was calculated to determine the significance of the effect sizes, Q statistic was computed to provide an estimation of the degree of homogeneity of the effect sizes of the different studies. The degree of inconsistency was signalized with the I^2 metric (I^2 >75% indicating large heterogeneity, >50% moderate heterogeneity and <50% low heterogeneity). To present the effect sizes of individual studies, a forest plot was created.

Next, to investigate potential sources of heterogeneity, three multivariate meta-analyses using a restricted maximum likelihood (REML) approach were conducted with a pre-specified a set of clinically and demographically relevant moderators. These analyses aimed to assess the impact of moderators on peripheral BDNF levels in SCHZ and BD patients, with serum and plasma BDNF levels analysed separately in the case of SCHZ. SMDs and corresponding variances were extracted from individual studies. The model included random effects to account for between-study variability and overlapping control groups.

Moderators included the stage of disorder (for schizophrenia studies) or episode of disorder (for BD studies), age of patients, as well as sex (only for SCHZ studies). The choice of moderators was guided by prior evidence and availability of data. Stage of disorder in SCHZ and episode of disorder in BD were included because previous studies indicate that peripheral BDNF levels may vary depending on illness stage i.e., first-episode vs. chronic SCHZ (326), and episode status i.e., depressed/manic episode vs. euthymic state (60). Age was examined given consistent reports of age-related decline in circulating BDNF (326), and sex was included in SCHZ analyses because research consistently demonstrates sex differences in circulating BDNF levels across various populations and conditions (327,328). The variance

components and residual heterogeneity were assessed, and tests for moderator significance were performed. Analyses were conducted using the rma.mv function from the 'metafor' package in RStudio (version 1.3.1093).

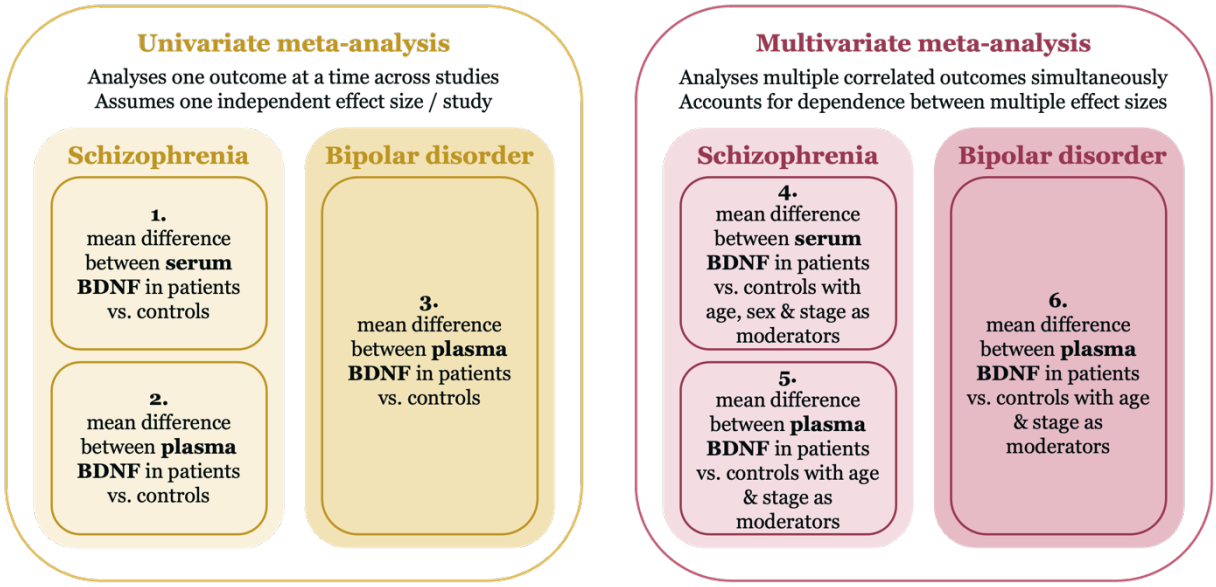

Figure 2. Summary of meta-analyses conducted to examine blood BDNF levels in patients vs. controls on the schizophrenia-bipolar spectrum

The yellow box shows the three univariate meta-analyses conducted; mean difference between serum and plasma BDNF levels in schizophrenia patients compared to controls, and mean difference between plasma BDNF levels in patients with bipolar disorder compared to controls. The red box shows the three multivariate meta-analyses conducted. In patients with schizophrenia, mean difference between serum and plasma BDNF levels compared to healthy controls were calculated with age and stage as moderators. In case of the serum analysis, sex was also included as a moderator. The final multivariate meta-analysis examined patient with bipolar disorder and looked at the mean difference between plasma BDNF in patients compared to controls with age and stage as moderators.

2.2.4.2. Pooled meta-analyses of cognitive impairment in patients compared to controls

In terms of cognitive functioning, two pooled, multivariate random-effects meta-analyses were conducted to evaluate differences between patients (SCHZ and BD separately) and HCs. Standardized mean differences (SMDs) and variances were extracted from each study across the available cognitive tests. Where multiple subtests assessed the same domain, priority was

given to (i) domain or composite scores (e.g., RBANS domain scores rather than the RBANS total) to avoid redundancy and overweighting, and (ii) well-established, gold-standard indices when overlapping measures were available (e.g., Stroop interference rather than word or colour naming alone; WCST perseverative errors rather than total or non-perseverative errors). This approach ensured that each study contributed a balanced and non-redundant representation of cognitive domains. Distinct tests tapping different domains (e.g., fluency, working memory, processing speed) were retained and subsequently pooled into a single study-level effect size. For each study, a random-effects meta-analysis was first conducted to pool SMDs across cognitive tests with moderators such as age, stage of disorder, and sex. These pooled SMDs, standard errors (SEs), and corresponding 95% confidence intervals (CIs) were then entered into the final meta-analysis, with results presented in forest plots. Analyses were conducted using the rma.mv function from the 'metafor' package in RStudio (version 1.3.1093).

2.2.4.3. Pooled meta-analyses of correlation between cognitive impairment and BDNF levels in patients with schizophrenia

Finally, the relationship between circulating BDNF levels and cognitive measures in patients with SCHZ was examined. To do this, first the reported correlation coefficients between BDNF levels (serum and plasma separately) and scores of cognitive tests were pooled within the studies. In case of studies where correlations for specific subgroups (e.g. males and females) were separately reported, the correlations were pooled within the respective subgroups, and each subgroup was treated as a separate entry in the pooled dataset. This approach preserved subgroup-level differences while maintaining consistency in the data structure. Next, the pooled correlations for each study were calculated using Fisher's Z transformation to stabilize variance, followed by back-transformation to correlation coefficients for reporting. Then, a multivariate meta-analysis was conducted using the pooled

correlation coefficients as effect sizes. This approach accounted for within-study dependencies, as multiple subgroups from the same study could be included in the analysis. The REML method was employed to estimate the model parameters, including between-study heterogeneity. In case of SCHZ serum studies, age, stage of disorder, and sex were included as moderators. Regarding SCHZ plasma studies, age, and stage of disorder, were included as moderators. Between-study heterogeneity was quantified using the variance component (τ^2) and I^2 statistics, and residual heterogeneity was assessed using a Q-test. No meta-analyses could have been conducted with BD patients. All statistical analyses were conducted in RStudio using the 'metafor' package. Forest plots were generated using the same package to visualize study-specific and overall effects.

2.3 Results

2.3.1. Search results

A summary of the article selection process for the systematic review and meta-analyses is presented in a PRISMA flow diagram (**Figure 3**). A total of 815 articles were identified via database and hand searches after removing duplicates. Out of these records, 69 were determined as potentially eligible to be included in the review based on the titles and abstracts. After evaluating the articles fully, 33 met the inclusion criteria as in several of them there was no control group present (21 studies) or the reporting on BDNF levels (6 studies) or cognitive impairment (9 studies) was inadequate, or it was a review article (1 study).

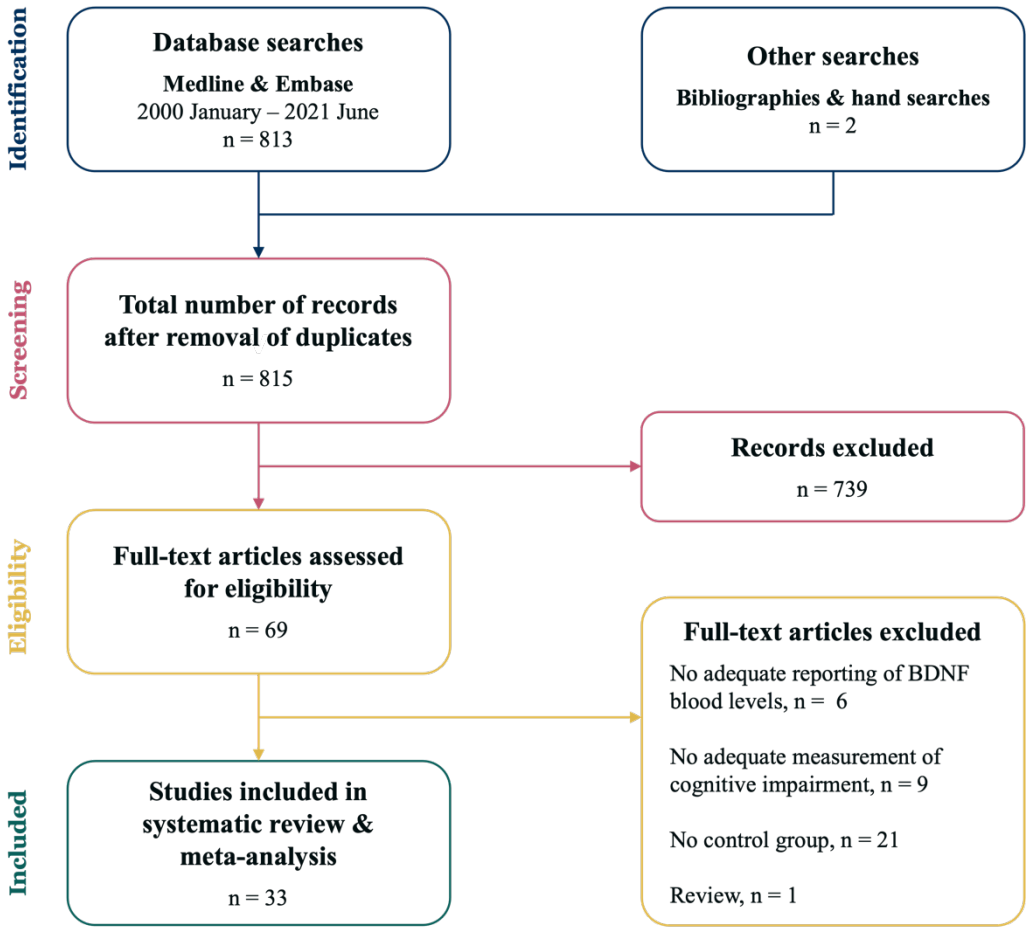

Figure 3. Summary of study identification and selection for the systematic review and meta-analyses of BDNF levels in patients with disorders on the schizophrenia-bipolar spectrum compared to healthy controls

The figure shows the steps of article selection for systematic review and meta-analyses from articles identification, through screening and eligibility to inclusion.

2.3.2. Study characteristics

2.3.2.1. Participant characteristics

Altogether, 4,971 SCHZ and 493 BD patients were compared to 3,461 HCs in the systematic review. No studies involving schizoaffective patients were obtained. Several schizophrenia studies had overlapping populations, especially regarding healthy controls (109,111,113,197,329–332) and potential duplicate publications from the same study were also detected (333,334). In terms of level of evidence, almost all studies (94%) were level "B" according to the rating system by Siwek et al. (2002), meaning that the design of the studies

were of lower quality, mostly being case-control studies, and there were only two randomized controlled trials (level A) (335–337).

The majority of studies (82%) included in the systematic review were focusing on different SCHZ populations; 15% on first-episode drug-naïve patients (FEDN) (105,110,338–340), 9% on first-episode patients (FEP) (341–343), and 39% on chronic schizophrenia patients (CH-SCHZ) (101,111,113,329,330,333,334,337,341,344–346). The rest of the studies (18%) were examining BD II patients (347) or BD I patients in euthymic state (EU) (123,348–350), manic (M) (123) or depressive (D) episodes (351). Study populations, number of patient and healthy controls, mean ages, and % of male patients are tabulated in **Table 9** (summarizing SCHZ studies) and **Table 10** (summarizing BD studies).

Table 9. Schizophrenia-BDNF study characteristics

Study	Participant characteristics				BDNF characteristics				Cognitive characteristics			Relationship between BDNF & cognition
	Study population	N	Mean age (SD), years	% male	Sample type	Collection time	Mean concentrations (SD), ng/ml	Difference* p-value	Domains & subdomains	Scales & tests	Difference* p-value	
Man et al. 2018	FEDN	80	25.7 (8.9)	53.8%	Serum	7.00 -9.00 a.m.	8.8 (3.1)	↓ < 0.001	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.001 except visuospatial domain	No association
	HC	80	34.9 (8.8)	57.5%			12.1 (2.2)					
Qu et al. 2020	FEDN	278	M: 26.3 (8.1) F: 28.1 (9.3)	57.6%	Serum	7.00 -9.00 a.m.	M: 9.1 (3.4) F: 9.2 (3.7)	↓ < 0.001	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.001	No association
	HC	389	M: 27.1 (7.8) F: 29.6 (7.4)	53.5%			M: 12.1 (2.2) F: 11.8 (2.4)					
Wu et a. 2020	FEDN	354	26.9 (9.4)	57.9%	Serum	7.00 -9.00 a.m.	9.1 (3.3)	↓ <0.001	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ <0.05	No association
	HC	152	28.3 (7.7)	52.0%			12.1 (2.2)					
Xiao et al. 2017	FEDN	58	25.0 (5.9)	53.4%	Serum	7.30 – 8.30 a.m.	10.0 (2.8)	↓ <0.01	Verbal fluency, attention, processing speed, working memory, motor speed, executive function	VFT, TMT, DS, SCT	↓ <0.05 except 1 test	Correlation with TMT-part B and VFT-animal in FEDN
	HC	55	26.5 (6.6)	60.0%			12.3 (1.6)					
Xiu et al. 2020	FEDN	327	26.9 (9.4)	48.9%	Serum	7.00 -9.00 a.m.	9.1 (3.6)	↓ <0.001	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.001 except visuospatial domain	No association
	HC	391	27.7 (7.4)	53.2%			11.8 (2.5)					
Ruiz de Azua et al. 2013	FEP	45	24.3 (8.5)	55.6%	Plasma	8.30 a.m.	6.1 (3.7)	↓ 0.002	Memory and learning, executive function, working memory, processing speed, attention, intelligence	TMT, SCT, WAIS-III, WCST etc.	↓ 15 out of 20 tests <0.01	Significant positive association at 6 months with several cognitive domains
	HC	45	24.0 (8.8)				9.2 (4.2)					
Theleritis et al. 2014	FEP	55	30.6 (9.3)	65.6%	Plasma	8.00 a.m.	0.03 (0.01)	NS	Verbal memory, visual memory, executive function,	WMS-III, TMT, WAIS-III	↓ <0.05	No association

	HC	87	32.1 (11.6)	48.7%			0.02 (0.01)		working memory, attention, concentration, processing speed, verbal fluency•			
Yang et al. 2019	FEP	34	22.3 (5.2)	55.9%	Plasma	7.00 -9.00 a.m.	44.4 (18.5)	↓ 0.044	Speed of processing, attention, working memory, verbal learning, visual learning, problem solving, social cognition	MCCB	↓ < 0.05	Significant correlation in visual learning, memory, and processing speed
	CH-SCHZ	31	27.4 (3.7)	51.6%			40.4 (19.5)					
	HC	35	25.6 (1.8)	45.7%			53.0 (20.9)					
Asevedo et al. 2013	SCHZ	30	33.7 (9.9)	83.3%	Plasma	-	0.03 (0.01)	↑ <0.001	Working memory, set shifting, inhibition, executive function, verbal learning, verbal fluency	VWM, KTT, LMT, PMT, NLT, SCT, SGT, ToL, WCST, HVLT, semantic and phonemic fluency	↓ 1 out of 15 <0.001	Correlation to semantic generation task
	HC	27	34.3 (10.6)	48.1%			0.03 (0.01)					
Dong et al. 2021	SCHZ, CLOZ	420	M: 46.8 (9.0) F: 52.7 (9.6)	85.0%	Serum	7.00 -9.00 a.m.	M: 8.0 (3.0) F: 10.6 (2.1)	↓ p < 0.01	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.001	Significant correlation only in male patients and female patients taking typical antipsychotics
	SCHZ, RIS	183	M: 49.1 (11.3) F: 45.0 (14.0)	73.8%			M: 8.0 (2.9) F: 9.3 (1.9)					
	SCHZ, TYP	215	M: 50.0 (9.2) F: 55.6 (9.6)	85.6%			M: 7.4 (3.2) F: 10.7 (2.3)					
	HC	467	M: 42.9 (15.1) F: 46.4 (12.3)	41.3%			M: 11.1 (4.3) F: 11.0 (4.3)					
Niitsu et al. 2011	SCHZ	63	35.9 (8.2)	41.3%	Serum	10.00 – 13.00 a.m.	15.3 (3.8)	NS.	Language, set shifting, attention, processing speed, inhibition, working memory	WAIS-R, VFT, WCST, TMT, SCT, DSDT	↓ 13 out of 14 < 05	Significant correlation in verbal working memory in patients
	HC	52	34.9 (7.3)	48.1%			14.6 (4.4)					
Penadés et al. 2018	SCHZ, CR	35	38.2 (11.9)	65.7%	Serum	-	29.5 (6.9)	↑ 0.004	Global cognition, working memory, processing speed, verbal memory,	DS, WAIS-III, TMT, WMS-III, WCST	-	No significant correlation
	SCHZ, SST	35	41.9 (12.3)	71.4%								

	HC	15	35.7 (11.1)	40.0%			27.7 (7.9)		non-verbal memory, executive function			
Zhang et al. 2012a	SCHZ	657	48.4 (13.7)	88.0%	Serum	7.00 – 9.00 a.m.	Val/Val: 9.6 (3.1) Met/Val: 9.5 (2.9) Met/Met: 9.8 (2.7)	↓ < 0.001	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.05	Significant correlation
	HC	445	44.9 (13.6)	59.1%			Val/Val: 11.8 (2.6) Met/Val: 11.8 (2.7) Met/Met: 11.9 (2.1)					
Zhang et al. 2017	SCHZ	216	28.7 (3.7)	53.2%	Plasma✦	7.00 – 9.00 a.m.	2.6 (0.8)	↓ < 0.01	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ <0.01	-
	HC**	72	26.2 (5.6)	55.6%			4.2 (1.1)					
Zhang et al. 2018	SCHZ	68	27.9 (3.3)	61.7%	Plasma✦	7.00 – 9.00 a.m.	3.4 (2.1)	↓ 0.006	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.01	Increase in plasma levels of BDNF is significantly correlated with the change in the RBANS total scores
	HC**	72	26.2 (5.6)	55.6%			4.2 (1.1)					
Carlino et al. 2011	CH-SCHZ	40	48.0 (-)	50.0%	Serum	8.00 – 9.00 a.m.	25.5 (3.5)	↓ 0.018	Processing speed, attention, executive function, and working memory	TMT, WAIS-III	↓ p < 0.0001	Significant correlation between reduced truncated-BDNF and cognitive performance
	HC	40	44.5 (-)	50.0%			28.9 (7.5)					
Hori et al. 2014	CH-SCHZ	86	35.1 (12.1)	50.0%	Serum	7.00 – 10.00 a.m.	11.8 (7.0)	NS	Decision-making	IGT	↓ < 0.001	Significant negative correlation between BDNF and mean net scores on the trials in the final two blocks
	HC	51	36.7 (9.9)	49.0%			14.1 (7.3)					
Hori et al. 2016	CH-SCHZ	145	33.6 (10.2)	51.0%	Serum	7.00 – 10.00 a.m.	9.6 (6.8)	NS	Verbal memory, working memory, motor function, verbal fluency, attention and processing speed, executive function	BACS	-	Negative correlations between BDNF and scores for verbal memory, attention and processing speed
	HC	51	36.7 (9.9)	49.0%			11.1 (3.9)					

Li et al. 2021	CH-SCHZ	418	46.5 (8.7)	88.8%	Serum	-	7.7 (3.0)	↓ < 0.01	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.01	Significant correlation between RBANS total score and domains in CH and control group
	CH-SCHZ, T2DM	54	52.7 (8.3)	74.1%			9.1 (2.6)					
	HC	225	47.8 (12.5)	44.0%			12.0 (2.3)					
Tang et al. 2019	D-CH	51	50.2 (6.9)	100%	Serum	7.00 – 9.00 a.m.	2.7 (1.9)	↓ < 0.001	Processing speed, attention, executive function, and working memory	DVT, VFT, SCT, WAIS-RC, PASAT	↓ < 0.001	No association
	ND-SCHZ	58	47.9 (6.8)				3.4 (1.7)					
	HC	40	46.8 (10.7)				9.9 (4.0)					
Vinogradov et al. 2009	CH-SCHZ	56	43.9 (9.3)	75.0%	Serum	-	25.3 (10.3)	↓ 0.04	Speed of processing, attention, working memory, verbal learning, visual learning, problem solving, social cognition	MCCB	↓ <.001	No associations
	HC	16	44.5 (11.7)	62.5%			31.3 (9.0)					
Wei et al. 2020▪	CH-SCHZ	189	50.7 (8.8)	66.1%	Serum	7.00 – 9.00 a.m.	M: 7.0 (2.3) F: 5.7 (1.9)	↓ < 0.001	Executive function+	WCST, VFT, SCT	↓ < 0.01	No association
	HC***	60	47.7 (4.5)	73.3%			M: 9.6 (5.1) F: 9.8 (3.6)					
Wu et al. 2015	CH-SCHZ	48	54.6 (5.3)	100%	Serum	7.00 – 9.00 a.m.	10.2 (1.8)	↓ < 0.001	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.001 except visuospatial domain	No association
	CH, TD	35	56.7 (6.6)				9.1 (2.5)					
	HC	52	56.2 (7.0)				11.6 (2.5)					
Xiu et al. 2019▪	CH-SCHZ	232	51.1 (8.8)	66.8%	Serum	8.00 a.m.	6.9 (2.4)	↓ < 0.001	Executive function+	WCST, VFT, SCT	↓ < 0.01	No association
	HC***	60	47.7 (4.5)	73.3%			9.7 (4.5)					
Zhang et al. 2012b▲	CH-SCHZ	251	52.1 (8.3)	74.5%	Serum	7.00 – 9.00 a.m.	9.9 (2.0)	↓ < 0.001	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.001	Significant correlation with immediate memory in patients
	HC	206	51.8 (9.2)	69.4%			11.9 (2.3)					
Zhang et al. 2014▲	CH-SCHZ	248	M: 51.8 (8.6) F: 53.0 (7.3)	74.6%	Serum	7.00 – 9.00 a.m.	M 9.9 (1.9) F: 10.9 (2.0)	↓ < 0.001	Immediate memory, visuospatial, language, attention, delayed memory	RBANS	↓ < 0.001	Significant correlation with RBANS total score in female patients
	HC	188	M: 46.8 (14.1) F: 48.4 (11.0)	52.1%			M: 11.9 (2.3) F: 11.9 (2.5)					

Zhang et al. 2016	CH-SCHZ	92	47.5 (4.4)	81.5%	Serum	7.00 – 9.00 a.m.	6.9 (2.4)	↓ < 0.001	Attention, memory, executive functioning	PANSS Cognitive factor	-	Low BDNF and TNF-a levels together were associated with poor performance on the PANSS cognitive factor
	HC***	60	47.7 (4.5)	73.3%			9.7 (4.5)					

** direction and significance of difference: patients compared to controls: ↓ means decreased in patients vs controls, ↑ means increased in patients vs controls*
*** same control group*
**** same control group*
● *based on 36 schizophrenia patients and 78 healthy controls*
✦ *based on 108 schizophrenia and 47 healthy controls*
★ *based on 47 healthy controls*
■ *studies are highly similar, likely to be from the same dataset*
✢ *based on 107 schizophrenia and 42 healthy controls*
▲ *studies are highly similar, likely to be from the same dataset*
BACS, Brief Assessment of Cognition in Schizophrenia; D-SCH, deficit schizophrenia; DS, digit span tests; DSDT, Digit Span Distraction Test; DVT, Digital Vigilance Test; CH-SCHZ, chronic schizophrenia; CLOZ, clozapine; CR, cognitive remediation; F, females; FEDN, first-episode drug-naïve; FEP, first-episode psychosis; HC, healthy controls; HVLT, Hopkins Verbal Learning Test; IGT, Iowa Gambling Task; KTT, Keep Track Task; LMT, Letter Memory Task; M, males; ND-SCHZ, non-deficit schizophrenia; NLT, Number-Letter Task; NS, non-significant; PASAT, Paced Auditory Serial Addition Test; PMT, Plus-Minus Task; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RIS, risperidone; SCHZ, schizophrenia; SGT, Semantic Generation Task; SST, social skills training; TD, tardive dyskinesia; TMT, Trail Making Test; ToL, Tower of London; TYP, typical antipsychotics; VFT, verbal fluency tests; VWM, Visual Working Memory; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale

Table 10. Bipolar disorder-BDNF study characteristics

Study	Participant characteristics				BDNF characteristics				Cognitive characteristics			Relationship between BDNF & cognition
	Study population	N	Mean age (SD), years	% male	Sample type	Collection time	Mean concentrations (SD), ng/ml	Difference* p-value	Domains & subdomains	Scales & tests	Difference* p-value	
Chang et al. 2018	BD II	228	35.2 (13.3)	46.0%	Plasma	7.00 -9.00 a.m.	13.9 (13.0)	↓ 0.048	Immediate memory delayed memory general memory, working memory	WMS-III	↓ 5 out 8 domains < 0.05	-
	HC	135	31.7 (7.9)	57.8%			16.5 (9.2)					
Chou et al. 2012	BD I - EU	23	36.5 (8.9)	26.1%	Plasma	-	0.3 (0.3)	NS	Attention, memory, executive function	TAP, WMS-III, CTT, WCST	↓ in in sub-items of the facial memory test and WCST < 0.05	No association
	HC	33	37.6 (7.8)	36.4%			0.3 (0.2)					
Dias et al. 2009	BD I - EU	65	37.8 (10.5)	36.9%	Serum level protein	-	0.28 (0.21)	NS	Attention, mental control, perceptual-motor skills, executive function, verbal fluency, verbal abstraction, visuospatial attention, memory	WMS, SDMT, TMT, SCWT, SCT, ToH, COWAT, WAIS-R	↓ 11 out of 16 < 0.05	Significant positive correlation with a test of verbal fluency (COWAT)
	HC	50	33.6 (9.7)	28.0%			0.24 (0.21)					
Rybakowski et al. 2010	BD I - EU	60	52.6 (10.2)	41.7%	Plasma	-	23.6 (13.3)	↓ 0.033	Executive functions, working memory, sustained attention	SSP, SWM, RVP, SOCS	↓ 6 out of 9 < 0.05	-
	HC	60	52.1 (13.6)	41.7%			28.9 (10.9)					
Mora et al. 2019	BD I/II- M	32	41.3 (12.9)	11.6%	Serum	8.00 – 9.00 a.m.	35.0 (10.6)	↓ < 0.0001	Executive functioning, inhibition, attention, processing speed, verbal memory, visual memory	TMT, FAS, WASI-III, WCST, CPT, SCT, CVLT, RCFT	↓ < 0.0001	Significant association with executive functioning and verbal memory
	BD I/II- EU	52	47.3 (11.9)	11.6%			40.0 (9.9)					
	HC	49	48.3 (12.1)	42.9%			45.9 (13.6)					
Dell'Osso et al. 2010	UD	17	46.1 (10.8)	23.5%	Plasma	8.00 – 9.00 a.m.	3.0 (1.8)	↓ < 0.01	Cognitive disturbances factor score	HRSD	-	No association
	BD I - D	16	46.8 (17.7)	50.0%			2.1 (1.3)					
	HC	15	46.9 (9.2)	20.0%			5.4 (2.3)					

** direction and significance of difference: patients compared to controls: ↓ means decreased in patients vs controls, ↑ means increased in patients vs controls*

BD I, Bipolar I disorder; BD II, Bipolar II disorder; CTT, Colour Trails Test; COWAT, Controlled Oral Word Association Test; D, depressive episode; EU, euthymic state; HC, healthy controls; M, manic episode; MCCCB, MATRICS™ Consensus Cognitive Battery; NS, non-significant; UD, unipolar depression; SCT, Stroop Colour Test; SCWT, Stroop Colour-Write Test; SDMT, Symbol Digit Modalities Test; SOCS, Stockings of Cambridge; SSP, Spatial Span; SWM, Spatial Working Memory; TAP, Test for Attentional Performance; TMT, Trail Making Test; ToH, Hanoi Towers Test; WAIS-R, Wechsler Intelligence Scale for Adults–Revised; WCST, Wisconsin Card Sorting Test; WMS-III, Wechsler Memory Scale-III

2.3.2.2. BDNF measurement characteristics

Most studies (70%) examined sBDNF, especially in SCHZ populations (21 out of 27 SCHZ studies). The rest of the studies analysed pBDNF (197,332,341–343,347,348,350–352). There was high consistency in collection time, with most studies (75%) collecting samples between 7.00 – 10.00 a.m. after fasting. Altogether, 21% of the studies failed to provide details on the collection time.

2.3.2.3. Cognitive measurement characteristics

There was high heterogeneity in the analysed cognitive domains and subdomains in the different studies. About one-third of the studies (36%) administered the RBANS scale to assess cognitive functioning, while the others applied an array of different cognitive tests such as the DS, the Trail Making Test (TMT), the SCT, the Wisconsin Card Sorting Test (WCST), or the Wechsler Adult Intelligence and Memory Scales (WAIS, WMS) just to name a few.

2.3.3. Blood BDNF levels in patients compared to controls

2.3.3.1. Systematic review

Most studies (76%) reported statistically significant reduction of circulating BDNF levels in patients with disorders on the schizophrenia – bipolar spectrum compared to HCs (21 SCHZ and 4 BD studies). Only two studies (6%) found patients to have significantly higher levels of circulating BDNF levels than HCs (336,352) both focusing on SCHZ patients, while the rest (18%) failed to detect any significant difference between the two populations (106,329,330,342,348,349).

Consistently, FEDN patients have been reported as having reduced sBDNF levels compared to age-matched controls ($p<0.01$) with mean levels ranging between 8.8 – 12.3 ng/ml (105,110,338–340). Studies focusing on FEP measured pBDNF samples with high

heterogeneity; mean BDNF levels were found to be 0.03 ng/ml in a study by Theleritis et al. (342) and 44.4 ng/ml in a study by Yang et al (341). In CH-SCHZ populations, only sBDNF levels were collected; Tang et al. found chronically ill deficit SCHZ patients to have 2.7 ng/ml mean serum BDNF levels (346), while Carlino et al. reported 25.5 ng/ml mean serum levels for the same population (101). Interestingly, in a comparison of male and female SCHZ patients, Dong et al. found female patients to have significantly higher sBDNF levels compared to men ($p<0.05$), however this difference was not observed in HCs (353). Another study by Zhang et al. reported patients with MetS to have significantly lower levels of pBDNF than those without ($p=0.012$) (197).

In studies focusing on BD patients, analysing pBDNF levels (347,348,350,351) were favoured compared to serum levels (123,349). Nonetheless, the two serum studies were still heterogenous; while Dias et al. reported 0.3 pg/µg mean serum protein concentrations in euthymic BD patients with no significant differences compared to controls (349), Mora et al. found 40.0 ng/ml BDNF in serum in the same patient population with significant differences in comparison to healthy controls (123). The studies reporting on plasma levels found significantly reduced BDNF levels in various BD populations, except one study where the difference between patients in EU state and HCs was not significant (348).

2.3.3.2. Meta-analyses of schizophrenia studies

Altogether, 18 SCHZ studies examining sBDNF levels in patients (N = 3,462) compared to HCs (N = 2,746) were included in the meta-analysis. In studies where the same control group was compared to multiple SCHZ groups, only the largest SCHZ group was included, therefore no overlap between the control groups were present in the model. According to the results, a moderate, but significant reduction of sBDNF levels was detected in SCHZ patients

compared to HCs (SMD = -0.80, 95% CI -1.00 to -0.59) (**Figure 4**). The level of heterogeneity was high (I^2=89%, p<0.01).

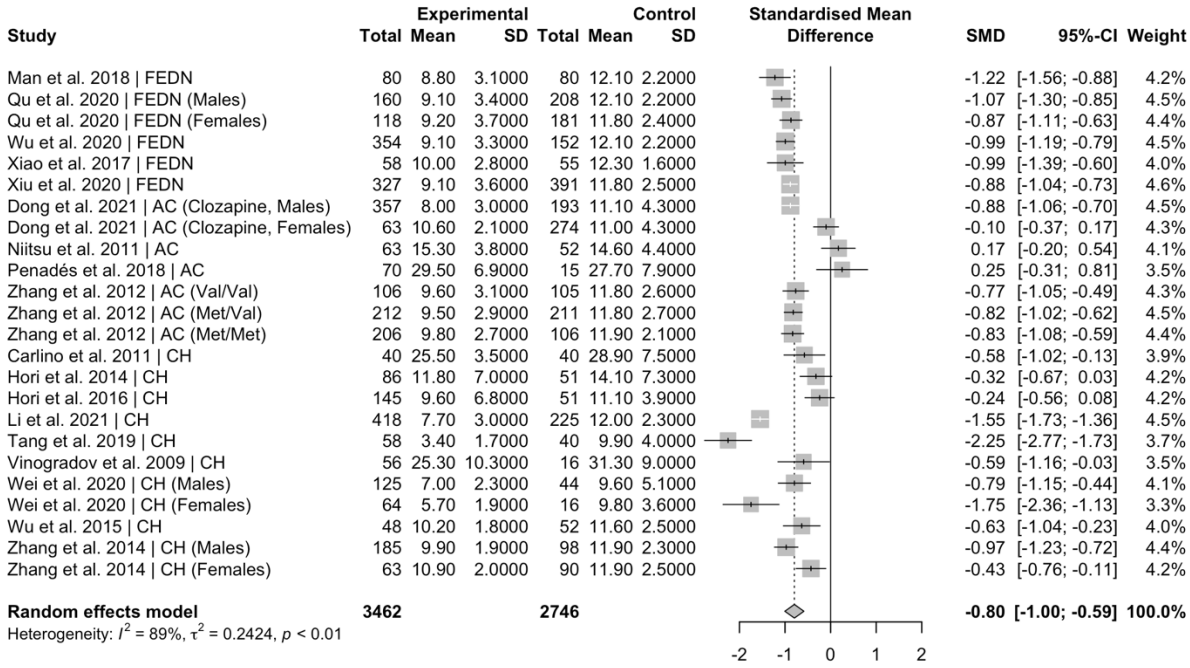

Figure 4. Forest plot of standardized mean differences in serum BDNF levels in patients with schizophrenia compared to healthy controls

Each study population is represented by a square, with the size reflecting its weight in the meta-analysis. Horizontal lines indicate 95% confidence intervals. A negative effect size indicates lower serum BDNF levels in patients with schizophrenia compared to healthy controls. The diamond represents the pooled estimate.

Studies examining pBDNF levels in SCHZ patients were analysed separately. Here, five studies comparing 272 SCHZ patients to 241 HCs were included. Similarly to the serum meta-analysis, studies with the same control group were excluded. A small reduction of pBDNF levels was found in SCHZ patients compared to HCs, however without statistical significance (SMD = -0.35, 95% CI -1.27 to 0.57) (**Figure 5**). The level of heterogeneity was high (I^2=96%, p<0.01).

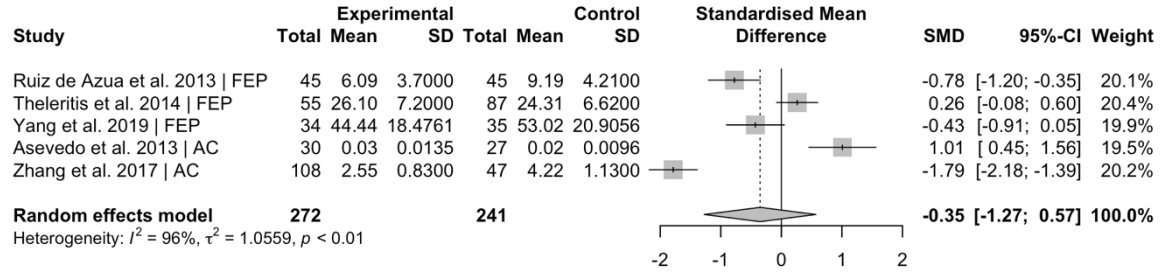

Figure 5. Forest plot of standardized mean differences in plasma BDNF levels in patients with schizophrenia compared to healthy controls

Each study is represented by a square, with the size reflecting its weight in the meta-analysis. Horizontal lines indicate 95% confidence intervals. A negative effect size indicates lower plasma BDNF levels in patients with schizophrenia compared to healthy controls. The diamond represents the pooled estimate.

Then, a multivariate random-effects model was fitted to examine SMDs in sBDNF levels between SCHZ patients and HCs, adjusting for stage of disorder (FEDN, acute (AC), and CH-SCHZ) sex, and age. Because the multivariate random-effects model accounts for overlapping control samples, 20 SCHZ studies examining sBDNF levels were included. Only one study by Zhang et al. from 2012 (334) examining CH-SCHZ patients was excluded since it seemed to be based on the same patient and HC population as the study by Zhang et al. from 2014 (333). As the latter reports on sBDNF levels separately for male and female patients, the decision to include it instead of the Zhang et al. 2012 was decided.

In the model, variance due to between-study heterogeneity was estimated to be 0.36 (SD = 0.60), indicating a moderate level of heterogeneity between studies. The test for residual heterogeneity revealed significant unexplained variability between studies (QE = 225.4, $p < 0.001$), confirming the presence of substantial heterogeneity that is not explained by the included moderators. The test of moderators revealed a significant overall effect (QM = 35.6, $p < 0.0001$), indicating that the moderators included in the model collectively explain a significant portion of the variation in effect sizes.

According to the results, sBDNF levels were found to be reduced in AC-SCHZ patients compared to HCs, however without statistical significance (SMD = -1.25, p = 0.103) (**Table 11**). In addition, sBDNF levels in CH-SCHZ patients were found to be lower than in AC-SCHZ patients (SMD = -0.68), but again, without statistical significance. Although sBDNF levels were found to be lower in the FEDN group compared to the AC group (SMD = -0.34), this difference was also not statistically significant. In addition, male SCHZ patients exhibited significantly lower sBDNF levels compared to female patients, with an SMD of -0.38 ($p < 0.001$). Finally, no association between age and sBDNF levels was found in SCHZ patients (SMD = 0.02). A forest plot summarizing the SMDs with the 95% confidence intervals is displayed in **Figure 6**.

Table 11. Multivariate meta-analysis results for BDNF serum levels in schizophrenia vs. controls

PARAMETER	ESTIMATE	SE	z-value	p-value	95% CI
Intercept	-1.25	0.76	-1.63	0.103	[-2.75, 0.25]
Stage (Chronic)	-0.68	0.37	-1.86	0.063	[-1.40, -0.04]
Stage (First-episode drug naive)	-0.34	0.47	-0.71	0.478	[-1.26, 0.59]
Sex (Males)	-0.38	0.08	-4.58	<0.0001	[-0.55, -0.22]
Sex (Males & Females)	-0.07	0.35	-0.19	0.846	[-0.76, 0.63]
Age	0.02	0.01	1.80	0.072	[-0.00, 0.05]
CI, confidence interval; SE, standard error					

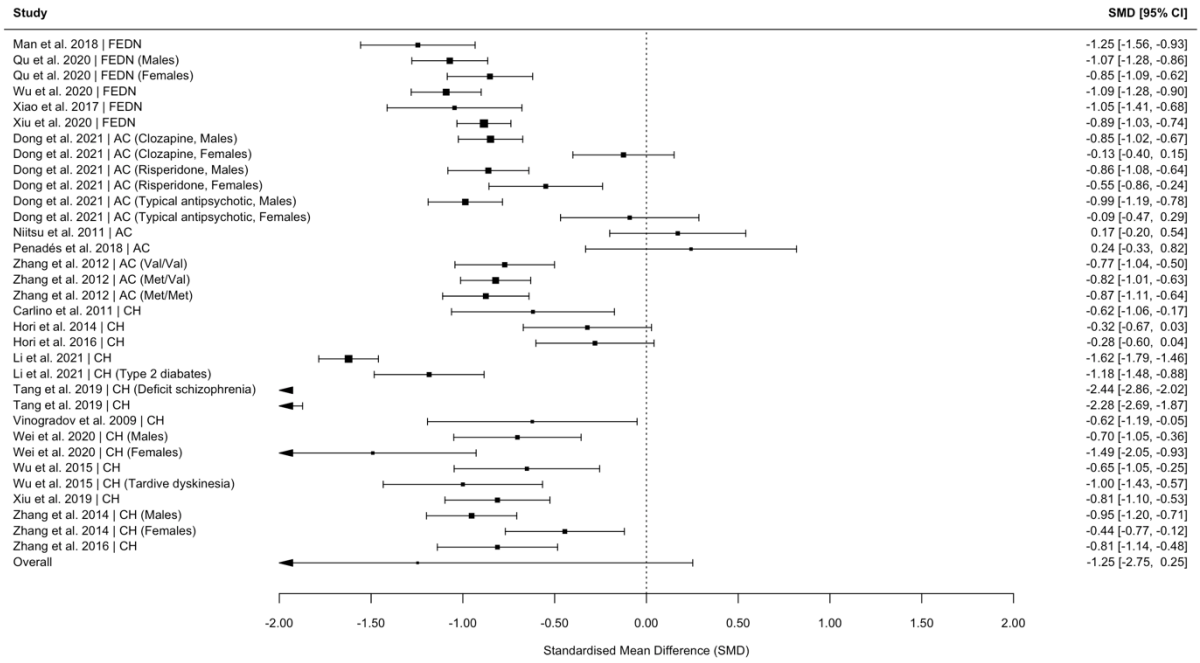

Figure 6. Forest plot displaying the results of a multivariate meta-analysis examining standardized mean differences in serum BDNF levels between patients with schizophrenia and healthy controls

Each study population is represented by a square, with size proportional to its weight in the multivariate model. Horizontal lines indicate 95% confidence intervals. Negative values reflect lower serum BDNF levels in patients compared to controls.

SMDs between SCHZ patients and HCs was also calculated for pBDNF levels using a multivariate random-effects model with two moderators: stage of disorder and age. All six pBDNF studies were included. Similarly to sBDNF studies, moderate level of heterogeneity was detected between studies ($\sigma^2 = 0.34$, SD = 0.58). In addition, substantial residual heterogeneity among the effect sizes was found (QE = 50.75, $p < 0.001$), suggesting that factors not included in the model might be contributing to variability. In addition, he moderators (stage and age) did not significantly explain the heterogeneity (QM = 3.28, p = 0.35).

All in all, pBDNF levels were lower in AC-SCHZ patients compared to HCs (SMD = -0.84, p = 0.126), however this result was not statistically significant (**Table 12**). Furthermore, pBDNF levels in FEP patients were higher than in AC-SCHZ patients (SMD = 0.93), while

CH-SCHZ patients had slightly lower pBDNF levels than acute patients (SMD = -0.20), though neither result was statistically significant. A borderline positive association was observed between age and pBDNF levels in SCHZ patients (SMD = 0.19, p = 0.086)). A forest plot summarizing the SMDs with the 95% CIs is displayed in **Figure 7**.

Table 12. Multivariate meta-analysis results for BDNF plasma levels in schizophrenia vs. controls

PARAMETER	ESTIMATE	SE	z-value	p-value	95% CI
Intercept	-0.84	0.55	-1.52	0.126	[-1.93, 0.24]
Stage (First episode)	0.93	0.85	1.09	0.274	[-0.73, 2.59]
Stage (Chronic)	-0.20	0.76	-0.27	0.787	[-1.68, 1.28]
Age	0.19	0.11	1.71	0.086	[-0.03, 0.42]

CI, confidence interval; SE, standard error

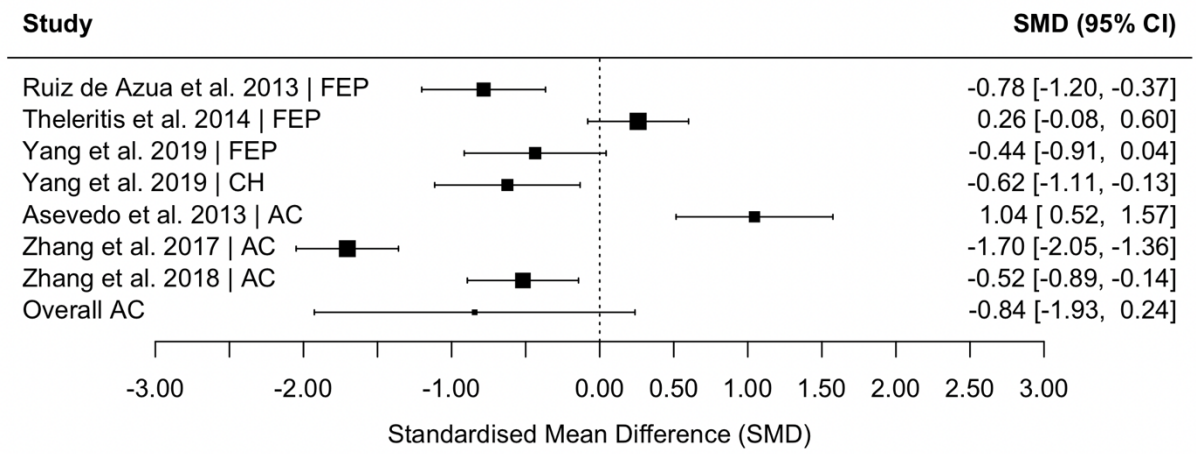

Figure 7. Forest plot displaying the results of a multivariate meta-analysis examining standardized mean differences in plasma BDNF levels between patients with schizophrenia and healthy controls

Each study population is represented by a square, with size proportional to its weight in the multivariate model. Horizontal lines indicate 95% confidence intervals. Negative values reflect lower plasma BDNF levels in patients compared to controls.

2.3.3.3. Meta-analyses of bipolar-disorder studies

Three studies comparing 99 BD patients to 108 HCs in terms of mean pBDNF levels were included in the meta-analysis (348,350,351). Where more patient populations were compared to the same control group, only the largest patient group was included. Since only two studies examined serum (protein) BDNF in BD patients, no meta-analysis could have been conducted

involving sBDNF data. According to the results, medium reduction of pBDNF levels was found in BD patients compared to HCs, however, without statistical significance (SMD = -0.67, 95% CI -1.63 to 0.29) (**Figure 8**). The level of heterogeneity was high (I^2=83%, p<0.01).

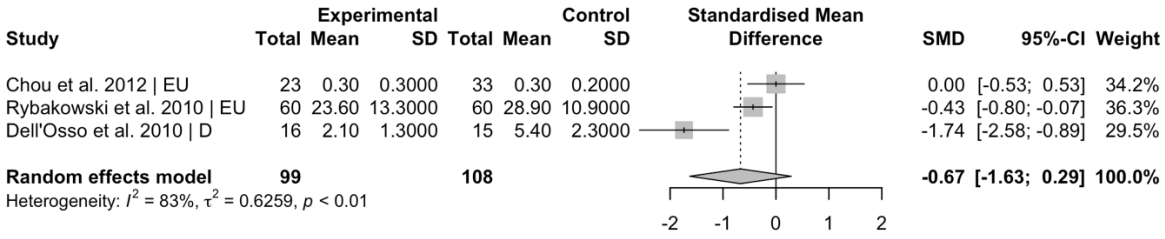

Figure 8. Forest plot of standardized mean differences in plasma BDNF levels in patients with bipolar disorder compared to healthy controls

Each study is represented by a square, with the size reflecting its weight in the meta-analysis. Horizontal lines indicate 95% confidence intervals. A negative effect size indicates lower plasma BDNF levels in patients with bipolar disorder compared to healthy controls. The diamond represents the pooled estimate.

Then, a multivariate analysis involving the same three studies with two moderators (episode of disorder and age) was conducted. The moderator analysis revealed a significant effect of the combined moderators on the outcome (QM = 16.21, p = 0.0003). This indicates that the moderators collectively explain a significant proportion of the variability in effect sizes. All in all, pBDNF levels were found to be reduced (SMD = -0.56) in BD patients in depressive episode compared to HCs, however this result was not statistically significant (p = 0.589) (**Table 13**). Nonetheless, bipolar I disorder might still significantly affect BDNF plasma levels, as patients in the euthymic state were found to display significantly higher levels than patients in depressive episode (SMD = 1.55, p = 0.001). Age, however, did not have a significant effect on pBDNF levels in patients with BD (SMD = -0.03, p = 0.188). A forest plot summarizing the SMDs with the 95% confidence intervals is displayed in **Figure 9**.

Table 13. Multivariate meta-analysis results for BDNF plasma levels in bipolar disorder patients vs. controls

PARAMETER	ESTIMATE	SE	z-value	p-value	95% CI
Intercept	-0.56	1.04	-0.54	0.589	[-2.59, 1.47]
Episode (Euthymic)	1.55	0.40	3.86	0.001	[0.76, 2.34]
Age	-0.03	0.02	-1.32	0.188	[-0.07, 0.01]

CI, confidence interval; SE, standard error

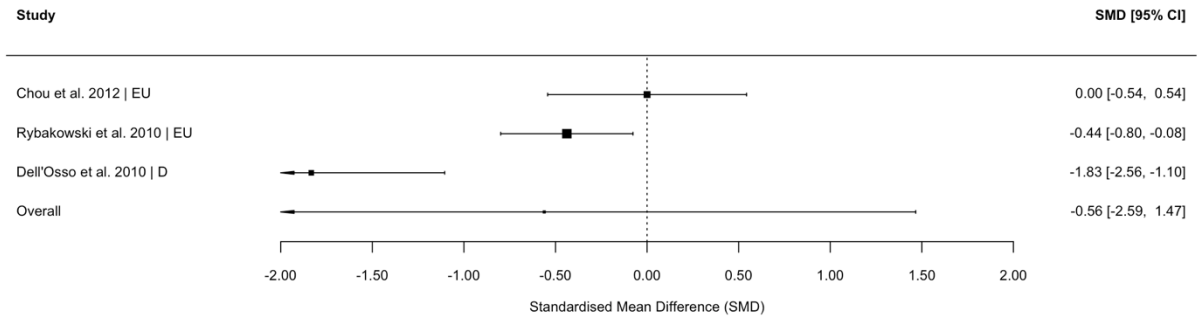

Figure 9. Forest plot displaying the results of a multivariate meta-analysis examining standardized mean differences in plasma BDNF levels between patients with bipolar disorder and healthy controls

Each study is represented by a square, with size proportional to its weight in the multivariate model. Horizontal lines indicate 95% confidence intervals. Negative values reflect lower plasma BDNF levels in patients compared to controls.

2.3.4. Cognitive impairment in patients with disorders on the schizophrenia-bipolar spectrum

2.3.4.1. Systematic review

All studies that reported a comparison between patients and controls in terms of cognitive functioning, found statistically significantly worse performance in patients in some, or in all cognitive tests. Only 12% of the studies did not provide details regarding the differences between patients and controls (330,331,336,351). From the SCHZ studies (27 studies), 44% evaluated cognitive impairment via the RBANS scale and 33% reported significantly worse performance of patients compared to HCs in all five domains of the RBANS scale (immediate memory, visuospatial index, language, attention, delayed memory) (110,112,197,332–334,340,353,354). The rest of the RBANS studies found no significant difference between

patients and controls on the visuospatial index (105,339,345). Similarly, studies comparing cognitive functioning of bipolar disorder patients to healthy controls failed to report statistical difference on tasks requiring visual memory (347), visual sustained attention (350), spatial planning (350), and verbal fluency (349). The remaining studies reported significantly worse performance in patients compared to controls on several different cognitive tests and scales such as the MCCB (337,341), TMT (101,106,123,338,342,343), or the SCT (106,111,123,338,343,344,346).

2.3.4.2. Pooled meta-analysis of schizophrenia studies

Altogether, 20 studies were eligible to be included in the pooled multivariate meta-analysis examining cognitive performance in patients with SCHZ compared to HCs. The rest of the studies were excluded due to the following reasons: no comparison of healthy subjects and patients (110,330,331), missing SDs (101,352), overlapping samples (111,334).

The model included three pre-specified moderators: age, sex, and stage of disorder. Considerable heterogeneity was detected, with a τ^2 value of 1.19 (SE = 0.13), suggesting significant variability across studies beyond sampling error. The I-squared (I^2) statistic was 98.3%, suggesting that the observed variability resulted from between-study heterogeneity rather than chance, and the H^2 value of 57.5 further confirmed this variability. The test for heterogeneity was also significant, providing strong evidence of substantial differences across studies.

The overall pooled SMD was -0.84 ($p < .0001$), indicating that individuals with SCHZ perform significantly worse on cognitive tasks than controls (**Figure 10**). If looking at the individual studies, SMDs varied between -11.57 (333) to 14.58 (345). Considerable differences in SMDs between males and females treated with different APs were noted in a

study by Dong et al. 2021 suggesting a complex interplay of sex, treatment, and illness stage in cognitive outcomes among patients with schizophrenia (353).

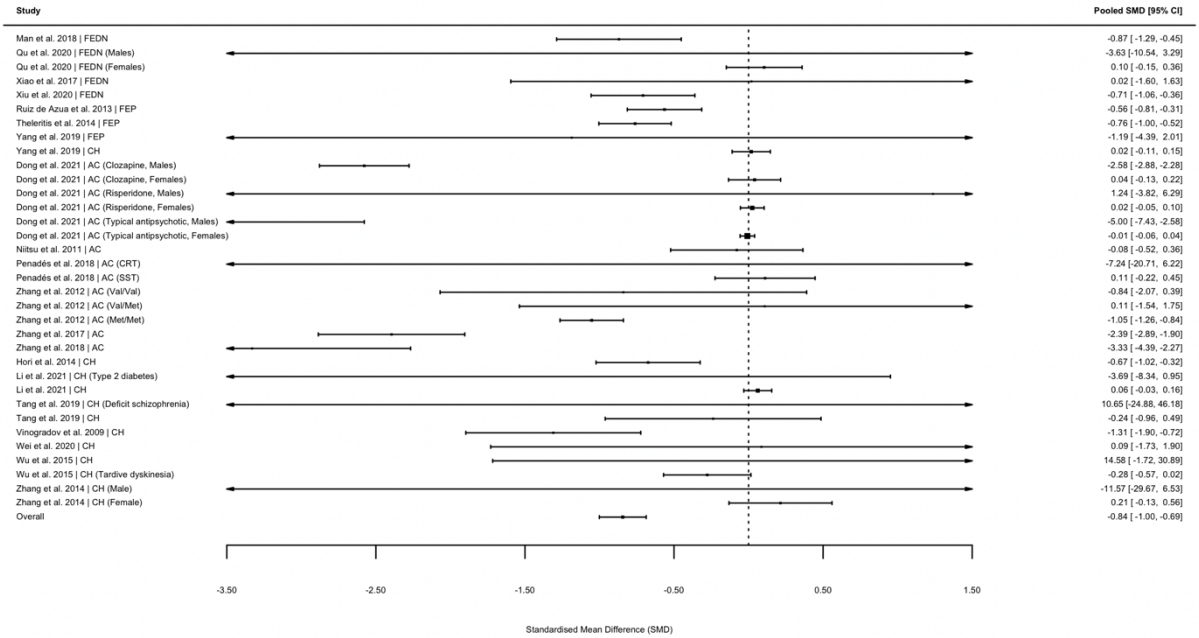

Figure 10. Forest plot displaying the results of a pooled multivariate meta-analysis examining standardized mean differences in cognitive functioning between patients with schizophrenia and healthy controls

Each study population is represented by a square, with size reflecting its weight in the analysis. Horizontal lines indicate 95% confidence intervals. Negative values indicate lower cognitive performance in patients compared to healthy controls.

2.3.4.3. Pooled meta-analysis of bipolar disorder studies

Five studies examining cognitive performance in BD patients compared to HCs were included in the pooled multivariate meta-analysis (**Figure 11**). This analysis incorporated age as a between-study moderator, as most studies did not report cognitive performance separately by sex, and nearly all examined BD patients in a euthymic or manic state.

The estimated amount of total heterogeneity (τ^2) across subgroups was 0.092 (SE = 0.085), indicating some variability beyond sampling error. The I^2 statistic was 76.2%, suggesting that most of the observed variability was due to between-study heterogeneity rather than chance, while H^2 was 4.20, further confirming moderate heterogeneity. The test for heterogeneity was

significant (Q(df = 5) = 26.28, p < 0.0001), indicating substantial differences across subgroups.

The model's pooled effect size estimate was -0.34, indicating a small but statistically significant effect (p = 0.026), suggesting that on average, patients with bipolar disorder performed worse in cognitive tasks compared to controls (**Figure 11**). Looking at the individual studies and subgroups, the study by Mora et al. showed subgroup differences, with euthymic patients demonstrating a moderate deficit (SMD = -0.48, 95% CI: [-0.90, -0.06]) and manic patients showing a larger deficit (SMD = -0.86, 95% CI: [-1.46, -0.27]).

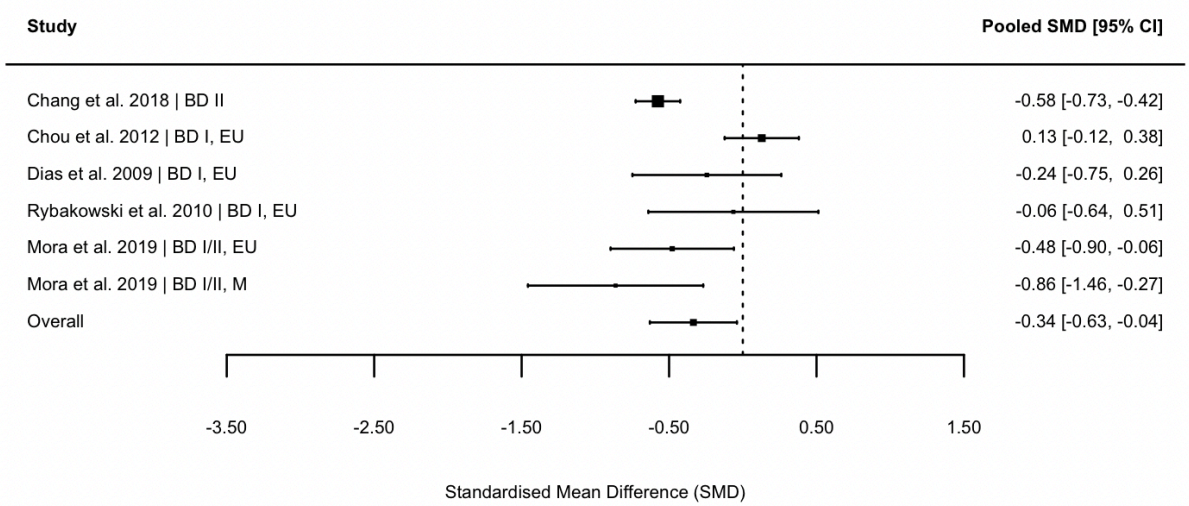

Figure 11. Forest plot displaying the results of a pooled multivariate meta-analysis examining standardized mean differences in cognitive functioning between patients with bipolar disorder and healthy controls

Each study population is represented by a square, with size reflecting its weight in the analysis. Horizontal lines indicate 95% confidence intervals. Negative values indicate lower cognitive performance in patients compared to healthy controls.

2.3.5. Relationship between BDNF levels and cognitive impairment in patients with disorders on the schizophrenia-bipolar spectrum

2.3.5.1. Systematic review

About half of the studies (52%) reported statistically significant association between circulating BDNF levels and cognitive impairment in patients with disorders on the

schizophrenia – bipolar spectrum. The rest of the studies found either no significant association (39%) or did not conduct correlation between these variables (9%). In BD patients, significant correlation was reported between sBDNF levels and verbal fluency (349), verbal memory, and executive functioning (123). No association between pBDNF levels and cognitive impairment was found in the rest of the BD studies (348,351). In SCHZ patients, significant correlation was mentioned between circulating BDNF and working memory (106,338), verbal fluency (338), visual learning and memory (341), processing speed (330,341), attention (330), immediate memory (334) as well as RBANS total score (112,332,354). Interestingly, Dong et al. reported significant correlation between sBDNF and cognitive impairment as measured by RBANS but only in male patients and in female patients taking typical antipsychotics (353). Additionally, Ruiz de Azua et al. found significant positive association after 6 months of the acute episode in FEP patients between pBDNF levels and several cognitive domains (343).

2.3.5.2. Meta-analysis of schizophrenia studies

Altogether, 16 SCHZ studies examining sBDNF and cognitive impairment were included in the pooled meta-analysis investigating the correlations between sBDNF levels and cognitive measures. The estimated amount of total heterogeneity (τ^2) was 0.021 (SE = 0.1441). The I^2 statistic indicated that 84% of the variability across studies was due to heterogeneity rather than sampling error, while the H^2 was estimated at 6.25, reflecting substantial heterogeneity among the included studies.

The pooled correlation coefficient was 0.28 ($p = 0.448$), indicating that the relationship between sBDNF and cognitive impairment is weak and statistically not significant (**Table 14**). Subgroup analysis revealed a significant effect for sex, with male groups showing lower correlations compared to females ($\beta = -0.20$, $p = 0.042$). No significant effects were found for

age or clinical stage, suggesting that these factors did not substantially moderate the association between sBDNF and cognitive measures. Despite the inclusion of moderators, significant residual heterogeneity remained (QE = 139.67, p < 0.0001). Examining individual studies, effect sizes varied widely, with several studies showing significant correlations, while others indicated no meaningful relationship (**Figure 12**).

Table 14. Pooled multivariate meta-analysis results for the correlation between BDNF serum levels and cognitive impairment in schizophrenia patients

PARAMETER	ESTIMATE	SE	z-value	p-value	95% CI
Intercept	0.28	0.37	0.76	0.448	[-0.44, 1.00]
Age	0.00	0.01	0.39	0.700	[-0.01, 0.02]
Stage (Chronic)	0.05	0.12	0.36	0.717	[-0.20, 0.29]
Stage (First episode)	-0.08	0.17	-0.50	0.618	[-0.42, 0.25]
Sex (Males)	-0.20	0.10	-2.04	0.042	[-0.38, -0.07]
Sex (Males & Females)	-0.31	0.20	-1.57	0.116	[-0.70, 0.08]

CI, confidence interval; SE, standard error

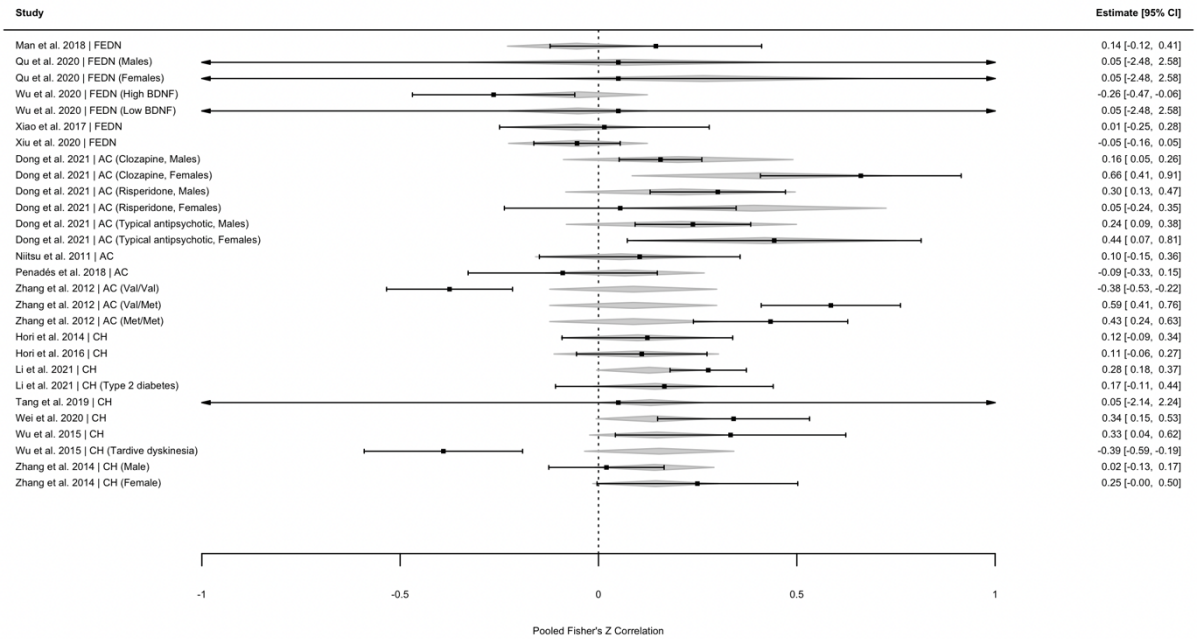

Figure 12. Forest plot displaying the results of a pooled multivariate meta-analysis examining Fisher's Z-transformed correlations between serum BDNF levels and cognitive measures across studies in schizophrenia

Individual cognitive outcomes within each study are represented by squares, with horizontal lines indicating 95% confidence intervals. Diamonds represent pooled correlation estimates for each study, summarizing multiple cognitive outcomes where applicable. Positive values indicate that higher serum BDNF levels are associated with better cognitive performance.

Four studies were included in the pooled meta-analysis investigating the correlations between pBDNF levels and cognitive measures. The estimated amount of total heterogeneity (τ^2) was 0, indicating no heterogeneity across the included studies. The I^2 statistic also reflected the absence of variability due to heterogeneity, emphasizing consistency in the findings across studies. The pooled correlation coefficient was 2.75 (p = 0.027), suggesting a statistically significant but modest relationship between pBDNF levels and cognitive impairment in SCHZ (**Table 15**). No significant effects were found for age or clinical stage, suggesting that neither clinical progression nor age does strongly influence the association between pBDNF and cognitive measures. Residual heterogeneity was not statistically significant (QE= 0.26, p = 0.613), further supporting the homogeneity of the data. Examining individual studies, effect sizes varied, with only two studies showing significant correlations, while others indicated no meaningful relationship (**Figure 13**).

Table 15. Pooled multivariate meta-analysis results for the correlation between BDNF plasma levels and cognitive impairment in schizophrenia patients

PARAMETER	ESTIMATE	SE	z-value	p-value	95% CI
Intercept	2.75	1.24	2.21	0.027	[0.31, 5.18]
Age	-0.07	0.04	-1-92	0.055	[-0.14, 0.00]
Stage (Chronic)	-0.78	1.16	-0.67	0.500	[-3.05, 1.49]
Stage (First episode)	-0.58	0.33	-1.76	0.078	[-1.22, 0.06]

CI, confidence interval; SE, standard error

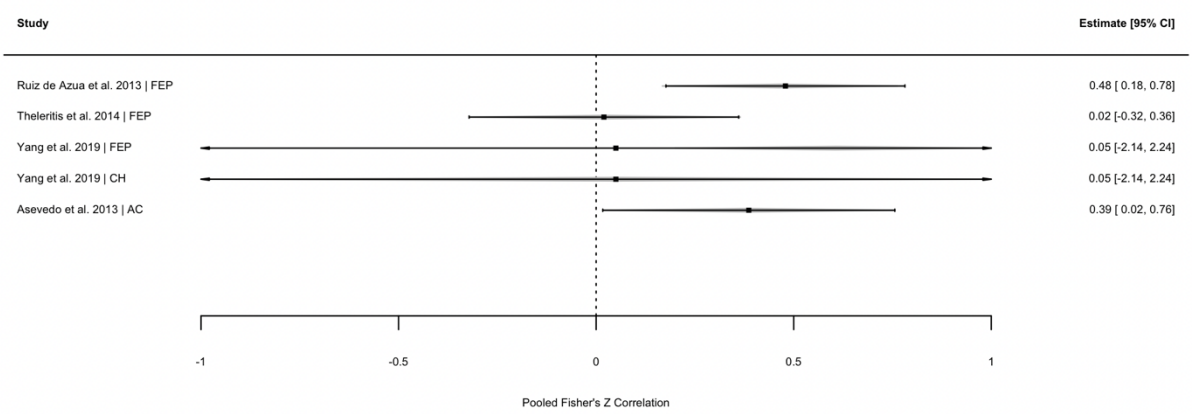

Figure 13. Forest plot displaying the results of a pooled multivariate meta-analysis examining Fisher's Z-transformed correlations between plasma BDNF levels and cognitive measures across studies in schizophrenia

Individual cognitive outcomes within each study are represented by squares, with horizontal lines indicating 95% confidence intervals. Diamonds represent pooled correlation estimates for each study, summarizing multiple cognitive outcomes where applicable. Positive values indicate that higher plasma BDNF levels are associated with better cognitive performance.

Unfortunately, no meta-analysis could be conducted regarding BD patients, as correlation was reported only in three studies, one of them examining plasma (348), the other two examining serum protein and serum BDNF levels (123,349).

2.4 Discussion

2.4.1. Summary of key findings

The present systematic review and meta-analysis aimed to evaluate whether circulating BDNF can act as a transdiagnostic biomarker for cognitive impairment in patients with disorders on the schizophrenia – bipolar spectrum by addressing the following objectives: a) to provide an updated review of circulating BDNF levels in patients with disorders on the schizophrenia – bipolar spectrum compared to healthy controls, b) to examine the severity of cognitive impairment in this patient population, and c) to evaluate the relationship between circulating BDNF and cognitive impairment in these patients.

The meta-analyses revealed significant reduction of sBDNF levels in SCHZ patients compared to HCs, however after adjusting for age, stage of disorder and sex, this result did not remain significant. In addition, further analysis showed that male SCHZ patients exhibited significantly lower sBDNF levels than female patients. Plasma BDNF levels were also found to be decreased compared to HCs in both SCHZ and BD patients but without statistical significance. Importantly, BD patients in euthymic state were found to have significantly higher levels of pBDNF than patients in depressive state.

The pooled analyses of cognitive performance indicated that both individuals with SCHZ and BD performed significantly worse on cognitive tasks than HCs. The severity of cognitive impairment however was found to be higher in patients with SCHZ. Finally, significant positive correlation was detected between pBDNF levels and cognitive impairment in patients with SCHZ. This was however not true for sBDNF levels in the same population.

2.4.2. Comparison of results to previous findings

The present results are somewhat consistent with the findings of previous reviews and meta-analyses. In terms of circulating BDNF levels, many studies reported serum and plasma BDNF to be reduced in patients with SCHZ compared to HCs (117,355). For instance, Green et al. found significant reduction of circulating BDNF levels in schizophrenia patients (Hedges g = -0.46, 95% $p < 0.004$) based on 16 studies (117), while the SMD in a meta-analysis by Zou et al. was -0.61 for sBDNF (95% CI: − 0.69, − 0.52) and -0.55 for pBDNF (95% CI: − 0.71, − 0.40) based on 25 studies (355). Although the present study also reports a reduction of both serum and plasma BDNF in SCHZ patients compared to HCs, the results were not statistically significant when moderators such as age or stage of disorders were included in the model. In addition, Green et al. did not find significant difference between

male and female schizophrenia patients in terms of circulating BDNF whereas this was one of the main results of the present analysis (117). In terms of BD, significantly higher pBDNF levels were detected in euthymic patients compared to patients in depressive state which is in line with previous studies where no significant difference between euthymic BD patients and HCs were found (125,127,128). This again suggests that BDNF alterations in BD may be state-dependent, fluctuating with mood episodes (127).

Most meta-analyses, including the present one, report a small, but statistically significant, positive correlation between (plasma) BDNF levels and cognitive performance in SCHZ (129,148). This suggests that higher BDNF levels are generally associated with better cognitive function, but the effect is subtle. For instance, Bora et al. found significant associations between BDNF and verbal memory, working memory, processing speed, and verbal fluency (129), while Amed et al. detected significant correlations only for reasoning and problem-solving abilities (148).

2.4.3. The role of BDNF as a biomarker in schizophrenia and bipolar disorder

One of the most important aspects of a biomarker is reliability and consistency: if measured, it should provide a stable and reproducible signal that consistently reflects the biological process it is intended to serve as a proxy for. With peripheral BDNF, this criterion is not fulfilled. One of the key findings of the present work is that serum and plasma BDNF are not interchangeable. Previous meta-analyses sometimes combined serum and plasma measures or did not distinguish between them, implicitly treating them as equivalent. However, the present results show that they yield different patterns, underscoring that they capture distinct biological information.

Specifically, in schizophrenia, sBDNF appeared significantly reduced compared to healthy controls (without moderators), whereas p BDNF did not show a statistically significant reduction. At the same time, only pBDNF — not sBDNF — correlated positively with cognitive impairment in this population. Furthermore, sex effects emerged only for sBDNF, with significantly lower levels in male patients, while in BD, stage effects were observed for pBDNF, where euthymic patients had significantly higher levels compared to those in a depressive state. These discrepancies highlight that serum and plasma BDNF cannot be treated as a single, unified measure. In addition, both sBDNF and pBDNF are strongly influenced by external factors such as sex, age, or stage of disorder, further reducing their stability. Taken together, the inconsistent findings, as well as their susceptibility to external influences, undermine their reliability and clinical utility as valid transdiagnostic biomarkers for cognitive impairment.

2.4.4. Limitations

The present study is not without limitations. First of all, the included studies exhibited substantial heterogeneity regarding BDNF measurement protocols, study populations as well as cognitive assessment methods, which complicated the synthesis and interpretation of results greatly. Second, many studies involved overlapping populations, and even though it was addressed in the model, it could have still potentially introduced bias. In addition, the inclusion and exclusion criteria focused on studies that measured both BDNF levels and cognitive impairments in SCHZ and BD. While this ensured relevance to the research question, it resulted in the exclusion of other relevant studies, potentially affecting the generalizability and significance of the findings. The meta-analytic approach also has inherent limitations. Causal relationships could not be established, and residual heterogeneity persisted despite incorporating moderators into the models. Furthermore, limited data in some areas

precluded specific analyses, such as those examining sBDNF levels or BDNF-cognition correlations in BD patients. In terms of the pooled meta-analysis of cognitive impairment, a limitation is that prioritizing domain scores (e.g., RBANS domains) over global totals, and selecting gold-standard indices (e.g., Stroop interference, WCST perseverative errors), may have excluded potentially informative total or subtest-level data. While this strategy reduced redundancy and minimized overweighting studies with many correlated measures, it also limited the ability to capture finer-grained variability (e.g., immediate vs. delayed memory, RBANS total cognitive performance). These pragmatic decisions were made to balance comprehensiveness with comparability across heterogeneous studies.

2.4.5. Future research

Given the inconsistency of the current evidence and the clear differences between serum and plasma BDNF, future research should carefully consider whether continued focus on peripheral BDNF is warranted or whether other candidate biomarkers may provide more reliable insights. If further investigation into BDNF is considered promising, then high-quality, longitudinal studies with standardized BDNF measurement practices and cognitive assessments will be essential. Such studies would improve the comparability of findings and help clarify whether BDNF is truly a transdiagnostic biomarker. Importantly, serum and plasma BDNF should not be used interchangeably in future research, and standardized procedures for blood collection and processing are critical, given the sensitivity of BDNF to methodological variation such as time of withdrawal. Moreover, studies should examine whether pBDNF relates differentially to specific cognitive subdomains, which could provide more nuanced insights into its potential role.

2.5 Conclusion

In conclusion, even with the limitations of the present systematic review and meta-analysis, peripheral BDNF levels do not appear to be reliable transdiagnostic biomarkers for cognitive impairment in schizophrenia or bipolar disorder. While there are some indications that pBDNF may be associated with cognition in schizophrenia, these findings are not convincing enough to establish clinical utility. The overall evidence remains inconsistent, heavily influenced by external factors, and dependent on whether serum or plasma is measured. Taken together, these limitations strongly undermine the reliability of BDNF as a biomarker. Given the inconsistency and methodological challenges, as things stand, future research may need to move beyond BDNF as a transdiagnostic biomarker of cognition and instead explore alternative biological pathways and markers.

3

Metabolic syndrome as a transdiagnostic biomarker for cognitive impairment in the schizophrenia-bipolar spectrum: A systematic review and database analysis

3.1 Introduction

In the previous chapter (**Chapter 2**), peripheral BDNF was explored as a potential transdiagnostic biomarker for cognitive impairment in patients with disorders on the schizophrenia – bipolar spectrum. While findings indicated a connection between pBDNF levels and cognitive function in SCHZ, circulating BDNF levels in general do not seem to be a reliable biomarker due to external influences and methodological problems. Variability in peripheral BDNF levels arises from factors such as sex, age, illness stage, type of BDNF (serum or plasma) and medication use. These limitations undermine BDNF's clinical utility as a valid and reproducible transdiagnostic biomarker for cognitive impairment. Given these challenges, there is a need to search for more practical, reliable, and clinically accessible biomarkers. One promising alternative could be MetS, a cluster of cardiovascular and metabolic abnormalities including obesity, hypertension, dyslipidaemia, and diabetes, which is highly prevalent in patients with different psychiatric disorders and is measured routinely in clinical settings (356).

3.1.1. Rationale

Evidence suggests an association between MetS and cognition across psychiatric disorders (168,169,357,358). In SCHZ, the presence of MetS and diabetes mellitus has been linked to more severe cognitive deficits, with additional evidence supporting significant associations between cognitive impairment and individual components of MetS, including hypertension, dyslipidaemia, abdominal obesity, and diabetes (168). Another meta-analysis reported that patients with SCHZ and MetS exhibited significantly greater cognitive impairment compared to those without the syndrome (169). Additionally, in a cross-sectional study by Dalkner et al., patients with BD and MetS also showed impaired executive function compared to those without (358). The association between MetS and cognitive impairment may be due to the fact that MetS and its components can lead to structural brain abnormalities, which in turn contribute to cognitive deficits (170). Furthermore, since the components of MetS are routinely measured in clinical settings, they offer practical and scalable means of identifying individuals at risk for cognitive decline. However, MetS has not yet been explored as a potential transdiagnostic biomarker for cognitive impairment across NPDs.

3.1.2. Aims and objectives

This chapter aims to examine the potential of MetS as a clinically useful transdiagnostic biomarker and/or modifiable risk factor for cognitive impairment in individuals with disorders on the schizophrenia – bipolar spectrum, through a systematic review of the literature and empirical analysis of a patient database.

The objectives are the following:

1. To conduct a systematic review of existing studies investigating the association between metabolic syndrome and cognitive impairment in individuals with disorders on the schizophrenia – bipolar spectrum.

2. To explore cognitive impairment, metabolic syndrome status, and antipsychotic medication history, and their associations in Hungarian schizophrenia patients using the SCHIZOBANK database.

3.2 Methods

The present study consists of two parts. The first part is a systematic review that summarizes existing evidence on the relationship between metabolic syndrome and cognitive impairment in individuals within the schizophrenia – bipolar spectrum. The second part involves the statistical analysis of a Hungarian database of schizophrenia patients, examining the association between cognitive impairment and metabolic syndrome, with a particular focus on antipsychotic medication history. While the systematic review is transdiagnostic in scope (schizophrenia – bipolar spectrum), the database analysis is necessarily restricted to patients with schizophrenia who were receiving antipsychotic treatment. This restriction reflects the available data, but it also provides a unique opportunity to examine the influence of antipsychotic medication on the association between metabolic syndrome and cognitive impairment — a factor that could not be addressed in the review.

3.2.1. Systematic review

3.2.1.1. Search strategy

A systematic literature search was conducted using the Medline and Embase databases for peer-reviewed, English-language studies published between January 2005 and January 2025, following PRISMA guidelines. The search terms were (‘schizo*’ OR ‘bipolar’) AND (‘metabolic syndrome’) AND (‘cognit*’). To ensure comprehensive coverage, the reference lists of identified studies were manually reviewed, and additional hand searches were performed. Only studies involving human participants were included.

3.2.1.2. Inclusion & exclusion criteria

Studies were included if they met the following criteria: (a) original research conducted with human participants; (b) involved individuals diagnosed with SCHZ, schizoaffective disorder, or BD, according to the DSM-IV, DSM-V, or ICD-10; (c) incorporated at least one cognitive assessment test or scale; and (d) provided a clear and well-defined assessment of MetS based on established diagnostic criteria. Studies were excluded if: (a) MetS status was not explicitly reported; (b) cognitive impairment was not sufficiently assessed or documented; and (c) if the relationship between MetS and cognitive impairment was not assessed or commented.

3.2.1.3. Recorded variables and data extraction

From each study, the following data were extracted: first author's name, year of publication, and participant characteristics, including diagnosis and sub-diagnosis, sample size, mean age, and sex. Information on MetS was collected, such as diagnostic criteria and MetS prevalence. Cognitive characteristics were extracted, detailing assessed domains and subdomains, measurement scales and tests used, and the reported associations between cognitive impairment and MetS. Study outcomes were systematically tabulated. In cases of duplicate publications (i.e., multiple reports from the same study), only unique contributions were considered, and non-overlapping data were included in the analysis.

3.2.2. Database analysis

3.2.2.1. Study design

This was a retrospective, cross-sectional, observational study analysing data from the SCHIZOBANK database. The SCHIZOBANK (Hungarian national schizophrenia biobank) is a database of 536 patients and 315 healthy controls from 5 Hungarian university sites (359).

The available data are general data (demographic characteristics, diagnostic information and specific information), laboratory test results, medication history, and PANSS scores.

3.2.2.2. Inclusion & exclusion criteria

Patients were included if they had a diagnosis of SCHZ and a documented history of exposure to at least one of the following APs at any point prior to the assessment date: metabolically challenging APs (clozapine, olanzapine, quetiapine, risperidone) or metabolically neutral APs (amisulpride, aripiprazole, fluphenazine, haloperidol) (360–362). Notably, this criterion does not imply that patients were exclusively treated with either metabolically challenging or neutral agents, as many may have been exposed to both categories and/or additional medications beyond those specified. To minimize the influence of brief medication exposure, only antipsychotic treatments administered for a minimum of 42 days (six weeks) were considered. This threshold was selected based on evidence indicating that the most pronounced AIWG typically occurs within the first six weeks of treatment and is rarely reversed thereafter (363–365). Patients were excluded if they had missing data on two or more of the five diagnostic criteria for metabolic syndrome (waist circumference, triglycerides, HDL cholesterol, blood pressure, fasting glucose). Metabolic syndrome status was determined according to the AHA/NHLBI-Modified NCEP-ATP III (2005) criteria (366).

3.2.2.3. Data

Information regarding birth date, age at onset, sex, weight, body mass index (BMI), waist circumference, weight belief, exercise pattern, blood pressure, disease status (coeliac disease, diabetes, endocrine disease, hyperlipidaemia, hypertonia, obesity), laboratory test results (blood sugar, HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides), date of diagnosis, antipsychotic medication history, and schizophrenia symptomatology measured by

the PANSS were analysed. The different symptom dimensions of schizophrenia were quantified using the PANSS Marder factor scores (367): PANSS Positive factor score (PANSS-P: items P1, P3, P5, P6, N7, G1, G9, G12), PANSS Negative factor score (PANSS-N: items N1, N2, N3, N4, N6, G7, G16), PANSS Disorganized thoughts factor score (PANSS-DT: items P2, N5, G5, G10, G11, G13, G15), PANSS Anxiety / Depression factor score (PANSS-AD: items G2, G3, G4, G6) and PANSS Uncontrolled excitement / Hostility factor score (PANSS-UEH: items P4, P7, G8, G14). Among these, the PANSS Disorganized thoughts factor was designated as the primary outcome of interest, given its central relevance to cognitive impairment. Analyses of PANSS total and the other factor scores were considered exploratory.

3.2.2.4. Statistical analyses

Patient characteristics, metabolic parameters, and antipsychotic medication history were summarized using descriptive statistics (means, percentages, and standard deviations). Data normality was assessed using the Shapiro-Wilk test, and homogeneity of variance was evaluated with Levene's test.

Group comparisons between MetS and non-MetS patients, as well as between those with a history of only metabolically challenging (OMC) versus only metabolically neutral (OMN) antipsychotic use, were conducted using appropriate statistical tests. Chi-square and Fisher's exact tests were used to compare categorical variables, while Wilcoxon rank tests assessed differences in the median duration of OMC and OMN antipsychotic use. Independent t-tests were applied to compare PANSS total and Marder factor scores between MetS and non-MetS patients, as well as between OMC and OMN groups.

To examine associations between MetS status and cognitive impairment, linear regression models were performed with the PANSS Disorganized thoughts factor score as the primary outcome. In the first model, sex, age, and illness duration were included as covariates, followed by BMI in a second model and antipsychotic history in a third model. These models were also conducted for individual MetS components and for males and females separately. Exploratory analyses using the PANSS total score and the remaining Marder factor scores were performed in the same way. To account for multiple comparisons across MetS components and PANSS outcomes, Bonferroni corrections were applied, and corrected p-values are reported alongside uncorrected values.

3.3 Results

3.3.1. Systematic review

This section presents the findings of the systematic review conducted to examine the association between MetS and cognitive impairment in individuals with disorders on the schizophrenia – bipolar spectrum. The results are organized as follows: first, the outcomes of the systematic search are described, including the number of studies identified, screened, and included. This is followed by a summary of study characteristics, an analysis of the prevalence of MetS across the included studies and a detailed examination of the relationship between MetS and cognitive performance.

3.3.1.1. Search results

A summary of the article selection process for the systematic review is shown in the PRISMA flow diagram (**Figure 14**). A total of 383 articles were identified through database searches after removing duplicates. No additional articles were identified through hand searches. Based on title and abstract screening, 42 articles were considered potentially eligible. Following full-

text evaluation, 25 studies met the inclusion criteria. Articles were excluded for the following reasons: insufficient information (n = 9), focus on MetS components only (n = 3), inclusion of MetS patients exclusively (n = 2), no report on the MetS-cognition association (n = 1), duplicate data from the same study (n = 1), or non-English language (n = 1).

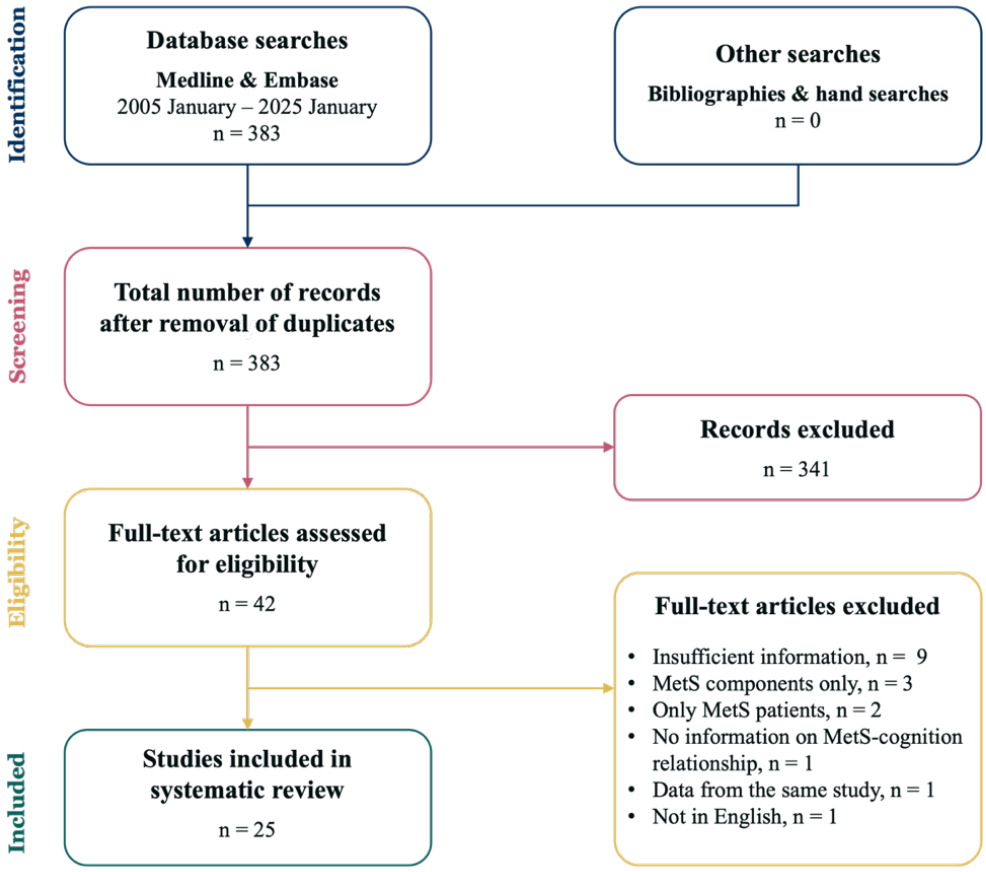

Figure 14. Summary of study identification and selection

The figure shows the steps of article selection for systematic review from articles identification, through screening and eligibility to inclusion.

3.3.1.2. Study characteristics

Altogether, 5,749 patients were included in the systematic review. Of the 25 included studies, 88% focused on patients with SCHZ, 16% on patients with BD, and 12% on patients with schizoaffective disorder (note: percentages exceed 100% because some studies included multiple patient populations) (**Table 16**). Some of the studies examining SCHZ patients reported on specific populations such as clozapine-resistant, FEP, or CH-SCHZ patients. The

mean age of patients ranged from 17.2 years (BD patients) to 63.8 years (CH-SCHZ patients). Where reported separately, patients with MetS had a slightly higher mean age (41.0 years on average) compared to those without MetS (39.4 years on average). The percentage of males ranged from 33.6% to 89.0%; in the total sample 55.3% were males.

Table 16. Summary of study characteristics included in the systematic review investigating the association between metabolic syndrome and cognitive impairment

Study	Participant characteristics				MetS characteristics		Cognitive characteristics		Relationship between MetS & cognition	Treatment characteristics
	Diagnosis	N	Mean age	% males	Criteria	% MetS	Domains & subdomains	Scales & tests		
Adamowicz et al. 2020	SCHZ	87	41.7	36.8%	IDF	69.0%	Verbal fluency, processing speed, verbal working memory, executive functions	Verbal fluency test, SCT, DS	Cognitive performance did not differ between patients with and without MetS	Olanzapine, clozapine, quetiapine, and aripiprazole
Bai et al. 2016	BD	143	44.8	33.6%	IDF (Asia criteria, 2005)	29.4%	Executive Function	WCST	Patients with MetS exhibited significantly greater impairment in executive function compared to those without MetS	Mood stabilizers (10.5% MetS), SGAs (36.0% MetS), SGAs + mood stabilizers (36.3% MetS)
Bosia et al. 2018	SCHZ	172	35.1 (MetS) 33.2 (no MetS)	62.2%	NCEP-ATP III	22.0%	Verbal memory, working memory, motor function, verbal fluency, attention and processing speed, executive function	BACS	No significant differences in cognitive domains between patients with and without MetS	Clozapine and other APs
Boyer et al. 2013	SCHZ	168	39.6 (MetS) 35.5 (no MetS)	73.8%	NCEP-ATP III	27.4%	Memory, attention, and executive functions	CVLT, TMT, SCT, WAIS-III, Category fluency, D2 attention	Among the various MetS components, hypertriglyceridemia and abdominal obesity were the only factors linked to cognitive impairment	90% SGAs
Cao et al. 2023	SCHZ	159	37.5 (MetS) 39.3 (no MetS)	53.5%	Diagnostic criteria proposed by the Diabetes Branch of the Chinese Medical Association	25.8%	Working memory, processing speed, attention and vigilance, verbal learning, visual learning, reasoning and problem solving, social cognition	MCCB	Patients with MetS showed significantly lower performance in processing speed, working memory, verbal and visual learning compared to those without MetS	No information
Chen et al. 2020	SCHZ	158	31.4 (MetS) 23.8 (no MetS)	49.4%	JIS	36.7%	Working memory, processing speed, attention and vigilance, verbal learning, visual learning, reasoning and problem solving, social cognition	MCCB	Patients without MetS had higher MCCB total and sub-scores than patients with MetS, however differences were not statistically significant	The use of hypolipidemic and hypoglycaemic drugs in patients with metabolic syndrome was higher than in the other two groups
Dalkner et al. 2021	BD - EU	148	39.5	52.5%	IDF	30.4%	Attention and processing speed, verbal memory, executive function	TMT, d2-R, SCT, CVLT	Patients MetS had impaired executive function compared to patients without MetS and healthy controls with and without MetS	Lithium, SGAs, antiepileptics, mood stabilizers
de Nijs et al. 2016	SCHZ	246	31.3 (MetS)	86.2%	IDF	42.3%	IQ, short- and long-term verbal memory, vigilance and processing speed	WAIS-III, WLT, CPT-HQ	MetS patients performed significantly worse on IQ, short- and long-term memory,	FGAs and SGAs

			30.8 (no MetS)						processing speed and vigilance than patients without MetS	
Dong et al. 2024	CR-TRS	69	45.9 (MetS) 48.7 (no MetS)	41.9%	NCEP-ATP III	44.9%	Immediate memory, visuospatial/constructional, attention, delayed memory	RBANS	Patients with MetS had significantly lower RBANS total and index scores compared to those without MetS	Clozapine (≥400 mg/day for ≥6 months)
Fang et al. 2019	SCHZ	174	35.8	47.1%	NCEP-ATP III	32.7%	Immediate memory, visuospatial/constructional, attention, delayed memory	RBANS	No significant differences in cognitive functions between MetS and non-Mets patients	100% SGAs
Goughari et al. 2015	SCHZ	68	42.4	67.6%	NCEP-ATP III	48.5%	Verbal memory, working memory, motor function, verbal fluency, attention and processing speed, executive function	BACS	Only hyperglycaemia and hypertension were found to be associated with cognitive functioning	Stable dose of primary FGAs or SGAs for at least 4 weeks
Grover et al. 2019	SCHZ	121	33.9	54.5%	NCEP-ATP III	56.2%	Processing speed, verbal fluency, cognitive flexibility, selective attention, auditory and verbal memory, executive functioning	TMT, COWAT, SCT, AVLT, ToL	MetS patients had significantly poorer performance in processing speed, selective attention, auditory and verbal memory than those without MetS	SGAs (95.9%), FGAs (4.1%)
Huang et al. 2023	SCHZ	358	40.6	68.2%	NCEP-ATP III	31.3%	Immediate memory, visuospatial/constructional, attention, delayed memory	RBANS	Sex differences: hyperglycaemia linked to immediate memory in males and dyslipidaemia associated with language, attention, delayed memory, and RBANS total score in females	SGAs (82.4%), FGAs (5.7%), SGA + FGA (7.4%)
Kraal et al. 2019	CH-SCHZ, CH-SCHZ-AF	226	44.7	62.8%	NCEP-ATP III	50.9%	Verbal memory, working memory, motor function, verbal fluency, attention and processing speed, executive function	BACS	Among eNOS-786C carriers only, metabolic syndrome was independently associated with lower scores in processing speed and verbal fluency	FGAs (85.4%) for at least 6 months
Lancon et al. 2012	SCHZ	168	36.6	73.8%	NCEP-ATP III	27.4%	Memory	CVLT	Association between MetS and memory impairment	SGAs & FGAs
Li et al. 2014	SCHZ	388	42.3	46.9%	MS of the Chinese Diabetes Society in 2004	46.4%	Immediate memory, visuospatial/constructional, attention, delayed memory	RBANS	RBANS total scale score and attention, immediate memory, and delayed memory scores in the MetS group were significantly lower than those in the non-MetS group	Risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, clozapine, chlorpromazine, perphenazine
Lindenmayer et al. 2012	SCHZ, SCHZ-AF	159	43.5	89.0%	NCEP-ATP III	43.3%	Working memory, processing speed, attention and vigilance, verbal learning, visual learning, reasoning and problem solving, social cognition	MCCB	Patients with MetS showed significantly worse processing speed, attention/vigilance, reasoning/ problem solving compared to patients without MetS	On stable antipsychotic medications prior to the start of the study
Luckhoff et al. 2024	FEP-SCHZ, FEP-SCHZ-AF	37	26.6	64.9%	JIS	8.0%	Immediate memory, visuospatial/constructional, attention, delayed memory	RBANS	Significant negative correlation between MetS features and immediate verbal memory, association between lower HDL	46% drug naïve, 54% risperidone, flupentixol, or low-dose haloperidol

									cholesterol and overall cognition and poorer performance in attention, language, immediate and delayed memory	
Meyer et al. 2005	SCHZ	1231	42.8 (MetS) 39.4 (no MetS)	74.0%	NCEP-ATP III	35.8%	Verbal memory, processing speed, working memory, reasoning, vigilance	WAIS-R, COWAT, CPT, WCST	No significant difference between MetS and non-MetS groups	13.4 years of average AP use
Naiberg et al. 2016	BD	34	17.2	41.2%	IDF	2.9%	Executive functioning, attention	CANTAB, IED	Association between elevated triglycerides and poorer executive function among adolescents with BD	SGAs, FGAs, SRRI, stimulant, non-SSRI antidepressant
Ren et al. 2022	CH-SCHZ	140	61.9 (MetS) 63.8 (no MetS)	78.6%	NCEP-ATP III	45.0%	Immediate memory, visuospatial/constructional, attention, delayed memory	RBANS	Patients with MetS tended to have better performances in coding test, attention span and delayed retention in RBANS compared to non-MetS patients	On average 26 months of clozapine treatment
Sánchez-Ortí et al. 2021	SCHZ, BD	30 SCH, 42 BD	49.9	52.0%	NCEP-ATP III	73.3% SCH, 47.6% BD	Verbal learning and memory, cognitive flexibility, verbal fluency, working memory, short-term memory, visual memory, processing speed	TAVEC, SCT, WCST, TMT, WAIS-III, ROCFT, FTT	Cognitive impairment was significantly greater in the MetS than in the non-MetS group	Prescribed treatment
Zhang et al. 2017	SCHZ	216	28.7	53.2%	NCEP-ATP III	44.0%	Immediate memory, visuospatial/constructional, attention, delayed memory	RBANS	MetS patients had lower immediate memory, attention, delayed memory and total scores in RBANS than patients without MetS	Long-term olanzapine monotherapy
Zhang et al. 2022	SCHZ	106	37.4 (MetS) 35.9 (no MetS)	51.8%	Guideline standards for the prevention and treatment of dyslipidaemia in Chinese adults in 2007 for MetS	45.3%	Memory, executive functioning, attention, language, visuospatial, orientation	MoCA	Cognitive function is worse in the MetS group than in the non-MetS group	Treated with olanzapine, clozapine, and risperidone for more than 3 months
Zhou et al. 2021	SCHZ	167	37.6	55.7%	IDF	27.5%	Working memory, processing speed, attention and vigilance, verbal learning, visual learning, reasoning and problem solving, social cognition	MCCB	An increase in allostatic load, even MetS, seems to be enough to affect brain cortical structure and cognitive performance	FGAs & SGAs (96.4%)

AP, antipsychotic medication; AVLT, Rey auditory and verbal learning test; BACS, Brief Assessment of Cognition in Schizophrenia; BD, bipolar disorder; CANTAB, Cambridge Neuropsychological Tests Automated Battery; CH-SCHZ, chronic schizophrenia; COWAT, Controlled Oral Word Association; CPT, Continuous Performance Task; CR-TRS, Clozapine-resistant treatment-refractory schizophrenia; CVLT, California Verbal Learning Test; d2-R, d2 Test of Attention Revised; D-KEFS, Delis-Kaplan Executive Function System for executive functioning; DS, digit span tests; EU, euthymic state; FEP, first-episode; FGA, First-generation antipsychotics; FTT, Finger tapping test; IDF, International Diabetes Federation; IED, intra/extra-dimensional set shift task; JIS, Joint Interim Statement; MCCB, MATRICS Consensus Cognitive Battery; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; ROCFT, Rey–Osterrieth Complex Figure; SCHZ, schizophrenia; SCT, Stroop Colour test; SGA, Second generation antipsychotics; SSRI, selective serotonin reuptake inhibitor; TAVEC, The California Verbal Learning Test (Spanish version of the CVLT); TICS, Telephone Interview for Cognitive Status; TMT, trail making tests; ToL, Tower of London; VLMT, Verbal Learning and Memory Test; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WLT, Word Learning Task

Most studies utilized the NCEP- ATP III (56%) or the International Diabetes Federation (IDF) criteria (24%) for diagnosing MetS. The IDF criteria require central obesity (waist circumference) as a mandatory component, while NCEP-ATP III treats all five components equally, requiring any three of five to diagnose metabolic syndrome. A comparison of the two diagnostic criteria is in **Table 17**.

Table 17. Comparison of the NCEP-ATP III and IDF criteria for metabolic syndrome

CRITERION	NCEP-ATP III		IDF	
	Men	Women	Men	Women
Waist circumference	≥ 102 cm	≥ 88 cm	≥ 94 cm	≥ 80 cm
Triglycerides*	≥ 150 mg/dL	≥ 150 mg/dL	≥ 150 mg/dL	≥ 150 mg/dL
HDL cholesterol*	< 40 mg/dL	< 50 mg/dL	< 40 mg/dL	< 50 mg/dL
Blood pressure*	≥ 130/85 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg
Fasting glucose*	≥ 110 mg/dl	≥ 110 mg/dl	≥ 100 mg/dl	≥ 100 mg/dl
DIAGNOSIS REQUIREMENT	3 out of 5 criteria		Central obesity + 2 out of 4 other criteria	
**or on treatment*				

In terms of cognitive impairment, the most commonly used cognitive scales were the RBANS (28%), the MCCB (16%), the WAIS (16%), and the BACS scale (12%). Additionally, the SCT (20%), TMT (16%), California Verbal Learning Test (CVLT) (12%) and WCST (12%) were also quite popular.

The most commonly reported treatments were SGAs (44%), followed by first-generation antipsychotics (FGAs) (24%). Among specific medications, clozapine was the most frequently mentioned (24% of studies), followed by olanzapine (16%) and risperidone (12%).

3.3.1.3. Prevalence of metabolic syndrome

The prevalence of MetS among patients across the 25 studies varied widely, ranging from 2.9% to 73.3%. The lowest prevalence (2.9%) was observed in adolescents with BD (368), while the highest prevalence (73.3%) was reported in schizophrenia patients (369). Most studies reported a MetS prevalence between 25% and 50%, with 18 studies (72%) falling

within this range. Four studies (16%) indicated a prevalence greater than 50%, suggesting a substantial metabolic burden in certain SCHZ patients, particularly those with CH-SCHZ (370). In contrast, three studies (12%) reported a prevalence below 25%, mostly in younger populations (368) or those in the early stages of illness (371). The average prevalence of MetS across all studies was approximately 32.8%, highlighting a high burden in patients on the schizophrenia-bipolar spectrum. Variations in prevalence may reflect differences in diagnostic criteria, treatment regimens, illness chronicity, and patient demographics. As anticipated, in studies where patients were treated with clozapine and olanzapine, the reported prevalences of MetS were at the higher end of the spectrum, approximately 45%.

3.3.1.4. Association between metabolic syndrome and cognitive impairment

The relationship between MetS and cognitive impairment across the included studies was mixed. While 52% of the studies reported significantly greater cognitive impairment in patients with MetS compared to those without (197,358,369,372–381), 20% found an association only between specific MetS components and cognitive difficulties (368,371,382–384). In contrast, 16% detected no difference in cognitive performance between the groups (194,385–387), and one study even reported better cognitive performance in patients with MetS than those without (186). In studies where MetS and its components were associated with poorer cognitive performance, the most affected domains were memory (32% of studies), attention/vigilance (28%), processing speed and executive function (16%).

About half of the studies found significant difference in cognitive impairment between patients with and without MetS. Bai et al. (2016) reported that patients with BD and MetS exhibited significantly more impaired executive function than those without (372), while Dalkner et al. (2021), found similar results in patients with euthymic BD (358). Among SCHZ patients, six studies consistently reported greater cognitive impairment in the MetS group,

with lower overall cognitive scores across various assessment tools, including the MCCB and RBANS (197,369,374,376,379,381). Three additional studies linked MetS status to difficulties in memory, problem-solving and processing speed (373,375,377,380). Indicating a possible gene-environment interaction, Kraal et al. (2019) showed that MetS was independently associated with lower scores in processing speed and verbal fluency among carriers of the eNOS-786C variant. Interestingly, Lancon et al. (2012) identified a dose-response relationship, where a greater number of MetS criteria was linked to increased memory impairment (378). In contrast, Ren et al. (2022) reported that MetS patients outperformed their non-MetS counterparts on specific cognitive tasks, including the coding test, attention span, and delayed retention (186).

Several studies identified specific MetS components to be associated with cognitive impairment. For example, Boyer et al. (2013) found that among the MetS components, hypertriglyceridemia and abdominal obesity were the only factors significantly linked to cognitive deficits in patients with SCHZ (382). Similarly, Naiberg et al. (2016) reported that elevated triglycerides were linked to poorer executive function in adolescents with BD (368). In contrast, Goughari et al. (2015) identified hyperglycaemia and hypertension as the sole MetS components associated with cognitive functioning (288). While Huang et al. (2023) observed sex differences in the MetS-cognition relationship, with hyperglycaemia associated with immediate memory deficits in males and dyslipidaemia linked to multiple cognitive impairments in females with schizophrenia (384). These findings suggests that the relationship between MetS and cognition in patients on the schizophrenia – bipolar spectrum may be domain-specific rather than a generalized cognitive deficit. In contrast, four studies could not report significant differences in cognitive performance between MetS and non-MetS patients (194,385–387). Furthermore, Zhou et al. (2021) suggested that elevated allostatic load, a marker of cumulative biological stress that overlaps with MetS, could

negatively affect cognitive performance and brain structure, even in the absence of MetS (388).

3.3.2. Database analysis

This section presents the results of the SCHIZOBANK database analysis exploring the association between MetS and cognitive impairment in Hungarian individuals with SCHZ. The findings are structured as follows: first, patient demographics and disease characteristics are detailed, followed by an overview of metabolic parameters, medication history, and symptom severity. Lastly, the relationship between MetS status, cognitive impairment and overall psychopathology, as well as medication history is examined.

3.3.2.1. Patient characteristics

The sample included 215 patients, with 118 being women (55.9%) and 97 men (45.1%) (**Table 18**). The mean age was 41.4 years, with women being older (mean = 43.9) than men (mean = 38.4). The mean age of onset was 27.3 years, and the mean duration of the disorder was 13.0 years. Based on the disorder stage, 17.2% patients were classified as early-stage (0–5 years), 31.2% as mid-stage (5–15 years), and 22.3% as late-stage (15+ years) (389), with the stage being unknown for 63 patients (29.3%).

Table 18. Characteristics of included patients from the SCHIZOBANK database

DEMOGRAPHICS	TOTAL	WOMEN	MEN
Patient number, n (%)	215 (100.0)	118 (55.9)	97 (45.1)
Age, mean (SD)	41.4 (12.1)	43.9 (12.1)	38.4 (11.4)
Age at onset, mean (SD)*	27.3 (7.9)	28.5 (8.3)	25.8 (7.2)
Duration of disorder, years, mean (SD)*	13.0 (9.3)	14.1 (9.5)	11.0 (8.9)
Stage, n (%)			
Early (0 – 5 years)	37 (17.2)	16 (13.6)	21 (21.6)
Mid (5 – 15 years)	67 (31.2)	36 (30.5)	31 (32.0)
Late (15+ years)	48 (22.3)	30 (25.4)	18 (18.6)
Unknown	63 (29.3)	36 (30.5)	27 (27.8)
**data for 63 (29.3%) patients unknown*			
SD, standard deviation			

Regarding disease status, diabetes was present in 16 patients (7.4%), with a higher prevalence in women (10.2%) compared to in men (4.1%) (**Table 19**). Hyperlipidaemia was found in 13.5% patients, and hypertension in 19.5% patients, with similar distributions between sexes. Other comorbidities included endocrine disorders (3.7%), hyperthyroidism (2.3%), and celiac disease (0.5%).

Table 19. Disease status of patients included from the SCHIZOBANK database

DISEASE STATUS	TOTAL	WOMEN	MEN
Coeliac disease, n (%)	1 (0.5)	1 (0.8)	0 (0.0)
Diabetes, n (%)	16 (7.4)	12 (10.2)	4 (4.1)
Endocrine disorders, n (%)	8 (3.7)	7 (5.9)	1 (1.0)
Hyperlipidaemia, n (%)	29 (13.5)	14 (11.9)	15 (15.5)
Hyperthyroidism, n (%)	5 (2.3)	5 (4.2)	0 (0.0)
Hypertension, n (%)	42 (19.5)	21 (17.8)	21 (21.6)

3.3.2.2. Metabolic characteristics

In terms of metabolic parameters, the mean weight of patients was 76.8 kg, with men being heavier (mean = 83.1 kg) than women (mean = 71.6 kg) (**Table 20**). The mean BMI was 26.5, with 32.1% of patients classified as overweight (BMI 25.0 – 29.9), and 14.0% as obese (BMI 30.0 – 34.9). Notably, the perception of patients about their own weight was quite similar to the BMI categories, with 29.8% considering themselves to be overweight and 14.4% to be obese. There were however differences between men and women, with 36.1% of men being overweight and 15.5% obese according to the BMI categories, while these numbers were 28.8% and 12.7% for women respectively. Despite this, less men thought themselves to be overweight or obese than women. Interestingly, doctors classified 28% of women and 15.5% of men to have obesity. The waist circumference averaged 92.6 cm in women and 96.6 cm in men. Physical activity levels varied, with 60.4% of patients reporting never exercising and only 5.6% exercising multiple times per week. The exercise patterns were similar among men and women. Blood pressure readings indicated a mean systolic value of 123.7 mmHg and a mean diastolic value of 80.6 mmHg. Men had slightly higher blood pressure (mean 125.5 /

82.3 mmHg) compared to women (mean 122.2 / 79.1 mmHg). Fasting glucose averaged 5.2 mmol/L for total and both sex groups. Cholesterol measurements showed mean HDL levels of 1.2 mmol/L, mean LDL levels of 3.0 mmol/L, and total cholesterol of 4.7 mmol/L, though HDL and LDL values were missing for 79 patients (36.7%). The mean triglyceride level was 1.7 mmol/L, with men showing higher values (mean = 1.9 mmol/L) than women (mean = 1.5 mmol/L).

Table 20. Metabolic characteristics of patients included from the SCHIZOBANK database

METABOLIC PARAMETERS	TOTAL	WOMEN	MEN
Weight, kg, mean (SD)	76.8 (17.7)	71.6 (16.6)	83.1 (17.1)
BMI, mean (SD)	26.5 (5.7)	26.3 (5.9)	26.7 (5.5)
BMI categories, n (%)			
Underweight (<18.5)	24 (11.2)	16 (13.6)	8 (8.2)
Normal (18.5 – 24.9)	75 (34.9)	42 (35.6)	33 (34.0)
Overweight (25.0 – 29.9)	69 (32.1)	34 (28.8)	35 (36.1)
Obese (30.0 – 34.9)	30 (14.0)	15 (12.7)	15 (15.5)
Extremely obese (35<)	16 (7.4)	10 (8.5)	6 (6.2)
Waist circumference, mean (SD)*	94.5 (16.0)	92.6 (15.1)	96.6 (16.8)
Obesity, n (%)	48 (22.3)	33 (28.0)	15 (15.5)
Weight belief, n (%)			
Underweight	34 (15.8)	13 (11.0)	21 (21.6)
Normal	77 (35.8)	41 (34.7)	36 (37.1)
Overweight	64 (29.8)	36 (30.5)	28 (28.9)
Obese	31 (14.4)	24 (20.3)	7 (7.2)
Unknown	9 (4.2)	4 (3.4)	5 (5.2)
Exercise, n (%)			
Never	130 (60.4)	75 (63.6)	55 (56.7)
Irregularly	39 (18.1)	19 (16.1)	20 (20.6)
Less often than monthly	9 (4.2)	3 (2.5)	6 (6.2)
Once monthly	5 (2.3)	3 (2.5)	2 (2.1)
Once weekly	8 (3.7)	6 (5.1)	2 (2.1)
Multiple times weekly	12 (5.6)	6 (5.1)	6 (6.2)
Daily	9 (4.2)	6 (5.1)	3 (3.1)
Unknown	3 (1.4)	0 (0.0)	3 (3.1)
Blood pressure, mean (SD)			
Systolic	123.7 (14.0)	122.2 (15.3)	125.5 (12.1)
Diastolic	80.6 (12.2)	79.1 (9.8)	82.3 (14.4)
Fasting glucose, mean (SD)	5.2 (1.5)	5.2 (1.6)	5.2 (1.4)
Cholesterol, mean (SD)			
HDL**	1.2 (0.3)	1.3 (0.3)	1.1 (0.3)
LDL**	3.0 (1.0)	2.9 (0.9)	3.1 (1.1)
Total	4.7 (1.1)	4.7 (1.0)	4.7 (1.2)
Triglycerides, mean (SD)	1.7 (1.2)	1.5 (0.9)	1.9 (1.4)

**31 missing values **79 missing values*
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation

Altogether, 70 individuals (32.6%) met the AHA/NHLBI-Modified NCEP-ATP III (2005) criteria for MetS (**Table 21**). While there were sex differences in the distribution of individual MetS components, the overall prevalence of MetS was comparable between both sexes (34.0% in males vs. 31.4% in females). Among the individual MetS components, the most common abnormalities in men were low HDL cholesterol (46.4%), elevated triglycerides (42.3%), and high blood pressure (37.1%). In women, the most frequent abnormalities were increased waist circumference (50.8%), low HDL cholesterol (38.1%), and high blood pressure (32.2%).

Table 21. Prevalence of metabolic syndrome and its components in patients included from the SCHIZOBANK database

METABOLIC SYNDROME CRITERIA	**TOTAL**, n (%) (n = 215)	**WOMEN**, n (%) (n = 118)	**MEN**, n (%) (n = 97)
Waist circumference above threshold (≥88 cm for women, ≥102 cm for men)	91 (42.3)	60 (50.8)	31 (32.0)
High triglycerides (≥1.7 mmol/L)	76 (35.3)	35 (29.7)	41 (42.3)
Low HDL cholesterol (<1.3 mmol/L for women, <1.0 mmol/L for men)	90 (41.9)	45 (38.1)	45 (46.4)
High blood pressure (≥130/85 mmHg)	74 (34.4)	38 (32.2)	36 (37.1)
High fasting glucose (≥5.6 mmol/L)	70 (32.6)	37 (31.4)	33 (34.0)
Metabolic Syndrome (≥3 criteria met)	70 (32.6)	37 (31.4)	33 (34.0)

Note: High triglycerides, low HDL, high blood pressure, and high fasting glucose include individuals with known diagnoses of hyperlipidaemia, hypertension, or diabetes.

3.3.2.3. Medication history

Among the 215 patients, risperidone was the most frequently used antipsychotic (32.6%), followed by olanzapine (20.9%), haloperidol (20.0%), quetiapine (19.1%), and clozapine (18.6%) (**Table 22**). Less commonly prescribed antipsychotics included aripiprazole (14.9%), amisulpride (9.8%), and fluphenazine (1.4%). Altogether, 60.0% of patients received metabolically challenging antipsychotics and 37.7% metabolically neutral throughout their lives. About a quarter of patients took metabolically challenging antipsychotics exclusively in the past (25.6%) and 11.2% metabolically neutral only. When comparing patients with and without MetS, the distribution of antipsychotic use was similar across groups. Interestingly,

patients with MetS had a slightly higher proportion of haloperidol (25.7% vs. 17.2%) and lower proportion of quetiapine (12.9% vs 22.1%) and risperidone (27.1% vs 35.2%) use compared to non-MetS patients. As expected, slightly more patients in the MetS group took metabolically challenging antipsychotics only (30.0% vs 23.4%). Nonetheless, the exclusive use of metabolically neutral antipsychotics was also higher in the MetS group (15.7% vs 9.0%). The chi-square & Fisher's exact test results indicated no statistically significant association between MetS status and the distribution of antipsychotic medications. Importantly, no significant association with MetS was observed in the OMC and OMN groups ($\chi^2 = 0.75$, p = 0.387 for OMC; $\chi^2 = 1.54$, p = 0.214 for OMN).

Table 22. Medication history of patients included from the SCHIZOBANK database

	TOTAL, n (%) (n = 215)	**MetS**, n (%) (n = 70)	**non-MetS**, n (%) (n = 145)	χ^2 / Fisher's exact	p-value
Metabolically neutral					
Amisulpride	21 (9.8)	7 (10.0)	14 (9.7)	0.00	1.000
Aripiprazole	32 (14.9)	6 (8.6)	26 (17.9)	2.57	0.109
Fluphenazine	3 (1.4)	1 (1.4)	2 (1.4)	*Fisher's exact*	1.000
Haloperidol	43 (20.0)	18 (25.7)	25 (17.2)	1.62	0.203
Total	81 (37.7)	26 (37.1)	55 (37.9)	0	1.000
Total OMN	24 (11.2)	11 (15.7)	13 (9.0)	1.54	0.214
Metabolically challenging					
Clozapine	40 (18.6)	12 (17.1)	28 (19.3)	0.04	0.845
Olanzapine	45 (20.9)	14 (20.0)	31 (21.4)	0.00	0.957
Quetiapine	41 (19.1)	9 (12.9)	32 (22.1)	2.03	0.154
Risperidone	70 (32.6)	19 (27.1)	51 (35.2)	1.04	0.307
Total	129 (60.0)	40 (57.1)	89 (61.4)	0.20	0.656
Total OMC	55 (25.6)	21 (30.0)	34 (23.4)	0.75	0.387

OMN, only metabolically neutral; OMC, only metabolically challenging
Note: Medication was taken for more than 42 days (6 weeks).

In terms of treatment duration, clozapine (mean = 1707 days), fluphenazine (mean = 1496 days) and haloperidol (mean = 1248 days) were used for the longest, while quetiapine (mean = 611 days), olanzapine (mean = 603 days), and aripiprazole (mean = 601 days) were prescribed for the shortest period (**Table 23**). There were no significant differences in the duration of metabolically neutral antipsychotic use between patients with and without MetS. The total duration of metabolically challenging antipsychotic use however showed a trend

toward significance p = 0.058, suggesting a potential association between prolonged exposure and MetS development. Among metabolically challenging antipsychotics, quetiapine was used for significantly longer durations in the MetS group compared to the non-MetS group (p = 0.007). In contrast, risperidone was taken significantly longer in the non-MetS group (p = 0.028).

Table 23. Medication duration of patients included from the SCHIZOBANK database

	TOTAL, mean days (SD) (n = 215)	**MetS**, mean days (SD) (n = 70)	**non-MetS**, mean days (SD) (n = 145)	Wilcoxon rank test	p-value
Metabolically neutral					
Amisulpride	853.1 (1132.4)	1144.6 (1635.8)	707.4 (818.0)	59	0.478
Aripiprazole	601.0 (671.4)	511.0 (696.4)	621.7 (677.9)	68	0.646
Fluphenazine	1496.3 (1869.6)	3653 (-)	418 (118.8)	-	-
Haloperidol	1247.7 (1656.4)	1095.1 (1146.6)	1357.5 (1959.6)	238.5	0.749
Total	1179.1 (1496.7)	1325.4 (1336.8)	1110.1 (1573.6)	845	0.190
Total OMN	1324.7 (1653.4)	1456.4 (1529.3)	1216.3 (1788.3)	138	0.468
Metabolically challenging					
Clozapine	1707.3 (1855.5)	1561.3 (1210.8)	707.4 (818.0)	191	0.512
Olanzapine	602.8 (725.1)	833.2 (1072.6)	621.7 (677.9)	250.5	0.418
Quetiapine	610.8 (647.1)	1179.2 (778.6)	418 (118.8)	230	0.007
Risperidone	772.8 (856.6)	1101.4 (989.4)	1357.5 (1959.6)	651	0.028
Total	1356.7 (1470.7)	1553.2 (1328.6)	1110.1 (1573.6)	2152.5	0.058
Total OMC	1274.0 (1401.4)	1428.6 (1232.0)	1216.3 (1788.3)	851.5	0.160

OMN, only metabolically neutral; OMC, only metabolically challenging; SD, standard deviation
Note: Medication was taken for more than 42 days (6 weeks).

3.3.2.4. Symptom composition and severity

The mean PANSS total score for the sample was 90.6, indicating moderate overall symptom severity (**Table 24**). Among the individual Marder factors, the Positive and Negative factor scores also reflected moderate severity, whereas the Disorganized thoughts, Anxiety/Depression, and Uncontrolled hostility/excitement factors indicated mild severity. Notably, patients without MetS had significantly higher PANSS total scores than those with MetS (p = 0.039) with a small effect size (Cohen's d = 0.30). While patients without MetS showed numerically higher scores across all Marder factors, these differences did not reach statistical significance.

Table 24. Comparison of PANSS total and factor scores between patients with and without MetS

	TOTAL n = 215 mean (SD)	**MetS** n = 70 mean (SD)	**non-MetS** n = 145 mean (SD)	**Test statistic**	**p - value**	**ES**
PANSS total score	90.6 (17.5)	87.1 (15.9)	92.3 (18.0)	2.07	0.039	0.30
Positive factor	27.6 (6.4)	26.5 (7.0)	28.1 (6.0)	1.73	0.085	0.25
Negative factor	21.9 (6.9)	20.9 (6.0)	22.4 (7.2)	1.54	0.124	0.22
Disorganized thoughts factor	20.2 (5.8)	19.8 (5.2)	20.4 (6.1)	0.82	0.413	0.12
Anxiety / Depression factor	11.0 (3.4)	10.7 (3.1)	11.2 (3.5)	1.12	0.264	0.16
Uncontrolled hostility / excitement factor	9.8 (3.7)	9.2 (3.2)	10.0 (3.9)	1.60	0.112	0.23

ES, effect size; MetS, Metabolic syndrome, PANSS, Positive and Negative Syndrome Scale; SD, standard deviation

When comparing symptom severity of patients with exclusive use of metabolically challenging and neutral antipsychotics, no statistical difference was detected neither in the PANSS total nor the Marder factor scores (**Table 25**).

Table 25. Comparison of PANSS total and factor scores between patients with exclusive use of metabolically challenging vs. neutral antipsychotics

	OMC n = 55 mean (SD)	**OMN** n = 24 mean (SD)	**Test statistic**	**p-value**	**ES**
PANSS total score	87.2 (14.6)	88.3 (18.7)	0.27	0.784	0.07
Positive factor	26.8 (6.3)	26.0 (6.2)	-0.55	0.584	-0.13
Negative factor	21.2 (5.7)	22.8 (7.7)	1.05	0.295	0.26
Disorganized thoughts factor	18.9 (4.2)	18.7 (5.7)	-0.13	0.900	-0.03
Anxiety / Depression factor	10.9 (3.3)	12.1 (4.1)	1.46	0.149	0.36
Uncontrolled hostility / excitement factor	9.5 (3.6)	8.6 (3.3)	-1.00	0.318	-0.25

AP, antipsychotic medication; ES, effect size; MetS, Metabolic syndrome, OMC, only metabolically challenging; OMN, only metabolically neutral; SD, standard deviation

3.3.2.5. Relationship between MetS status and cognitive impairment

Linear regression analyses were conducted to examine the relationship between MetS status and its components with cognitive impairment, as measured by the PANSS Disorganized thoughts factor scores, while controlling for sex, age, and years of disorder. The results indicate no significant association between MetS and cognitive impairment (estimate = -0.92, p = 0.377; Bonferroni-corrected p = 1.000), suggesting that MetS did not contribute to cognitive dysfunction (**Table 26**). Similarly, none of the individual MetS components — including HDL cholesterol, waist circumference, triglycerides, diastolic blood pressure, systolic blood pressure, fasting glucose, or BMI — remained significantly associated with

cognitive impairment after Bonferroni correction, although systolic blood pressure (estimate = -0.12, uncorrected p = 0.027, corrected p = 0.216) showed trends in the expected direction. The relationship between systolic blood pressure and PANSS Disorganized thoughts factor score is shown in **Figure 15**.

Table 26. Linear regression analysis of MetS status/components and PANSS Disorganized thoughts factor

VARIABLES	ESTIMATE	SE	t-value	p-value	corrected p-value
Metabolic syndrome*	-0.92	1.03	-0.89	0.377	1.000
Waist circumference (cm)*	-0.03	0.03	-0.93	0.353	1.000
Triglycerides (mmol/L) *	-0.26	0.37	-0.70	0.487	1.000
HDL cholesterol (mmol/L) *	-1.14	1.87	-0.61	0.546	1.000
Systolic blood pressure (mmHg)**	-0.12	0.05	-2.28	0.027	0.216
Diastolic blood pressure (mmHg)*	-0.06	0.04	-1.59	0.115	0.920
Fasting glucose (mmol/L)*	0.10	0.31	0.33	0.744	1.000
BMI (kg/m^2)***	-0.22	0.10	-2.21	0.031	0.248

**Controlling for sex, age, and disorder years.*
***Controlling for sex, age, disorder years, BMI and antipsychotic medication history (OMN vs. OMC)*
**** Controlling for sex, age, disorder years and antipsychotic medication history (OMN vs. OMC)*
OMC, only metabolically challenging; OMN, only metabolically neutral; SE, standard error

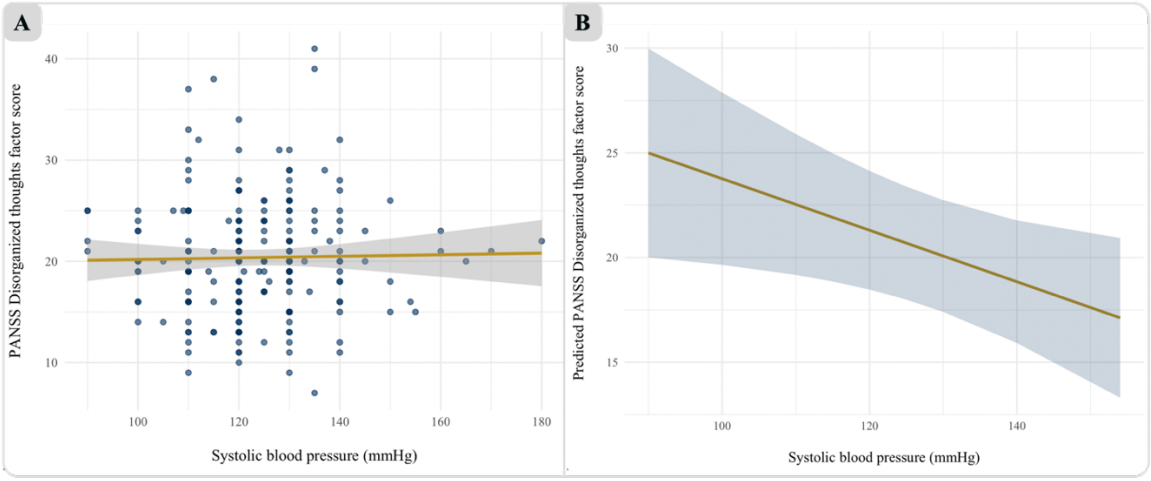

Figure 15. Relationship between systolic blood pressure and PANSS Disorganized thoughts factor

In Figure 16A, the unadjusted association between systolic blood pressure and the PANSS Disorganized Thoughts factor is shown. In Figure 16B, this association is presented after adjustment for relevant covariates.

Sex, BMI, and years of disorder remained significant predictors in several models, suggesting their potential influence on cognitive outcomes. When analysed separately, BMI was significantly associated with cognitive impairment (estimate = -0.22, p = 0.031), however, this

effect was no longer significant after Bonferroni correction. The relationship between BMI and PANSS Disorganized thoughts factor score is shown in **Figure 17**.

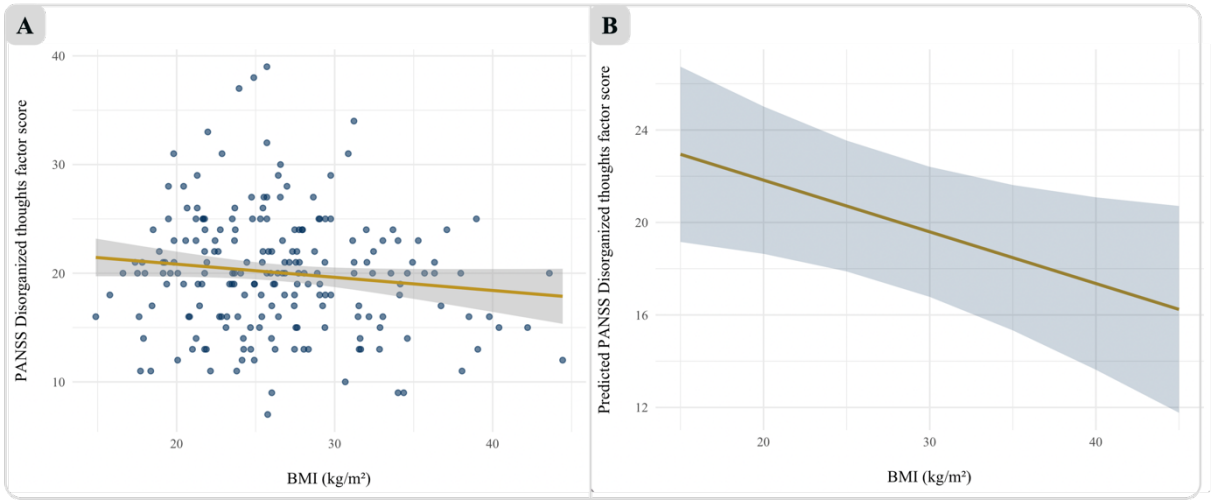

Figure 16. Relationship between BMI and PANSS Disorganized thoughts factor

In Figure 17A, the unadjusted association between body mass index (BMI) and the PANSS Disorganized Thoughts factor is shown. In Figure 17B, this association is presented after adjustment for relevant covariates.

3.3.2.6. Relationship between MetS status and overall psychopathology

Linear regression analysis was conducted to examine the relationship between MetS status and its components with overall psychopathology, as measured by PANSS total scores, while controlling for sex, age, and years of disorder. The results indicated no significant association between MetS and PANSS total scores (estimate = -6.02, p = 0.054, corrected p = 0.432) (**Table 27**). Similarly, none of the individual MetS components showed a significant relationship with overall symptom severity after Bonferroni correction. However, sex and BMI consistently emerged as significant predictors across all models, suggesting their potential role in influencing symptom severity in schizophrenia. Given this, an additional analysis was conducted to assess the direct impact of BMI on PANSS total scores. The findings confirmed that higher BMI was significantly associated with lower PANSS total

scores (estimate = -0.94, p = 0.004, corrected p = 0.032), suggesting a potential protective effect. The relationship between BMI and PANSS total score is shown in **Figure 17**.

Table 27. Linear regression analysis of MetS status/components and PANSS Total score

VARIABLES	ESTIMATE	SE	t-value	p-value	corrected p-value
Metabolic syndrome*	-6.02	3.11	-1.94	0.054	0.432
Waist circumference (cm)*	-0.16	0.10	-1.57	0.120	0.960
Triglycerides (mmol/L) *	-1.89	1.13	-1.67	0.097	0.776
HDL cholesterol (mmol/L) *	-3.71	5.81	-0.64	0.525	1.000
Systolic blood pressure (mmHg)*	-0.04	0.10	-0.39	0.699	1.000
Diastolic blood pressure (mmHg)*	-0.16	0.11	-1.44	0.152	1.000
Fasting glucose (mmol/L) *	0.12	0.95	0.13	0.896	1.000
BMI (kg/m^2)**	-0.94	0.31	-2.98	0.004	0.032

**Controlling for sex, age, and disorder years.*
*** Controlling for sex, age, disorder years and antipsychotic medication history (OMN vs. OMC)*
OMC, only metabolically challenging; OMN, only metabolically neutral; SE, standard error

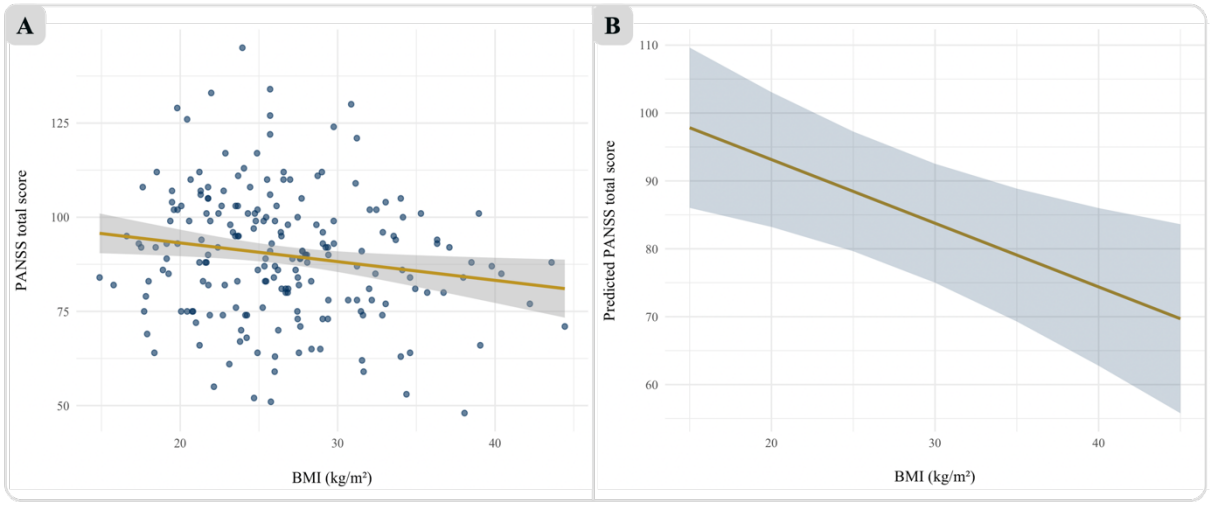

Figure 17. Relationship between BMI and PANSS Total score

In Figure 15A, the unadjusted association between BMI and total PANSS score is shown. In Figure 15B, the association is presented after adjustment for relevant covariates.

3.3.2.7. Sex differences in the relationship between MetS status and psychopathology

The results indicate that MetS status was not significantly associated with PANSS total scores or individual Marder factor scores in women (**Table 28**). In men, MetS appeared to be associated with lower PANSS total scores (estimate = -11.34, p = 0.003) and lower positive factor scores (estimate = -5.82, p < 0.001), when uncorrected. However, after Bonferroni

correction and further adjustment for BMI and antipsychotic medication history, these associations were no longer statistically significant, suggesting that BMI and medication may mediate the observed effects.

Table 28. Linear regression analysis of MetS status and PANSS total and factor scores by sex

	WOMEN (n = 118)					**MEN** (n = 97)				
	Estimate	SE	t	p	corrected p	Estimate	SE	t	p	corrected p
PANSS total score*×	-0.72	5.02	-0.14	0.887	1.000	-11.34	3.68	-3.08	0.003	0.018
Positive factor*×	-0.27	1.66	-0.16	0.871	1.000	-5.82	1.43	-4.05	<0.001	0.006
Negative factor*	0.72	1.89	0.38	0.704	1.000	-1.82	1.62	-1.13	0.264	1.000
Disorganized thoughts factor*	-0.33	0.73	-0.19	0.851	1.000	-1.60	1.17	-1.37	0.175	1.000
Anxiety / Depression factor *	0.20	0.85	0.24	0.813	1.000	-0.96	0.92	-1.04	0.301	1.000
Uncontrolled hostility / excitement factor*	-1.04	1.10	-0.95	0.344	1.000	-1.14	0.75	-1.52	0.134	0.804

**Controlling for sex, age, and disorder years.*
× Not significant anymore when controlling for sex, age, disorder years, BMI and antipsychotic medication history (OMN vs. OMC) in male patients.
PANSS, Positive and Negative Syndrome Scale; SE, standard error

Associations between MetS components and PANSS Disorganized thoughts factor scores by sex were also analysed (**Table 29**). In women, none of the MetS components showed significant associations with cognitive impairment after correction. In men, higher BMI was significantly associated with lower PANSS Disorganized thoughts factor scores in the uncorrected model (estimate = -0.29, p = 0.035) (**Figure 18**), but this association did not remain significant after Bonferroni correction. While no other associations reached statistical significance, the direction of effects differed between men and women for certain components, such as HDL cholesterol and fasting glucose, highlighting potential sex-specific patterns in the relationship between metabolic health and cognitive symptoms.

Table 29. Linear regression analysis of MetS components and PANSS Disorganized thoughts factor by sex

	WOMEN (n = 118)					**MEN** (n = 97)				
	Estimate	SE	t	p	corrected p	Estimate	SE	t	p	corrected p
Metabolic syndrome*	-0.33	0.73	-0.19	0.851	1.000	-1.60	1.17	-1.37	0.175	1.000
Waist circumference (cm)*	0.01	0.06	0.129	0.898	1.000	-0.07	0.04	-1.91	0.060	0.480
Triglycerides (mmol/L) *	-0.67	0.83	-0.81	0.421	1.000	-0.09	0.36	-0.26	0.798	1.000
HDL cholesterol (mmol/L) *	-3.06	3.72	-0.82	0.417	1.000	0.31	1.93	0.16	0.872	1.000
Systolic blood pressure (mmHg)*	-0.01	0.05	-0.22	0.827	1.000	-0.04	0.05	-0.91	0.365	1.000
Diastolic blood pressure (mmHg)*	-0.10	0.08	-1.28	0.203	1.000	-0.05	0.04	-1.45	0.152	1.000
Fasting glucose (mmol/L)*	0.55	0.44	1.25	0.216	1.000	-0.78	0.44	-1.79	0.078	0.624
BMI (kg/m^2)**	-0.13	0.17	-0.76	0.457	1.000	-0.29	0.13	-2.23	0.035	0.280

**Controlling for sex, age, and disorder years.*
*** Controlling for sex, age, disorder years and antipsychotic medication history (OMN vs. OMC)*
BMI, body mass index; SE, standard error

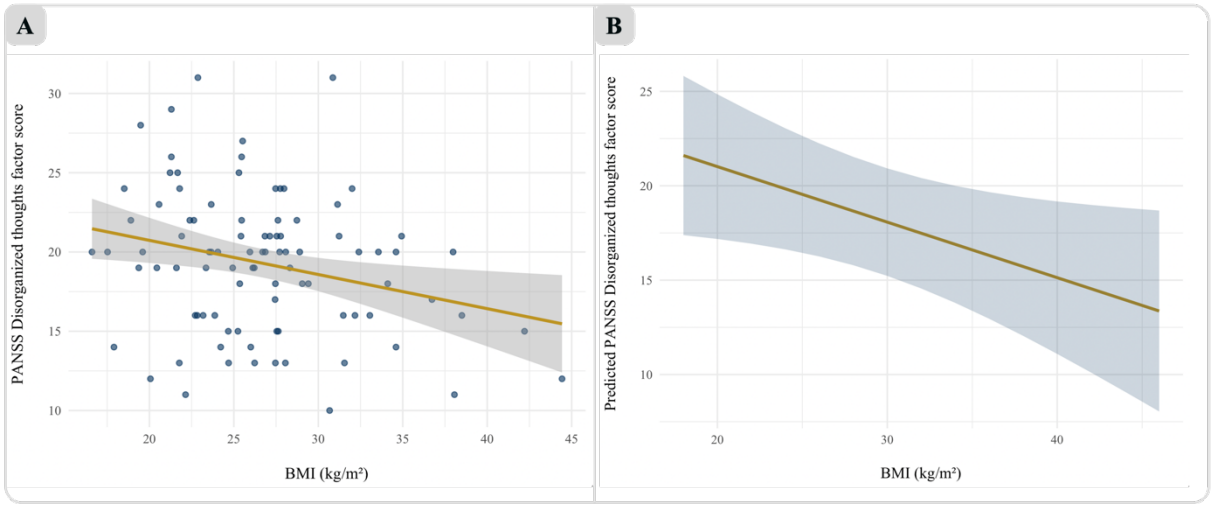

Figure 18. Relationship between BMI and PANSS Disorganized thoughts factor in men

In Figure 18A, the unadjusted association between body mass index (BMI) and the PANSS Disorganized Thoughts factor is shown for male participants. In Figure 18B, this association is presented after adjustment for relevant covariates.

3.4 Discussion

3.4.1. Summary of key findings

The present study explored whether MetS could act as a biomarker or modifiable risk factor for cognitive impairment in patients with disorders on the schizophrenia – bipolar spectrum through a systematic literature review and a real-world database analysis of Hungarian schizophrenia patients. Taken together, the systematic review highlights the potential transdiagnostic relevance of metabolic dysfunction for cognition, while the database analysis demonstrates how this relationship manifests in antipsychotic-treated schizophrenia patients. This complementary approach allows both a broad synthesis and a more focused, clinically grounded analysis.

According to the results of the systematic review, the mean prevalence of MetS across studies was 32.8% which is almost identical to the findings of the SCHIZOBANK database analysis, where MetS prevalence was 32.6%. In terms of the relationship between antipsychotic medication history and MetS, findings were not consistent anymore. Although several studies have reported a higher prevalence of MetS in patients treated with clozapine or olanzapine, this pattern was not observed in the SCHIZOBANK database, where the proportion of patients with MetS was not higher among those receiving these metabolically challenging antipsychotics. Indeed, no significant differences were observed in terms of antipsychotic medication history or duration of antipsychotic exposure between MetS and non-MetS patients, with only two exceptions: patients with MetS had longer exposure to quetiapine, while non-MetS patients had longer exposure to risperidone. While both medications are classified as metabolically challenging in this study, risperidone is often considered metabolically intermediate in the literature - a point also addressed in the limitations.

Group comparisons between MetS and non-MetS patients revealed a statistically significant difference in overall psychopathology: patients with MetS had lower PANSS total scores compared to those without MetS. In contrast, no significant group differences were observed for the Marder factor scores, including the Disorganized thoughts factor (all $p > 0.05$). This stands in partial contrast to the systematic review, where more than half of the included studies reported worse cognitive performance in patients with MetS.

In the primary analysis, examining the PANSS Disorganized thoughts factor score, none of the MetS components remained significant predictors of cognitive impairment after Bonferroni correction. Although systolic blood pressure was initially significant in the full sample, this association did not survive correction and was not observed when stratified by sex, suggesting that its relationship with cognitive symptoms is not robust.

Exploratory analyses examining BMI indicated that higher BMI was associated with lower overall psychopathology even after controlling for multiple comparisons. Despite this, the findings still suggest that neither MetS nor its individual components show consistent or strong associations with cognitive or general symptom severity when multiple testing is considered.

3.4.2. The relationship between MetS and cognitive impairment

Several review and meta-analytic studies have explored the association between MetS and cognitive impairment in individuals with disorders on the schizophrenia – bipolar spectrum (168,169,390–392). Regarding prevalence, a systematic review of 86 studies by Chadda et al. reported that MetS was significantly more prevalent among antipsychotic-treated SCHZ patients (32–68%) compared to antipsychotic-naïve individuals (3.3–26%) (393). Notably,

and in contrast to the findings from the present database analysis, their review found higher MetS prevalence among patients treated with SGAs, particularly clozapine, olanzapine, and risperidone (393). Supporting these observations, a meta-analysis by Torres et al. examining 18 studies found the prevalence of MetS among drug-naïve FEP patients to be 13.2%, a figure consistent with findings from the current systematic review (394).

With respect to the relationship between MetS and cognitive impairment, the results of two systematic reviews (390,392) and three meta-analyses (168,169,391) stand in contrast to the present study's findings, reporting significantly greater cognitive deficits in patients with SCHZ and MetS compared to those without. Specifically, Bora et al. and Hagi et al. both identified significantly worse cognitive functioning in patients with MetS, albeit with small effect sizes (ES=0.28 and 0.31, respectively) (168,169). Similarly, Zheng et al., focusing exclusively on case-control studies that utilized the RBANS, conducted a meta-analysis of six studies (all from China) reporting significant cognitive impairment among SCHZ patients with MetS (391). In the context of BD, only one systematic review was identified that specifically investigated the relationship between MetS and cognitive outcomes (392). This review, which included 36 studies (six of which focused on MetS, while the remainder examined individual metabolic components), found associations between MetS and poorer global functioning, reduced treatment response, and increased frequency of rapid cycling (392).

3.4.3. The relationship between BMI and cognitive impairment

An unexpected finding from the SCHIZOBANK database analysis was the inverse association between BMI and overall psychopathology, with higher BMI emerging as a potential protective factor. This association was observed for PANSS total scores and remained statistically significant after Bonferroni correction. In contrast, for cognitive

impairment, as measured by the PANSS Disorganized thoughts factor score, the association with BMI in men did not survive correction, indicating that the relationship with cognitive symptoms was weaker or more exploratory.

These findings align with previous literature. For instance, Wei et al. reported a negative association between BMI and overall psychopathology in patients with SCHZ, with effects primarily driven by male participants (344). Tian et al. also reported that obese SCHZ patients had significantly lower PANSS total and cognitive factor scores compared to their non-obese counterparts, alongside a significant negative correlation between BMI and both PANSS total and cognitive factor scores (395). Hui et al. also echoed these findings, noting stronger inverse correlations between BMI and PANSS scores in males but not in females (396).

Several explanations may account for this phenomenon. First, antipsychotic medications are known to promote weight gain through interactions with serotonin pathways, particularly via 5-HT_{2C} receptor blockade, which is also implicated in the improvement of clinical symptoms (395,397). Second, as clinical symptoms improve with treatment, patients may adopt healthier dietary habits and increase nutrient intake, thereby supporting cognitive function (395). Third, considering that women in the current sample exhibited higher rates of abdominal obesity (as measured by waist circumference) as well as higher rates of both clinician-rated and self-reported obesity, BMI may not serve as a reliable indicator of metabolic dysfunction. In male patients, in particular, higher BMI may reflect greater muscle mass or better physical condition rather than excess adiposity, potentially explaining its protective association with cognitive outcomes.

3.4.4. Limitations

3.4.4.1. Systematic review

A key limitation of the systematic review is the variability in the criteria used to define MetS across the included studies. While most definitions were similar, differences in diagnostic thresholds and criteria could have contributed to heterogeneity in the findings. This variability makes direct comparisons between studies more challenging and may have influenced the overall conclusions.

Another major limitation is the substantial variability in the cognitive domains assessed, as well as the methods used to measure cognitive function. Studies used a wide range of neuropsychological tests, assessing different cognitive domains and subdomains with varying degrees of sensitivity and specificity. Additionally, the statistical methods used to evaluate the relationship between MetS and cognitive impairment were inconsistent across studies. These methodological differences limit the ability to draw definitive conclusions and may have contributed to discrepancies in reported findings.

Standard limitations of systematic reviews also apply. Despite a comprehensive search strategy, there is a possibility of publication bias, where studies reporting significant findings are more likely to be published than those with null results. Additionally, although efforts were made to include all relevant studies, some studies may have been missed due to language restrictions or incomplete indexing in databases.

Furthermore, most included studies had cross-sectional designs, limiting causal interpretations. Longitudinal studies would be better suited to determine whether metabolic syndrome contributes to cognitive decline over time. Lastly, while this review aimed to

synthesize available evidence, the heterogeneity in study designs, populations, and methodologies limits the generalizability of the findings.

3.4.4.2. Database analysis

A key limitation of the SCHIZOBANK database analysis is the measurement of cognitive impairment. The PANSS Disorganized thoughts factor score was used as a proxy for cognitive dysfunction, as no specific cognitive assessment was available in the dataset. While previous literature suggests that this factor has some reliability in reflecting cognitive impairment, it is not a comprehensive measure of cognition and does not capture the full spectrum of cognitive deficits seen in schizophrenia (398,399).

Another limitation is the lack of information regarding medications used for the management of MetS. While the dataset included diagnostic status for conditions such as diabetes (fasting glucose), hyperlipidaemia (HDL cholesterol), and hypertension (blood pressure), it did not contain details on whether patients were receiving pharmacological treatment for these conditions. The use of medications such as antihypertensives, lipid-lowering agents, or antidiabetic drugs could have influenced metabolic parameters and, consequently, the observed associations.

Regarding antipsychotic medication history, most patients were exposed to a combination of metabolically challenging and metabolically neutral antipsychotics, leading to relatively small subgroup sizes for the exclusive-use groups (55 patients in the metabolically challenging only group and 24 in the metabolically neutral only group, out of 215 total). The limited sample sizes may have reduced statistical power and contributed to the absence of significant associations between MetS, antipsychotic medication history, and symptom severity.

Additionally, the classification of antipsychotic medications into metabolically challenging and neutral groups itself also presents a limitation, as the metabolic risk profile of antipsychotics is not always clear-cut. Notably, risperidone was classified as metabolically challenging, although its metabolic impact is generally considered intermediate, potentially influencing the observed associations (361).

Missing data also pose a limitation. Patients with missing values for two or more metabolic syndrome components were excluded from the analysis, yet some remaining variables still contained missing values, which could have influenced the results. Additionally, to minimize the influence of brief medication exposure, only antipsychotic treatments taken for at least 42 days (six weeks) were considered. While this criterion helps ensure a more stable medication history, it may also exclude cases where shorter exposure periods had meaningful metabolic effects.

Finally, as this study was based on a clinical registry rather than a controlled research setting, several potential confounders were unaccounted for. The timing and conditions of blood sample collection were not documented, which could introduce variability in metabolic parameter measurements. Furthermore, relevant lifestyle factors, such as smoking status, were not available in the dataset, despite their known impact on metabolic health.

3.4.5. Future research

To more accurately assess the potential role of MetS as a biomarker or modifiable risk factor for cognitive impairment in SCHZ, future research should adopt longitudinal study designs that follow patients from the time of diagnosis. Early identification of metabolic status, coupled with regular monitoring of antipsychotic medication use and the emergence of MetS,

would allow for a clearer understanding of temporal and causal relationships. Importantly, cognitive functioning should be assessed using validated neuropsychological instruments rather than symptom-based proxies.

Future studies therefore should also account for key moderating factors such as sex, age, education level, smoking status, and other environmental and lifestyle variables. Such rigorous, well-controlled, and adequately powered longitudinal studies with standardized cognitive and metabolic assessments would be essential to determine whether MetS or its individual components can any way serve as clinically meaningful predictors or markers of cognitive decline in individuals with disorders on the schizophrenia – bipolar spectrum.

3.5 Conclusion

In conclusion, while numerous prior studies support an association between MetS and cognitive impairment, particularly in domains such as memory, processing speed, attention, and executive functioning, the findings of the present study do not provide evidence to support this relationship. Based on the results of the systematic review and SCHIZOBANK database analysis, MetS as a unified construct may not serve as a reliable biomarker or modifiable risk factor for cognitive dysfunction in this population.

Although it might be possible that specific components of MetS contribute to cognitive impairment, the interplay of additional factors such as sex differences, gene–environment interactions, antipsychotic medication effects, and the cumulative burden of metabolic and psychiatric comorbidities likely adds complexity to this relationship. Despite the established role of certain antipsychotics in increasing metabolic risk, this study did not identify a significant association between medication history and MetS status.

Interestingly, the findings also revealed an inverse association between BMI and overall psychopathology. While counterintuitive, this observation aligns with previous research suggesting that higher BMI may reflect better physical condition or nutritional status rather than metabolic dysfunction in some cases. These results underscore the complexity of interpreting BMI in psychiatric populations and suggest that weight-related measures may not uniformly indicate health risk, but rather interact with other factors such as sex, treatment response, and lifestyle changes during illness management.

The variability in findings across studies, including this one, may reflect differences in sample characteristics, diagnostic thresholds, cognitive assessment tools, and treatment regimens. Ultimately, these results underscore the need for future research to disentangle the multifactorial relationship between metabolic dysfunction and cognitive impairment, with greater attention to longitudinal designs, standardized assessments, and the moderating role of individual patient characteristics.

4

The development & application of the Transdiagnostic Global Impression Psychopathology scale

Most of the content in this chapter has been published in the *European Neuropsychopharmacology* "The Transdiagnostic Global Impression - Psychopathology scale (TGI-P): Initial development of a novel transdiagnostic tool for assessing, tracking, and visualising psychiatric symptom severity in everyday practice" (400) and in *European Psychiatry* "Advancing measurement-based care through triangle of care: Development and feasibility of the Transdiagnostic Global Impression - Psychopathology scale for patients and informants" (401).

4.1. Introduction

The preceding chapters examined the potential of two transdiagnostic biomarkers (BDNF (**Chapter 2**) and MetS (**Chapter 3**)) as proxy indicators of cognitive impairment that could be feasibly implemented in routine clinical practice. Although both biomarkers appeared promising in theory, the findings indicated that neither BDNF nor MetS demonstrated the necessary specificity or reliability for everyday clinical use. These results underscore and reinforce a broader challenge discussed in **Chapter 1**: the lack of practical, scalable tools for measuring transdiagnostic symptoms, particularly cognitive impairment, in real-world psychiatric settings (402,403).

As highlighted in **Chapter 1**, MBC is a critical component of high-quality psychiatric practice (207). When routinely implemented, it is associated with improved clinical outcomes and more personalized treatment planning (203,207,208). However, despite its clear benefits,

MBC is not always feasible in fast-paced clinical environments (247). In both outpatient and inpatient settings, time constraints and high caseloads often prevent clinicians from conducting comprehensive interviews or administering lengthy symptom rating scales (250). It is also important to note, that MBC is not a substitute for clinical judgment but rather a tool to enhance and objectively support the assessment and monitoring of a patient's progress by experienced clinicians (214). Yet, to gain a meaningful and holistic understanding of a patient's mental state, it is essential to assess multiple symptom domains, not just the core diagnostic criteria. Brief tools that provide broad symptom coverage can help identify key areas of concern, which can then be explored in more depth if needed (214,247).

4.1.1. Rationale

Given the limitations of current biomarker approaches (404), there is a pressing need to return to the gold standard of clinical assessment, psychiatric rating scales that can meaningfully support decision-making without overburdening clinicians or patients (405). Most of the existing cognitive assessment scales however, even in their abbreviated forms, require significant time and training, making them difficult to integrate into routine psychiatric visits (248,406,407). As a result, many clinicians forego cognitive assessment altogether, missing critical insights that could inform treatment planning (247,408).

While the focus of this thesis is cognitive impairment, it is important to recognise that cognitive symptoms do not occur in isolation. Cognitive dysfunction is often closely linked to other transdiagnostic symptoms, such as affective and negative symptoms, which may interact and compound overall functional impairment (15). As such, any meaningful assessment of cognition should ideally occur within a broader clinical framework that acknowledges and evaluates these interconnected symptom domains.

To support this approach, there is a pressing need for a new type of clinical instrument: one that is brief, intuitive, and feasible to use across diagnostic categories (214,247). Such a tool should facilitate the rapid identification of problematic domains, including cognition, and help clinicians determine when more detailed evaluation is warranted. Importantly, it should also align with the growing movement toward MBC in psychiatry, allowing for consistent symptom monitoring without increasing clinical workload. Thus, the development and application of such a multidimensional, transdiagnostic assessment tool is the focus of the present chapter.

4.1.2. Aims & objectives

The overarching aim of this chapter is to describe the development and preliminary validation of the Transdiagnostic Global Impression – Psychopathology (TGI-P) scale, a novel rating instrument designed to measure and visualize the severity of key symptom domains independent of diagnosis and to be feasible for use in everyday clinical practice.

The objectives of the chapter are:

1. To provide an overview of the methodology behind developing a psychiatric rating scale.
2. To present the development process of the TGI-P scale.
3. To explore the clinical applicability and feasibility of the TGI-P scale in a sample of inpatients with psychotic disorders.
4. To evaluate the feasibility of the TGI-P scale by comparing administration time with established measures.
5. To examine the psychometric properties of the TGI-P scale, including internal consistency, inter-rater reliability, and construct validity.

4.2 Methods

4.2.1. The process of scale development

As outlined by Boateng and colleagues, the development of psychiatric rating scales follows a structured process (409). It is comprised of three key phases: Phase I: item development; Phase II: scale construction; and Phase III: scale evaluation (409). The first phase involves defining the construct of interest, then the development of items using deductive and inductive approaches such as literature search, as well as the expert evaluation of content validity with potential feedback from the target population (409). Then, scale construction (Phase II) includes the pre-testing of items to assess clarity and comprehension and the administration of the survey to a representative sample (409). By taking the results of these steps into consideration, the scale is then refined accordingly i.e., redundant or poorly performing items are removed through statistical techniques such as item analysis and exploratory factor analysis (409). The last phase, scale evaluation, involves the real-world testing of the scale thus ensuring reliability through measures like internal consistency and test-retest reliability, and establishing validity by assessing criterion validity and construct validity (409). Adhering to this rigorous, multi-step process ensures the reliability and validity of the scale, as well as enhances its quality and applicability, facilitating effectiveness when used in research and everyday clinical settings (409). A summary of the scale development process is presented in **Figure 19**.

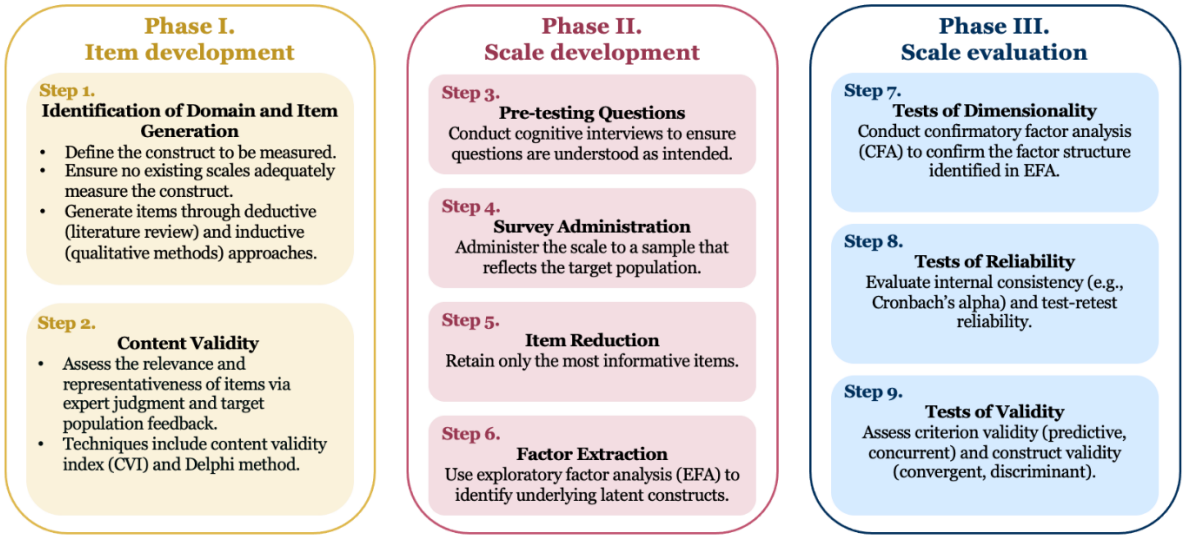

Figure 19. The process of scale development

The figure shows the steps of psychiatric rating scale development as outlined by Boateng et al. 2018.

4.2.2. Phase I. Item development

4.2.2.1. Identification of domain & item generation

The scale development process began with the identification of the domain of interest. Reviewing the literature, a gap was identified in the availability of transdiagnostic scales that are capable of assessing a broad range of symptoms across multiple psychiatric disorders. The aim was to develop a simple yet comprehensive scale that is applicable in everyday clinical settings, therefore allowing psychiatrists to use it instead of choosing disorder-specific instruments. The choice of domains was guided primarily by expert consensus rather than a systematic review, with the goal of capturing the most common and clinically relevant psychiatric symptoms. Since simplicity and quickness were top priority, six initial items were identified at this step by the author of the thesis and then discussed with senior colleagues (Dr Ágota Barabássy and Dr György Nemeth) at Gedeon Richter Plc.

4.2.2.2. Content validity

To establish content validity, qualitative feedback was gathered through video interviews with two professors (Professor Roger S. McIntyre (R.S.M.), University of Toronto and Professor Christoph U. Correll (C.U.C.), Charite University Medicine), who have extensive experience in both scale development and treatment of various psychiatric disorders. These experts were asked to evaluate the scale's comprehensiveness and identify any missing symptom domains. Through multiple discussions and iterative feedback, they suggested expanding the initial item set to improve coverage while maintaining brevity. Based on their recommendations, four additional items were incorporated, bringing the total number to ten. This approach ensured that the scale remained clinically practical while capturing a broad spectrum of psychopathology. Based on their feedback, patient- and caregiver-filled versions were also developed. In addition, the name of the scale, Transdiagnostic Global Impression – Psychopathology (TGI-P) scale was decided.

4.2.3. Phase II. Scale development

4.2.3.1. Pre-testing questions

The pre-testing of the transdiagnostic scale was conducted via an anonymous, online survey involving 36 psychiatrists from three countries: the United States, Germany, and Poland. The aim was to gain a deeper understanding of the initial impression on the clarity and comprehensibility of the items as well as gather opinions on the scale's content and visual elements. Participants were recruited through a research agency, ensuring anonymity. The research was funded by Gedeon Richter Plc. The survey questions (**Appendix A**) and a ten-minute explanatory video about the scale was developed by the author of the thesis. The video was provided to introduce the scale's background, which was then followed by survey questions assessing the clinicians' perceptions of the scale, asking about potential missing elements, and the perceived utility of the visual components. Additionally, further questions

addressed the general attitudes towards psychiatric scales, confirming the hypothesis that only a minority of clinicians (approximately 20% according to existing literature (250)) utilize symptom rating scales in routine practice. Participants also had the chance to try out the new scale by rating a fictional patient (**Appendix B**).

4.2.3.2. Survey administration

The following step was the administration of a survey to a sample representative of the target population, comprising 50 participants including 25 patients and 25 caregivers. The included patients had diagnoses of SCHZ, BD or MDD. The caregivers were not matched with the patients; however, they were also caring for patients with these psychiatric disorders. The patients and caregivers were approached by the same research company and their identity remained anonymous. This study was also funded by Gedeon Richter Plc. In the online survey, participants were first asked to interact with the scale by self-rating (for patients) or rating the patient they cared for (for caregivers) and second, to provide feedback on the clarity and acceptability of the wording of the questions, the usefulness of the visual format, and their general attitudes towards the use of scales during clinical visits (**Appendix C**). Given that the scale was in English, the participants were drawn from English-speaking populations (the United States (n = 25) and the United Kingdom (n = 25)) to account for potential cultural differences in perception.

4.2.3.3. Item finalization

Instead of item reduction, which is typically performed to eliminate redundant items, the focus of this stage was to fine-tune and finalize the scale based on the feedback of participants. Adjustments were made to enhance clarity and relevance while maintaining the original number of items.

4.2.4. Phase III. Scale validation

4.2.4.1. Protocol

The final phase of scale development as described by Boateng et al., is the evaluation of the psychometric properties of the scale through tests of dimensionality, reliability, and validity (409). To achieve this, a comprehensive study protocol was developed. The protocol outlines the procedures for examining the internal consistency, reliability and validity of the scale. Validity assessment will include test of concurrent validity, as well as criterion validity to examine the scale's ability to predict relevant clinical outcomes. Reliability will be assessed through internal consistency measures, such as Cronbach's alpha. This psychometric testing process is a lengthy process and therefore it is still ongoing. Results are expected to be available at a later stage before the finalization of the thesis. The protocol is presented in a table format, summarizing the planned methods, statistical analyses, and criteria for evaluating each psychometric property (**Table 30**).

Table 30. Protocol for testing the validity and reliability of the TGI-P scale clinician version

SCALE
TGI – Psychopathology scale: Clinician, Patient & Informant version
INDICATION
• Adult individuals with a diagnosis of **schizophrenia** • Adult individuals with a diagnosis of **bipolar disorder** (including bipolar mania patients) • Adult individuals with a diagnosis of **major depressive disorder**
AIM
To evaluate the validity and reliability of the TGI-P scales
OBJECTIVES
• To evaluate the **concurrent validity** of TGI-P by comparison with established scales • To evaluate the **internal consistency** of TGI-P by using Cronbach's alpha to evaluate the consistency of items • To evaluate the **sensitivity to change** of TGI-P by measuring how well TGI-P detects changes over time, particularly in response to treatment
STUDY DESIGN
Prospective cohort study
STUDY RATIONALE
There is a high need for a brief, reliable and valid transdiagnostic instrument to assess the diverse symptoms of psychiatric disorders.

NUMBER OF SUBJECTS

90 participants (30 / diagnostic group – 15 inpatients & 15 outpatients)

- 30 schizophrenia patients
- 30 major depression patients
- 30 bipolar disorder patients with at least 8 bipolar mania patients

ENTRY CRITERIA

Diagnosis of schizophrenia, bipolar disorder, or major depressive disorder according to the DSM-V criteria.

PI

TBD

STUDY SITES:

UK / US / Canada / Australia (raters with experience)

TIMELINE

- Baseline Visit (**Visit 1**): Initial assessment.
- Follow-Up Visit (**Visit 2**): Assess test-retest reliability and initial sensitivity to change. For inpatients, this would be at discharge (not shorter than 1 week), for outpatients this would be at their next regular visit.

CRITERIA FOR EVALUATION

- Transdiagnostic Global Impression – Psychopathology (TGI-P)
- Positive and Negative Syndrome Scale (PANSS)
- Young Mania Rating Scale (YMRS)
- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Drug Abuse Screening Test (DAST-10)

STATISTICS

1. Pearson correlation between TGI-P items & total- and sub-scores of validated rating scales:

TGI – Positive	• PANSS Positive factor score • YMRS item 8
TGI – Manic	• YMRS total score
TGI – Hostility	• PANSS Uncontrolled hostility/ Excitement factor score • YMRS item 5 & 9
TGI – Addiction	• DAST-10 total score
TGI – Sleep	• MADRS item 4 • YMRS item 4
TGI – Self-harm	• MADRS item 10
TGI – Anxiety	• PANSS Anxiety-Depression factor score • MADRS item 3
TGI – Cognitive	• PANSS Disorganized factor score • MADRS item 6 • YMRS item 7
TGI – Negative	• PANSS Negative factor score • MADRS items 7 & 8
TGI – Depressive	• PANSS Anxiety-Depression factor score • MADRS total score

2. Effect size of changes in TGI-P, PANSS, YMRS, MADRS, DAST-10 scores from baseline to last visit

3. Cronbach's Alpha: To assess internal consistency

4. Bland-Altman Plot: To assess agreement between scales

5. Multivariate Analysis of Variance (MANOVA): To compare scores across diagnostic groups.

4.2.5. Small-scale cross-sectional feasibility study

Although a formal validation of the TGI-P scale is planned, to gain preliminary hands-on experience with the scale in real world setting was also important. Therefore, a small-scale cross-sectional feasibility study was conducted in an acute psychiatric ward. The purpose of the study was not to establish definitive psychometric properties, but rather to test the scale in clinical practice, assess its feasibility, and provide the author with direct experience of its use in everyday psychiatric care.

4.2.5.1. Study design

This was a small-scale cross-sectional feasibility study conducted in the Acute Psychiatric Ward of the Department of Psychiatry and Psychotherapy at Semmelweis University in Budapest, Hungary. All participants provided written informed consent to take part in the study. The study was reviewed and approved by the local institutional ethics committee.

As per protocol, after admission, patients underwent a structured clinical assessment conducted by a consultant psychiatrist (Dr Levente Hermán) and the author of the thesis (Zs.B.D.). The assessment was composed of three parts; first, a short interview was conducted where patients were asked about their clinical background. Next, the PANSS was administered by the clinician with the author of the thesis participating as a silent observer. Finally, the cognitive functioning of patients was assessed by the author using the ACE scale. Both the clinician and the author completed the TGI-P scale independently following the clinical interview. The results of the PANSS and ACE scales were only visible to the investigators after scoring the TGI-P, therefore minimising bias. As one of the aims of the feasibility study was to assess the practical burden of psychiatric instruments in real-world settings, the duration of each assessment phase was measured.

4.2.5.2. Inclusion & exclusion criteria

Participants were eligible for inclusion if they were adult inpatients (aged 18 years or older) with a diagnosis of a psychotic disorder, including schizophrenia, schizoaffective disorder, psychotic bipolar disorder, or other non-affective psychotic disorders, as diagnosed by their treating clinical team. All participants were receiving inpatient psychiatric care at the time of assessment and were considered clinically stable enough to participate in a structured interview. Exclusion criteria included the presence of a primary neurodegenerative disorder, a diagnosis of intellectual disability, or any condition that impaired the patient's capacity to provide informed consent. Patients were also excluded if they were unable to engage with the assessment procedures due to the severity of their psychiatric symptoms, cognitive impairment, or physical health issues.

4.2.5.3. Scales

A detailed description of the TGI-P scale is in **Chapter 4**. The TGI-P is composed of ten symptom domains, rated on a Likert scale from 1 (normal / absent) to 7 (extreme severity), similarly to the CGI-S scale. The scores are then mapped on a symptom-web, therefore providing a visual summary of the patient's clinical status.

The PANSS is a clinician-rated instrument widely used to assess symptom severity in individuals with psychotic disorders. It consists of 30 items divided into three subscales: Positive Symptoms (7 items), Negative Symptoms (7 items), and General Psychopathology (16 items). Each item is rated on a 7-point scale ranging from 1 (absent) to 7 (extreme). In the present study, the PANSS was administered through a semi-structured clinical interview conducted by an experienced psychiatrist. The Marder factor model was used to derive domain-specific scores (Positive, Negative, Disorganized Thoughts, Hostility/Excitement,

Anxiety/Depression) (367), allowing for item-level comparisons with corresponding domains in the TGI-P scale.

The ACE is a brief, structured cognitive screening tool used to assess global cognitive functioning across multiple domains (254). It includes items assessing orientation, concentration, memory, verbal fluency, language, and visuospatial abilities, with a total possible score of 100. The ACE has been validated in both neurological and psychiatric populations and is sensitive to cognitive impairments in schizophrenia and related disorders (275,276,278–280). In this study, the ACE was administered by the author following standard instructions. The total and MMSE score were used as an index of global cognitive function and correlated with the Cognitive symptom domain item of the TGI-P.

4.2.5.4. Statistical analyses

Given the small sample size, the statistical analyses were primarily descriptive and exploratory in nature. Means, standard deviations, and percentages were calculated for demographic characteristics and scores on the TGI-P, PANSS, and ACE, as well as for the time required to administer each scale.

Internal consistency of the TGI-P for both raters was assessed using Cronbach's alpha, calculated across all ten symptom domains. Since the TGI-P assesses multiple distinct symptom domains rather than a single unified construct, a low Cronbach's alpha is expected and appropriate in this context.

Inter-rater reliability was evaluated by comparing TGI-P scores independently rated by L.H. and Zs.B.D. Intraclass correlation coefficients (ICC) were calculated using a two-way random effects model with absolute agreement. Additionally, for cognitive symptoms, a Bland–

Altman plot was generated to visually assess the degree of agreement between raters and to identify any systematic bias across the range of scores.

To examine construct validity, Spearman's rank correlations were computed between TGI-P items and matched PANSS Marder factor scores (367) and individual PANSS items, based on theoretical overlap (**Table 31**). Except three TGI items (addiction, sleep and self-harm symptoms), all items were matched with a factor or total score or individual item. Strong correlations between related constructs were interpreted as evidence of convergent validity, while low correlations with unrelated domains suggested divergent validity. Correlations were also calculated between the TGI-P Cognitive symptom domain item and the PANSS Disorganized Thoughts factor, and ACE total and MMSE scores to explore its alignment with established measures of cognitive impairment. The feasibility of administering the TGI-P was assessed by comparing the time required to complete the TGI-P with that of the PANSS and ACE. Descriptive statistics were used to summarize administration times across patients.
All quantitative analyses were conducted using RStudio version 2024.04.2+764.

Table 31. TGI-P items matched with establish scales

TGI – Psychopathology items	Established scales for comparison
Positive symptoms	PANSS Positive factor score
Manic symptoms	PANSS P5 – Grandiosity
Hostility symptoms	PANSS Uncontrolled excitement / Hostility factor score
Addiction symptoms	-
Sleep symptoms	-
Self-harm symptoms	-
Anxiety symptoms	PANSS Anxiety / Depression factor score
	PANSS G2 - Anxiety
Cognitive symptoms	PANSS Disorganized thoughts factor score
	ACE Total score
	ACE MMSE score
Negative symptoms	PANSS Negative factor score
Depressive symptoms	PANSS Anxiety / Depression factor score
	PANSS G6 – Depression

ACE, Addenbrooke's Cognitive Examination; MMSE, Mini Mental State Examination; PANSS, Positive and Negative Syndrome Scale; TGI, Transdiagnostic Global Impression

4.3 Results

4.3.1. Item development

Originally, six transdiagnostic symptom domains were identified as items through the literature review. These items were positive symptoms, negative symptoms, manic symptoms, depressive symptoms, addiction symptoms and cognitive symptoms.

4.3.1.1. Positive symptoms

Positive symptoms are composed of delusions, hallucinations, disorganised thinking, disorganised speech, and abnormal motor behaviour. While these symptoms are traditionally linked to schizophrenia (6), they are now widely recognized as transdiagnostic features occurring across various psychiatric disorders (410). Indeed, a community-based study involving three thousand adolescents and young adults with depressive or anxiety disorders, but no history of psychotic disorder, found that 27% exhibited at least one psychotic symptom, compared to 14% of those without these disorders (411). Furthermore, research also reports the occurrence of positive symptoms in borderline personality disorder, BD, PTSD, as well as schizoaffective disorder (412–414) (**Table 32**).

4.3.1.2. Negative symptoms

The term, negative symptoms, derives from the concept of a diminished or impaired capacity for normal functioning, reflecting deficits in typical emotional, cognitive, or behavioural processes (415,416). Negative symptoms encompass apathy, avolition, asociality, alogia, and affective blunting, collectively referred to as the '5-As' (415). Although these symptoms are primarily associated with schizophrenia spectrum disorders including schizoaffective and schizotypal personality disorder (415,417), they are also core features of numerous other disorders, such as BD, MDD, and PTSD, albeit not explicitly labelled as negative symptoms (417). In addition, apathy frequently appears in neurodegenerative disorders such as HD or

PD (418,419), while (social) anhedonia is common in anxiety disorders, eating disorders, ASD, and substance use disorders (SUD) (417,420–424).

4.3.1.3. Manic symptoms

Mania is characterized by expansive mood, grandiosity, racing thoughts, increased energy, and excessive engagement in pleasurable activities (425). While it is a distinct syndrome, it is also a core feature of BD (425). Beyond BD, studies have identified significant associations between manic symptoms and PTSD (426,427), as well as attention deficit hyperactivity disorder (ADHD) and ASD in children (428,429). Additionally, a substantial proportion of patients with SCHZ (25%) exhibit subthreshold manic symptoms, which correlate with positive symptoms (430). This overlap may stem from the phenotypic similarities between psychotic mood disorders and SCHZ, leading to misdiagnoses where patients with mania are classified as schizophrenic due to their psychotic features (430). Manic symptoms are also reported in unipolar depression and anxiety disorders, where they are associated with greater illness severity and a higher risk of suicide attempts (431). A strong link exists with SUD, largely due to the increased likelihood of mania leading to substance dependence (432). In neurodegenerative disorders, mania is more prevalent in conditions affecting the ventral frontal and temporal regions, such as frontotemporal dementia (433,434).

4.3.1.4. Depressive symptoms

Depressive symptoms, including low mood, consummatory anhedonia, sadness, hopelessness and helplessness, are core features of unipolar and bipolar depression (6) as well as SCHZ (435). Additionally, depressive symptoms are strongly associated with anxiety disorders (436), eating disorders (437,438), neurodevelopmental disorders such as ASD and ADHD (439,440), neurodegenerative disorders including HD and PD (441), personality disorders, particularly borderline personality disorder (BPD) (442), PTSD (443) and SUD (444).

Importantly, depressive symptoms are often associated with more severe symptoms in anxiety disorders (445) and SCHZ (446), decreased treatment response in generalized and social anxiety disorder (436), as well as increased risk of relapse in SUD (447). All in all, depressive symptoms can truly be regarded as transdiagnostic symptoms, as they are shared across mental health disorders and may be better targeted by biomarkers that map onto these shared symptoms (23).

4.3.1.5. Addiction symptoms

Symptoms of addiction are impaired control over substance use or behaviours, craving, physical or psychological dependence, compulsive engagement, and symptoms of withdrawal. These symptoms are central to SUD and also manifest in eating disorders such as bulimia nervosa and binge eating disorder in the form of food addiction (448–451). Among psychiatric populations, the most common substance addictions involve alcohol, tobacco, cannabis, and cocaine (452,453). Behavioural addictions, such as pathological gambling, problematic internet use, online gaming, compulsive sexual behaviour, and compulsive buying, frequently co-occur with depressive, anxiety, and BD (453–455) as well as ASD (456). Depressive disorders, in particular, are often comorbid with addictive behaviours, as individuals may use substances to cope with feelings of sadness and anxiety (457). Substance use is also highly prevalent among individuals with ADHD (458), BPD (459,460), schizophrenia spectrum disorders (461) and PTSD (462). In PTSD and SCHZ, frequent substance use may align with the self-medication hypothesis, where substances are used to alleviate distressing symptoms (463,464). Importantly, approximately 78% of adults with BPD experience a substance-related disorder or addiction during their lifetime (459). In neurodegenerative disorders, especially in PD, addiction-like behaviours can emerge due to dopamine dysregulation (465).

4.3.1.6. Cognitive symptoms

Cognitive symptoms can be described as problems with learning and memory, language, perceptual-motor function, executive function, attention and social cognition (32). As discussed in **Chapter 1**, cognitive impairment is continuously reported to be transdiagnostic symptom domain, as it is present in multiple psychiatric disorders independently from diagnosis (15,31). It is considered to be a core symptom in SCHZ, BD, MDD, PTSD (466), SUD (467,468), neurodegenerative disorders such as AD or HD (403) as well as neurodevelopmental disorders like ASD or ADHD (77,469,470). Furthermore, it is strongly associated with anxiety disorders (471), eating disorders (472), and personality disorders (473,474). Evidence suggests that shared mechanisms may underlie cognitive dysfunction across diagnostic boundaries, though these impairments could also stem from distinct underlying causes converging on common final pathways (475). Notably, cognitive symptoms and functional outcomes are interconnected. For instance, cognitive impairment in MDD is associated with poorer general functioning, including unemployment and decreased psychosocial functioning (476,477).

Table 32. The prevalence of the identified six symptom domains in major psychiatric disorders

SYMPTOMS / DISORDERS	Positive	Negative	Manic	Depressive	Addiction	Cognitive
Anxiety disorders	●	●	●	●	●	●
Bipolar disorders	●	X	X	X	●	X
Eating disorders	○	●	○	●	X	●
Depressive disorders	●	X	●	X	●	X
Neurodevelopmental disorders*	●	●	●	●	●	X
Neurodegenerative disorders**	○	●	○	●	○	X
Personality disorders	●	X	○	●	●	●
PTSD	X	X	●	●	●	X
Schizophrenia spectrum disorders	X	X	●	X	●	X
Substance use disorders	○	●	○	●	X	X

X – *core symptom;* ● – *associated symptom;* ○ – *rare symptom*
**Autism spectrum disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Intellectual Disabilities (ID)*
***Alzheimer's disease and dementias, Huntington's disease (HD), Parkinson's disease (PD)*

4.3.2. Content validity

Expert feedback highlighted the gaps in the initial six-item scale, leading to the addition of anxiety, sleep, hostility, and self-harm symptom domains. One expert (R.M.) emphasized the relevance of anxiety and sleep symptoms, while the other expert (C.U.C.) recommended hostility and self-harm symptoms to enhance the scale's applicability. With these additions, both experts agreed that the revised ten-item scale provides a comprehensive yet concise tool for assessing transdiagnostic psychiatric symptoms (**Table 33**).

4.3.2.1. Anxiety symptoms

Symptoms of anxiety include nervousness, tension, hypervigilance, panic, social inhibition, anxious withdrawal, and ruminative thoughts. Anxiety symptoms are prevalent across psychiatric disorders, with studies showing that 40-60% of patients with schizophrenia spectrum, BD, MDD, eating disorders, SUD, and neurodegenerative disorders such as AD or PD report experiencing frequent or persistent anxiety (478–482). Moreover, anxiety is a core symptom of anxiety disorders such as panic disorder, generalized anxiety disorder, social anxiety disorder and PTSD, where it plays a central role in diagnosis and disease progression (483). Symptoms of anxiety, especially particularly generalized and separation anxiety, are also common in children with autism and ADHD (484). In terms of personality disorders, a prospective, 7-year study involving 499 individuals reported specific associations between schizotypal, avoidant, obsessive-compulsive, and borderline personality disorders with the progression, remission, and chronicity of various anxiety disorders (485).

4.3.2.2. Sleep symptoms

Although hypersomnia and insomnia are not psychiatric symptoms per se, they are highly prevalent in psychiatric disorders and have a significant impact on symptom presentation and disease progression (486–488). Indeed, recent evidence shows that sleep disturbances, often

viewed as a secondary symptom of PTSD, are in fact a core feature, frequently persisting even after successful PTSD treatment (489). Sleep symptoms are also integral to BD, with different phases of the disorder being characterized by distinct sleep disturbances: manic episodes are linked to reduced sleep need and insomnia, depressive episodes to hypersomnia and insomnia, and mixed episodes to a variety of sleep disturbances (490,491). Sleep disturbances and circadian rhythm disruptions are a core feature of neurodegenerative disorders as well, often occurring early in disease progression and potentially serving as preclinical signs (492,493). In addition, nearly all patients with MDD report experiencing insomnia, and in those with SCHZ, insomnia often serves as an early sign of worsening psychotic symptoms (487). Sleep disturbances are also linked to anxiety, personality and eating disorders, ADHD and SUD (494).

4.3.2.3. Hostility symptoms

Hostile behaviours such as anger, tension, uncooperativeness, impulsivity, aggression, irritability are integral to several psychiatric disorders such as schizophrenia spectrum (495,496) and personality disorders (497). Hostility is also associated with depressive (498), anxiety (499) and eating disorders (500), BD (501), as well as SUD (502,503). Importantly, research showed that patients with psychiatric disorders and concurrent substance use have a higher risk of violent behaviour compared to those with former or no substance use (504). In anxiety disorders, increased hostility towards others, especially in panic and agoraphobia is common, though socially anxious individuals tend to exhibit less aggressive behaviour (499). High levels of hostility, especially anger and aggression are commonly experienced by veterans with PTSD (505,506). In addition, aggression, including physical harm, and verbal abuse is well-documented in AD and emerging research suggests a similar prevalence in PD, while irritability and unpredictable anger outbursts are common in HD, affecting 38-73% of gene carriers (507–510). Nonetheless, children with ASD show less aggression compared to a

clinic-referred comparison group, and their aggression is more likely to be reactive rather than proactive (511).

4.3.2.4. Self-harm symptoms

The engagement in s non-suicidal self-injury is highly prevalent in patients with SCHZ (512,513), MDD, BD, anxiety, eating disorders (514) and personality disorders, ADHD, PTSD as well as SUD (513–518). Importantly, individuals with BD have a higher prevalence of self-harm and a stronger association with impulsivity compared to those with unipolar depression (519). In patients with SCHZ and concomitant substance misuse, self-harm is associated with specific psychotic symptoms, particularly command hallucinations and threat control override symptoms (520). Research also indicates that around 90% of individuals who die by suicide have a diagnosed psychiatric disorder (515). The psychiatric conditions most commonly linked to suicide include mood disorders, especially MDD, personality disorders as well as SUD and SCHZ (521,522).

Table 33. The prevalence of the four additional symptoms in major psychiatric disorders

SYMPTOMS / DISORDERS	Anxiety	Sleep	Hostility	Self-harm
Anxiety disorders	**X**	●	●	●
Bipolar disorders	●	X	●	●
Eating disorders	●	●	●	●
Depressive disorders	●	●	●	●
Neurodevelopmental disorders*	●	●	○	●
Neurodegenerative disorders**	●	X	●	●
Personality disorders	●	●	**X**	●
PTSD	**X**	X	●	●
Schizophrenia spectrum disorders	●	●	**X**	●
Substance use disorders	●	●	●	●

X – *core symptom;* ● – *associated symptom;* ○ – *rare symptom*

**Autism spectrum disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Intellectual Disabilities (ID)*

***Alzheimer's disease and dementias, Huntington's disease (HD), Parkinson's disease (PD)*

4.3.3. Pre-testing of questions

A survey was conducted among 36 psychiatrists from three countries (the United States, Poland, and Germany) to capture varying perspectives on psychiatric rating scales in general as well as to understand the first impression regarding the TGI-P scale. These countries were selected in order to represent different patterns and opinions. The sample consisted predominantly of male participants (69%), with most psychiatrists having 10 - 20 years of professional experience (44%) and various patient sizes (**Table 34**).

Table 34. Participant characteristics of the clinician survey

	TOTAL	United States	Poland	Germany
Sex, n (%)				
Male	69	75	33	100
Female	31	25	67	0
Clinical experience, n (%)				
Less than 10 years	31	67	8	17
10 -20 years	44	33	33	67
More than 20 years	25	0	58	17
Total patient size				
Less than 500	33	25	50	25
500 – 1000	33	50	33	17
More than 1000	33	25	17	58

4.3.3.1. General attitudes towards rating scales

The survey regarding the general attitudes towards rating scales among clinicians in the U.S., Poland, and Germany highlights notable trends and barriers (**Table 35**). According to the responses, the majority (47%) of doctors use rating scales occasionally, while 33% use them frequently but not always, and only 8% utilize them at every visit. The primary reasons for using rating scales include diagnosis support (69%), monitoring symptom severity (69%), and tracking disease progression (50%). However, significant barriers to their use include limited time during visits (89%), patient discomfort (36%), and perceived lack of additional value (25%). Indeed, most clinicians (67%) spend less than 10 minutes on rating scales and 19% between 10 to 20 minutes. Importantly, 36% of physicians always explain the results to patients or caregivers, with another 28% doing so frequently.

When evaluating symptoms, clinicians predominantly rely on patient observation (89%) and direct questioning (83%), while only 53% incorporate rating scales. Similarly, for monitoring disorder progression, most clinicians refer to previous reports (75%) and question the patient or caregiver (75%), whereas only 56% use rating scales. Regarding the preferred characteristics of rating scales, validity and reliability are deemed the most important factors (42%), followed by time efficiency (39%) and simplicity (14%). In terms of format, the majority (56%) prefer a combination of physician- and patient-rated scales, while 28% favour physician-rated tools, and only 3% prefer exclusively patient-rated scales. Notably, a small minority (3%) prefer not to use rating scales at all.

Across countries, Polish clinicians show a higher tendency to use rating scales for monitoring disease progress (75%). In addition, the U.S. shows a higher preference for time-efficient tools (67%), while German respondents prioritize validity and reliability (67%). Overall, the findings indicate that while rating scales are recognized as valuable tools in clinical practice, practical constraints, particularly time limitations, hinder their consistent implementation.

Table 35. General attitudes of psychiatrists towards rating scales

General attitudes towards rating scales, N (%)	TOTAL	U.S.	Poland	Germany
Usage frequency of rating scales*				
Almost never	4 (11)	1 (8)	1 (8)	2 (17)
Occasionally	17 (47)	(42)	3 (25)	4 (33)
Frequently, but not always	12 (33)	5 (42)	8 (67)	4 (33)
Every time	3 (8)	1 (8)	-	2 (17)
Top reasons of using rating scales**				
Diagnosis support	25 (69)	10 (83)	8 (67)	7 (58)
Monitoring severity of symptoms	25 (69)	11 (92)	10 (83)	9 (75)
Quantification of symptoms	10 (56)	9 (75)	2 (17)	9 (75)
Monitoring disease progress	18 (50)	6 (50)	9 (75)	7 (58)
Top barriers of using rating scales**				
Limited time at visit	32 (89)	(100)	11 (83)	11 (83)
Bothersome for patients	13 (36)	5 (42)	5 (42)	3 (25)
Does not bring any additional value	9 (25)	1 (8)	3 (25)	5 (42)
High costs	3 (8)	1 (8)	2 (17)	-
Average time spent on rating scales at visits*				
Less than 10 minutes	24 (67)	(83)	7 (58)	7 (58)
10 – 20 minutes	7 (19)	1 (8)	4 (33)	2 (17)
20 – 40 minutes	4 (11)	1 (8)	1 (8)	2 (17)
No use of scales	1 (3)	-	-	1 (8)
Explaining results to patients / caregivers*				
Always	13 (36)	5 (42)	3 (25)	5 (42)
Not always, but frequently	10 (28)	2 (17)	3 (25)	5 (42)
Sometimes	12 (33)	5 (42)	5 (42)	2 (17)
Do not to use scales	1 (3)	-	1 (8)	-
Symptom evaluation at visits**				
By observing the patient	32 (89)	11 (92)	12 (100)	9 (75)
By questioning the patient	30 (83)	9 (75)	12 (100)	9 (75)
By questioning the caregiver	23 (64)	(67)	9 (75)	6 (50)
Using rating scales	19 (53)	5 (42)	5 (42)	9 (75)
Disorder progress monitoring at visits**				
Reading previous visit reports	27 (75)	9 (75)	11 (92)	7 (58)
By questioning the patient / caregiver	27 (75)	8 (67)	10 (83)	9 (75)
Remembering the previous visit	21 (58)	7 (58)	7 (58)	7 (58)
Using rating scales	20 (56)	7 (58)	4 (33)	9 (75)
Most important need in a rating scale***				
Validity & reliability	15 (42)	3 (25)	4 (33)	8 (67)
Time	14 (39)	8 (67)	4 (33)	2 (17)
Simplicity	5 (14)	1 (8)	3 (25)	1 (8)
Popularity	2 (6)	-	1 (8)	1 (8)
Preference of rating scale types*				
Both physician- and patient-rated scale	20 (56)	8 (67)	4 (33)	8 (67)
Physician-rated scale	10 (28)	2 (17)	5 (42)	3 (25)
Patient-rated scale	1 (3)	1 (8)	0 (0)	0 (0)
No preference	4 (11)	1 (8)	2 (17)	1 (8)
Prefer not to use scales	1 (3)	-	1 (8)	-

**single choice question; **multiple choice question; ***ranked as most important*

4.3.3.2. Opinions about the TGI-P scale

Regarding opinions on the TGI-P scale, 14% of psychiatrists rated it "very positively," and 67% rated it "positively" (**Table 36**). Most respondents (75%) appreciated that the scale is based on the CGI-S scale, and 94% approved of its 10 symptom dimensions, with 92% indicating no desire to modify them. The visualization component of the scale received strong

approval, with 75% agreeing that it enhances understanding of symptomatology and facilitates communication with patients and caregivers. In terms of future use, 70% of psychiatrists expressed willingness to adopt the TGI-P scale in either online or paper form, while 25% were uncertain, and 6% declined usage. The primary concerns regarding adoption centred on the scale's ongoing validation process.

Table 36. Opinions of psychiatrists on the TGI-P scale

Opinion about the TGI-P scale, N (%)	TOTAL	U.S.	Poland	Germany
Overall opinion				
Very positive	5 (14)	1 (8)	2 (17)	2 (17)
Positive	24 (67)	7 (58)	8 (67)	9 (75)
Neutral	6 (17)	3 (25)	2 (17)	1 (8)
Negative	1 (3)	1 (8)	-	-
Very negative	-	-	-	-
Opinion about CGI-based rating				
Very positive	7 (19)	2 (17)	2 (17)	3 (25)
Positive	20 (56)	7 (58)	6 (50)	7 (58)
Neutral	7 (19)	3 (25)	3 (25)	1 (8)
Negative	6 (17)	-	1 (8)	1 (8)
Very negative	-	-	-	-
Opinion about dimensions				
Very positive	10 (28)	3 (25)	3 (25)	4 (33)
Positive	24 (67)	8 (67)	8 (67)	8 (67)
Neutral	2 (6)	1 (8)	1 (8)	-
Negative	-	-	-	-
Very negative	-	-	-	-
Role of the symptom shape: overall understanding				
Very positive	6 (17)	1 (8)	1 (17)	3 (25)
Positive	21 (58)	6 (50)	8 (67)	7 (58)
Neutral	7 (19)	3 (25)	2 (17)	2 (17)
Negative	2 (6)	2 (17)	-	-
Very negative	-	-	-	-
Role of the symptom shape: patient support				
Very positive	6 (17)	2 (17)	1 (8)	3 (25)
Positive	21 (58)	6 (50)	9 (75)	6 (50)
Neutral	8 (22)	3 (25)	2 (17)	3 (25)
Negative	1 (3)	1 (8)	-	-
Very negative	-	-	-	-
Willingness to use the scale				
Yes, in online version	14 (39)	4 (33)	5 (42)	5 (42)
Yes, in pen & paper version	11 (31)	3 (25)	5 (42)	3 (25)
No	2 (6)	1 (8)	1 (8)	-
I am not sure yet	9 (25)	4 (33)	1 (8)	4 (33)

4.3.3.3. Mock rating

A total of 86% of participants engaged in a mock TGI-P rating exercise, though data regarding the reasons for non-participation among the remaining 14% were unavailable. The results indicated that positive, self-harm, sleep, and depressive symptoms were rated most

consistently across participants, while greater variability was observed in the ratings of manic, addiction, and hostility symptoms (**Table 37**). The highest degree of rating inconsistency was noted for negative, cognitive, and anxiety symptoms. Notably, symptom ratings varied across countries, with Polish psychiatrists tending to rate depressive, manic, hostility, cognitive, and anxiety symptoms lower compared to their U.S. and German counterparts. German psychiatrists assessed hostility and anxiety symptoms as more severe, while U.S. psychiatrists provided lower severity ratings for positive symptoms than their European peers.

Table 37. Results of the mock rating of the TGI-P scale by 31 psychiatrists

	Mean score	% of doctors rating each score						
		Normal	Minimal	Mild	Moderate	Marked	Severe	Extreme
		1	2	3	4	5	6	7
Positive symptoms	6.0	-	-	-	-	16	**71**	13
Self-harm symptoms	1.3	**84**	6	6	3	-	-	-
Sleep symptoms	1.7	**71**	10	6	6	6	-	-
Depressive symptoms	1.7	**45**	39	13	3	-	-	-
Manic symptoms	2.4	**45**	16	10	19	6	3	-
Addiction symptoms	3.2	10	16	**45**	6	19	3	-
Hostility symptoms	2.9	13	**32**	26	13	13	3	-
Negative symptom	2.9	26	16	13	**32**	13		-
Cognitive symptoms	3.5	3	19	**32**	19	16	10	-
Anxiety symptoms	3.6	6	23	16	19	**29**	6	-

N = 31; USA (n = 8), Poland (n=11), Germany (n=12)

4.3.4. Patient-caregiver survey

The survey involving patients and caregivers aimed to understand the acceptability of the scale by the target population. A total of 50 participants were included in the study, comprising 25 patients and 25 caregivers. Among the patients, 12 were based in the UK and 13 in the US; for caregivers, 13 were from the UK and 12 from the US (**Table 38**). The sample was predominantly female (72%), with identical sex distributions between patients and caregivers. Participants ranged in age from 18 to over 60 years, with a mean age of 44.5 years (SD = 9.9). Nearly half (46%) were aged 18–39, followed by 26% aged 40–49, 20%

aged 50–59, and 8% aged 60 or older. Caregivers were more likely to fall into the youngest age bracket (52%), while patients were primarily distributed between the 18–39 and 40–49 age groups (40% each).

Educational attainment across the sample was high, with 68% holding a university degree. An additional 24% had completed high school, and 8% reported vocational training. Household composition varied: 30% lived in households of four or more people, 26% lived with one other person, 22% with two others, and 22% lived alone. Notably, 36% of patients lived alone compared to only 8% of caregivers, while caregivers were more likely to live in three-person households (36% vs. 8% of patients). In terms of clinical characteristics, MDD was the most common diagnosis among patients (40%), followed by BD (36%) and SCHZ (24%). Caregivers most frequently reported supporting individuals with SCHZ (44%), followed by BD (32%) and MDD (24%).

Table 38. Participant characteristics of the patient-caregiver survey

	TOTAL, n = 50	**PATIENTS,** n = 25	**CAREGIVERS,** n = 25
Country, n (%)			
from UK	25 (50.0)	12 (48.0)	13 (52.0)
from US	25 (50.0)	13 (52.0)	12 (48.0)
Sex, n (%)			
Male	14 (28.0)	7 (28.0)	7 (28.0)
Female	36 (72.0)	18 (72.0)	18 (72.0)
Age groups, n (%)			
18 – 39 years	23 (46.0)	10 (40.0)	13 (52.0)
40 – 49 years	13 (26.0)	10 (40.0)	3 (12.0)
50 – 59 years	10 (20.0)	3 (12.0)	7 (28.0)
60+	4 (8.0)	2 (8.0)	2 (8.0)
Age, mean (SD)	44.5 (9.9)	44.5 (10.8)	44.4 (9.1)
Education, n (%)			
High school	12 (24.0)	5 (20.00)	7 (28.0)
Vocational school	4 (8.0)	2 (8.0)	2 (8.0)
University	34 (68.0)	18 (72.0)	16 (64.0)
Household size, n (%)			
1	11 (22.0)	9 (36.0)	2 (8.0)
2	13 (26.0)	6 (24.0)	7 (28.0)
3	11 (22.0)	2 (8.0)	9 (36.0)
4+	15 (30.0)	8 (32.0)	7 (28.0)

Diagnosis of patients / patients whom caregivers provide care for, n (%)			
Bipolar disorder	17 (34.0)	9 (36.0)	8 (32.0)
Major depression	16 (32.0)	10 (40.0)	6 (24.0)
Schizophrenia	17 (34.0)	6 (24.0)	11 (44.0)

Participants demonstrated varied experiences with and attitudes toward using rating scales (**Table 39**). Only a small proportion (8%) reported completing rating scales frequently (weekly), while 44% used them occasionally (monthly) and 36% reported rare use (less than monthly). A minority (12%) indicated they had never completed a rating scale. Notably, caregivers were more likely than patients to report occasional use (56% vs. 32%), whereas rare use was more commonly reported by patients (48% vs. 24%).

Overall perceptions of rating scale usefulness were positive. While 26% of participants found them very helpful and 34% somewhat helpful, patients were more likely to endorse the "somewhat helpful" option (40%) compared to caregivers (28%). Approximately 28% of participants felt neutral, and a small proportion described rating scales as somewhat (8%) or very exhausting (4%).

Preferences for visual feedback were strong across the sample. A majority (58%) expressed a clear preference for visual outputs, with an additional 28% indicating a slight preference. Only 14% reported no preference. Format preferences were also assessed: 58% of participants preferred digital formats, 12% preferred paper, and 30% were comfortable with both. Caregivers were slightly more inclined toward digital formats (64%) compared to patients (52%).

Table 39. General attitudes of patients and caregivers towards rating scales

	Total, n = 50	**Patients,** n = 25	**Caregivers,** n = 25
Frequency of filling out rating scales, n (%)			
Frequently / Weekly	4 (8)	2 (8)	2 (8)
Occasionally / Monthly	22 (44)	8 (32)	14 (56)
Rarely / Less than monthly	18 (36)	12 (48)	6 (24)
Never	6 (12)	3 (12)	3 (12)
Helpfulness of rating scales, n (%)			
Very helpful	13 (26)	5 (20)	8 (32)
Somewhat helpful	17 (34)	10 (40)	7 (28)
Neutral	14 (28)	6 (24)	8 (32)
Somewhat exhausting	4 (8)	2 (8)	2 (8)
Very exhausting	2 (4)	2 (8)	0 (0)
Preference for visual output, n (%)			
Much more preferred	29 (58)	14 (56)	15 (60)
Little more preferred	14 (28)	8 (32)	6 (24)
Not preferred	7 (14)	3 (12)	4 (16)
Format of scale, n (%)			
Digital	29 (58)	13 (52)	16 (64)
Paper	6 (12)	3 (12)	3 (12)
Both	15 (30)	9 (36)	6 (24)

The results of the survey indicate that the TGI-P scale is generally well-received, with most respondents finding its aim clear and its instructions easy to follow (**Table 40**). The majority of participants (76%) felt completely confident when completing the scale, and 72% were able to finish it in less than five minutes, suggesting that it is both user-friendly and efficient. The response options were considered appropriate by 86% of respondents, and 58% found the visual output very helpful, though a notable proportion (40%) found it only somewhat helpful. Regarding the emotional and cognitive burden, most respondents did not find the scale overwhelming or burdensome, but 30% reported feeling slightly triggered, highlighting a potential area of sensitivity. Compared to other psychiatric scales, 76% rated the TGI-P as better or much better, reinforcing its overall positive reception. However, suggestions for improvement included a shorter format (50%), simpler wording (36%), and clearer instructions (18%), indicating that while the scale is effective, minor refinements could enhance its usability further.

Table 40. Results of the patient-caregiver survey

Opinion about the TGI-P scale, N (%)	TOTAL, n = 50	PATIENTS, n = 25		CAREGIVERS, n = 25	
		UK, n = 12	U.S., n = 13	UK, n = 13	U.S., n = 12
Understandability of aim					
Yes, very clear	34 (68)	7 (58)	7 (54)	13 (100)	7 (58)
Somewhat clear	16 (32)	5 (42)	6 (46)	0 (0)	5 (42)
Not clear	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Understandability of instructions					
Very easy to follow	40 (80)	10 (83)	11 (85)	13 (100)	6 (50)
Easy to follow	8 (16)	2 (17)	2 (15)	0 (0)	4 (33)
Neutral	2 (4)	0 (0)	0 (0)	0 (0)	2 (17)
Confusing	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Level of confidence when filling the scale					
Yes, completely	38 (76)	7 (58)	11 (85)	12 (92)	8 (67)
Somewhat	12 (24)	5 (42)	2 (15)	1 (8)	4 (33)
No, I needed help	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Length of filling out					
Less than 5 minutes	36 (72)	10 (83)	9 (69)	8 (62)	9 (75)
5 – 10 minutes	13 (26)	2 (17)	4 (31)	5 (38)	2 (17)
More than 10 minutes	1 (2)	0 (0)	0 (0)	0 (0)	1 (8)
Easiness of filling out					
Very easy	31 (62)	6 (50)	8 (62)	11 (85)	6 (50)
Easy	16 (32)	5 (42)	5 (38)	1 (8)	5 (42)
Neutral	3 (6)	1 (8)	0 (0)	1 (8)	1 (8)
Difficult	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Very difficult	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Difficulties during filling out					
No difficulties	48 (96)	11 (91)	13 (100)	13 (100)	11 (91)
A few minor difficulties	2 (4)	1 (8)	0 (0)	0 (0)	1 (8)
Many difficulties	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Understandability of wording*					
Question 1 – Positive symptoms	3 (6)	1 (8)	0 (0)	2 (15)	0 (0)
Question 2 – Hostility symptoms	1 (2)	0 (0)	0 (0)	1 (8)	0 (0)
Question 3 – Manic symptoms	4 (8)	2 (17)	0 (0)	2 (15)	0 (0)
Question 4 – Addiction symptoms	3 (6)	1 (8)	0 (0)	1 (8)	1 (8)
Question 5 – Sleep symptoms	1 (2)	0 (0)	0 (0)	1 (8)	0 (0)
Question 6 – Negative symptoms	1 (2)	0 (0)	0 (0)	1 (8)	0 (0)
Question 7 – Self-harm symptoms	5 (10)	1 (8)	1 (8)	2 (15)	1 (8)
Question 8 – Depressive symptoms	1 (2)	0 (0)	0 (0)	1 (8)	0 (0)
Question 9 – Cognitive symptoms	1 (2)	0 (0)	0 (0)	1 (8)	0 (0)
Question 10 – Anxiety symptoms	1 (2)	0 (0)	0 (0)	1 (8)	0 (0)
Evaluation of scale response options					
Very appropriate	43 (86)	9 (75)	13 (100)	11 (85)	10 (83)
Somewhat appropriate	7 (14)	3 (25)	0 (0)	2 (15)	2 (17)
Not appropriate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Evaluation of visual output					
Very helpful	29 (58)	6 (50)	7 (54)	10 (77)	6 (50)
Somewhat helpful	20 (40)	6 (50)	6 (46)	3 (23)	5 (42)
Not helpful	1 (2)	0 (0)	0 (0)	0 (0)	1 (8)
Overwhelmingness					
Not at all overwhelmed	37 (74)	8 (67)	11 (85)	10 (77)	8 (67)
Slightly overwhelmed	13 (26)	4 (33)	2 (15)	3 (23)	4 (33)
Very overwhelmed	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Burden					
Not at all burdensome	43 (86)	10 (83)	12 (92)	12 (92)	9 (75)
Slightly burdensome	7 (14)	2 (17)	1 (8)	1 (8)	3 (25)
Very burdensome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Emotional trigger					
Not at all triggered	34 (68)	7 (58)	9 (69)	10 (77)	8 (67)
Slightly triggered	15 (30)	4 (33)	4 (31)	3 (23)	4 (33)
Very triggered	1 (2)	1 (8)	0 (0)	0 (0)	0 (0)

Comparison to other scales					
Much better	16 (32)	2 (17)	2 (15)	9 (69)	3 (25)
Better	22 (44)	7 (58)	6 (46)	4 (31)	5 (42)
About the same	11 (22)	3 (25)	5 (38)	0 (0)	3 (25)
Worse	1 (2)	0 (0)	0 (0)	0 (0)	1 (8)
Much worse	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Future improvements					
Shorter formats	25 (50)	4 (33)	4 (31)	9 (69)	8 (67)
Simpler wording	18 (36)	6 (50)	3 (23)	7 (54)	2 (17)
Clearer instructions	9 (18)	4 (33)	1 (8)	2 (15)	2 (17)
Other	2 (4)	0 (0)	1 (8)	0 (0)	1 (8)
**only 'No' answers displayed*					

4.3.5. The Transdiagnostic Global Impression Psychopathology scale

4.3.5.1. The base

The Transdiagnostic Global Impression of Psychopathology (TGI-P) scale is based on the widely used Clinical Global Impression-Severity (CGI-S) scale (227,400). The CGI-S is well-established in clinical practice due to its simplicity and ease of use, making it a familiar tool for clinicians. In the CGI-S, a rating of 1 indicates a normal state, while a rating of 7 represents being among the most severely ill. Utilizing the CGI-S as the foundation for the TGI-P scale ensures that clinicians can easily adapt to it without extensive training. A distinctive feature of the TGI-P scale is its visual output, where symptom severity is represented not only numerically but also graphically through a series of seven circles of increasing size (**Figure 20**) (400). The smallest circle corresponds to a severity rating of 1 (normal), then 2 means minimal severity, 3 means mild severity, 4 means moderate severity, 5 means marked severity, 6 means severe severity and the largest circle represents the most severe level of symptomatology (extreme) (400). This visual representation enhances intuitive understanding and facilitates quick clinical assessments.

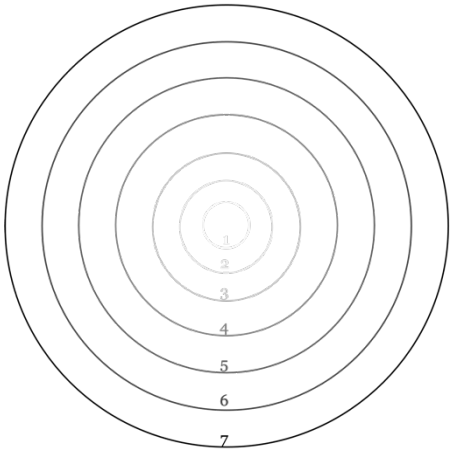

Figure 20. The base of the TGI-P scale

Each circle represents a severity level with 1 representing normal and 7 representing extreme severity of symptoms, in line with the Clinical Global Impression – Severity scale.

4.3.5.2. The items

The TGI-P scale consists of 10 final items, each representing key symptom domains that are commonly observed across various psychiatric disorders (400). These items were selected based on their clinical relevance and broad applicability, recognizing the need for a brief yet effective assessment tool. The scale aims to provide a practical alternative to more comprehensive measures that may be time-consuming and impractical in everyday clinical settings. The selected items include positive symptoms, negative symptoms, manic symptoms, depressive symptoms, addiction symptoms, cognitive symptoms, anxiety symptoms, sleep symptoms, hostility symptoms, and self-harm symptoms (400). The objective was not to capture every possible symptom but to provide a concise and clinically useful tool that covers the most critical areas of psychiatric evaluation. The decision to limit the scale to 10 items ensures that it remains feasible for routine use without overburdening clinicians.

4.3.5.3. The lines

The organization of symptoms within the visual representation of the TGI-P scale is systematic and meaningful, with symptoms arranged along specific lines that reflect their clinical relationships (**Figure 21**) (400). Pairs of symptoms have been positioned to highlight

their conceptual linkages. For example, positive and negative symptoms are paired to reflect opposing aspects of psychotic disorders, while depressive and manic symptoms capture the bipolar spectrum. Similarly, addiction and cognitive symptoms, hostility and self-harm symptoms, and anxiety and sleep symptoms are paired, emphasizing their interconnectedness and potential influence on each other. These pairings provide clinicians with additional insight into the patient's overall symptom profile and help in recognizing symptom patterns across disorders.

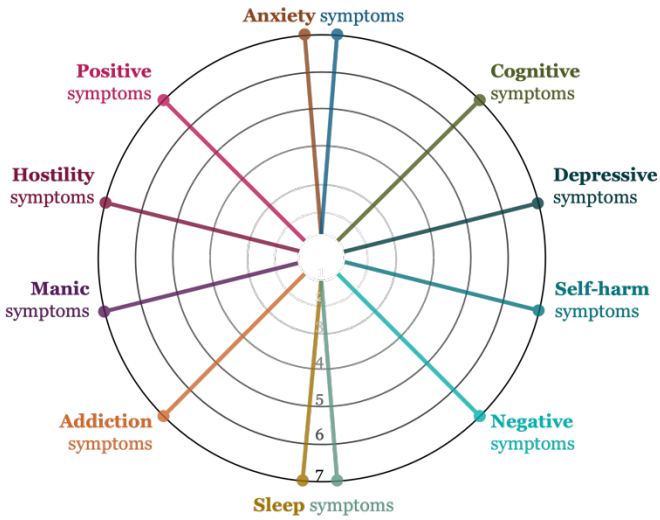

Figure 21. The TGI-P scale

The Transdiagnostic Global Impression – Psychopathology scale is composed of the seven severity circles and the ten symptom domains.

4.3.5.4. The poles

Beyond symptom pairings, the TGI-P scale also features two overarching poles, representing distinct dimensions of psychopathology (**Figure 22**) (400). The left pole, referred to as the hyper pole, encompasses symptoms associated with heightened activity or expression, such as positive symptoms, hostility, manic symptoms, addiction symptoms, and aspects of anxiety and sleep symptoms. Conversely, the right pole, known as the hypo pole, captures symptoms related to diminished functioning, including negative symptoms, depressive symptoms, cognitive symptoms, and self-harm symptoms, with certain aspects of anxiety and sleep

symptoms also falling within this spectrum. The placement of anxiety at the top and sleep at the bottom of the visual representation reflects their potential to contribute to both hyper- and hypo-states, making their classification flexible. This structured visual arrangement enhances the interpretability of the TGI-P scale and aids clinicians in rapidly identifying key symptom dimensions. The final composition of the TGI-P scale is summarized in **Table 41**, while the final pen-and-paper format of the clinician (**Appendix D**), patient (**Appendix E**) and caregiver (**Appendix F**) versions are in the Appendices.

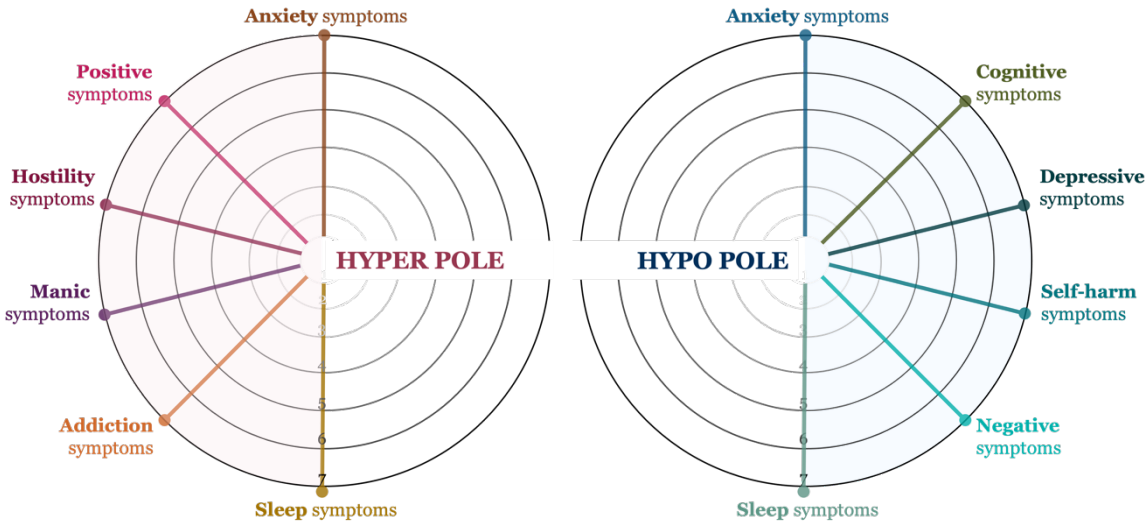

Figure 22. The poles of the TGI-P scale

The ten symptom domains are organized on the two poles of the severity circles; on the left side are the symptoms belonging to the hyper pole, while on the right side are the symptoms belonging to the hypo pole.

Table 41. The composition of the TGI-P scale

LINES \ POLES	HYPER	HYPO
Psychotic symptom spectrum	**Positive symptoms** *Delusions, hallucinations, disorganised thinking, disorganised speech, abnormal motor behaviour*	**Negative symptoms** *Blunted affect, alogia, asociality, avolition, anticipatory anhedonia**
Harmful behaviour	**Hostility symptoms** *Anger, tension, uncooperativeness, impulsivity, aggression, irritability*	**Self-harm symptoms** *Non-suicidal self-injury, suicidal ideation, intent, or attempt*
Mood dysregulation	**Manic symptoms** *Expansive mood, grandiosity, racing thoughts, increased energy, excessive involvement in pleasurable activities*	**Depressive symptoms** *Low mood, consummatory anhedonia, sadness, hopelessness, helplessness*
Dependence and thinking	**Addiction symptoms** *Impaired control over substance-use or behaviours, craving, physical or psychological dependence, compulsive engagement, and withdrawal symptoms*	**Cognitive symptoms** *Problems with concentration, attention, memory*
Sleep disturbance	**Insomnia** *Initial, middle or terminal insomnia*	**Hypersomnia** *Hypersomnia*
Anxious behaviour	**Hypervigilance** *Feeling nervous, tense, hypervigilant, panicky*	**Anxiety** *Social inhibition, anxious withdrawal, ruminations*

**Rate as negative symptom if present without depressed mood*

4.3.6. Small-scale cross-sectional feasibility study

Following the description of the finalized TGI-P scale, the findings of the small-scale cross-sectional feasibility study is reported. The intention of this pilot was to explore how the scale performs when applied in a routine clinical setting, to generate initial data on feasibility and usability, and to provide a practical illustration of its potential application prior to completion of the full validation study.

4.3.6.1. Demographic & clinical characteristics

Six inpatients with psychotic disorders participated in the study (mean age = 45.8 years, 66.7% male) (**Table 42**). The majority of patients were single (83.3%) and had a mean of 11.3 years of education. Most were diagnosed with SCHZ (83.3%), with one patient diagnosed with schizoaffective disorder.

The TGI-P symptom ratings by the clinician indicated high severity in positive (mean = 5.5), negative (mean = 4.0), and anxiety symptoms (mean = 3.5), followed by cognitive and hostility symptoms (means = 3.3). The total PANSS score (mean = 104.5) indicated severe overall symptomatology with high levels of positive (mean = 36.0), negative (mean = 22.2) and cognitive symptoms (mean = 23.8), based on the corresponding Marder factor scores. Nonetheless, the ACE total scores (mean = 75.8) and MMSE scores (mean = 27.3) reflected only mild cognitive impairment, with significant impairment in memory (mean = 18.7) and verbal fluency (mean = 8.5). The individual TGI-P symptom maps are presented in **Figure 23**.

Table 42. Demographic & clinical characteristics of the TGI-P pilot study participants

Demographic characteristics	
Total number of patients, n (%)	6 (100.0)
Age, mean (SD)	45.8 (13.5)
Men, n (%)	4 (66.7%)
Marital status, n (%)	
Single	5 (83.3%)
Married	1 (16.7%)
Educational years, mean (SD)	11.3 (2.1)
Clinical characteristics	
Diagnosis, n (%)	
Schizophrenia	5 (83.3%)
Schizoaffective disorder	1 (16.7%)
TGI-P scores, mean (SD)*	
Positive symptoms	5.5 (1.0)
Manic symptoms	3.0 (1.7)
Hostility symptoms	3.3 (0.5)
Addiction symptoms	1.7 (1.6)
Sleep symptoms	1.7 (1.0)
Self-harm symptoms	1.8 (1.0)
Anxiety symptoms	3.5 (0.5)
Cognitive symptoms	3.3 (0.8)
Negative symptoms	4.0 (0.9)
Depressive symptoms	3.3 (1.2)
PANSS, scores, mean (SD)	
Positive factor score	36.0 (5.0)
Negative factor score	22.2 (7.1)
Disorganized thoughts factor score	23.8 (2.5)
Anxiety / Depression factor score	11.0 (2.8)
Uncontrolled excitement / Hostility factor score	11.5 (0.8)
Total score	104.5 (9.2)
ACE scores, mean (SD)	
Orientation	9.8 (0.4)
Concentration	8.0 (0.0)
Memory	18.7 (6.4)
Verbal fluency	8.5 (3.4)
Language	26.8 (1.5)
Visuospatial	4.0 (1.1)
Total score	75.8 (7.6)

MMSE score	27.3 (0.8)

**scores rated by L.H.*
ACE, Addenbrooke's Cognitive Examination; MMSE, Mini Mental State Examination; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; TGI, Transdiagnostic Global Impression

Figure 23. Individual TGI-P symptom maps

The figure shows the individual Transdiagnostic Global Impression – Psychopathology symptom web plots for the six patients included in the pilot study. The individual points on the seven circles represent the severity of the different symptom domains with 1 indicating the absence of symptoms, while seven represents extreme severity.

4.3.6.2. Internal consistency

Internal consistency of the TGI-P items was assessed using Cronbach's alpha separately for ratings by the clinician and the author. The clinician-rated scale yielded a negative alpha value (raw $\alpha = -3.4$), indicating low internal consistency, while ratings by ZS.B.D. showed a low but positive alpha (raw $\alpha = 0.12$) (**Table 43**). Neither Cronbach's alpha reached statistical significance, as indicated by confidence intervals that included zero.

Table 43. Internal consistency

Rater	Cronbach's alpha	Standardized alpha	Mean item score	95% CI
Clinician – L.H.	-3.40	-0.88	2.6	-11.66 to 0.28
Author – Zs.B.D.	0.12	0.26	3.1	-1.51 to 0.86

CI, confidence interval

4.3.6.3. Inter-rater reliability

The inter-rater reliability of the TGI-P items was evaluated using ICCs, calculated via a two-way random effects model with absolute agreement. As shown in **Table 44**, ICC values ranged from 0.47 (depressive symptoms) to 1.00 (positive and addiction symptoms), indicating variable agreement across domains. Perfect agreement was observed for positive and addiction symptoms (ICC = 1.00, $p < 0.001$) and high agreement was noted for self-harm (ICC = 0.85, $p < 0.01$) and hostility symptoms (ICC = 0.80, $p < 0.01$). The agreement was rather moderate for manic (ICC = 0.64, $p < 0.05$), cognitive (ICC = 0.62, $p < 0.05$), and anxiety symptoms (ICC = 0.62, $p = 0.076$), while the least agreement was seen for negative (ICC = 0.55, $p = 0.071$), sleep (ICC = 0.52, $p = 0.073$), and depressive (ICC = 0.47, $p = 0.145$) symptoms. F-tests were statistically significant for several domains, though 95% confidence intervals for some ICCs included zero, reflecting the limited sample size and associated uncertainty. A Bland–Altman plot showed moderate agreement between raters on the TGI-P cognitive symptom domain, with differences falling within the 95% limits of agreement (**Figure 24**).

Table 44. Inter-rater reliability of the TGI-P scale

TGI-P symptom domains	ICC	F-test	p-value	95% CI
Positive symptoms	1.00	-	< 0.001	1.00 to 1.00
Manic symptoms	0.64	5.68	0.037	-0.07 to 0.94
Hostility symptoms	0.80	9.00	0.009	0.20 to 0.97
Addiction symptoms	1.00	-	< 0.001	1.00 to 1.00
Sleep symptoms	0.52	4.56	0.073	-0.16 to 0.91
Self-harm symptoms	0.85	10.90	0.008	0.28 to 0.98
Anxiety symptoms	0.62	3.82	0.076	-0.32 to 0.94
Cognitive symptoms	0.62	4.81	0.044	-0.10 to 0.93
Negative symptoms	0.55	3.73	0.071	-0.20 to 0.92
Depressive symptoms	0.47	2.64	0.145	-0.49 to 0.91

CI, confidence interval; ICC, Interclass correlation coefficient; TGI-P, Transdiagnostic Global Impression - Psychopathology

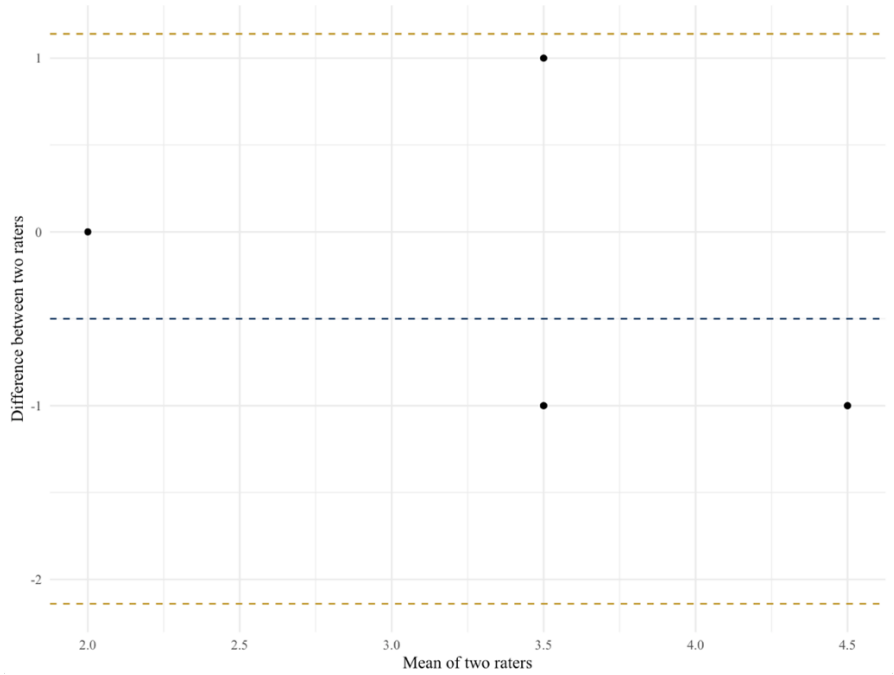

Figure 24. Bland–Altman plot of cognitive symptom ratings from the TGI-P, comparing scores between clinician and the author of the thesis for the six participants

Each black dot represents an individual participant, with the x-axis showing the mean of the two raters' scores and the y-axis showing the difference between the clinician's and the author's ratings for that participant. The plot includes the mean difference (blue dashed line), indicating any systematic bias between raters, and the 95% limits of agreement (gold dashed lines), which represent the range within which most differences between the two raters are expected to lie.

4.3.6.4. Construct validity

Construct validity was explored using Spearman's rank correlation between TGI-P symptom domain scores and PANSS Marder factor or item scores, and ACE Total and MMSE scores (**Table 45**). For each symptom domain, correlations were calculated separately for the ratings of the author (Zs.B.D.) and the consulting psychiatrist (L.H.). Strong and significant correlations were observed for the Positive symptom domain with the PANSS Positive factor ($\rho = 0.95$, $p < 0.01$for both raters), for the Manic symptom domain with PANSS P5 – Grandiosity item ($\rho = 0.86$, $p < 0.05$ for Zs.B.D.), and for the Anxiety symptom domain with PANSS Anxiety / Depression factor score ($\rho = 0.89$, $p < 0.05$ for Zs.B.D.). Furthermore, the TGI Cognitive symptom domain showed strong inverse correlations with ACE MMSE scores ($\rho = –0.83$, $p < 0.05$ for Zs.B.D.), but no significant correlation was found neither with ACE

Total nor PANSS Disorganized thoughts factor score, suggesting some convergence with cognitive performance. Other domains such as Hostility, Negative, and Depressive symptoms showed variable correlations with relevant PANSS factor and item scores, without reaching statistical significance. Three symptom domains (Addiction, Sleep and Self-harm symptoms) had no clear reference measures and were thus not assessed.

Table 45. Spearman's correlation

TGI-P symptom domains	Reference scale	Rater	ρ	p-value
Positive symptoms	PANSS Positive factor score	L.H.	0.95	0.003
		Zs.B.D.	0.95	0.003
Manic symptoms	PANSS P5 – Grandiosity	L.H.	0.81	0.052
		Zs.B.D.	0.86	0.027
Hostility symptoms	PANSS Uncontrolled excitement / Hostility factor score	L.H.	0.12	0.817
		Zs.B.D.	-0.27	0.600
Addiction symptoms	-	-	-	-
Sleep symptoms	-	-	-	-
Self-harm symptoms	-	-	-	-
Anxiety symptoms	PANSS Anxiety / Depression factor score	L.H.	0.79	0.060
		Zs.B.D.	0.89	0.016
	PANSS G2 - Anxiety	L.H.	0.74	0.094
		Zs.B.D.	0.13	0.689
Cognitive symptoms	PANSS Disorganized thoughts factor score	L.H.	0.62	0.191
		Zs.B.D.	0.35	0.492
	ACE Total score	L.H.	-0.31	0.552
		Zs.B.D.	-0.53	0.280
	ACE MMSE score	L.H.	-0.48	0.332
		Zs.B.D.	-0.83	0.042
Negative symptoms	PANSS Negative factor score	L.H.	0.42	0.402
		Zs.B.D.	0.13	0.803
Depressive symptoms	PANSS Anxiety / Depression factor score	L.H.	0.63	0.183
		Zs.B.D.	0.19	0.722
	PANSS G6 – Depression	L.H.	0.06	0.908
		Zs.B.D.	0.09	0.866

ACE, Addenbrooke's Cognitive Examination; MMSE, Mini Mental State Examination; PANSS, Positive and Negative Syndrome Scale; TGI-P, Transdiagnostic Global Impression - Psychopathology

4.3.6.5. Feasibility

The average time to complete the TGI-P rating was 3 minutes, compared to 36 minutes for the PANSS and 15 minutes for the ACE (**Table 46**).

Table 46. Time requirement for administration of scales

Scales	**Duration in minutes,** mean (SD)
TGI-P*	3.0 (1.10)
PANSS	36.3 (9.46)
ACE	15.5 (2.66)

**time for L.H.*
ACE, Addenbrooke's Cognitive Examination; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; TGI-P, Transdiagnostic Global Impression - Psychopathology

4.5 Discussion

4.5.1. Summary of key findings

The TGI-P is a novel tool for assessing, tracking, and visualizing symptom severity across psychiatric conditions and comorbidities, with significant potential even before psychometric testing (400). Given that humans process complex visual stimuli in as little as 13 milliseconds (523), the TGI-P enables a rapid, intuitive understanding of complex psychopathology. With a single glance, psychiatrists can identify symptom domains requiring attention or detect shifts in symptom composition. Repeated use of the TGI-P may also facilitate communication with patients and caregivers, improving understanding of overall psychopathology and treatment goals.

Survey results support this potential, as most psychiatrists expressed willingness to integrate the tool into clinical practice. Additionally, the mock rating provided insights into the scale's reliability and validity. Importantly, the general impression of both patients and caregivers was quite positive regarding the TGI-P, with the majority of survey participants reporting it to be better compared to other scales measuring symptom severity. Additionally, most of them did not feel overwhelmed or triggered when using the scale and over half of them appreciated the visual output.

The small-scale cross-sectional feasibility study was the first to explore the utility, internal consistency, inter-rater reliability, and construct validity of the TGI-P scale in a real-world inpatient psychiatric setting. Despite the very limited sample size (n = 6), the findings offer initial support for the potential of the TGI-P as a rapid symptom assessment tool.

Internal consistency, assessed using Cronbach's alpha, yielded a negative value which is commonly interpreted as having poor reliability (524). Nonetheless, in the present context, it rather reflects the intended multidimensionality and heterogeneity of the scale, as it was designed to cover a broad spectrum of symptom domains. The discrepancy between Cronbach's alpha values across raters (clinician vs. author) may be explained by several factors, including the small sample size, which makes such estimates unstable, and the raters' differing levels of clinical experience. The experienced clinician may have identified a wider range of symptom severity, leading to greater variability and lower item correlations. In contrast, the author, a novice rater, likely applied more cautious and uniform scoring.

Indeed, inter-rater reliability was stronger for symptoms that are more outwardly observable, such as positive, manic, and hostile symptoms. Concerning these domains, agreement between the two raters was high. In contrast, symptoms like negative, depressive, and sleep disturbances showed lower agreement. This discrepancy likely reflects the fact that such symptoms are less readily identifiable during brief interviews and require longitudinal observation, which the author did not have access to (525–527). These findings illustrate how symptom visibility and rater experience shape perceived symptom severity and underscore the importance of rater training and contextual knowledge.

Construct validity analyses also supported these findings. Strongest correlations between TGI-P items and reference measures were seen for domains such as positive and manic symptoms, and to a lesser extent, anxiety and cognitive symptoms. Notably, cognitive symptoms rated by the author correlated significantly with MMSE scores, but not with other cognitive indicators or with clinician ratings. The weakest correlations were found for depressive and negative symptoms, especially in the author's ratings. This aligns with existing

literature, where negative symptoms such as anhedonia, blunted affect and avolition are notoriously difficult to assess reliably in short clinical interviews (525–527). Measuring depressive symptoms also present challenges due to their episodic nature and overlap with other symptom domains (528,529). Importantly, these low correlations are likely reflective of a general measurement challenge inherent to psychiatric assessment rather than a specific flaw in the TGI-P. Objective measures, such as facial expression analysis or ecological momentary assessment, as well as patient-reported outcomes, may complement clinician ratings and improve reliability in future studies (530,531).

Finally, the feasibility of the TGI-P was strongly supported. The scale required an average of only 3 minutes to complete, compared to 36 minutes for the PANSS and 15 minutes for the ACE. Given the fact that the average visit time in the field of psychiatry is 9 minutes (532), the TGI-P scale shows clear advantage over the more comprehensive scales and offers a feasible solution to implement MBC in clinical practice.

4.5.1. The potential of the TGI-P scale

The TGI-P scale has already gained significant attention in the psychiatric community. It was published in European Neuropsychopharmacology and European Psychiatry and presented at major international congresses, including the Annual Congress of the College of European Neuropsychopharmacology (ECNP) and the European Psychiatric Association (EPA) congresses in 2024. Despite not yet being tested psychometrically, the scale is freely accessible online, allowing clinicians and researchers to explore its potential in practice. The substantial interest is evident, with over 3,000 unique website visits, and numerous inquiries from professionals eager to validate the scale in their respective languages, such as Slovak, Hungarian, Japanese, and Latvian. This enthusiasm underscores the scale's potential for widespread adoption.

The TGI-P aligns with the growing transdiagnostic paradigm in psychiatry, emphasizing symptom dimensions over traditional diagnostic categories. Its simplicity and brevity make it particularly suitable for clinical practice, where time constraints often limit the use of more comprehensive scales. Its patient-centered design provides a concise, holistic overview of symptom severity, supporting individualized and comprehensive care models.

Preliminary findings indicate that the TGI-P can serve as a useful proxy measure in high-paced clinical environments. Requiring only three minutes to complete, it provides a structured overview across multiple domains, allowing clinicians to detect symptom changes over time and adjust treatment accordingly. While it is not designed to replace comprehensive scales like the PANSS, it can flag symptom areas needing attention and guide further assessment.

Encouragingly, the TGI-P also shows potential for detecting cognitive difficulties. The cognitive item correlated significantly with MMSE scores in the author's ratings, suggesting that clinical impression alone can offer insight into cognitive impairment when formal testing is not feasible. While not a substitute for detailed cognitive assessment, the TGI-P may serve as a practical flag in everyday clinical practice.

4.5.2. Limitations

The primary limitation of the TGI-P scale is that the psychometric testing is still in progress. However, its structure is based on the CGI-S scale, which is widely recognized for its strong correlations with validated psychiatric rating scales, such as the PANSS. Additionally, disorder-specific CGI versions, such as CGI for schizophrenia (CGI-SCH) and CGI for

bipolar disorder (CGI-BP), have demonstrated validity and reliability, suggesting that the TGI-P scale may also exhibit strong psychometric properties once validation is complete.

Another potential limitation is the selection of the 10 symptom domains. One of the most frequent criticisms from clinicians has been the absence of certain symptom clusters, such as obsessive-compulsive symptoms or catatonia. However, given that the scale was designed to be concise, a cut-off was necessary. While the TGI-P scale does not provide an exhaustive symptom assessment, this is not necessarily a drawback, as its primary purpose is to offer a broad transdiagnostic overview rather than a detailed symptom breakdown. Similarly, it does not specify the precise nature of symptoms within a domain, for example, in the case of negative symptoms, it does not differentiate between asociality, anhedonia, avolition, or apathy. However, for a rapid, high-level assessment, this trade-off is justified. Therefore, the TGI-P scale can also be regarded as a clinical checklist or thermometer that helps to evaluate the most important symptom domains and signalizes if something requires more attention. Those domains can be then measured by more detailed symptom-specific scales if necessary.

Additionally, the TGI-P scale is best utilized in a digital format, as the visual representation of the seven circles can be cumbersome when used in a traditional pen-and-paper format. While this may be seen as a limitation, it can also be a strength, as the scale fits well within modern digital health frameworks, which are increasingly being integrated into clinical practice.

Regarding the limitations of the scale development methods, two surveys were conducted to understand the content validity and feasibility of the TGI-P scale. In terms of the survey with the psychiatrists, the sample was small and limited to only three countries, US, Germany and Poland, which hinders the generalizability of the results. This is also a relevant limitation of

the patient-caregiver survey where the study sample was also relatively small and restricted to participants from the UK and US. Furthermore, the high level of educational attainment among patients and caregivers may have introduced a positive bias in perceptions of scale clarity and usability. Additionally, patients and caregivers were not matched pairs, preventing direct comparison between their responses. Finally, psychiatric diagnoses were based on self-report rather than clinical verification.

The primary limitation of the feasibility study is its extremely small sample size. With only six inpatients included, statistical power was very limited, and findings must be interpreted with caution. The study was exploratory in nature, aiming to test feasibility rather than draw firm conclusions about validity or reliability. Additionally, the lack of rater training and clinical experience on the part of the author (Zs.B.D.) likely contributed to variability in scoring, especially in comparison to the experienced psychiatrist (L.H.). This is particularly relevant in the inter-rater reliability findings, where discrepancies may reflect both differences in observation context and clinical judgment. Nonetheless, the results can also be interpreted as evidence that even with limited experience, the TGI-P can be administered with considerable correlation with ratings by an experienced clinician. Therefore, the TGI-P could be utilized by GPs, nurses and other healthcare professionals. Lastly, the cross-sectional design also represents a limitation, which precludes conclusions about the TGI-P's sensitivity to change over time, an important feature for any tool intended for use in longitudinal care.

4.5.3. Future research

While there is preliminary support for the feasibility and utility of the TGI-P, the above-mentioned limitations limit the generalizability of the findings. It is important to note however that at this stage, the scale does not require major revisions; rather, further large-scale feasibility testing and formal psychometric validation are warranted. Future studies should

include a broader range of patients, including those with bipolar disorder and major depression, and employ additional reference measures for domains that currently lack gold-standard assessments. Such studies will clarify whether low correlations in certain domains reflect persistent measurement challenges or can be improved through rater training and scale refinement.

Building on the success of the TGI-P scale, further developments are underway to expand the transdiagnostic approach beyond symptom measurement. Currently, the author of the thesis leads the development of five additional scales that follow the same visual analogy of seven circles, focusing on functioning (TGI-F) and caregiver burden (TGI-CB), adverse events (TGI-AE), and patient satisfaction with life (TGI-SL) and with care (TGI-SC). Together, these scales (TGI-P, TGI-F, TGI-AE and TGI-S) form the Transdiagnostic Pyramid, a novel framework aimed at providing a more holistic understanding of mental health measurement and treatment (**Figure 25**). This approach recognizes that true recovery extends beyond symptom reduction, it also involves the patient's overall well-being, daily functioning, and ability to reintegrate into society. Additionally, adverse events and physical health must be considered, as they significantly impact mental health treatment adherence and quality of life. By validating and integrating these new scales, the Transdiagnostic Pyramid has the potential to redefine how mental health is assessed and managed, ultimately promoting a more comprehensive and patient-cantered approach to psychiatric care.

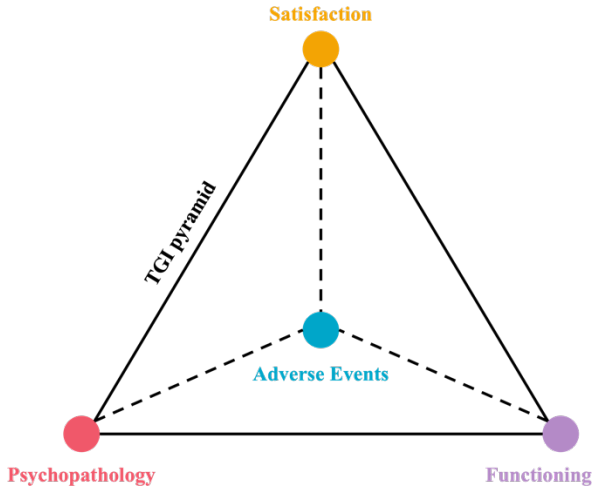

Figure 25. The Transdiagnostic Global Impression pyramid

Composed of four transdiagnostic scales, the TGI pyramid approach provides a novel framework for implementing measurement-based care holistically in everyday clinical practice.

4.6 Conclusion

This chapter presented the development and initial validation of the Transdiagnostic Global Impression – Psychopathology (TGI-P) scale, a novel assessment tool designed to provide a brief yet structured overview of key symptom domains, including cognition, based on routine clinical anamnesis. The TGI-P is not intended to replace formal cognitive or psychiatric testing, but rather to flag potential impairments, track symptom changes, and support measurement-based care (MBC).

By integrating cognitive functioning into a global clinical impression framework, the TGI-P addresses a critical gap in current psychiatric assessment tools, particularly in transdiagnostic research and clinical care. Although formal psychometric validation is still ongoing, the scale demonstrates strong face validity, positive initial user feedback, and promising feasibility in real-world inpatient settings.

The TGI-P offers a practical compromise between comprehensiveness and brevity. It provides a rapid, structured snapshot of multiple symptom domains, allowing clinicians, caregivers, and patients to quickly identify areas requiring attention and monitor changes over time. This approach aligns with MBC principles, emphasizing systematic symptom assessment to improve treatment outcomes.

Importantly, the TGI-P showed preliminary utility in assessing cognitive difficulties, correlating with MMSE scores in the exploratory feasibility study. While performance-based cognitive assessments remain the gold standard, the TGI-P can highlight cognitive impairments and track their progression, supporting timely clinical interventions.

Overall, the TGI-P represents a novel, transdiagnostic tool that is feasible, informative, and patient-centred. It has the potential to enhance clinical decision-making, facilitate communication, and improve outcomes in routine psychiatric practice while further validation studies are being conducted.

5 Cariprazine as a transdiagnostic treatment candidate for cognitive impairment: A systematic review & meta-analysis

5.1. Introduction

As emphasized in the previous chapters, measuring (**Chapter 2** & **Chapter 3**) and assessing (**Chapter 4**) cognitive impairment in individuals with NPDs is essential for understanding their symptom profile and clinical needs (533). However, effective assessment and measurement must be followed by targeted treatment strategies that can meaningfully improve cognitive functioning (77,533). Given its transdiagnostic nature and profound impact on daily functioning, quality of life, and other patient-reported outcomes (281,282,533), cognitive impairment remains a critical and largely unmet treatment target (77,534). Despite its clinical significance, there is currently no approved pharmacological intervention for cognitive impairment neither in SCHZ nor in other NPDs (535–537). Among the available medication classes, antipsychotics are the most viable candidates due to their diverse receptor profiles, which allow them to influence a broad range of brain processes relevant to cognition (294,538–540).

5.1.1. Rationale

As highlighted in **Chapter 1**, the cognitive effects of antipsychotics are highly variable, shaped by drug type, dose, treatment duration, polypharmacy, and patient characteristics.

Some SGAs such as clozapine, olanzapine, risperidone, and quetiapine may modestly enhance cognitive function in NPDs (283), with risperidone showing benefits in executive functioning in BD (284). However, findings are inconsistent, with several studies detecting no clear differences between typical and atypical agents (285), and some linking higher doses or prolonged use to cognitive worsening (286–288). Indeed, Osugo et al. provided evidence that sustained modulation of dopamine D_2-D_3 receptors with amisulpride or aripiprazole impairs visuospatial working memory in healthy participants, suggesting that dopamine receptor manipulation by antipsychotics may have a detrimental impact on specific cognitive domains (541). Furthermore, Mancini et al. (2025) showed through a meta-analysis that anticholinergic burden is strongly associated with impairments across multiple cognitive domains, and that tapering anticholinergic drugs can yield cognitive improvements (542). Importantly, while antipsychotics are predominantly known as dopamine modulators, many agents such as clozapine also exert anticholinergic effects (543).

Interestingly, a large-scale network meta-analysis by Feber et al. indicated that, while antipsychotics are not true pro-cognitive agents, treatment as a whole is associated with small but significant improvements in cognition compared to placebo, likely driven by reductions in disorganized thought processes rather than direct cognitive enhancement (544). Taken together, these mixed findings underscore the need to carefully review antipsychotics in terms of cognitive effects and determine which agents are least likely to worsen cognition or even improve certain domeians. In this regard, TGAs are emerging as promising candidates for cognitive improvement in NPDs (290).

Among TGAs, cariprazine has attracted particular interest due to its unique receptor profile. Cariprazine is a D_3-D_2 partial agonist, with the highest affinity for D_3 receptors among all currently available antipsychotics (545,546). The D_3 receptor is thought to play a critical role

in cognitive processes, particularly those related to motivation, reward, and executive function (539,547). Although no clinical trials to date have been designed specifically to evaluate the cognitive effects of cariprazine, post-hoc analyses of clinical trials in SCHZ and BD as well as case reports have indicated a potential pro-cognitive effect (293,547–549). These findings position cariprazine as a promising candidate for the transdiagnostic treatment of cognitive impairment. Indeed, Olivola et al. explored the efficacy of cariprazine as well as lurasidone in improving cognition in a mini systematic review focusing on both animal models and human studies (547), whereas García-Fernández et al. conducted a systematic review of randomized controlled trials (RCTs) that assessed the effects of cariprazine on cognition in patients with SCHZ or BD (549). Both reviews concluded that cariprazine is a promising agent for improving cognition.

5.1.2. Aims and objectives

The aim of the present chapter is to evaluate the potential of cariprazine as a transdiagnostic treatment candidate for cognitive impairment in NPDs. In contrast to the previous reviews, this systematic review and meta-analysis aims to evaluate evidence from both clinical trials and real-world studies including case reports and synthesize the evidence beyond the approved indications, SCHZ, BD and MDD.

The objective of the systematic review and meta-analysis is the following:

1. To conduct a systematic review and meta-analysis of existing evidence investigating the impact of cariprazine on cognitive functioning in individuals with NPDs.
2. To explore whether based on the available evidence, cariprazine can act as a transdiagnostic cognitive enhancer.

5.2 Methods

5.2.1. Search strategy

A systematic electronic search was conducted in the Embase, PubMed, and Scopus databases for English-language articles published in peer-reviewed journals between January 1, 2015, and January 31, 2025, following PRISMA guidelines. The search employed the following terms: (‘cariprazine’) AND (‘cognit*’). In addition to database searches, reference lists of the identified articles were manually screened, and supplementary hand searches were conducted to capture any additional relevant studies.

5.2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria: (a) original research conducted with human participants; (b) inclusion of at least one validated cognitive assessment tool, test, or scale that provides a proxy for cognitive function or sufficient description of cognitive improvements; and (c) investigation of cariprazine as the primary treatment intervention or clear descriptions that the treatment effect is attributed to cariprazine. Studies were excluded if they were review articles, preclinical (animal) studies, or did not address cognitive outcomes adequately. Additionally, studies that combined cariprazine with other pharmacological treatments in a way that prevented the independent evaluation of their cognitive effects were also excluded.

5.2.3. Recorded variables and data extraction

From each included study, the following information was extracted: first author, year of publication, study design, participant characteristics (including diagnosis, sample size, (mean) age, and sex distribution), details of cariprazine treatment (maintenance dose and polytherapy), cognitive characteristics (symptoms, scales and tests) and key findings related to cognitive outcomes. Study results were systematically organized and presented in tabular

format. In cases where multiple publications were derived from the same study such as post hoc analyses or companion papers reporting different aspects of the same dataset, care was taken to identify overlapping content. To avoid redundancy, only the publication most relevant to the aims of this systematic review and meta-analysis was included. Data were directly extracted from the text or tables; no values were estimated from graphs. In one instance, study authors were contacted to clarify specific data.

5.2.4. Statistical analyses

Only clinical trials comparing cariprazine to placebo were included in the meta-analysis, which was conducted to evaluate the efficacy of cariprazine in alleviating symptoms of cognitive impairment. Data were extracted from post-hoc analyses of randomized controlled trials, including both individual study-level and pooled results. The included studies covered various psychiatric indications and investigated different doses of cariprazine.

The primary outcome analysed in this meta-analysis was the change from baseline in cognitive symptom scores, rather than raw end-point scores. This approach was chosen because cognitive impairment was typically assessed as post-hoc outcome in the included clinical trials, which reported least squares mean change values for both cariprazine and placebo groups. To enable comparison across trials using different cognitive assessment scales, these change scores were standardized by converting effect sizes to Cohen's *d*.

For each included trial or dose arm, the following variables were recorded: author and publication year, clinical indication, study identifier, cognitive scale used, cariprazine dose, number of participants in the cariprazine and placebo groups, least squares (LS) mean change from baseline for each group, and the corresponding SEs (**Appendix G**). Cohen's d was

calculated as: Cohen's d = (LS mean change (Cariprazine) – LS mean change (Placebo) / pooled SD, with the pooled standard deviation estimated from the reported SEs and group sizes. The standard error of Cohen's d was also computed for each comparison. Where available, the LS mean difference (LSMD) between cariprazine and placebo and its SE and 95% CIs were extracted directly. In cases where LSMD and SE were not reported, they were calculated manually in Excel using the following formulas:

$$\text{LSMD} = \text{LS mean change (Cariprazine)} - \text{LS mean change (Placebo)}$$

$$\text{SE} = \sqrt{(\text{SE\_Cariprazine}^2 + \text{SE\_Placebo}^2)}$$

Where necessary, study authors were contacted to request missing information, and they provided the data upon request.

The meta-analysis was conducted in RStudio (version 2024.04.2+764) using the *metafor* package. A multilevel random-effects model was employed to account for the hierarchical structure of the data and to address the non-independence introduced by overlapping placebo groups, which occurred in studies reporting multiple cariprazine dose arms sharing a single placebo sample. Cognitive outcomes were frequently analysed post hoc and sometimes reported as pooled data across multiple trials, limiting the availability of separate trial-level results. To accommodate this, comparisons within the same study were grouped using a random intercept structure (i.e., random = ~1 | STUDY), allowing for the correlation between effect sizes sharing a common placebo group. Subgroup analyses by dose or individual trial were not feasible due to limited data. Effect sizes are reported as pooled standardized mean differences (Cohen's d) with 95% confidence intervals. Between-study heterogeneity was assessed using the Q-statistic, I^2, and the estimated variance component (τ^2) from the multilevel model. Forest plots illustrate individual and pooled estimates of the cognitive effects of cariprazine versus placebo.

5.3 Results

5.3.1. Search results

A summary of the article selection process for the systematic review and meta-analyses is presented in a PRISMA flow diagram (**Figure 26**). A total of 139 articles were identified via database searches before removing duplicates. Additionally, seven studies were identified via hand searches. Removing the duplicates, a total of 85 records were screened. Based on the abstracts, twenty-three were chosen to be evaluated as full text of whom 20 was included in the systematic review and 2 in the meta-analysis. The three articles excluded did not provide sufficient information on the effects of cariprazine on cognitive impairment to be included.

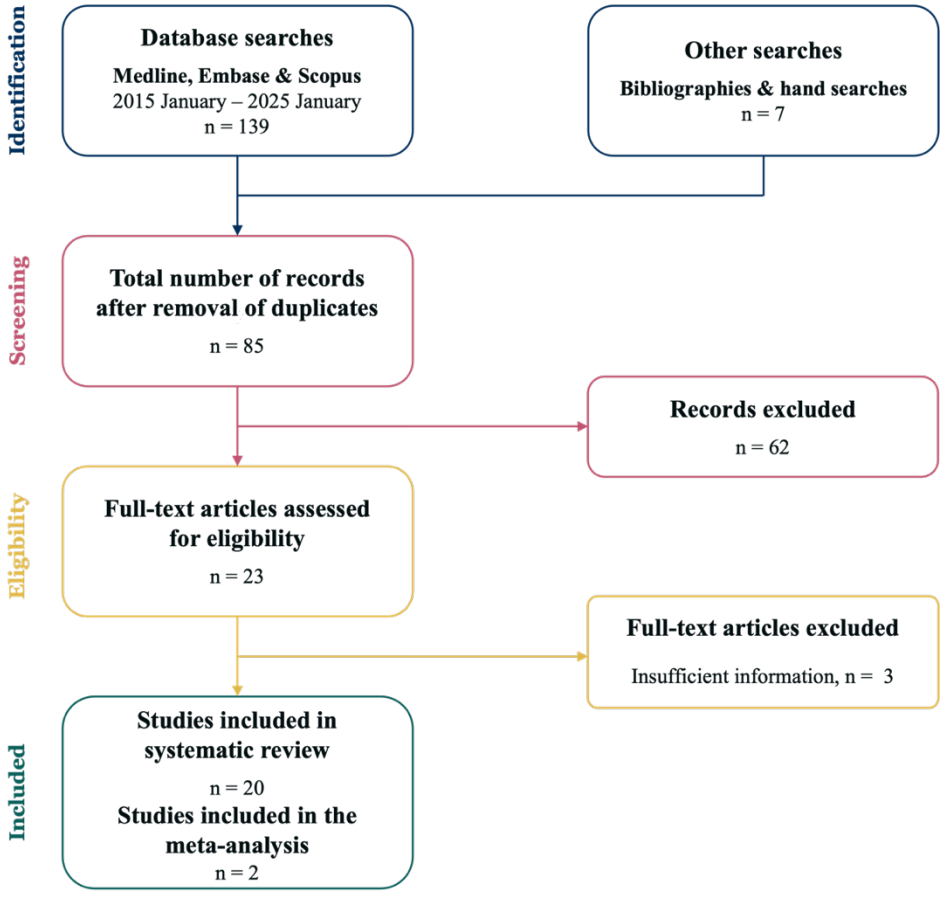

Figure 26. Summary of study identification and selection

The figure shows the article dentification and selection process for the systematic review and meta-analysis according to the PRISMA guidelines.

5.3.2. Study characteristics

The included studies are tabulated in **Table 47**. Out of the 20 included studies, 85% were real-world evidence including case reports (12 studies), case series (4 studies), and one observational study, while 15% (2 studies) were post-hoc analyses of clinical trials, where cognitive impairment was not the primary outcome.

Table 47. Cariprazine – cognition study characteristics

Study	Study design	Patient characteristics				Cariprazine treatment		Cognitive characteristics		Effect of cariprazine on cognition
		Diagnosis	N	(Mean) age	% males	Maintenance dose	Concomitant medication	Symptoms	Scales & tests	
Amore et al. 2019	Case report	Schizophrenia	1	24	Unknown	3.0 mg/day	-	The capacity to maintain attention, especially active attention, and concentration was markedly reduced.	-	The patient showed an increase in personal initiative, good skills of future planning, and regular implementation of daily life activities.
Aubel et al. 2021	Case study	Paranoid schizophrenia	1	32	100%	4.5 mg/day	-	Concentration difficulties.	-	Improvement in cognitive performance, concentration, and alertness
Balicza et al. 2024	Case study	Mitochondrial disease	1	34	100%	3.0 mg/day	Venlafaxine, Procyclidine	Delayed speech development, learning disabilities, cognitive slowing.	ACE, MOCA, MMSE	ACE scores improved (02/2021: 87, 07/2021: 96).
Bogren et al. 2022	Case study	Schizoaffective disorder	1	45	100%	6.0 mg/day	Clozapine (275 mg), Valproate (1,200 mg), Sertraline (200 mg)	Prominent sustained cognitive symptoms with clozapine therapy.	-	Recovery of attentional cognitive processes
Boydstun et al. 2023	Case series	Treatment-resistant schizophrenia	1	26	100%	3.0 mg/day	Haloperidol decanoate (200 mg)	Significant cognitive/memory impairments with ongoing treatment.	-	Perceived improvements in memory and attention.
			1	43	100%	6.0 mg/day	Paliperidone palmitate	Significant cognitive decline.	-	Rapid improvements in organization of thought processes and perceived gains in memory and concentration.
Carmassi et al. 2019	Case series	Schizophrenia	1	39	100%	6.0 mg/day	Benzodiazepines	Concentration deficit		Improvement in his cognitive profile with gradual improvement in concentration.
			1	20	100%	3.0 mg/day	Biperiden (4 mg)	Cognitive deficiency	-	Gradual improvement in cognitive performance.
Cruz et al. 2021	Case stduy	Schizophrenia	1	30	100%	4.5 mg/day	Quetiapine (900 mg), Clonazepam (2 mg), Propranolol	Dysfunction in attention, working memory, cognitive flexibility and spontaneity.	-	Cariprazine add-on to quetiapine treatment improved cognitive functioning.
De Berardis et al. 2021	Case study	Schizophrenia	1	35	100%	3.0 mg/day	Clozapine (300 mg)	Considerable problem in functioning (lost his job).	-	The patient reported that he “felt better” especially on functioning and cognitions without adverse effects.

Di Sciascio et al. 2019	Case study	Schizophrenia	1	22	0%	6.0 mg/day	-	Blockages and glitches in her thinking, which appeared to be conceptually fragmented and disorganized.	-	Clear improvement in the disorganized thinking, the ability to focus and relate to other people. Returned to work.
Fleischhacker et al. 2019	Post hoc analysis of a clinical trial	Schizophrenia	230	40.2	54%	3.0 – 6.0 mg/day	-	Unknown	PANSS Disorganized thoughts factor score	Change from baseline to week 26 was significantly different for cariprazine versus risperidone on Disorganized thoughts factor score (LS mean change = -0.63, $p < 0.01$).
Jimoh et al. 2020	Case study	Wernicke encephalopathy	1	32	0%	3.0 mg/day	-	Memory impairment and incoherent thinking process.	ACE	ACE score improved from 81 to 86 after 6 months. Started working again.
Marder et al. 2019	Pooled post hoc analyses	Schizophrenia	1024	36.9	69.6%	1.5 – 9.0 mg/day	-	Unknown	PANSS Disorganized thoughts factor score	The largest treatment effect was observed in the disorganized thought factor (ES = 0.47, $P < 0.0001$).
McIntyre et al. 2022	Post hoc analyses of clinical trials	Bipolar I depression	1383	Unknown	Unknown	1.5 mg/day, 3.0 mg/day	-	88.4% of patients had at least mild cognitive symptoms and 66.0% had at least moderate cognitive symptoms. 75.8% of patients had baseline cognitive symptoms.	MADRS item 6, FAST Cognitive score	Greater improvement was observed for cariprazine vs placebo on measures of cognition in the overall population and in sub-sets of patients with greater cognitive symptoms.
		Bipolar I mania	1012	Unknown	Unknown	3.0 – 12.0 mg/day	-	More than half of all patients had a baseline PANSS Cognitive subscale score at or above the median (11), whereas 17.2% of patients had PANSS Cognitive subscale score ≥15.	PANSS Cognitive subscale	In patients with manic or mixed bipolar I disorder episodes and cognitive symptoms at baseline, significant improvement for cariprazine vs placebo was observed in cognitive symptoms (i.e., change from baseline in PANSS Cognitive subscale and on 4 of 5 individual subscale items).
		Schizophrenia	520	Unknown	Unknown	3.0 mg/day, 6.0 mg/day	-	The high cognitive impairment subsets included patients with scores above or equal to the median PoA time (≥1545.1 ms) and below or equal to the median CoA score (≤88).	CDR	In patients with baseline attentional impairment, significantly greater median change from baseline on the PoA was noted for cariprazine 3 mg/day vs placebo, as well as for cariprazine 3 mg/day vs the active-comparator aripiprazole. Significantly greater median change from baseline was seen for both

										cariprazine 3 and 6 mg/day vs placebo.
Mencacci et al. 2019	Case series	Schizophrenia	1	51	100%	4.5 mg/day	-	Poor capacity of concentration.	-	Lack of concentration, gradually improved; the patient was again able to attend a job-related course as well as church-related activities.
			1	49	0%	4.5 mg/day	Biperiden (4.5 mg), Lorazepam (6 mg)	Unknown		Concentration skills are subjectively improved.
Molnar et al. 2020	Case study	Early-onset schizophrenia	1	23	0%	3.0 mg/day	Anticholinergic medication	Thinking, memory, and concept formation, were severely impaired.	-	16 weeks after the first contact cognitive functions, such as memory and abstract thinking had improved remarkably.
Molnár et al. 2022	Observational study	Huntington's disease	16	48.1	25%	1.5 mg/day (87.5%) 3.0 mg/day (6.2%) 4.5 mg/day (6.2%)	Tetrabenazine, benzodiazepine, antidepressants or antipsychotics	Cognitive alterations including executive dysfunction, planning difficulties, cognitive decline.	ACE, UHDRS	ACE increased from 75.1 + 11.0 (baseline) to 86.7 + 9.3 (week 12) (LS mean change 11.5+/−1.4 $p < 0.0001$). Cognitive Verbal fluency score (UHDRS) was 6.2 + 2.5 at the baseline, increased to 7.7 + 2.7 by week 12 (LS mean change 1.5+/−0.5, $p = 0.0103$). The mean baseline score of 9.2 + 6.9 on the Symbol Digit test increased to 12.3 + 8.9 by week 12 (LS mean change 3.1 +/−0.7, $p = 0.0009$).
Probo et al. 2023	Case study	Treatment-resistant schizophrenia	1	34	100%	6.0 mg/day	Clozapine (400 mg), Lorazepam (2.5 mg)	Unknown	WAIS IV	Slight improvement in the overall WAIS score (+6.2%), visual perceptive reasoning (+11%), and processing speed (+13%), and a slight worsening in working memory (-7.5%) and visual understanding (-3.1%).
Sanders et al. 2019	Case study	Bipolar I disorder, ADHD, alcohol and cannabis use disorder	1	20	0%	3.0 mg/day	Quetiapine (25 mg), Clonazepam (0.5 mg), Methylphenidate XR (72 mg)	Failed out of college, difficulty communicating.	-	Significant improvement: organized thought processes. Graduated at the top of her class in an aesthetician training program.
Siwek et al. 2024	Case series	Treatment-resistant schizophrenia	1	38	100%	4.5 mg/day	Clozapine (200 mg)	Low severity of cognitive dysfunction	-	Improvement in global functioning in terms of overall activity, independence, ability to make

										purchases independently, participation in household activities.
			1		100%	4.5 mg/day	Clozapine (500 mg)	Moderate severity of cognitive dysfunction		Improvement in global functioning in terms of overall activity.
			1		100%	4.5 mg/day	Clozapine (375 mg)	Low severity of cognitive dysfunction		Improvement in formal thought disorders, better social contacts and communication.
			1		0%	6.0 mg/day	Clozapine (150 mg)	Low severity of cognitive dysfunction		-
			1		100%	4.5 mg/day	Clozapine (200 mg)	Low severity of cognitive dysfunction		Improved cognitive functions.
Vannucchi et al. 2022	Case study	Schizophrenia	1	38	100%	3.0 mg/day	Amitriptyline (10 mg), Perphenazine (4 mg)	Attention and concentration difficulties	-	Less confusion, more fluid and organized speech. Concentration difficulties disappeared.

ACE, Addenbrooke Cognitive Examination; ADHD, Attention-Deficit/Hyperactivity Disorder; CDR, Cognitive Drug Research; CoA, Continuity of Attention; FAST, Functional Assessment Short Test; LS, Least Squares; MADRS, Montgomery–Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; PANSS, Positive and Negative Syndrome Scale; PoA, Power of Attention; UHDRS, Unified Huntington's Disease Rating Scale; WAIS IV, Wechsler Adult Intelligence Scale – Fourth Edition

5.3.2.1. Post-hoc analyses of clinical trials

Three post-hoc analyses of clinical trials were identified, analysing large samples across SCHZ (total n = 1,774) and BD (total n = 2,395) populations with manic, mixed or depressive episodes (293,550,551). In these clinical trials, change in cognition was not the primary outcome, therefore this aspect was analysed post-hoc. Understanding the impact of cariprazine on cognition, Fleischhacker et al. analysed data from a clinical trial that included 230 patients with SCHZ and predominant negative symptoms (mean age 40.2 years, 54% male) post hoc (292,550). Patients were randomly assigned to be treated with either fixed doses of cariprazine (3.0, 4.5 or 6.0 mg/day) or risperidone (3.0, 4.0 or 6.0 mg/day) for 26 weeks (292). The post-hoc study evaluated changes in cognition via the Marder Disorganized thoughts factor score (550). Similarly, Marder et al. used this factor score as an anchor for cognition in a pooled post hoc analysis involving data from three clinical trials encompassing 1024 patients with SCHZ (mean age 36.9 years, 69.6% male) (551). Doses of cariprazine ranged between 1.5 to 9.0 mg/day (fixed dose in two and flexible dose in one of the trials) in these 6-week, double-blind and placebo controlled clinical trials with acute patients (551). Finally, McIntyre et al. analysed data from 1383 patients with BD (pooled from three 6-week randomized, double-blind, and placebo-controlled clinical trials), 1012 patients with manic or mixed episodes associated with BD (pooled from three 3-week randomized, double-blind, and placebo-controlled clinical trials), and 520 patients with acute SCHZ (one randomized, double-blind, and placebo-controlled clinical trial) (293). The anchors for cognition in this post hoc were changes from baseline to week 6 in MADRS Concentration Item (item 6) score (in BD depression studies), changes from baseline to day 21 in PANSS Cognitive subscale score (in BD mania studies), and median changes in Cognitive Drug Research (CDR) system attention battery (in the SCHZ study) (293).

5.3.2.2. Real-world evidence

The 12 case reports and 4 case series summarise a total of 23 patient cases (**Table 48**). Most of the patients were male (69.6%) and the ages of the patients ranged between 20-51 years (mean age= 34.2). In terms of diagnosis, the majority of cases were diagnosed with SCHZ (82.6%) (552–563), including treatment-resistant (34.7%) (560,562,563), paranoid (4.3%) (559), and early-onset forms (4.3%) (561). Other diagnoses included BD (564), schizoaffective disorder (565), Wernicke encephalopathy (566), mitochondrial disease (567), ADHD (564), and SUD (564) (each 4.3%). One patient had more than one diagnosis (564). The most common cariprazine maintenance dose was 3.0 mg/day (39.1%), followed by 4.5 mg/day (34.8%) and 6.0 mg/day (26.1%). Concomitant medications were reported in 78.3% of cases, most frequently antipsychotics (60.8%), including clozapine (34.8%), quetiapine (13.0%), haloperidol, paliperidone, and perphenazine (each 4.3%). Benzodiazepines were used in 21.7% of cases, antidepressants in 13.0%, anticholinergics in 17.4%, mood stabilizers in 4.3%, and other medications in 8.7%.

In addition to the case-based evidence, one observational study evaluated cariprazine treatment in patients with HD (294). The observational study by Molnár et al. (2022) included 16 patients with HD with a mean age of 48.1 years (294). Of the sample, 25% were male (294). Cariprazine was administered at a maintenance dose of 1.5 mg/day in 87.5% of patients, with 6.2% each receiving 3.0 mg/day and 4.5 mg/day (294). Concomitant medications included tetrabenazine, benzodiazepines, antidepressants, or antipsychotics (294).

Table 48. Summary of patient cases included in the systematic review

Total number of patient cases, n (%)	23 (100)
Age (years)	
Range	20 – 51
Mean	34.2
Men, n (%)	16 (69.6)
Diagnosis, n (%)*	
Schizophrenia	19 (82.6)
Treatment-resistant schizophrenia	8 (34.7)
Paranoid schizophrenia	1 (4.3)
Early-onset schizophrenia	1 (4.3)
Bipolar I disorder	1 (4.3)
Schizoaffective	1 (4.3)
Wernicke encephalopathy	1 (4.3)
Mitochondrial disease	1 (4.3)
ADHD	1 (4.3)
SUD	1 (4.3)
Cariprazine maintenance dose, n (%)	
3.0 mg/day	9 (39.1)
4.5 mg/day	8 (34.8)
6.0 mg/day	6 (26.1)
Concomitant medication, n (%)	18 (78.3)
Antipsychotics	14 (60.8)
Clozapine	8 (34.8)
Quetiapine	3 (13.0)
Haloperidol	1 (4.3)
Paliperidone	1 (4.3)
Perphenazine	1 (4.3)
Benzodiazepines	5 (21.7)
Antidepressants	3 (13.0)
Anticholinergics	4 (17.4)
Mood stabilizers	1 (4.3)
Other medications	2 (8.7)

*one patient had more than one diagnosis
ADHD, Attention-Deficit/Hyperactivity Disorder; SUD, Substance use disorder

5.3.3. The impact of cariprazine on cognitive functioning

5.3.3.1. Schizophrenia

The effectiveness of cariprazine in alleviating cognitive impairment is most thoroughly documented in patients with SCHZ, with evidence drawn from three post-hoc analyses and 19 individual patient cases. A pooled post-hoc analysis of three 6-week randomized controlled trials demonstrated a significant reduction in the PANSS Disorganized thought factor score for cariprazine compared to placebo (ES = 0.47, $p < 0.0001$) (551). Similarly, a separate post-hoc analysis of a 26-week clinical trial involving patients with predominant negative

symptoms found a significantly greater improvement in the same factor score for cariprazine compared to risperidone (LS mean change = –0.63, $p < 0.01$) (550). Finally, a post-hoc analysis by McIntyre et al. examined a subset of SCHZ patients with baseline cognitive impairment. In this subgroup, cariprazine 3.0 mg/day was associated with significantly greater improvements in Power of Attention (PoA) scores compared to both placebo and the active comparator, aripiprazole (293).

Evidence from case reports and case series further supports the potential benefits of cariprazine in cognitive impairment related to SCHZ, although these data are almost solely based on subjective descriptions. Only one case employed a standardized cognitive assessment tool, the WAIS, which showed slight improvements in overall score, visual perceptive reasoning, and processing speed (562). However, this was accompanied by mild declines in working memory and visual understanding, indicating mixed results (562). Cognitive symptoms reported across cases included concentration difficulties (552,553,557–559), memory impairment (554,560,561), and dysfunction in attention (552,554,557). In some cases, cognitive impairment manifested through functional consequences such as job loss, fragmented thinking, and reduced ability to perform daily tasks (555,556,558). Cariprazine treatment either as monotherapy or added on top of the established treatment regimen resulted in subjective and functional improvements such as enhancements in concentration, attention, memory, and abstract thinking (556–558). Functional improvements included returning to work, improved participation in household activities, and better planning and organizational skills (552,556,558).

5.3.3.2. Bipolar & schizoaffective disorder

The impact of cariprazine on cognitive symptoms in BD is highlighted through two post-hoc analyses and one case report. A pooled post-hoc analysis of three 6-week randomized, double-

blind, placebo-controlled trials in bipolar depression demonstrated significantly greater improvements with cariprazine compared to placebo (293). Importantly, at baseline, 88.4% of participants exhibited at least mild cognitive symptoms, and 66% had symptoms rated as moderate (293). In terms of bipolar mania, over half of the participants had PANSS Cognitive Subscale scores at or above the median at baseline (293). Among this subgroup, cariprazine was associated with significantly greater improvements in total score, as well as in four out of five individual items, compared to placebo (293).

In addition to clinical trial data, case reports offer further insight. One described a patient with BD, ADHD, and comorbid SUD who showed marked cognitive and functional improvement after cariprazine was added to a regimen of quetiapine, clonazepam, and methylphenidate (564). Previously struggling with communication and academic challenges, the patient ultimately graduated at the top of her class in an aesthetician training program (564). Another case, involving a patient with schizoaffective disorder and persistent cognitive symptoms despite clozapine treatment, reported notable improvements in attention and cognitive functioning following the addition of cariprazine (565).

5.3.3.3. Neurological disorders

Findings from an observational study and individual case reports support the potential of cariprazine to improve cognitive impairment in neurological disorders. In a 12-week observational study involving 16 patients with HD, cognitive outcomes were assessed using the ACE and the cognitive subscale of the UHDRS (294). By the end of the treatment period, mean ACE scores increased from 75.1 to 86.7 (LS mean change = 11.5, $p < 0.0001$), while the UHDRS Verbal Fluency subscale improved from 6.2 to 7.7 (LS mean change = 1.5, $p = 0.0103$) (294). Performance on the Digit Symbol Test also significantly increased, from 9.2 at baseline to 12.3 at week 12 (LS mean change = 3.1, $p = 0.0009$) (294).

Further support comes from two case reports. In one patient with Wernicke encephalopathy, ACE scores improved from 81 to 86 over a six-month period of cariprazine treatment, with the individual subsequently able to return to work (566). Another case involved a patient with mitochondrial disease, characterized by delayed speech development, learning difficulties, and cognitive slowing (567). ACE scores in this patient improved from 87 to 96 (567).

5.3.4. Meta-analysis of cariprazine versus placebo for cognitive symptom improvement

Data for the meta-analysis on cognitive impairment were drawn from two publications summarizing post-hoc analyses of clinical trials investigating cariprazine against placebo. The third post-hoc analysis by Fleischhacker et al. (2019) was excluded, since cariprazine was compared to risperidone rather than placebo (550). The publication by Marder et al. (2019) reported on three short-term schizophrenia trials (551). Of these, two fixed-dose studies were included in the meta-analysis to allow evaluation of dose-specific effects, while the third (a flexible-dose trial) was excluded due to unreported data. The authors were not available to provide the missing data. For the 3.0 mg/day dose, the results of the two included schizophrenia trials were pooled by the authors and entered into the analysis as a single data point. The second source, McIntyre et al. (2022), reported pooled data from trials in bipolar depression, bipolar mania, and schizophrenia (293). As the schizophrenia data overlapped with the Marder publication, only data on bipolar disorder were included. For bipolar depression, three studies were pooled, and data were available separately for the 1.5 mg/day and 3.0 mg/day doses. For bipolar mania, three studies were pooled, but dose-specific estimates were not reported. Notably, within the pooled data a 12 mg/day dose of cariprazine was also included, which is above the typical therapeutic range. This dataset was retained in

the analysis to ensure representation of mania patients and to preserve the transdiagnostic scope of the meta-analysis. Cognitive outcomes varied by diagnostic indication: the PANSS Disorganized Thought Factor score was used in schizophrenia trials, the MADRS concentration item in bipolar depression, and the PANSS Cognitive subscale in bipolar mania.

The multilevel meta-analysis included seven comparisons and was conducted using a random-effects model, accounting for clustering at the study level due to overlapping placebo groups. The pooled standardized mean difference (Cohen's d) between cariprazine and placebo was –0.34 (SE = 0.048, $p < .0001$), with a 95% confidence interval of –0.43 to –0.24, indicating a statistically significant and moderate improvement in cognitive symptoms with cariprazine compared to placebo. Between-study heterogeneity was also significant ($Q = 13.84$, $p = 0.031$), with an estimated variance component (σ^2) of 0.0064.

Inspection of the forest plot revealed that the largest standardized effects were observed in schizophrenia at the higher doses: 4.5 mg/day (d = –0.51, 95% CI –0.72 to –0.31) and 6.0 mg/day (d = –0.48, 95% CI –0.68 to –0.28). The smallest effect was seen in bipolar depression at 3.0 mg/day, with a Cohen's d of –0.14 (95% CI –0.27 to –0.01), as shown in **Figure 27**.

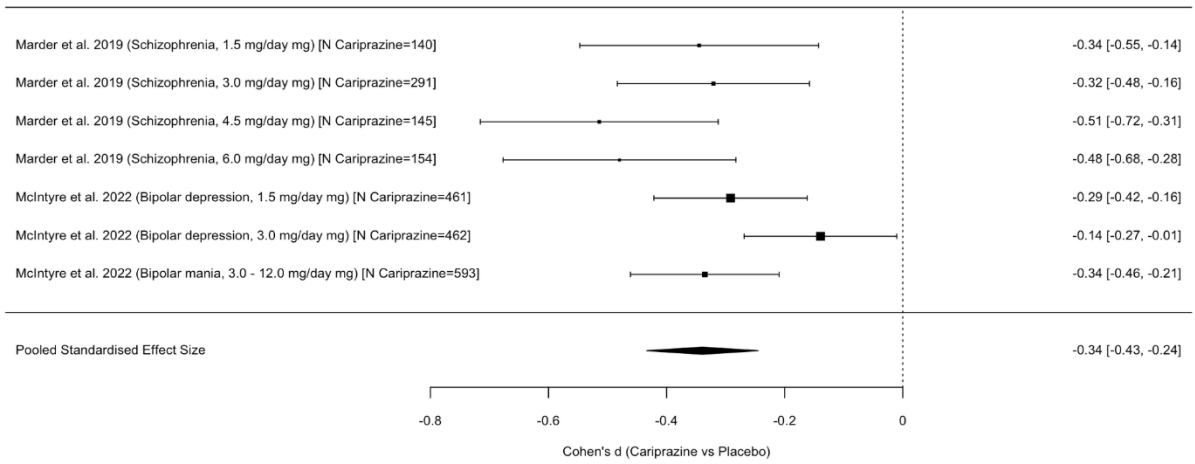

Figure 27. Forest plot of the efficacy of cariprazine versus placebo on cognitive symptoms across psychiatric disorders

This forest plot presents standardized mean differences (Cohen's d) in cognitive symptom outcomes between cariprazine and placebo, derived from pooled post-hoc analyses of randomized controlled trials in schizophrenia, bipolar depression, and bipolar mania. Effect sizes are organized by dose and clinical indication, with 95% confidence intervals. Negative values indicate greater improvement in cognitive symptoms with cariprazine relative to placebo. Some entries reflect pooled analyses across multiple trials. To account for shared placebo groups and multiple arms within studies, a multilevel meta-analytic model with a random intercept for study was applied.

5.4 Discussion

5.4.1. Summary of key findings

This is the first systematic review and meta-analysis to evaluate the impact of cariprazine on cognitive impairment across a broad range of NPDs, extending beyond its approved indications. By incorporating both clinical trial data and real-world evidence (including observational studies, case series, and case reports) this review offers a comprehensive overview of cariprazine's potential cognitive benefits.

The findings of the meta-analysis indicate that cariprazine is significantly better in reducing symptoms of cognition compared to placebo in patients with SCHZ, bipolar depression and bipolar mania. This is supported by the systematic review results where evidence showed that cariprazine may improve key cognitive symptoms such as concentration difficulties, memory

impairment, and attentional dysfunction across several neuropsychiatric conditions. These cognitive improvements are often associated with enhanced functional outcomes, including patients' ability to return to work and re-engage with daily life. The most robust and consistent evidence to date comes from studies in SCHZ. However, emerging data in BD, HD, and individual cases of other conditions also support its potential transdiagnostic utility.

5.4.2. Cariprazine as a transdiagnostic medication for cognitive impairment

As highlighted in the **Rationale** of the present chapter, cariprazine's potential as a transdiagnostic treatment for cognitive impairment stems from its unique pharmacological profile (293). As a dopamine D_3-D_2 partial agonist with high affinity for D_3 receptors (545,546), it targets a system strongly implicated in cognition across both healthy and clinical populations (568–571). D_3 receptor modulation may enhance memory, attention, and executive function, consistent with improvements observed in individual cases (571).

The results of the present meta-analysis appear somewhat larger than what has been reported for SGAs in prior work (572), though not as large as the most favourable effect sizes identified in a recent NMA (573). Indeed, Feber et al. (2025) reported advantages for specific antipsychotics and cognitive domains, with medium-sized effects observed for sertindole (SMD = –0.41) and paliperidone (SMD = –0.57) (573). In comparison, the present meta-analysis yielded a pooled effect size of –0.34 across disorders, with higher-dose cariprazine in schizophrenia reaching values of –0.48 to –0.51.

Several differences may account for these discrepancies. First, Feber and colleagues focused exclusively on schizophrenia spectrum disorders, whereas the present study adopted a transdiagnostic scope, also incorporating bipolar depression and mania. Second,

methodological approaches diverged: Feber used a frequentist network meta-analysis with receptor-class groupings, while the present work applied a random-effects model to post-hoc pooled trial data. Third, the sample sizes were markedly different: for example, paliperidone's estimate in Feber was based on 106 participants, whereas the present meta-analysis encompassed several thousand patients across diagnostic groups. Finally, cariprazine was not included in Feber's analysis, but given its serotonergic–dopaminergic profile, it would likely have fallen into one of the more favourable receptor classes identified.

Together, these comparisons suggest that while cariprazine's cognitive effects are in line with or somewhat smaller than the largest domain-specific benefits reported for other antipsychotics, its transdiagnostic efficacy, larger evidence base, and consistent improvements across multiple disorders distinguish it as a promising candidate for addressing cognitive impairment in NPDs.

5.4.3. Limitations

This systematic review is notably limited by the type and quality of the included evidence, most of which comprised case reports or case series and an observational study, with the remainder consisting of post-hoc analyses of clinical trials. Case reports are inherently subjective (574), often lack standardized or validated cognitive assessment tools, and are prone to publication bias; positive or dramatic outcomes are more likely to be published than negative or inconclusive ones (575). These factors collectively limit the generalizability and robustness of the findings. One observational study was also included in the review. Although this provides a useful perspective on real-world treatment effects, observational designs inherently lack the ability to determine causality (576), making it difficult to establish a clear temporal or causal link between cariprazine treatment and cognitive improvements.

The meta-analysis is limited by its reliance on data from post-hoc analyses of clinical trials. While post-hoc analyses offer valuable insights, they are constrained by their retrospective nature (577). These analyses are not prospectively designed to evaluate specific outcomes such as cognitive impairment and often rely on proxy measures that may only partially reflect cognitive functioning (577). For example, the use of the PANSS Disorganized thoughts factor score may offer indirect evidence of cognitive effects but cannot substitute for comprehensive assessments like the MoCA (399). This concern is supported by several studies; Good et al. demonstrated that the correlation of the PANSS cognitive factor with standardized cognitive test performance was modest, leaving two-thirds of the variance in cognition unexplained (578). Similarly, Nielsen et al. found that PANSS cognitive factors lacked discriminant validity and primarily reflected verbal IQ rather than domains known to be impaired in schizophrenia, such as memory, attention, and processing speed (399). These findings highlight that PANSS-derived measures might lack the sensitivity and specificity required to robustly capture cognitive deficits. Moreover, post-hoc analyses frequently fail to control for relevant confounders such as illness stage, medication exposure, and polypharmacy, which increases the risk of biased estimates (577).

Additional limitations of the meta-analysis include the considerable heterogeneity of studies (study populations, cognitive measures used, trial design and dosing differences), although given the aim of examining the transdiagnostic potential of cariprazine, this was expected. Finally, data extraction was conducted by a single reviewer, rather than in duplicate as is typically recommended to minimize error. However, given the relatively small number of included studies and the clarity of the reported data, the risk of extraction errors is likely to be low.

5.4.4. Future research

Future research should prioritize well-designed, double-blind, placebo-controlled and/or active comparator trials specifically targeting cognitive outcomes using validated cognitive measures. Longitudinal study designs are also essential, as cognitive changes do not occur overnight.

5.5 Conclusion

To conclude, cariprazine demonstrates considerable promise as a transdiagnostic treatment for cognitive impairment. However, further research is necessary before definitive conclusions can be drawn. The current evidence base is primarily derived from post-hoc analyses of clinical trials and individual case reports; forms of evidence that, while valuable, are considered lower in the hierarchy of scientific rigor. Future studies, including prospective clinical trials specifically designed to assess cognitive outcomes, are essential to validate and expand upon these preliminary observations.

6

Cariprazine as a transdiagnostic treatment candidate for cognitive impairment in neuropsychiatric disorders: A 12-week observational study

6.1. Introduction

In **Chapter 5**, the potential of cariprazine as a transdiagnostic treatment option for cognitive impairment was evaluated through a systematic review and meta-analysis. The strongest evidence emerged from post-hoc analyses of clinical trials involving patients with schizophrenia, bipolar depression, and bipolar mania. In contrast, evidence from other NPDs was more limited and primarily derived from case reports and a single observational study. Overall, the review suggested that cariprazine may improve core cognitive symptoms such as concentration difficulties, memory deficits, and attentional dysfunction across diagnostic boundaries.

6.1.1. Rationale

Building on these findings, it would be particularly valuable to further explore cariprazine's impact on cognitive impairment in patients from the more neurologically rooted end of the NPD spectrum, including those with HD and PD. These populations experience significant cognitive deficits for which there are currently no approved treatments (579–583). In HD, for

instance, cognitive symptoms can emerge as early as the second decade of life, severely affecting daily functioning and quality of life (584,585).

Although MetS and its components were not found to be a reliable biomarker for cognitive impairment in patients on the schizophrenia-bipolar spectrum in **Chapter 3**, this relationship may differ in the above-mentioned disorders. Importantly, cariprazine is considered to be a metabolically neutral antipsychotic with minimal to no associated weight gain (295), prompting the question of whether its potential pro-cognitive effects may, in part, be influenced by its favourable metabolic profile. To date, however, no study has simultaneously examined the impact of cariprazine on both cognitive functioning and metabolic parameters.

6.1.2. Aims & objectives

The primary aim of this chapter is to investigate the effects of cariprazine on cognitive impairment in patients from the more neurologically rooted end of the NPD spectrum during a 12-week observational period.

The objectives of the chapter are the following:

1. Primary objective: To analyse changes in cognitive functioning, assessed using the Addenbrooke's Cognitive Examination (ACE), during 12 weeks of cariprazine treatment.
2. Secondary objective: To evaluate the changes in metabolic parameters over the same 12-week period.
3. Exploratory objective: To examine the relationship between cognitive functioning and metabolic characteristics in this patient population.
4. Exploratory objective: To assess the long-term effects of cariprazine on both cognitive impairment and metabolic parameters in a subset of patients followed for approximately one year.

6.2 Methods

6.2.1. Study design

The present study was a retrospective observational study conducted at the Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary, between January 2023 and December 2024. Although clinical data were originally recorded prospectively as part of routine care, the study involved a retrospective analysis of anonymized patient records. Eligible patients were identified based on predefined inclusion and exclusion criteria. In standard clinical practice, follow-up visits for patients receiving cariprazine treatment are typically scheduled at approximately 6 and 12 weeks. In case of patients who continued cariprazine treatment beyond 12 weeks, longitudinal assessment (around one year after initiation) was also included in the analyses. All participants were granted permission for the off-label use of cariprazine by the Hungarian National Institute of Pharmacy and Nutrition. The study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients prior to inclusion.

6.2.2. Inclusion & exclusion criteria

Adult patients (18–65 years old) with NPDs who exhibited cognitive and affective symptoms, for whom cariprazine was therefore prescribed, were eligible for inclusion. Additional inclusion criteria were the ability to provide informed consent, taking cariprazine for the first time, and receiving ambulatory care (**Table 49**). Patients were excluded if they expressed acute suicidal ideation, had comorbid psychiatric disorder including SUD or had any other serious somatic problems such as kidney or liver failure, non-controlled diabetes or epilepsy, or serious cardiovascular disease. Pregnant or breastfeeding women were also ineligible to be included.

Table 49. Inclusion and exclusion criteria

Inclusion criteria
1. Adult patient (age 18-65) with a diagnosis of a neurological disorder.
2. Being able to provide informed consent.
3. Exhibiting cognitive and affective symptoms.
4. Starting cariprazine treatment for the first time.
5. Receiving ambulatory care.
Exclusion criteria
1. Acute suicidal ideation.
2. Comorbid psychiatric disorder.
3. Kidney failure (GFR < 30).
4. Liver failure (Child-Pugh score >= 10).
5. Non-controlled diabetes (HbA1c > 11%).
6. Non-controlled epilepsy.
7. Serious cardiovascular disease (abnormal ECG, QTc > 450 ms, instable arrhythmia etc.).
8. Pregnancy or breast feeding.

6.2.3. Study measures & outcomes

Data were collected at baseline, week 6, and week 12, as well as after approximately 1-year after the initiation of cariprazine treatment (**Table 50**). In the present analysis, baseline was defined as the visit when cariprazine treatment was decided. Demographic information was recorded at baseline. Various neurological (UHDRS and Unified Parkinson's Disease Rating Scale (UPDRS)), and psychiatric scales (Apathy Evaluation Scale (AES), Beck Anxiety Inventory (BAI), and Beck Depression Inventory (BDI)), were administered as per clinical practice at the Institute. However, as the focus of this thesis is on cognitive function and metabolic outcomes, these neurological and psychiatric scales were not analysed in the present thesis. The primary outcome was cognitive performance, assessed using the ACE total and subdomain scores at all time points. The secondary outcomes were metabolic parameters, including triglycerides, HDL cholesterol, fasting glucose, waist circumference, blood pressure, weight, and BMI, assessed at baseline, week 12, and long-term. The exploratory outcomes included the relationship between cognition and metabolic parameters. Adverse events were also monitored and recorded at both follow-up visits.

Table 50. Outcome measures of the 12-week cariprazine observational study

		Baseline	Week 6	Week 12	Long-term
Demographics		x			
Neurological scales					
	UHDRS	x	x	x	x
	UPDRS	x	x	x	x
Psychiatric scales					
	ACE	x	x	x	x
	AES	x	x	x	x
	BDI	x	x	x	x
	BAI	x	x	x	x
Metabolic syndrome					
	Triglycerides	x		x	x
	HDL cholesterol	x		x	x
	Fasting glucose	x		x	x
	Waist circumference	x		x	x
	Blood pressure	x		x	x
	Weight	x		x	x
	BMI	x		x	x
Adverse events			x	x	x

ACE, Addenbrooke's Cognitive Examination; AES, Apathy Evaluation Scale; BAI, Beck's Anxiety Inventory; BDI, Beck's Depression Inventory; BMI, body mass index; UHDRS, Unified Huntington's Disease Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale

6.2.4. Statistical analyses

Descriptive statistics, including means, SDs, counts, and percentages, were used to summarize demographic, clinical, metabolic, and treatment-related characteristics. The primary analysis assessed within-subject changes in cognition (ACE total and subdomain scores) across all time points (baseline, week 6, week 12, and long-term) using LS mean changes. The secondary analysis examined changes in metabolic parameters between baseline and week 12 using paired t-tests. For the exploratory analyses, linear regression models were performed with ACE total score as the dependent variable and metabolic parameters (weight, BMI, waist circumference, triglycerides, HDL cholesterol, systolic and diastolic blood pressure, and fasting glucose) as predictors, adjusting for age, sex, and disorder duration. These models were applied both at baseline and week 12. All analyses were repeated for both the full sample (n = 21) and the long-term subsample (n = 8). Statistical analyses were conducted using RStudio version 2024.04.2+764.

6.3 Results

6.3.1. Demographic & clinical characteristics

A total of 21 patients were included in the study. The mean age was 53.3 years, and 13 participants (61.9%) were male (**Table 51**). Regarding marital status**,** 71.4% of patients were married, 19.0% were single, and one patient was divorced. Employment status varied: about one third of the participants were employed full-time the other third was retired, three patients were unemployed, and 28.6% had unknown employment status. Educational attainment showed that 23.8% of the participants completed secondary school, 42.9% had a vocational school or bachelor's degree, and 19.0% held a master's degree. The average number of years in education was 14.6 years. Most participants were diagnosed with Huntington's disease (71.4%), followed by Parkinson's disease (23.8%), and mitochondrial disease (4.8%). The average duration of illness was 5.1 years.

Table 51. Demographic & clinical characteristics

Demographic characteristics	
Total number of patients, n (%)	21 (100.0)
Age, mean (SD)	53.3 (13.9)
Men, n (%)	13 (61.9)
Marital status, n (%)	
Single	4 (19.0)
Married	15 (71.4)
Divorced	1 (4.8)
Unknown	1 (4.8)
Employment status, n (%)	
Full-time job	6 (28.6)
Retired	6 (28.6)
Unemployed	3 (14.3)
Unknown	6 (28.6)
Educational status, n (%)	
Secondary school	5 (23.8)
Bachelor's degree / Vocational school	9 (42.9)
Master's degree	4 (19.0)
Unknown	3 (14.3)
Educational years, mean (SD)	14.6 (1.9)
Clinical characteristics	
Diagnosis, n (%)	
Huntington's disease	15 (71.4)
Parkinson's disease	5 (23.8)
Mitochondrial disease	1 (4.8)
Duration of disorder, mean (SD)	5.1 (3.2)

SD, standard deviation

6.3.2. Treatment characteristics

All patients initiated cariprazine treatment at a dose of 1.5 mg/day (**Table 52**). By the week 6 visit, four patients had discontinued cariprazine, though no specific reasons were reported. One patient required a dose increase to 3.0 mg/day. At the final visit (week 12), 88.2% of patients remained on 1.5 mg/day, one patient continued at 3.0 mg/day, and one decided to discontinue treatment after the visit.

In addition to cariprazine, seven patients received supplementary antipsychotic medications during the study. Furthermore, benzodiazepine use was common at baseline, with nearly half of the patients receiving them; however, this decreased to 29.4% by both week 6 and week 12. Antidepressants were used consistently by two patients at each timepoint. Use of anti-Parkinsonian medications declined from 28.6% at baseline to 23.5% by the end of the observational period. Other medications taken included cardiovascular and cognitive enhancers, though these were no longer present by week 12.

Table 52. Treatment characteristics

Treatment	Baseline (n = 21)	Week 6 (n = 17)	Week 12 (n = 17)
Cariprazine, n (%)			
1.5 mg/day	21 (100.0)	16 (76.2)	15 (88.2)
3.0 mg/day	0 (0.0)	1 (4.8)	1 (5.9)
Discontinued	0 (0.0)	4 (19.0)	1 (5.9)
Other medications, n (%)			
Antipsychotics	7 (33.3)	7 (41.2)	7 (41.2)
Benzodiazepines	10 (47.6)	5 (29.4)	5 (29.4)
Antidepressants	2 (9.5)	2 (11.8)	2 (11.8)
Anti-Parkinsonian	6 (28.6)	3 (17.6)	4 (23.5)
Cardiovascular	3 (14.3)	0 (0.0)	2 (11.8)
Cognitive / Neuro	2 (9.5)	2 (11.8)	0 (0.0)
Other	3 (14.3)	0 (0.0)	0 (0.0)

6.3.3. Metabolic characteristics & outcomes

At baseline, the mean body weight of participants was 75.7 kg, and the mean BMI was 25.1 kg/m², indicating a slightly overweight population (**Table 53**). Regarding metabolic parameters, the mean systolic blood pressure was above the threshold at 131.0 mmHg, while

other parameters remained within normal ranges: the mean diastolic blood pressure was 83.8 mmHg, fasting glucose was 5.2 mmol/L, HDL cholesterol was 1.5 mmol/L, triglycerides were 1.3 mmol/L, and the average waist circumference was 87.8 cm.

The paired t-test conducted on the 17 participants who completed the study revealed a significant increase in waist circumference (mean change = 3.10 cm, p = 0.01). However, no other parameters demonstrated statistically significant changes, despite observing numerical increases in mean weight, BMI, fasting glucose, and triglycerides, as well as numerical decrease in both systolic and diastolic blood pressure.

Table 53. Metabolic characteristics & outcomes

Metabolic characteristics	**Baseline** (n = 21)	**Week 12** (n = 17)	**Paired t-test*** (t)	**p-value**
Weight, kg, mean (SD)	75.7 (15.6)	77.1 (13.2)	0.41	0.688
BMI, mean (SD)	25.1 (5.1)	25.6 (4.9)	0.39	0.704
Waist circumference, mean (SD)	87.8 (15.2)	95.5 (14.8)	3.10	0.010
Systolic blood pressure, mmHg, mean (SD)	131.0 (13.3)	128.7 (15.6)	0.19	0.856
Diastolic blood pressure, mmHg, mean (SD)	83.8 (5.5)	80.5 (6.8)	-1.25	0.251
Fasting glucose, mmol/L, mean (SD)	5.2 (0.8)	5.7 (1.0)	1.82	0.103
HDL cholesterol, mmol/L, mean (SD)	1.5 (0.3)	1.5 (0.2)	0.88	0.398
Triglycerides, mmol/L, mean (SD)	1.3 (0.6)	1.4 (0.6)	0.24	0.818

**based on 17 patients*
SD, standard deviation

In terms of BMI categories, at baseline, 38.1% of participants were classified as overweight, 28.6% fell within the normal range, and 14.3% were underweight, while two individuals met criteria for obesity or extreme obesity (**Table 54**). A similar distribution was observed at the final assessment at week 12, with the majority of participants being classified as either overweight (41.2%) or within the normal BMI range (23.5%). Regrading MetS, only two patients met the criteria at baseline (9.5%), however, this proportion increased to 23.5% by week 12. This change may have been primarily driven by the rise in the proportion of individuals with elevated fasting glucose, which increased from 9.5% at baseline to 35.3% at week 12.

Table 54. BMI categories & metabolic syndrome criteria

Metabolic characteristics	Criteria	Baseline (n = 21)	Week 12 (n = 17)
BMI			
Underweight	<18.5	3 (14.3)	2 (11.8)
Normal	18.5 – 24.9	6 (28.6)	4 (23.5)
Overweight	25.0 – 29.9	8 (38.1)	7 (41.2)
Obese	30.0 – 34.9	1 (4.8)	0 (0.0)
Extremely obese	35<	1 (4.8)	1 (5.9)
Metabolic syndrome			
Waist circumference	≥88 cm for women, ≥102 cm for men	6 (28.6)	6 (35.3)
High triglycerides	≥1.7 mmol/L	4 (19.0)	5 (29.4)
Low HDL cholesterol	<1.3 mmol/L for women, <1.0 mmol/L for men	1 (4.8)	0 (0.0)
High blood pressure	≥130/85 mmHg	7 (33.3)	6 (35.3)
High fasting glucose	≥5.6 mmol/L	2 (9.5)	6 (35.3)
Metabolic syndrome	≥3 criteria met	2 (9.5)	4 (23.5)

6.3.4. Cognitive characteristics & outcomes

Patients were considered to have moderate cognitive impairment at baseline (mean ACE total score = 74.3). Over the 12-week observational period, participants demonstrated small but statistically significant improvements in global cognitive performance, as measured by the ACE total score (LS mean change = 3.62, $p = 0.048$, Cohen's $d = 0.14$) (**Table 55**). The largest cognitive improvement was observed in the memory sub-score (LS mean change = 3.80, $p = 0.028$, $d = 0.33$), with modest gains in visuospatial ability approaching significance (LS mean change = 0.33, $p = 0.055$, $d = 0.31$). No significant changes were detected in orientation, concentration, verbal fluency, language, or MMSE scores. Interestingly, LS mean scores for ACE total, MMSE, memory, orientation, and verbal fluency sub-scores were higher at week 6 than were at week 12, suggesting a peak in cognitive performance mid-treatment (**Figure 28**).

Table 55. LS mean changes in ACE total and sub-scores by week 12

	Baseline, mean (SD) (n = 21)	**Week 12,** mean (SD) (n = 17)	**LS mean change** (SE)	**p-value**	**ES** (Cohen's d)
Total score	74.3 (14.8)	76.5 (15.6)	3.62 (1.68)	0.048	0.14
MMSE score	25.4 (4.4)	26.0 (4.2)	0.63 (0.52)	0.251	0.14
Orientation	9.0 (1.5)	9.0 (1.6)	0.00 (0.24)	1.000	0.00
Concentration	6.7 (1.9)	6.3 (1.8)	-0.33 (0.32)	0.313	-0.22
Memory	20.5 (9.2)	23.5 (8.8)	3.80 (1.55)	0.028	0.33
Verbal fluency	6.4 (2.7)	5.9 (3.2)	-0.13 (0.40)	0.744	-0.17
Language	27.0 (1.1)	27.6 (1.0)	0.73 (0.45)	0.127	0.57
Visuospatial	3.8 (1.3)	4.2 (1.3)	0.33 (0.16)	0.055	0.31

ACE, Addenbrooke's Cognitive Examination; ES, effect size; MMSE, Mini-Mental State Examination; SD, standard deviation; SE, standard error

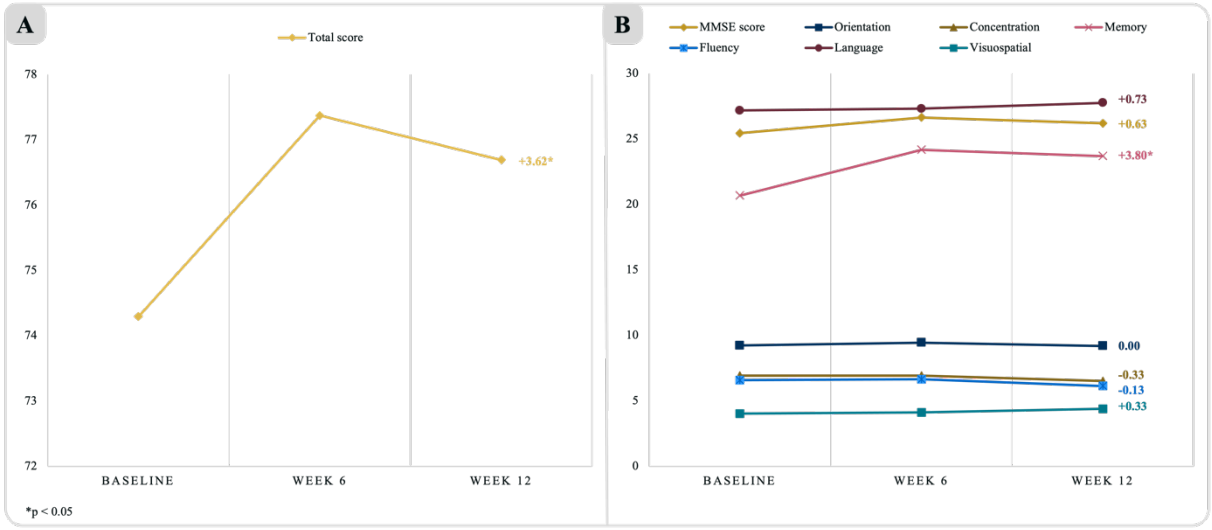

Figure 28. Mean scores and LS Mean changes in ACE Total and Subdomain scores over 12 weeks

Figure A displays mean scores at baseline, week 6, and week 12, and the LS mean change from baseline to week 12 in the Addenbrooke's Cognitive Examination (ACE) total score. Figure B presents mean scores at baseline, week 6, and week 12, and the LS mean changes from baseline to week 12 in the six ACE subdomains (orientation, concentration, memory, fluency, language, and visuospatial abilities) and the MMSE score. Y-axes represent raw mean scores, with LS mean changes from baseline annotated numerically. Increases in scores reflect improvements in cognitive function.

6.3.5. Associations between cognitive & metabolic characteristics

At baseline, linear regression analyses (**Table 56**) examining the association between metabolic parameters and ACE total score (controlling for sex, age, and duration of illness) suggested that higher systolic and diastolic blood pressure were associated with better cognitive performance (systolic: β = 0.62, raw p = 0.031; diastolic: β = 1.47, raw p = 0.029) (**Figure 29 & 30**). However, these associations did not remain statistically significant after

correction for multiple comparisons (Bonferroni-adjusted p = 0.248 and 0.232, respectively; FDR-adjusted p = 0.124 for both). Other metabolic variables, including weight, BMI, waist circumference, triglycerides, HDL cholesterol, and fasting glucose, were not significantly associated with cognitive outcomes, although most estimates showed a numerically positive relationship.

Table 56. Linear regression analysis of metabolic parameters and ACE total score at baseline controlling for sex, age, and disorder years

Variables	Estimate	SE	t-value	p-value	corrected p-value
Weight (kg)	0.26	0.25	1.04	0.320	1.000
BMI (kg/m^2)	0.70	0.83	0.84	0.420	1.000
Waist circumference (cm)	0.27	24.36	1.56	0.151	1.000
Triglycerides (mmol/L)	4.54	11.28	0.40	0.698	1.000
HDL cholesterol (mmol/L)	8.75	12.87	0.68	0.514	1.000
Systolic blood pressure (mmHg)	0.62	0.24	2.60	0.031	0.248
Diastolic blood pressure (mmHg)	1.47	0.56	2.65	0.029	0.232
Fasting glucose (mmol/L)	1.19	7.54	0.16	0.878	1.000

BMI, body mass index; SE, standard error

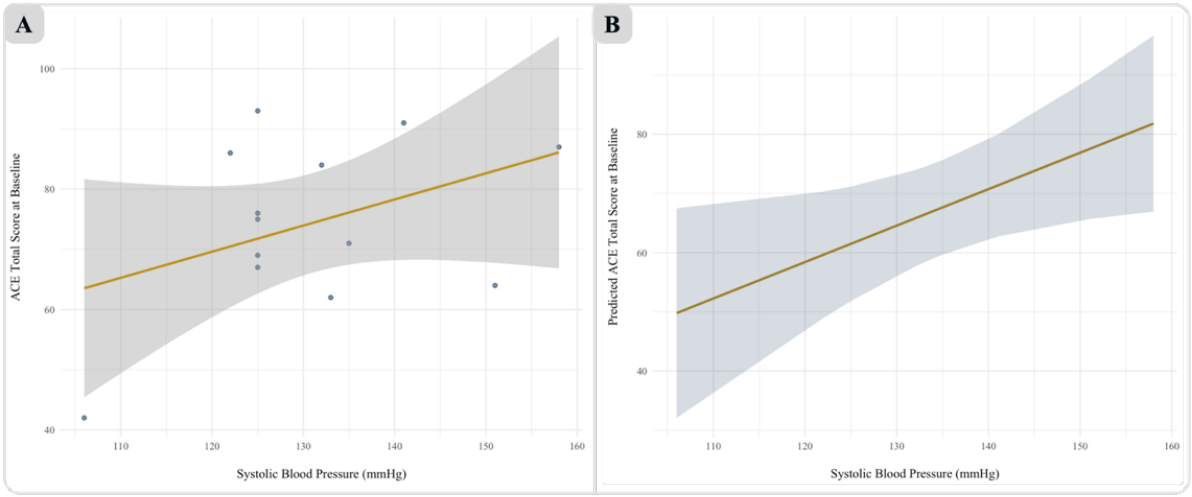

Figure 29. Relationship between systolic blood pressure and ACE total score

Figure A illustrates the unadjusted association between systolic blood pressure and ACE total score. Figure B presents the adjusted association, accounting for age, sex, and disorder years. Higher ACE scores indicate better cognitive functioning. Lines represent the fitted regression models with 95% confidence intervals.

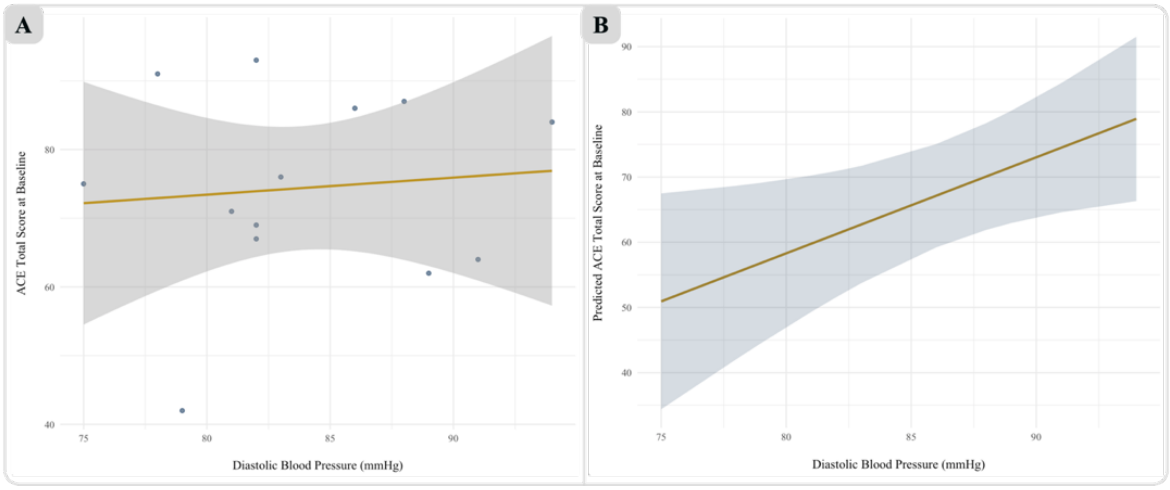

Figure 30. Relationship between diastolic blood pressure and ACE total score

Figure A illustrates the unadjusted association between diastolic blood pressure and ACE total score. Figure B presents the adjusted association, accounting for age, sex, and disorder years. Higher ACE scores indicate better cognitive functioning. Lines represent the fitted regression models with 95% confidence intervals.

At week 12, none of the metabolic parameters were significantly associated with ACE total scores after controlling for sex, age, and duration of illness (**Table 57**). While most metabolic variables showed numerically positive but non-significant associations with cognitive scores, systolic (β = -0.20) and diastolic (β = -0.75) blood pressure as well as fasting glucose (-3.70) were non-significantly and negatively associated. This represents a change from baseline, where all correlations were positive.

Table 57. Linear regression analysis of metabolic parameters and ACE total score at week 12 controlling for sex, age, and disorder years

Variables	Estimate	SE	t-value	p-value	corrected p-value
Weight (kg)	0.34	0.43	0.80	0.454	1.000
BMI (kg/m^2)	1.26	1.67	0.76	0.478	1.000
Waist circumference (cm)	0.52	0.55	0.96	0.376	1.000
Triglycerides (mmol/L)	13.17	13.8	0.96	0.393	1.000
HDL cholesterol (mmol/L)	13.21	21.92	0.60	0.569	1.000
Systolic blood pressure (mmHg)	-0.20	0.43	-0.47	0.655	1.000
Diastolic blood pressure (mmHg)	-0.75	0.76	-0.99	0.363	1.000
Fasting glucose (mmol/L)	-3.70	4.16	-0.89	0.408	1.000

BMI, body mass index; SE, standard error

6.3.6. Long-term follow-up

The long-term follow-up sample consisted of 8 patients with a mean age of 57.4 years (**Table 58**). No information is available regarding why the remainder of the sample was not followed up long-term. The majority of patients were male (62.5%). The average years spent in education was 14.0 years. Almost all patients were diagnosed with HD (87.5%), with only one case of mitochondrial disease (12.5%). The average duration of illness was 4.7 years.

Table 58. Demographic & clinical characteristics of the long-term follow-up sample

Demographic characteristics	
Total number of patients, n (%)	8 (100.0)
Age, mean (SD)	57.4 (9.7)
Men, n (%)	5 (62.5)
Educational years, mean (SD)	14.0 (2.0)
Clinical characteristics	
Diagnosis, n (%)	
Huntington's disease	7 (87.5)
Mitochondrial disease	1 (12.5)
Duration of disorder, mean (SD)	4.7 (2.6)
SD, standard deviation	

The long-term follow-up point was on average 270 days after the week 12 visit (**Table 59**). Most patients (75.0%) were still on 1.5 mg/day cariprazine and the remainder on 3.0 mg/day. Half of the sample were taking additional antipsychotics, while other psychotropic or somatic medications, including benzodiazepines, antidepressants, anti-Parkinsonian, and cardiovascular agents were also noted.

Table 59. Long-term treatment characteristics

Treatment duration	
Days since week 12 visit, mean (SD)	269. 9 (121.5)
Treatment type	
Cariprazine, n (%)	
1.5 mg/day	6 (75.0)
3.0 mg/day	2 (25.0)
Discontinued	0 (0.0)
Other medications, n (%)	
Antipsychotics	4 (50.0)
Benzodiazepines	1 (12.5)
Antidepressants	1 (12.5)
Anti-Parkinsonian	1 (12.5)
Cardiovascular	1 (12.5)
Cognitive / Neuro	0 (0.0)
Other	1 (12.5)

Metabolic parameters remained stable between baseline and the long-term follow-up visit, with no significant differences observed (**Table 60**). Although a numerical decrease in body weight and BMI was observed, these changes were not statistically significant. In contrast, waist circumference and systolic blood pressure showed a non-significant increase, while diastolic blood pressure, fasting glucose, and HDL cholesterol levels remained virtually the same. Triglyceride comparisons could not be assessed due to missing data.

Table 60. Long-term metabolic characteristics & outcomes

Metabolic characteristics	Baseline (n = 8)	Long-term (n = 8)	Paired t-test* (t)	p-value
Weight, kg, mean (SD)	83.0 (10.4)	78.0 (15.8)	-2.80	0.353
BMI, mean (SD)	27.4 (4.5)	25.8 (6.1)	-1.05	0.371
Waist circumference, mean (SD)	97.6 (13.1)	101.2 (15.6)	3.10	0.149
Systolic blood pressure, mmHg, mean (SD)	131.2 (11.8)	136.4 (6.9)	2.00	0.828
Diastolic blood pressure, mmHg, mean (SD)	84.6 (6.3)	84.2 (8.6)	0.25	0.942
Fasting glucose, mmol/L, mean (SD)	5.4 (0.3)	5.3 (0.7)	0.03	0.923
HDL cholesterol, mmol/L, mean (SD)	1.3 (0.2)	1.3 (0.2)	-0.08	0.531
Triglycerides, mmol/L, mean (SD)*	1.6 (0.8)	1.8 (0.4)	-	-

**sample size too small due to missing values to conduct a t-test*
BMI, body mass index; SD, standard deviation

Cognitive outcomes showed a trend toward improvement in ACE total scores, with a mean increase of 4.62 points (p = 0.079) (**Table 61**). Importantly however, significant improvement was detected in memory performance (mean change = 5.88, p = 0.048). Small and non-significant changes were observed in other ACE sub-domains, including MMSE, orientation, verbal fluency, language, and visuospatial ability. Across the observational period, LS mean scores showed overall stability or mild improvement in cognitive functioning, with peaks distributed between week 6 and 12 visits except for the memory and concentration sub-domain where the increase was gradual (**Figure 31**).

Table 61. Long-term LS mean changes in cognitive outcomes

	Baseline, mean (SD) (n = 8)	**Long-term,** mean (SD) (n = 8)	**LS mean change** (SE)	**p-value**	**ES** (Cohen's d)
Total score	74.1 (15.4)	78.8 (13.0)	4.62 (2.25)	0.079	0.33
MMSE	26.3 (4.9)	25.5 (5.1)	-0.75 (0.59)	0.244	-0.16
Orientation	9.1 (1.4)	9.3 (1.4)	0.13 (0.35)	0.732	0.14
Concentration	6.5 (2.1)	6.6 (1.9)	0.13 (0.67)	0.857	0.05
Memory	20.5 (9.4)	26.4 (5.1)	5.88 (2.46)	0.048	0.78
Fluency	6.4 (3.3)	5.8 (3.3)	-0.63 (0.75)	0.435	-0.18
Language	27.3 (0.9)	27.0 (1.5)	-0.25 (0.31)	0.451	-0.24
Visuospatial	4.4 (0.7)	3.8 (1.4)	-0.63 (0.38)	0.140	-0.54

ACE, Addenbrooke's Cognitive Examination; ES, effect size; MMSE, Mini-Mental State Examination; SD, standard deviation; SE, standard error

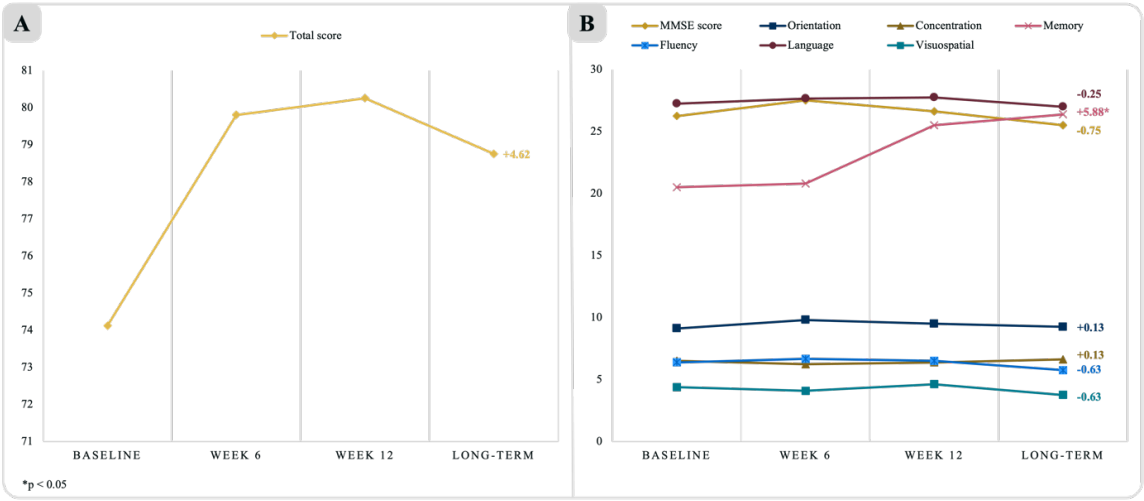

Figure 31. *Mean scores and LS Mean changes in ACE Total and Subdomain scores over the observational period*

Figure A displays mean scores at baseline, week 6, week 12 and long-term, and the LS mean change from baseline to long-term in the Addenbrooke's Cognitive Examination (ACE) total score. Figure B presents mean scores across the same period, and the LS mean changes from baseline to long-term in the six ACE subdomains (orientation, concentration, memory, fluency, language, and visuospatial abilities) and the MMSE score. Y-axes represent raw mean scores, with LS mean changes from baseline annotated numerically. Increases in scores reflect improvements in cognitive function.

6.4 Discussion

6.4.1. Summary of key findings

This retrospective observational study conducted at the Institute of Genomic Medicine and Rare Disorders, Semmelweis University examined the cognitive and metabolic effects of cariprazine treatment in 21 patients, most of whom were diagnosed with HD. Cariprazine was initiated based on clinically significant cognitive and affective symptoms, with scheduled

follow-ups at weeks 6 and 12. Of the original cohort, 17 patients remained on treatment by week 12, with 1.5 mg/day being the most common dose. Concomitant use of antipsychotics and benzodiazepines was frequent. While the prevalence of MetS increased from two to four patients over 12 weeks, no significant changes were detected in most metabolic parameters, apart from a statistically significant increase in waist circumference. In terms of cognitive outcomes, a significant improvement was observed in the ACE total score and memory domain between baseline and week 12, with visuospatial abilities showing a trend-level improvement. Notably, cognitive scores peaked at week 6 before a slight decline by week 12. Linear regression analyses suggested a positive association between ACE total scores and both systolic and diastolic blood pressure at baseline, although these did not remain significant after correction for multiple comparisons; by week 12, the associations had reversed in direction and remained non-significant. In the long-term subsample of eight patients, who continued cariprazine treatment for an average of 270 days after the week 12 visit, cognitive outcomes remained largely stable, with a significant improvement observed only in the memory domain. Metabolic parameters did not show significant changes over the long term.

6.4.2. Cariprazine as a transdiagnostic treatment candidate for cognitive impairment

The effects of a 12-week cariprazine treatment on cognitive symptoms associated with HD was previously explored by Molnár et al. in the same research institute as the current study (294). At baseline, the severity of cognitive impairment was similar (ACE total score: 75.1), however greater improvement was detected by week 12 (ACE total score: 86.7, LS mean change:11.5, $p < 0.0001$) compared to the present analysis (ACE total score: 76.5, LS mean change: 3.6, $p < 0.05$) (294). Nonetheless, it is important to note, that there were considerable differences in the two samples. First, in the Molnár study, only patients with HD were

included with a mean age of 48.13 years (294), whereas in the present observation, patients with other NPDs were also eligible to be included and the mean age was also higher, potentially influencing the cognitive abilities. Additionally, 75.0% of their sample was female, while in the current study most patients were male (61.9%). Indeed, research indicates significant sex differences in cognitive impairment associated with neurological disorders; for instance, males with PD progress more rapidly to MCI and dementia compared to females (586). Additionally, there is growing recognition that oestrogen may play a neuroprotective role in various neurological disorders, including PD and HD (587). Furthermore, the present sample showed frequent antipsychotic polypharmacy and benzodiazepine use, which were less pronounced in the previous study. Importantly, both antipsychotic polypharmacy and long-term benzodiazepine use are associated with cognitive impairment (588,589), potentially limiting the cognitive improvements that might otherwise have occurred. Nonetheless, while the magnitude of cognitive improvement differed in the two studies, both resulted in statistically significant change from baseline, supporting the notion that cariprazine might be a good candidate for alleviating cognitive symptoms in these patient populations.

In general, the findings of the present observational study align with the results of the systematic review and meta-analysis presented in **Chapter 5**, which indicated the ability of cariprazine to alleviate cognitive symptoms such as concentration difficulties, memory impairment, and attentional dysfunction across various NPDs. Notably, memory improvement emerged as a consistent and sustained effect in the present study as well, including in the long-term follow-up sample. This may be attributable to cariprazine's receptor profile, particularly its high affinity for dopamine D_3 receptors. Indeed, Xing et al. demonstrated that aged D_3 receptor knockout mice outperformed wild-type controls in spatial learning and memory tasks, suggesting that D_3 receptor blockade may mitigate age-associated memory deficits (590). Additionally, research has shown that D_3 receptors in the medial prefrontal

cortex contribute to impairments in novel object recognition memory (591). Tropea et al. further proposed D_3 receptor inhibition as a potential therapeutic strategy for cognitive dysfunction in aging and patients with AD (592). Therefore, it is plausible that the observed cognitive improvements are attributable to cariprazine's mechanism of action; however, the possibility of measurement error cannot be ruled out. Although the ACE has been reported as a useful tool for detecting change over time (593), it has not typically been used at short intervals such as six weeks, raising the possibility that familiarity with the test may have influenced the results. Finally, when looking at the results of the long-term sample, after initial improvement a slight decline was detected, albeit the long-term follow-up visit scores were still higher than those at baseline. Such trend is also evident in studies examining acetylcholinesterase inhibitors for cognitive decline in AD, where they have been shown to initially improve cognition, followed by maintenance above baseline for up to a year before declining (594).

6.4.3. Effects of cariprazine on metabolic parameters

The results indicate that after 12 weeks of cariprazine treatment, there were no significant changes in metabolic parameters aside from an increase in waist circumference. However, the long-term follow-up sample revealed no statistically significant alterations, and parameters such as weight and BMI showed a numerical decline. These findings are consistent with a pooled analysis of eight Phase II/III studies, which reported a mean weight gain of approximately 1 kg among patients receiving cariprazine in both short- and long-term treatment, with weight gain noted as an adverse event in 5.1% of cases (295). Additionally, the pooled analyses also showed total cholesterol, HDL cholesterol, and fasting triglyceride levels to decrease from baseline in the overall cariprazine treatment group, with no apparent dose-dependent effects observed for any of these parameters (295). Furthermore, in a meta-

analysis comparing 32 antipsychotics, cariprazine ranked sixth best with respect to minimal weight gain (362). Taking the above-mentioned findings into consideration, and the fact that about half of the patients in the present sample were receiving antipsychotic polypharmacy, the statistically significant increase in waist circumference might have been due to other factors than cariprazine. Nonetheless, waist circumference is one of the strongest predictors of MetS (595), therefore further studies are warranted.

6.4.4. Cognitive impairment & metabolic syndrome in neurological disorders

In line with the findings from **Chapter 3**, the present analyses did not reveal significant associations between metabolic parameters and cognitive performance. In Chapter 3, cognition was approximated using the PANSS Disorganized Thoughts factor in a schizophrenia dataset, whereas here a performance-based measure (ACE) was applied in patients with predominantly Huntington's and Parkinson's disease. Despite methodological and population differences, the results converge in showing no robust relationship between metabolic parameters and cognition. This consistency strengthens the conclusion that, within the datasets examined in this thesis, previously suggested associations between metabolic syndrome and cognitive impairment were not confirmed.

6.4.5. Limitations

The present study has several limitations. The primary limitation is its retrospective and observational design, which precludes any conclusions about causality; thus, the observed results cannot be definitively attributed to cariprazine treatment. In addition, missing data pose a notable limitation, as is often the case when analysing clinical records. Data collection during routine care visits can be inconsistent, contributing to gaps in the dataset.

6.4.6. Future research

In order to establish the role of cariprazine as a viable transdiagnostic treatment option for cognitive impairment, large-scale, longitudinal, prospective, and placebo- or active comparator-controlled clinical trials are warranted with adequate and detailed cognitive measures. Investigating the impact of cariprazine on metabolic parameters, especially waist circumference is also needed in order to draw definite conclusions.

6.5 Conclusion

Despite being a small-scale, retrospective observational study involving primarily patients with Huntington's and Parkinson's disease and only one case of mitochondrial disease, the findings suggest that cariprazine may hold promise as a transdiagnostic treatment option for cognitive impairment. Improvements in memory were observed by week 12 and appeared sustained in the limited long-term subsample, while the treatment was associated with a metabolically neutral profile. However, these findings should be interpreted with caution given the small effect sizes, incomplete follow-up data, heterogeneity of the sample, and the influence of polypharmacy. Taken together, the results are consistent with previous reports indicating potential cognitive benefits and favourable metabolic safety of cariprazine, but larger and more methodologically rigorous studies (ideally randomized, placebo- or comparator-controlled trials) are needed to confirm and expand upon these preliminary observations.

7 Discussion

The overarching aim of the present thesis was to comprehensively investigate cognitive impairment, a crucial symptom domain in neuropsychiatry, from a transdiagnostic perspective. To achieve this, a diverse set of methodological approaches was utilized, focusing on three core aspects of cognitive impairment: measurement, assessment, and treatment.

7.1. Transdiagnostic measurement of cognitive impairment

This section of the thesis focused on how cognitive impairment can be measured quantitatively without relying on clinical rating scales, which was addressed later, in the section on transdiagnostic assessment. Here, the goal was to explore potential biological and physiological proxies, namely, biomarkers (57). As outlined in **Chapter 1**, biomarker research in neuropsychiatry is still in the early stages (63,65). Although several types of biomarkers have been proposed form diagnostic to prognostic (58,59), reliable and accessible markers are still lacking in routine clinical use. In AD, tau protein represents an established biomarker (64), but for other NPDs, progress is still ongoing (63,65). In this thesis, two potential biomarkers were explored: BDNF and MetS.

The first investigation was a systematic review and meta-analysis of peripheral BDNF. Overall, the results did not support blood BDNF as a reliable or practical biomarker for

cognitive impairment in patients with disorders on the schizophrenia – bipolar spectrum. Nonetheless, some of the findings were supporting the presence of a connection between BDNF and cognition in this patient population. In patients with SCHZ, a moderate but significant reduction of sBDNF was reported compared to healthy controls which was influenced by sex; significantly lower sBDNF was reported in male vs. female SCHZ patients. In patients with BD, no significant difference was found between patients and controls. Importantly, only about half of the reviewed studies reported a statistically significant association between BDNF and cognitive impairment. The results of the meta-analyses reflected the mixed connection, only pBDNF showed a modest but significant association with cognitive impairment in SCHZ. In BD, this relationship could not be adequately assessed due to data limitations.

Although pBDNF appeared to be a more promising candidate than sBDNF, the overall findings clearly indicate that peripheral BDNF levels are influenced by multiple confounding factors, raising substantial concerns about their reliability as biomarkers. These results reinforce critiques that BDNF may be state-sensitive but lacks trait stability (60,61), limiting its potential as a standalone biomarker in clinical psychiatry. Furthermore, given the logistical issues related to its storage and processing (93,94), BDNF is not likely to be included in the routine measurement panel in clinical practice. Therefore, BDNF does not fulfil the criteria of a reliable, stable, or accessible biomarker for cognitive impairment in neuropsychiatric conditions.

Given these limitations, the thesis next examined whether MetS or its components could serve as proxies for cognitive impairment. MetS is associated with cognitive dysfunction not only in patients with neuropsychiatric disorders but also in the general population (596). Importantly,

metabolic parameters are routinely assessed in clinical settings, which makes them a potentially attractive and time-efficient proxy.

This part of the work included a systematic review and an analysis of the SCHIZOBANK database. Both sources indicated that about one third of patients with SCHZ or BD are affected by MetS. While clozapine and olanzapine were associated with higher MetS prevalence in the literature, this was not supported by the database, which showed no significant differences in antipsychotic history or duration. Importantly, no significant differences in PANSS total or Disorganized thoughts factor scores were found between groups (MetS vs. non-MetS), contrasting with the results of the systematic review. Only higher BMI was associated with lower overall symptom severity. This may reflect the confounding role of effective but weight-promoting antipsychotics, an interpretation that aligns with literature on the therapeutic-metabolic trade-off in antipsychotic prescribing (597). Nevertheless, neither MetS as a whole, nor individual components, were robustly or consistently associated with cognitive impairment in a way that would make them practical proxies in clinical care.

In summary, the research conducted did not identify any biomarker of cognitive impairment in neuropsychiatric disorders that could be considered reliable, accessible, and valid. While some associations were identified, these findings were inconsistent and heavily influenced by confounding variables such as sex, episode polarity, medication effects, and disorder heterogeneity. Indeed, one of the core challenges in biomarker research lies in disentangling biological signal from clinical and lifestyle confounders (598). These limitations underscore the need for longitudinal designs, standardized protocols, and more stratified analyses in future studies. In the meantime, the case for returning to traditional assessment tools is strong.

Cognitive rating scales, despite their time demands, remain essential, especially in the context of MBC, where systematic symptom tracking is linked to improved outcomes (204,207). This also justifies the development of the TGI-P scale as a transdiagnostic tool designed for routine clinical use, bridging the current gap between ideal biomarkers and practical assessment.

7.2. Transdiagnostic assessment of cognitive impairment

The second part of the thesis therefore turned towards the assessment of cognitive impairment via psychiatric rating scales, and more specifically, the development, initial validation and testing of a novel instrument: the TGI-P (400,401). The idea behind the TGI-P was inspired by several considerations. First and foremost, a robust body of literature supports the use of MBC, demonstrating that systematically tracking symptoms through structured tools leads to better outcomes than standard care (207,599). Second, in real-world clinical practice, such tools are rarely used, as clinicians often lack the capacity to administer lengthy scales during short appointments (248,249). This was also the experience of the author of the thesis during data collection involving patients with neuropsychiatric disorders; administering multiple assessments was a clear burden on patients, as completion often took 60 to 90 minutes. Third, there is an overwhelming number of available scales, many of which are diagnosis- or symptom-specific, making it difficult for clinicians to determine which to select (215). Fourth, transdiagnostic approaches in psychiatry, i.e., new frameworks that address the limitations of categorical diagnostic systems by focusing on broad, interrelated dimensions of psychopathology, are gaining prominence (17,28,203,410). However, the clinical translation of these frameworks has been limited by a lack of available tools. In response to these challenges, the TGI-P was developed as a transdiagnostic scale designed to be quick, acceptable, and clinically useful, offering a practical compromise between comprehensiveness and feasibility (400).

The TGI-P comprises the ten most important symptom domains of psychiatric disorders, including cognitive impairment, each rated on a 7-point Likert scale identical to the CGI-S rating (400). Although cognitive impairment is an independent, transdiagnostic symptom domain (also referred to as the C-factor), it does not exist in isolation, it is interwoven with broader psychopathology (400). The TGI-P was therefore designed to reflect this clinical reality, offering a single metric that captures how symptom domains evolve together as the disorder progresses and in response to treatment (400). One of the unique features of the TGI-P is its visual presentation of ratings on a symptom map, enabling rapid and intuitive understanding of the results (400).

While the CGI-S remains a widely used and practical tool for assessing global illness severity, its strength lies in its simplicity rather than its specificity. By contrast, the TGI-P extends the CGI framework by preserving its ease of use while embedding it in a multidimensional structure that allows clinicians to track cognition and other domains simultaneously. This provides richer clinical information than the CGI-S alone, without substantially increasing assessment burden.

Supporting this, the TGI-P has demonstrated strong acceptability among clinicians, patients, and caregivers, with feedback highlighting its ease of use and clinical relevance (400). As part of the TGI-P development process, content validity was established through input from 36 psychiatrists, most of whom indicated they would use the scale in clinical practice (400). Furthermore, the feasibility of the patient and informant versions were supported by findings from a survey involving 50 patients and caregivers.

Finally, a pilot study explored the applicability of the TGI-P in real-world settings and its relationship to validated scales such as the PANSS and the ACE. The results were promising, with strong symptom correlations (including for cognitive impairment) and clear evidence that, after minimal familiarization, the TGI-P could be administered in just 2–3 minutes. Overall, the TGI-P offers a feasible and clinically meaningful way to complement — and in some cases surpass — the CGI-S by providing a domain-level perspective that remains sensitive to transdiagnostic features such as cognitive impairment, thereby addressing a critical gap in routine psychiatric care.

7.3. Transdiagnostic treatment of cognitive impairment

The final chapters of the thesis turned towards the treatment of cognitive impairment related to NPDs. While assessing and measuring cognitive impairment is essential, the next critical step is determining how to address it. Given that cognitive impairment is a transdiagnostic symptom domain (31), it raises an important question: can it also be treated transdiagnostically?

To answer the question, one of the third-generation antipsychotics, cariprazine was put under the microscope. Being a dopamine D_3-D_2 and serotonin 5-HT_{1A} partial agonist, as well as an antagonist at serotonin 5-HT_{2A} and 5-HT_{2B} receptors, cariprazine is a promising candidate to alleviate symptoms such as executive function deficits or memory problems (293,545,547,549). Additionally, cariprazine is often considered a transdiagnostic medication, as it is approved in the US for the treatment of schizophrenia, bipolar I depression, manic or mixed episodes associated with bipolar I disorder, and as an adjunctive treatment for major depressive disorder. Indeed, this broad utility suggests a potential for cognitive benefit across diagnostic categories.

The systematic review conducted supported this possibility: although much of the data came from post-hoc analyses or case reports, consistent subjective and functional improvements were observed in domains such as attention, memory, concentration, and abstract thinking, particularly in SCHZ and BD (293,551). The results of the meta-analysis also confirmed a significant cognitive benefit compared to placebo. To extend these findings, an observational study was carried out in patients with disorders on the more neurological end of the NPD spectrum. Results indicated cognitive improvement by week 12, especially in memory, with some benefits sustained longer term. Therefore, current evidence justifies considering cariprazine as a promising transdiagnostic candidate for addressing cognitive symptoms in NPDs.

7.4. Strengths & limitations

The present thesis employed a multi-method approach, incorporating systematic review, meta-analysis, database analysis, and original observational research. While each method has its own limitations, the diversity of approaches represents a strength, offering a well-rounded view of cognitive impairment across NPDs. Meta-analyses are considered a high level of evidence, though their reliability depends on the quality of included studies (600), an issue carefully addressed in the respective chapters. The observational studies were limited primarily by small sample sizes, while the real-world database analysis was constrained by missing data, a common limitation in naturalistic datasets. Nonetheless, these limitations were transparently acknowledged, ensuring that findings are interpreted in context. The transdiagnostic perspective adopted throughout the thesis is relatively novel in psychiatry and although it introduces additional heterogeneity, but this conceptual shift is important and necessary for advancing the field.

7.5. Future research directions

Further research is needed to build on the foundations laid in this thesis. First, biomarker research should continue and expand beyond disorder-specific targets toward markers that cut across diagnoses. The goal should be to identify feasible, valid, and low-burden markers that can be realistically implemented in routine care. Without practicality, even the best-researched markers are unlikely to be used, a reality underscored throughout this work.

Next, psychometric testing of the TGI-P scale should continue, particularly in diverse clinical settings. Digital integration and implementation of the TGI-P is also an important next step, especially to evaluate how it can support clinical decision-making. Considering the advancements in artificial intelligence–driven tools, it may become feasible in the future to generate a TGI-P symptom map directly from descriptive visit reports. Finally, clinical trials should explore treatments that target shared symptoms, such as cognitive impairment or anhedonia, rather than disorder-specific endpoints. The use of transdiagnostic measurement tools like the TGI-P in such trials would also be a welcome development.

7.6. Concluding remarks

Cognitive impairment is a deeply transdiagnostic symptom with far-reaching consequences for patients' functional outcomes and societal reintegration. Recognizing its ubiquity across psychiatric diagnoses helps underscore its importance and supports a more symptom-focused approach to assessment and treatment. Although BDNF and metabolic syndrome did not meet the criteria for reliable biomarkers in this work, ruling them out remains a valuable contribution that can guide future investigations. Clinically, the development and implementation of pragmatic tools like the TGI-P scale represent meaningful progress toward bridging the gap between ideal assessment practices and real-world constraints. Furthermore,

exploring treatment options based on their receptor profiles, rather than focusing solely on the indications for which they are approved, promotes a more patient-cantered approach and reduces reliance on decisions shaped by commercial interests. Ultimately, moving beyond rigid diagnostic categories and focusing instead on the symptoms most impactful for each individual offers a clearer path toward truly personalized psychiatry: one that is grounded in what patients experience, not just how they are labelled.

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Appendices

Appendix A. Survey questions for psychiatrists

Part I. Current measurements used in everyday practice					
Q1	**How often do you use psychiatric rating scales in your everyday practice?** *(Single answer)*				
	Never	*Almost never*	*Occasionally*	*Frequently but not always*	*Every time*
Q2	**What are the most common reason(s) for using psychiatric rating scales in your everyday practice?** *(Multiple answers)*				
	Quantification of symptoms	*Diagnosis support*	*Monitoring severity of symptoms*	*Monitoring disease progress*	*Other, specify:*
Q3	**What are the most common reason(s) for not using psychiatric rating scales in your everyday practice?** *(Multiple answers)*				
	Limited time at visit	*High costs*	*Does not bring any additional value*	*Bothersome for patients*	*Other, specify:*
Q4	**How much time do you spend with using psychiatric rating scales in a visit on average?** *(Single answer)*				
	N/A.	*less than 10 minutes*	*10 – 20 minutes*	*20 – 40 minutes*	*more than 40 minutes*
Q5	**Do you explain the results of the psychiatric rating scales to patients or caregivers?** *(Single answer)*				
	Always	*Not always but frequently*	*Sometimes*	*Never*	*I do not use scales*
Q6	**If you do not use any psychiatric rating scales, how do you evaluate symptoms?** *(Multiple answers)*				
	By questioning the patient	*By observing the patient*	*By questioning the caregiver*	*I use rating scales*	*Other, specify:*
Q7	**If you do not use any psychiatric rating scales, how do you monitor disorder progress?** *(Multiple answers)*				
	Remembering the previous visit	*Reading previous visit reports*	*By questioning the patient / caregiver*	*I use rating scales*	*Other, specify:*
Q8	**What are the most important aspects for you in a psychiatric rating scale?** *(Make a ranking based on the importance of aspects)*				
	Time	*Simplicity*	*Validity & reliability*	*Popularity*	
Q9	**Do you prefer patient-rated or physician-rated psychiatric scales?** *(Single answer)*				
	I prefer patient-rated scale	*I prefer physician-rated scale*	*I prefer both*	*I do not have a preference*	*I prefer not using any scales*
Part II. Opinion about the new scale					
Q10	**What is your overall opinion on the new scale?** *(Single answer)*				
	Very negative	*Negative*	*Neutral*	*Positive*	*Very Positive*
Q11	**Do you like that the new scale is based on the CGI Severity rating (1 to 7)?** *(Single answer)*				
	Very much not	*No*	*Neutral*	*Yes*	*Very much*
Q12	**Do you like that the new scale has 10 dimensions (positive, negative, depressive, manic, cognitive, addictive, sleep, anxiety, hostility and self-harm)?** *(Single answer)*				
	Very much not	*No*	*Neutral*	*Yes*	*Very much*
Q13	**Is there any dimension you would remove / add?** *(Multiple answer)*				
	No	*Yes, I would remove this one:*	*Yes, I would add this one:*		
Q14	**Do you agree that the symptom shape aids to the overall understanding of the symptomatology and over time, of the disorder progress?** *(Single answer)*				
	Strongly disagree	*Disagree*	*Neither agree nor disagree*	*Agree*	*Strongly agree*

Q15	**Do you agree that the symptom shape might help in explaining the symptomatology to patients & caregivers?** *(Single answer)*				
	Strongly disagree	*Disagree*	*Neither agree nor disagree*	*Agree*	*Strongly agree*
Q16	**Would you use the new scale in your everyday practice?** *(Choose one)*				
	No, because of the following reasons:	*I am not sure yet because of the following reasons:*	*Yes, in online version*	*Yes, in pen & paper version*	
Q17	**Which name would you prefer for the new scale?** *(Single answer)*				
	Symptomila Scale (SS)	*Transdiagnostic Symptom Scale (TSS)*	*Overall Psychopathology Scale (OPS)*	*SYMMPLE – SYmptom Measurement Made simPLE*	*Other, specify:*

Appendix B. Description of a fictional patient for the mock rating

31-year-old, well-known, male patient, presenting with delusions and acoustic hallucinations. Patient believes neighbour wants to harm him, sending poisonous gas to his apartment; hears neighbour's voice everywhere in the apartment, on the streets, here in the office. Patient believes that the neighbour is influencing his thoughts and can extract them as he pleases. Concentration is slightly impaired; patient has difficulty following the conversation; and believes this is the neighbour's fault. Outward appearance is somewhat neglected, personal hygiene impaired. Patient is awake, oriented to time, location, situation and to personal data. Memory is intact. Thinking is laborious, narrowed on the issues with the neighbour. Mood is mostly euthymic; patient is somewhat agitated when talking about the neighbour but can otherwise be modulated nicely (affective oscillation capacity preserved). Patient shows psychomotor restlessness, rocks in his chair, but does not feel bothered by it (no antipsychotic medication at this point; patient has deliberately stopped treatment half a year ago). Sleep and appetite are not impaired. Patient has a normal body mass index. No obsessive-compulsive behaviour, no specific phobias, panic attacks or generalized anxiety. No suicidal ideations, plans or behaviour. When specifically asked about consuming substances, patient discloses smoking around 5-10 cigarettes per day and 1-2 joints.

Appendix C. Survey questions for patients and caregivers

Part I. Understandability					
Q1	**Is it clear what the scale aims to measure?** *(Single answer)*				
	a. Yes, very clear	*b. Somewhat clear*	*c. Not clear*		
Q2	**Were the instructions for using the scale clear and easy to follow?** *(Single answer)*				
	a. Very clear	*b. Clear*	*c. Neutral*	*d. Confusing*	*e. Very confusing*
Q3	**Did you feel confident using the scale without additional explanation?** *(Single answer)*				
	a. Yes, completely confident	*b. Somewhat confident*	*c. No, I needed help*		
Part II. Ease of use					
Q4	**How long did it take to complete the scale?** *(Single answer)*				
	a. Less than 5 minutes	*b. 5-10 minutes*	*c. More than 10 minutes*		
Q5	**How easy was it to complete the scale?** *(Single answer)*				
	a. Very easy	*b. Easy*	*c. Neutral*	*d. Difficult*	*e. Very difficult*
Q6	**Did you encounter any difficulties while completing the scale?** *(Single answer)*				
	a. No difficulties	*b. A few minor difficulties, please specify:*	*c. Many difficulties*		
Part III. Wording and visual aids					
Q7	**Did the wording of the question make sense to you? Please, evaluate all the listed questions!** *(Each question is rated one by one)*				
	a. Yes, completely	*b. Yes, somewhat*	*c. No*		
Q8	**Were the response options appropriate for the questions?** *(Single answer)*				
	a. Yes, very appropriate	*b. Somewhat appropriate*	*c. No, not appropriate*		
Q9a	**Was the visual output helpful in understanding the symptoms you experience in relation to your psychiatric diagnosis?** *(Single answer)*				
	a. Yes, very appropriate	*b. Somewhat appropriate*	*c. No, not appropriate*		
Q9b	**Was the visual output helpful in understanding the symptoms experienced by the person you provide care for in relation to their psychiatric diagnosis?** *(Single answer)*				
	a. Yes, very appropriate	*b. Somewhat appropriate*	*c. No, not appropriate*		
Part IV. Emotional and cognitive load					
Q10	**Did you feel overwhelmed while completing the scale?** *(Single answer)*				
	a. Not at all overwhelmed	*b. Slightly overwhelmed*	*c. Very overwhelmed*		
Q11	**Did the scale feel like a burden to complete?** *(Single answer)*				
	a. Not at all burdensome	*b. Slightly burdensome*	*c. Very burdensome*		
Q12	**Did you feel emotionally triggered while completing the scale?** *(Single answer)*				
	a. Not at all triggered	*b. Slightly triggered*	*c. Very triggered*		
Part V. Comparison to current practices					
Q13	**How often do you fill out similar questionnaires?** *(Single answer)*				
	a. Frequently	*b. Occasionally*	*c. Rarely*	*d. Never*	
Q14	**Do you usually find such questionnaires helpful or exhausting?** *(Single answer)*				
	f. Very helpful	*g. Somewhat helpful*	*h. Neutral*	*i. Somewhat exhausting*	*j. Very exhausting*
Q15	**How does this scale compare to others you've used?** *(Single answer)*				
	f. Much better	*g. Better*	*h. About the same*	*i. Worse*	*j. Much worse*

Q16	**Do you prefer scales that have a visual output compared to those with numeric output?** *(Single answer)* *e. Yes, much more* *f. Yes, little more* *g. No*
Part VI. Future improvements	
Q17	**What feature(s) would you like to see added to improve the scale?** *(Single answer)* *f. Clearer instructions* *g. Simpler wording* *h. Shorter format* *i. Other, please specify:*
Q18	**Would you prefer this scale as a digital tool or paper format?** *(Single answer)* *j. Digital tool* *k. Paper format* *l. No preference*
Q19	**If you found any part of the scale particularly helpful or challenging, please describe it below**

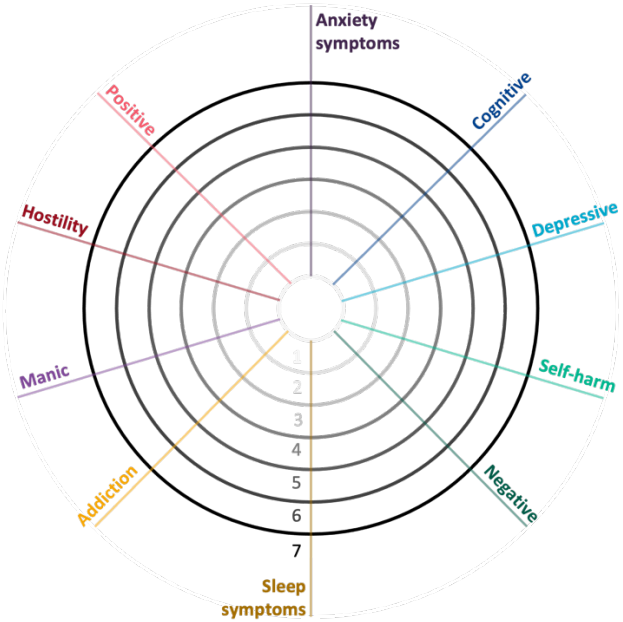
Appendix D. TGI-P Clinician version

TRANSDIAGNOSTIC GLOBAL IMPRESSION
Psychopathology scale for Clinicians

The TGI-P scale provides a **global overview** of your patient's symptom profile over the past 7 days, **based on your clinical impression**.

Please rate each item using the 1–7 scale (**1 = normal / not at all, 7 = extreme)**, reflecting the **average severity of symptoms** within each domain.

After rating each item, **plot the scores onto the symptom map** by marking the corresponding value for each domain and connecting the points to form the patient's **clinical footprint**. Higher scores on the left side of the visual indicate a **more hyper-symptomatology**, while higher scores on the right reflect a **more hypo-symptomatology** profile.



SYMPTOM DOMAIN	YOUR GLOBAL IMPRESSION ON THE SEVERITY OF…	LEVEL OF SEVERITY*
Positive	… **delusions**, **hallucinations**, disorganised thinking, disorganised speech, abnormal motor behaviour	1 2 3 4 5 6 7
Hostility	… **anger**, tension, uncooperativeness, impulsivity, **aggression**, irritability	1 2 3 4 5 6 7
Manic	… **expansive mood**, **grandiosity**, racing thoughts, increased energy, excessive involvement in pleasurable activities	1 2 3 4 5 6 7
Addiction	… **impaired substance use control**, craving, physical dependence	1 2 3 4 5 6 7
Sleep**	… initial, middle or terminal **insomnia** *(hyper-pole symptom)*	1 2 3 4 5 6 7
	… **hypersomnia** *(hypo-pole symptom)*	1 2 3 4 5 6 7
Negative	… **blunted affect**, alogia, asociality, **avolition**, anhedonia *(rate as negative symptom if present without depressed mood)*	1 2 3 4 5 6 7
Self-harm	… non-suicidal **self-injury**, **suicidal** ideation, intent, or attempt	1 2 3 4 5 6 7
Depressive	… **low mood**, anhedonia, **sadness**, hopelessness, helplessness	1 2 3 4 5 6 7
Cognitive	… **problems with concentration**, attention, memory	1 2 3 4 5 6 7
Anxiety**	… feeling nervous, **tense**, **hypervigilant**, panicky *(hyper-pole symptom)*	1 2 3 4 5 6 7
	… social inhibition, **anxious withdrawal**, ruminations *(hypo-pole symptom)*	1 2 3 4 5 6 7

*1 – normal / not at all; 2 – minimal; 3 – mild; 4 – moderate; 5 – marked; 6 – severe; 7 – extreme
**Plot the one (hyper- or hypo-pole symptom) with the highest severity

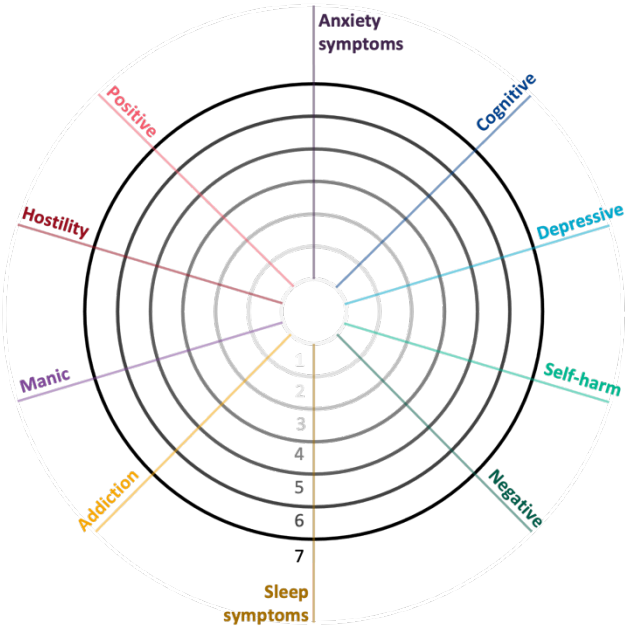
Appendix E. TGI-P Patient version

TRANSDIAGNOSTIC GLOBAL IMPRESSION
Psychopathology scale for Patients

The TGI-P scale is designed to provide a global overview of your symptoms and mental health experiences over the past 7 days.

Please read each question carefully and **rate how severe these symptoms and/or experiences** have been for you **on average** during the past week, using a scale from **1 (not at all / normal)** to **7 (extreme)**. If you did not experience a particular symptom, please select 1.

Your responses will be plotted onto a **symptom map**, creating a **clinical footprint** of your current state – helping your care team better understand your overall symptom profile and areas that may need attention.



SYMPTOM DOMAIN	IN THE PAST WEEK, HOW SEVERE WERE YOUR EXPERIENCES OF…	LEVEL OF SEVERITY*
Positive	… having strong beliefs that others didn't share, **seeing or hearing things that others could not**, or finding it difficult to think or speak clearly?	1 2 3 4 5 6 7
Hostility	… feeling being **tense, irritable, angry**, or **easily annoyed**, or noticing changes in how you reacted, like being **more impulsive** or **aggressive**?	1 2 3 4 5 6 7
Manic	… feeling unusually **happy, confident**, or **energetic**, having racing thoughts, or becoming involved in **fun or exciting activities**?	1 2 3 4 5 6 7
Addiction	… being unable to control your use of substances like **tobacco, alcohol, or cannabis** — including experiencing **strong cravings** or **feeling you needed them to get through the day**?	1 2 3 4 5 6 7
Sleep**	… having **trouble falling asleep** or staying asleep, or waking up early?	1 2 3 4 5 6 7
	… sleeping much more than usual or feeling very sleepy during the day?	1 2 3 4 5 6 7
Negative	… feeling **less motivated** or **interested in social activities**, or not enjoying activities as much as before?	1 2 3 4 5 6 7
Self-harm	… having thoughts about **hurting yourself** or **ending your life** and making any plans or attempts to do so?	1 2 3 4 5 6 7
Depressive	… feeling **down**, **sad**, or **hopeless**, or finding it difficult to enjoy things you used to like?	1 2 3 4 5 6 7
Cognitive	… having **trouble concentrating**, paying attention, **remembering** things or making decisions alone?	1 2 3 4 5 6 7
Anxiety**	… feeling **nervous, restless**, **tense** or **panicky,** or feeling unable to relax and needing to pace around?	1 2 3 4 5 6 7
	… feeling constantly **worried**, or fearful of interacting with others and needed to **withdraw from usual activities**?	1 2 3 4 5 6 7

*1 – normal / not at all; 2 – minimal; 3 – mild; 4 – moderate; 5 – marked; 6 – severe; 7 – extreme
**Note for clinicians: plot the one (hyper- or hypo-pole symptom) with the highest severity

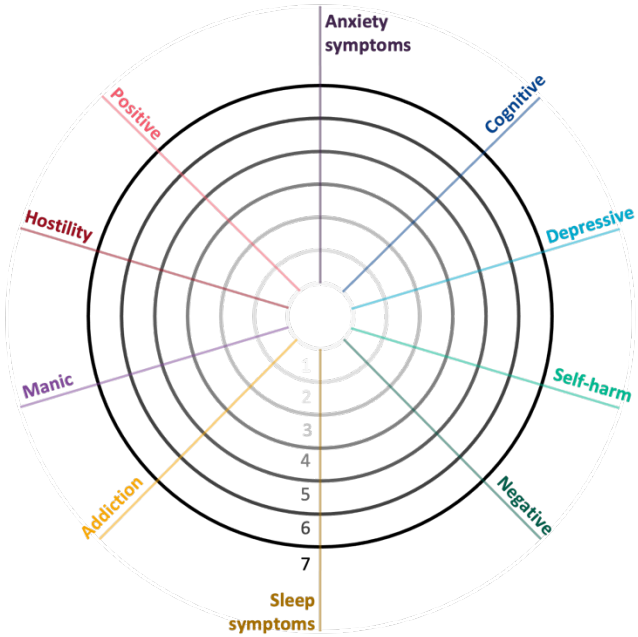
Appendix F. TGI-P Informant version

TRANSDIAGNOSTIC GLOBAL IMPRESSION
Psychopathology scale for Informants

The TGI-P scale is designed to provide a global overview of the symptoms and mental health experiences of the one you provide care for over the past 7 days.

Please read each question carefully and **rate how severe these symptoms and/or experiences** have been for the one you provide care for **on average** during the past week, using a scale from **1 (not at all / normal)** to **7 (extreme).** If they did not experience a particular symptom, please select 1.

Your responses will be plotted onto a **symptom map,** creating a **clinical footprint** of their current state – helping the care team better understand their overall symptom profile and areas that may need attention.



SYMPTOM DOMAIN	In the past week, how SEVERE were the SYMPTOMS / EXPERIENCES of the person you care for in terms of…	LEVEL OF SEVERITY*
Positive	… having strong beliefs that others didn't share, **seeing or hearing things that others could not**, or finding it difficult to think or speak clearly?	1 2 3 4 5 6 7
Hostility	… feeling being **tense, irritable, angry**, or **easily annoyed**, or noticing changes in how they reacted, like being **more impulsive** or **aggressive**?	1 2 3 4 5 6 7
Manic	… feeling unusually **happy, confident**, or **energetic**, having racing thoughts, or becoming involved in **fun or exciting activities**?	1 2 3 4 5 6 7
Addiction	… being unable to control their use of substances like **tobacco, alcohol, or cannabis** — including experiencing **strong cravings** or **feeling you needed them to get through the day**?	1 2 3 4 5 6 7
Sleep**	… having **trouble falling asleep** or staying asleep, or waking up early?	1 2 3 4 5 6 7
	… sleeping much more than usual or feeling very sleepy during the day?	1 2 3 4 5 6 7
Negative	… feeling **less motivated** or **interested in social activities**, or not enjoying activities as much as before?	1 2 3 4 5 6 7
Self-harm	… having thoughts about **hurting themselves** or **ending their life** and making any plans or attempts to do so?	1 2 3 4 5 6 7
Depressive	… feeling **down**, **sad**, or **hopeless**, or finding it difficult to enjoy things they used to like?	1 2 3 4 5 6 7
Cognitive	… having **trouble concentrating**, paying attention, **remembering** things or making decisions alone?	1 2 3 4 5 6 7
Anxiety**	… feeling **nervous, restless, tense** or **panicky,** or feeling unable to relax and needing to pace around?	1 2 3 4 5 6 7
	… feeling constantly **worried**, or fearful of interacting with others and needed to **withdraw from usual activities**?	1 2 3 4 5 6 7

*1 – normal / not at all; 2 – minimal; 3 – mild; 4 – moderate; 5 – marked; 6 – severe; 7 – extreme
**Note for clinicians: plot the one (hyper- or hypo-pole symptom) with the highest severity

Appendix G. Extracted data for the cariprazine meta-analysis

AUTHOR	STUDY	DIAG	SCALE	CARIPRAZINE				PLACEBO			LS mean diff.	SE	95% CI
				DOSE	N	LS mean	SE	N	LS mean	SE			
Marder et al. 2019	MD-16	SCHZ	PANSS Disorganized thought factor	1.5	140	-3,9	0,3	297	-2,7	0,2	-1,2	0,4	-2,0 to -0,5
Marder et al. 2019	MD-16, MD-04	SCHZ	PANSS Disorganized thought factor	3.0	291	-3,8	0,2	297	-2,7	0,2	-1,2	0,4	-1,7 to -0,6
Marder et al. 2019	MD-16	SCHZ	PANSS Disorganized thought factor	4.5	145	-4,5	0,3	297	-2,7	0,2	-1,8	0,6	-2,5 to -1,0
Marder et al. 2019	MD-04	SCHZ	PANSS Disorganized thought factor	6.0	154	-4,4	0,3	297	-2,7	0,2	-1,7	0,5	-2,4 to -1,0
McIntyre et al. 2022	MD-53, MD-54, MD-56	BD	MADRS Concentration Item	1.5	461	-1,6	0,1	460	-1,2	0,1	-0,4	0,1	-
McIntyre et al. 2022	MD-53, MD-54, MD-56	BD	MADRS Concentration Item	3.0	462	-1,4	0,1	460	-1,2	0,1	-0,2	0,1	-
McIntyre et al. 2022	MD-31, MD-32, MD-33	BM	PANSS Cognitive subscale	3.0 - 12.0	593	-2,2	0,1	419	-1,3	0,1	-0,9	0,2	-1,2 to -0,6

BD, bipolar depression; BM, bipolar mania; CI, confidence interval; LS, least square; SCHZ, schizophrenia; SE, standard error