

Transdiagnostic psychiatry: a systematic review

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The usefulness of current psychiatric classification, which is based on ICD/DSM categorical diagnoses, remains questionable. A promising alternative has been put forward as the “transdiagnostic” approach. This is expected to cut across existing categorical diagnoses and go beyond them, to improve the way we classify and treat mental disorders. This systematic review explores whether self-defining transdiagnostic research meets such high expectations. A multi-step Web of Science literature search was performed according to an a priori protocol, to identify all studies that used the word “transdiagnostic” in their title, up to May 5, 2018. Empirical variables which indexed core characteristics were extracted, complemented by a bibliometric and conceptual analysis. A total of 111 studies were included. Most studies were investigating interventions, followed by cognition and psychological processes, and neuroscientific topics. Their samples ranged from 15 to 91,199 (median 148) participants, with a mean age from 10 to more than 60 (median 33) years. There were several methodological inconsistencies relating to the definition of the gold standard (DSM/ICD diagnoses), of the outcome measures and of the transdiagnostic approach. The quality of the studies was generally low and only a few findings were externally replicated. The majority of studies tested transdiagnostic features cutting across different diagnoses, and only a few tested new classification systems beyond the existing diagnoses. About one fifth of the studies were not transdiagnostic at all, because they investigated symptoms and not disorders, a single disorder, or because there was no diagnostic information. The bibliometric analysis revealed that transdiagnostic research largely restricted its focus to anxiety and depressive disorders. The conceptual analysis showed that transdiagnostic research is grounded more on rediscoveries than on true innovations, and that it is affected by some conceptual biases. To date, transdiagnostic approaches have not delivered a credible paradigm shift that can impact classification and clinical care. Practical “TRANSD”agnostic recommendations are proposed here to guide future research in this field.

Key words: Transdiagnostic, diagnosis, classification, bibliometric analysis, conceptual analysis, anxiety, depression, psychosis, recommendations

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Diagnosis, which is the medical application of the process of classification, ubiquitous in science, has been the cornerstone of modern clinical knowledge and practice¹. Diagnosis in psychiatry started in Europe in the late 17th century, informed by systems that classified animal and plant species as part of other natural sciences². Psychiatric nosology, traditionally represented by the ICD and DSM (gold standard), is based on categorical diagnoses that are intertwined with the key clinical dichotomies that characterize the realm of clinical medicine (e.g., to treat or not to treat)^{3,4}.

Since its inception, psychiatric nosology has always been under fire. This is documented by several lines of evidence, including two recent issues of this journal^{3,5}. Although current diagnostic categories have demonstrated moderate to almost perfect reliability⁶, their usefulness has remained questionable⁷.

A promising avenue has been put forward by the so-called transdiagnostic approach. The prefix “trans” comes from Latin and it can either mean across/through (e.g., transatlantic) or beyond (e.g., transcend)⁸. Therefore, a transdiagnostic approach in psychiatry is expected to cut across existing categorical diagnoses and go beyond them, to produce a better classification system, compared to the existing gold standard.

Transdiagnostic approaches originated from cognitive behavioral theories and treatments for eating disorders^{9,10}, which were then extended to anxiety^{11–13} and depressive disorders¹⁴. The initial transdiagnostic rationale leveraged two core points:

a) these disorders share common etiological and maintenance processes^{9,10,13,15} as well as cognitive-affective, interpersonal, and behavioral features^{9,10,15} (e.g., the general psychopathology latent factor – p factor¹⁶), and b) the ever-growing number of disorder-specific treatment manuals is a barrier to the implementation of cognitive behavioral treatments^{10,13,15}.

The rationale for extending the transdiagnostic paradigm to anxiety and depressive disorders included an additional point that was not originally acknowledged¹⁰: c) disorder-specific interventions rely on heterogeneous diagnostic categories and pay relatively limited attention to comorbidity, which is high¹⁵.

Transdiagnostic research aims at tackling these limitations to introduce a novel approach that could improve the way we classify, formulate, treat, and prevent¹⁵ mental disorders. Moving away from a single-diagnosis approach towards a transdiagnostic conceptualization and treatment of mental disorders would thus be a significant paradigm shift¹⁵. Recently, transdiagnostic approaches have been endorsed by other paradigms that cut across different mental disorders, such as the Research Domain Criteria (RDoC) initiative¹⁷ and the clinical staging model¹⁸. At present, however, it is unclear whether transdiagnostic research meets such high expectations for delivering a radical paradigm shift that impacts classification and clinical care.

To address this issue, we present here a broad systematic review of transdiagnostic research in psychiatry. We systematically assess the transdiagnostic literature against several

empirical variables which index core characteristics as well as potential pitfalls. A bibliometric and conceptual analysis complements the empirical findings, along with practical recommendations to guide future research in this field.

METHODS

The PRISMA compliant¹⁹ protocol for this study was registered on PROSPERO (CRD42018108613).

Search strategy, selection criteria and data extraction

A multi-step literature search was performed. First, systematic searches were conducted in the Web of Science (which includes Web of Science Core Collection, BIOSIS Citation Index, KCI - Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index), until May 5, 2018, with no restrictions on language or publication date. The keyword “transdiagnostic” was used, filtering for the category “psychiatry” through the Web of Science categories function. Second, we searched the reference lists of retrieved articles. Third, abstracts identified by this process were then screened and full-text articles were inspected against the inclusion and exclusion criteria.

The literature search, study selection and data extraction were conducted by two authors (MS, NB) independently. During all stages, in the case of disagreement, consensus was reached through discussion with a third author (PFP).

Studies were eligible for inclusion when the following criteria were fulfilled: a) original individual articles, with no restriction on study design (including interventional and observational studies) or topic; b) a clear and primary focus on a transdiagnostic approach, demonstrated by using the word “transdiagnostic” in the title.

The exclusion criteria were: a) reviews, meta-analyses, study protocols, abstracts and any other non-original data; b) lacking a clear primary focus on transdiagnostic approaches, defined as above; and c) studies with less than ten participants²⁰.

Descriptive variables

For each study, we extracted descriptive variables relating to: a) general information, b) definition of gold standard diagnostic criteria, c) outcome measures, d) definition of the transdiagnostic approach, and e) quality assessment.

General information variables included: first author and year of publication; study domain (classification, treatment, clinical prediction, neuroscience, cognition and psychological processes); study design (observational, uncontrolled interventional, controlled interventional); type of design (cross-sectional, longitudinal, unrandomized, randomized); total sample size (total pool of participants recruited at baseline, including non-clinical samples); and mean age (or age range).

Variables relating to the definition of the gold standard diagnostic criteria included: whether the study explicitly acknowledged the type of gold standard used (DSM or ICD, any version); the specific type of primary diagnoses of mental disorders and their specific ICD or DSM codes; the presence of any other clinical condition as defined by each individual study; the presence of a non-clinical sample (e.g., healthy controls); the total number of ICD/DSM mental disorders investigated by the study; the total number of diagnostic spectra (defined according to the ICD-10 diagnostic blocks: organic, including symptomatic mental disorders; mental and behavioral disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood (affective) disorders; neurotic, stress-related and somatoform disorders; behavioral syndromes associated with physiological disturbances and physical factors; disorders of adult personality and behavior; mental retardation; disorders of psychological development; behavioral and emotional disorders with onset usually occurring in childhood and adolescence; unspecified mental disorders); and the type of psychometric instrument employed to define the gold standard.

Variables relating to the outcomes included: whether the primary outcome of the study was clearly acknowledged in the manuscript; the specific type of instruments employed to define it; and the total number of primary outcomes.

Variables relating to the transdiagnostic approach included: the exact definition of the transdiagnostic construct as provided by each study; the number of transdiagnostic constructs (single or multiple)²¹; whether the transdiagnostic construct was descriptive (a construct which is present in multiple disorders, without regard to how or why²²) or mechanistic (a construct that may reflect an underlying physiological, neurobiological or functional mechanism²²); whether the construct was causally associated with the outcome (to rule out the possibility that a construct may just be epiphenomenal²¹); whether the transdiagnostic construct was present in all clinical conditions and spectra (universal transdiagnostic process) and in how many of them. We also extracted the type of statistical analysis used to probe the transdiagnostic construct; whether there was a formal statistical assessment of the impact of the transdiagnostic approach compared to the specific-diagnostic approach; and the results of such a test.

Quality assessment was performed by recording if an *a priori* protocol had been made available, if funding was provided by industry, and if the core findings had been externally replicated in an independent sample.

Analysis

The descriptive variables were used to perform different types of analyses.

First, descriptive summary data and statistics (i.e., frequencies, means/medians, ranges) of the above variables were narratively presented in the text and in informative tables.

Second, each study was assessed against the criteria introduced by Mansell et al²¹ to define transdiagnostic approaches

in psychiatry: a) presence of a clinical population, b) presence of at least four different mental disorders, c) presence of a non-clinical sample, and d) demonstration of the transdiagnostic construct in all mental disorders investigated.

Third, the conceptual definition of the transdiagnostic approach was empirically deconstructed. The main aim was to explore the extent to which each transdiagnostic approach related to the existing diagnostic categorical system. As indicated in Figure 1, the simplest transdiagnostic approach – defined as “across-diagnoses” – was to compare different ICD/DSM categorical diagnoses against each other, to test their diagnostic boundaries and cross-cutting features. The across-diagnoses model could include one diagnostic spectrum, multiple spectra and/or non-clinical samples, including also healthy individuals. A more elaborated approach involved the definition of new diagnostic-like constructs, for example based on bio-types or clinical types, and then testing the relatedness of these newly defined constructs against the gold standard. These approaches were termed “beyond-diagnoses”, because they employed standard ICD/DSM diagnostic information but went beyond it, to test new diagnostic constructs. When studies did not fit within any of the above two categories, the specific approach was described.

Fourth, we conducted a bibliometric analysis using the list of specific ICD/DSM mental disorders that were analyzed by each study (when available). These data were then loaded into R software and cleaned with the Bibliometrix and TM packages. The processed data were then loaded into Gephi software to generate the network map of the specific ICD/DSM mental disorders investigated by transdiagnostic research. Each node indicated a specific mental disorder, with the node’s size reflecting how many different connections (frequency) with other nodes were present. The thickness of the edges reflected the number of connections between a pair of nodes/mental disorders. For graphical purposes, nodes that had frequen-

cy ≤ 6 and number of co-occurrent connections ≤ 3 were filtered out.

RESULTS

Studies identified

The literature search identified 627 potential records that were screened on the basis of title and abstract reading. Of these, 239 were considered eligible for full screening. At this stage, 128 studies were further excluded, leaving a sample of 111 studies, which represented the final database for the current systematic review (Figure 2).

Characteristics of transdiagnostic studies in psychiatry

General information

The first study, published in 2004 by Norton et al¹¹, addressed the effects of a transdiagnostic psychological intervention for different types of anxiety disorders. Since then, there was one study published in 2006, six in 2008, four in 2009, six in 2012, six in 2013, thirteen in 2014, eleven in 2015, eighteen in 2016, thirty-four in 2017, and eleven up to May 2018.

Most studies (45%) were investigating interventions (of which 50% were controlled, 48% uncontrolled²³⁻⁴⁶, and 2% unclear⁴⁷). Less than half (46%)^{11,43,48-68} of the interventional studies were randomized. All interventional studies focused on neurotic, stress-related and somatoform disorders or mood (affective) disorders, while other mental disorders were rarely investigated (Table 1).

Cognition and psychological processes was the second most frequent topic (28%), followed by neuroscientific topics

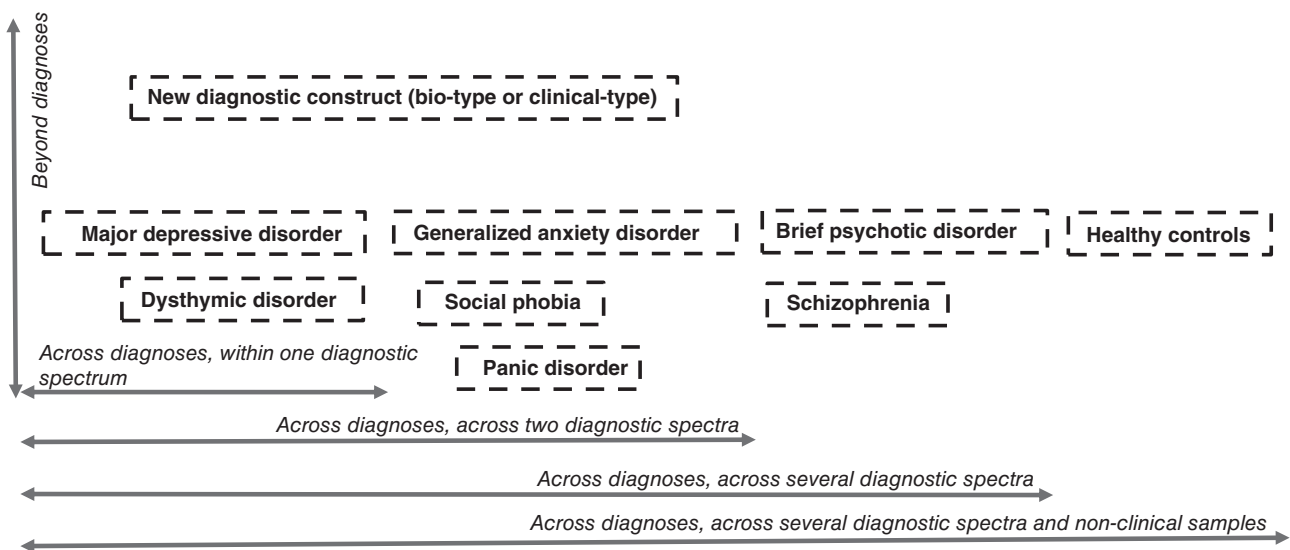


Figure 1 Conceptual classification of transdiagnostic approaches most widely employed in psychiatry, with some prototypical diagnostic examples

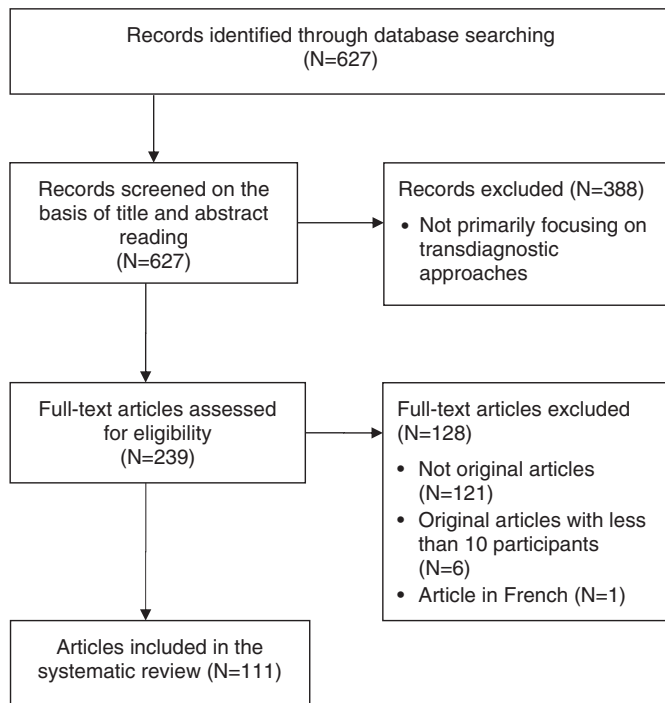


Figure 2 Study identification and selection (PRISMA flow chart)

(13%). Classification and prediction studies were more infrequent (4% and 10% respectively) (Table 1).

The vast majority of non-interventional studies (79%) were cross-sectional, and only 21%⁶⁹⁻⁸¹ longitudinal. There was a large variability in study sample size, ranging from 15 participants in the smallest study⁴² to 91,199 in the largest⁷³ (median: 148 participants). The mean age of individuals (when available) ranged from 10⁴⁴ to more than 60²³ (median: 33 years).

Definition of gold standard diagnostic criteria

A substantial proportion (27%) of studies^{24,29,36,40,48,49,64,69-71,73,78,80,82-98} did not acknowledge using any psychometric interview to establish their gold standard diagnoses. Several studies (16%)^{29,34,54,70,71,78,82,83,85-88,92,93,95,97,99,100} did not refer to a gold standard diagnostic manual, but speculated on comparative benefits of the transdiagnostic approach over specific diagnoses^{29,71}.

Some studies reported non-existent (e.g., DSM-IV-TR bipolar II disorder with psychotic features⁸⁴) or incorrect diagnoses (e.g., suicidality³⁴, marijuana abuse/dependence^{76,101}, late onset schizophrenia-like psychosis¹⁰⁰, social anxiety disorder and social phobia as two distinct DSM-IV disorders¹⁰¹). Other studies included health anxiety within mental disorders, confusingly defined either as not relating to a specific diagnosis⁹⁰, as hypochondriasis²³, or as “health-based anxiety predominant in individuals with illness anxiety disorders and somatic symptom disorders”⁹⁰.

One interventional study stated that the participants were not diagnosed at all⁸⁸. The study addressed this issue by sim-

ply noting that “it would have been informative to know client diagnoses”⁸⁸, raising concerns about unnecessary or excessive treatments in this sample¹⁰².

Some studies used comorbid (as opposed to primary) diagnoses to validate the transdiagnostic construct^{50,52,56,59-63,99,103}. In about one third of studies (28%)^{34,36,54,69,70,72,74,75,82,85,87,89,104-107}, the boundaries between primary and secondary diagnoses were not completely clear.

There was also some confusion between the measurement of symptoms as opposed to categorical disorders. This was mainly due to the use of continuous measurements that were not translated into ICD/DSM diagnostic categories through the use of *a priori* cut-offs⁸³. Three studies measured DSM-related items in non-clinical samples without applying cut-offs to establish the intake of specific diagnostic categories^{86,90,91}. The results were there interpreted in the context of the disorder-oriented literature⁹¹, arguing that findings were related to specific categorical diagnoses^{86,90}. These studies concurrently acknowledged a transdiagnostic approach in their title – as for any other study included in the current review – and “the lack of diagnostic measures” in the study itself⁹¹.

An interventional study which did not use cut-offs to define post-traumatic stress disorder concluded that treating distress was better than treating the categorical disorder²⁹. Another interventional study which measured symptoms but not disorders tautologically concluded that the potential advantage of transdiagnostic interventions was a reduced need for disorder-based assessments⁸⁸. Some studies did apply cut-offs but eventually did not use them for their main analyses^{48,94}.

Frequently, studies did not specify the exact ICD/DSM types of mental disorders that were investigated, but only referred to the general domains of psychotic disorders^{34,106}, substance induced disorders^{28,34,108}, anxiety disorders^{23,28,54,88,93,104}, mood disorders^{23,28,48,49,54,64,88,93}, or mood and anxiety disorders^{54,93}. The specific ICD/DSM diagnostic codes were hardly ever reported.

The number of primary mental disorders investigated by each study was highly variable and overall relatively low, ranging from no evidence of mental disorders at all (13% of studies)^{24,29,70,78,82,85-88,90-92,95,97} and one mental disorder (8% of studies)^{50,59-63,96,109,110}, up to 353 mental disorders⁷³ (median: four mental disorders per study). Similarly, the number of ICD-defined diagnostic spectra was heterogeneous, ranging from zero (12% of studies)^{29,70,78,82,85-88,90-92,95,97} to ten⁷³ (median: one spectrum) per study. The largest transdiagnostic study published to date leveraged an electronic case register to include 353 mental disorders clustered across ten spectra, representing all ICD-10 mental disorders except organic mental disorders⁷³. About one third of the studies (35%)^{29,40,70,74,76,78,81,82,85-87,90-92,94-98,100,101,103,105-107,111-124} included at least one non-clinical sample.

Outcome measures

Only a minority (35%)^{23-25,32,34-36,40,48,49,51-53,56-62,64,66-68,73,74,83,84,88,100,103,111,112,115,125-128} of studies explicitly acknowledged

Table 1 Studies included in the systematic review

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Van Dijk et al ²³	2018	Treatment	53 and 64	>60	DSM-IV-TR	Psychotherapeutic day treatment and activating day treatment	Across diagnoses, across spectra	No
Samtani et al ¹⁰⁹	2018	Prediction	183	23	DSM-IV	Repetitive negative thinking	Within the same diagnosis	No
Pellizzer et al ⁶⁹	2018	Prediction	78	27	DSM-5	Body image flexibility	Across diagnoses, within spectrum	No
Nota & Coles ¹⁰⁴	2018	Neuroscience	52	36	DSM-IV-TR	Repetitive negative thinking	Across diagnoses, across spectra	No
McEvoy et al ⁸²	2018	Prediction	2,088	20	NA	Repetitive negative thinking	A-diagnostic	No
Grisanzio et al ¹¹¹	2018	Classification	420	40	DSM-IV	Subtypes based on neuro-cognition, brain activation and functional capacity	Beyond diagnoses	No
Goldschmidt et al ¹²⁵	2018	Classification	636	15	DSM-5	Eating disorders symptoms network	Across diagnoses, within spectrum	No
Dear et al ²⁴	2018	Treatment	28	41	DSM-IV	Cognitive behavioral therapy	Across physical and mental health diagnoses	No
Curzio et al ¹²⁹	2018	C&P processes	419	15	DSM-IV-TR	Binge eating, dietary restraint, affective, interpersonal problems and perfectionism	Across diagnoses, within spectrum	No
Ciaramidaro et al ¹⁰⁵	2018	Neuroscience	78	22	ICD-10	Facial recognition	Across diagnoses, across spectra and non-clinical samples	No
Capobianco et al ⁴⁸	2018	Treatment	40	28	DSM-IV	Metacognitive and mindfulness meditation therapies	Across diagnoses, across spectra	No
Zwerenz et al ⁴⁹	2017	Treatment	82	40	ICD-10	Psychodynamic web-based self-help intervention	Across diagnoses, across spectra	No
Zemestani et al ⁵⁰	2017	Treatment	43	23	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Wigman et al ⁷⁰	2017	C&P processes	293	19	NA	Interconnectedness of psychotic and affective experiences	A-diagnostic	No
Talkovsky et al ²⁵	2017	Treatment	129	33	DSM-IV-TR	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Talkovsky et al ²⁶	2017	Treatment	120	33	DSM-IV-TR	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Smith et al ²⁷	2017	Treatment	49	33	DSM-IV	Anxiety symptoms questionnaire	Across diagnoses, within spectrum	No
Shinn et al ⁷¹	2017	Classification	91	21	NA	Clinical service	Across diagnoses, across spectra	No
Sheffield et al ¹¹²	2017	Neuroscience	576	35	DSM-IV	Functional brain network integrity	Across diagnoses, across spectra and non-clinical samples	No
Sharma et al ⁵¹	2017	Treatment	63	14	ICD-10	Group cognitive behavioral therapy	Across physical and mental health diagnoses	No
Schroder et al ⁵²	2017	Treatment	179	37	DSM-IV	Internet intervention	Across diagnoses, within spectrum	No
Riccardi et al ⁵³	2017	Treatment	28	29	DSM-IV	False safety behavior elimination therapy	Across diagnoses, within spectrum	No
Platt et al ⁷²	2017	Prediction	4,925	13-18	DSM-IV	Timing of menarche and internalizing factors	Across diagnoses, across spectra	No
Pitman et al ²⁸	2017	Treatment	73	29	DSM-IV	Short-term psychodynamic psychotherapy	Across diagnoses, across spectra	No

Table 1 Studies included in the systematic review (*continued*)

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Newby et al ⁸³	2017	Treatment	2,109	40	DSM-IV	Internet-based cognitive behavioral therapy	Across diagnoses, across spectra	No
Maia et al ⁵⁴	2017	Treatment	67	>18	DSM-IV, ICD-10	Cognitive behavioral therapy	Across diagnoses, across spectra	No
MacNamara et al ¹¹³	2017	Neuroscience	199	26	DSM-IV	Affective face processing	Across diagnoses, across spectra and non-clinical samples	No
Lee et al ⁸⁴	2017	Prediction	163	20	DSM-IV-TR	Neuropsychological functioning	Across diagnoses, across spectra	No
LeBouthillier & Asmundson ⁵⁵	2017	Treatment	48	33	DSM-5	Aerobic exercise and resistance training	Across diagnoses, within spectrum	No
Keil et al ¹¹⁴	2017	C&P processes	108	12	DSM-5	Emotions regulation	Across diagnoses, across spectra and non-clinical samples	No
Jauhar et al ¹¹⁵	2017	Neuroscience	60	24	DSM-IV	Dopamine synthesis capacity	Across diagnoses, across spectra and non-clinical samples	No
Hankin et al ⁸⁵	2017	C&P processes	1,125	11	NA	Temperamental and psychopathology factors	A-diagnostic	No
Hamblen et al ²⁹	2017	Treatment	342	57	NA	Cognitive behavioral therapy	Across symptoms	No
Gros et al ³⁰	2017	Treatment	16	47	DSM-5	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Gong et al ¹¹⁶	2017	Neuroscience	272	34	DSM-IV	Intra/inter-network connectivity	Across diagnoses, across spectra and non-clinical samples	No
Gibson et al ⁸⁶	2017	C&P processes	2,342	21	NA	Exposure to traumatic life events	Across symptoms	No
Fusar-Poli et al ⁷³	2017	Prediction	91,199	33	CAARMS, ICD-10	Risk model of transition to psychosis	Across diagnoses, across spectra	No
Forbush et al ¹²⁶	2017	Classification	207	25	DSM-5	Distress and fear-avoidance internalizing factors	Beyond diagnoses	No
Feldker et al ¹¹⁷	2017	Neuroscience	134	28	DSM-IV	Brain response to visual threat	Across diagnoses, within spectrum and non-clinical samples	Yes
Espejo et al ³¹	2017	Treatment	48	45	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Ellard et al ⁵⁶	2017	Treatment	29	44	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Chen et al ¹¹⁸	2017	Neuroscience	60	41	DSM-IV	Functional connectivity density	Across diagnoses, across spectra and non-clinical samples	No
Chasson et al ⁸⁷	2017	C&P processes	3,094	15	NA	Emotional vulnerabilities	A-diagnostic	No
Berger et al ⁵⁷	2017	Treatment	139	42	DSM-IV	Internet-based cognitive behavioral therapy	Across diagnoses, within spectrum	No
Barlow et al ⁵⁸	2017	Treatment	233	31	DSM-IV, DSM-5	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Talkovsky & Norton ³²	2016	Treatment	151	33	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Sunderland et al ¹¹⁹	2016	C&P processes	8,871	16-85	DSM-IV	Two factor internalizing-substance dependence model	Across diagnoses, across spectra and non-clinical samples	No
Stanton et al ¹⁰⁶	2016	C&P processes	299	47	DSM-5	Emotion regulation and basic personality dimensions	Across diagnoses, across spectra and non-clinical samples	No

Table 1 Studies included in the systematic review (*continued*)

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Sabharwal et al ¹⁰⁸	2016	Neuroscience	82	45	DSM-IV	Behavioral and neural measures of emotion-related working memory	Across diagnoses, across spectra	No
Reininghaus et al ¹³⁰	2016	Classification	1,168	42	RDoC	Bifactor model with general and specific psychosis dimensions	Beyond diagnoses	No
Philip et al ⁷⁴	2016	Prediction/ neuroscience	46	39	DSM-IV-TR	Thalamic connectivity in early life stress	Across diagnoses, across spectra and non-clinical samples	No
Morris et al ⁸⁸	2016	Treatment	108	41	NA	Group based psychological intervention	Across symptoms	No
McIntosh et al ⁵⁹	2016	Treatment	112	35	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
McEvoy & Erceg-Hurn ³³	2016	Treatment	256	34	DSM-IV	Intolerance of uncertainty	Across diagnoses, across spectra	No
Kristjánadóttir et al ³⁴	2015	Treatment	287	39	DSM-IV, ICD-10	Group cognitive behavioral therapy	Across diagnoses, across spectra	No
Ito et al ³⁵	2016	Treatment	28	35	DSM-IV	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Holliday et al ⁸⁹	2016	C&P processes	783	29	DSM-5	Distress tolerance	Across diagnoses, across spectra	No
Hadjistavropoulos et al ³⁶	2016	Treatment	458	39	DSM-IV	Internet-based cognitive behavioral therapy	Across diagnoses, across spectra	No
Fogliati et al ⁶⁰	2016	Treatment	145	41	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Dear et al ⁶¹	2016	Treatment	233	42	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Conway et al ⁷⁵	2016	C&P processes	815	15	DSM-IV	Internalizing and externalizing factors mediating appraisal biases	Transdiagnostic outcome	No
Conway et al ¹⁰⁷	2016	Prediction	700	20	DSM-IV	Latent model of personality disorder	Across diagnoses, across spectra and non-clinical samples	No
Asnaani et al ³⁷	2016	Treatment	107	33	DSM-5	Anxiety sensitivity, depression, rumination as moderators of cognitive behavioral therapy	Across diagnoses, within spectrum	No
Titov et al ⁶²	2015	Treatment	290	44	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Thibodeau et al ⁹⁰	2015	C&P processes	1,255	22	DSM-IV-TR	Intolerance of uncertainty	Across symptoms	No
Tang-Smith et al ⁹¹	2015	C&P processes	612	21	DSM-III	Dominance behavioral system	Across symptoms	No
Rodriguez-Seijas et al ¹²⁷	2015	C&P processes	5,191	NA	DSM-IV	Internalizing and externalizing factors	Across diagnoses, across spectra	No
Pietrzak et al ¹¹⁰	2015	C&P processes	267	54	DSM-IV	Loss symptoms, threat symptoms and somatic symptoms	Within the same diagnosis	No
Maia et al ⁹⁹	2015	Treatment	48	18-58	DSM-IV, ICD-10	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Latack et al ⁷⁶	2015	C&P processes	34,653	>18	DSM-IV	Internalizing and externalizing factors	Across diagnoses, across spectra and non-clinical samples	No
Hsu et al ¹³¹	2015	C&P processes	51	33	DSM-IV	Self-reported attentional control and rumination	Across diagnoses, across spectra	No

Table 1 Studies included in the systematic review (*continued*)

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Dear et al ⁶³	2015	Treatment	366	44	DSM-IV	Cognitive behavioral therapy	Within the same diagnosis	No
Corral-Frías et al ¹⁰¹	2015	Neuroscience	906	20	DSM-IV	Ventral striatal reactivity to reward	Across diagnoses, across spectra and non-clinical samples	No
Bedwell et al ¹²⁰	2015	Neuroscience	48	36	DSM-IV	Visual evoked potentials	Across diagnoses, across spectra and non-clinical samples	No
Vann et al ¹²⁸	2014	C&P processes	27	26	DSM-IV-TR	Metacognitions	Across diagnoses, within spectrum	No
Talkovsky & Norton ³⁸	2014	Treatment	256	33	DSM-IV	Negative affectivity, anxiety sensitivity, intolerance uncertainty	Across diagnoses, within spectrum	No
Starr et al ⁷⁷	2014	Prediction	1,630	28	DSM-IV	Latent internalizing factors for psychopathology	Transdiagnostic outcome	No
Spielberg et al ¹²¹	2014	Neuroscience	179	27	DSM-IV	Dimensions of anxiety and depression	Across diagnoses, across spectra and non-clinical samples	No
Queen et al ³⁹	2014	Treatment	59	15	DSM-IV	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Pietrzak et al ¹⁰³	2014	Neuroscience	35	29	DSM-IV-TR	Threat and loss symptoms	Across diagnoses, across spectra and non-clinical samples	No
Newby et al ⁴⁰	2014	Treatment	707	40	DSM-IV	Internet-based cognitive behavioral therapy	Across diagnoses, across spectra and non-clinical samples	No
McLaughlin et al ⁷⁸	2014	Prediction	1,065	12	NA	Rumination	A-diagnostic	No
McEvoy et al ¹²²	2014	C&P processes	786	28	DSM-IV	Repetitive negative thinking	Across diagnoses, across spectra and non-clinical samples	No
Gros ⁴¹	2014	Treatment	29	50	DSM-IV	Cognitive behavioral therapy	Across diagnoses, across spectra	No
Cameron et al ⁹²	2014	C&P processes	41	28	NA	Emotion perception and semantic memory	A-diagnostic	No
Bullis et al ⁴²	2014	Treatment	15	32	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Bohnke et al ⁹³	2014	C&P processes	11,939	38	DSM-IV	Negative affectivity	Across diagnoses, across spectra	No
Norton et al ⁴⁷	2013	Treatment	79	33	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
McEvoy et al ¹³²	2013	C&P processes	513	37	DSM-IV	Repetitive negative thinking	Across diagnoses, across spectra	No
McEvoy & Mahoney ¹³³	2013	C&P processes	99	NA	DSM-IV	Intolerance of uncertainty and negative metacognitive beliefs	Across diagnoses, within spectrum	No
Johnson et al ⁹⁴	2013	C&P processes	334	19	DSM-IV	Impulsive responses to emotion	Across diagnoses, across spectra and non-clinical samples	No
Ebert et al ⁶⁴	2013	Treatment	400	45	ICD-10	Internet-based maintenance treatment	Across diagnoses, across spectra	No
Boswell et al ⁴³	2013	Treatment	54	30	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Norton & Barrera ⁶⁵	2012	Treatment	46	31	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No

Table 1 Studies included in the systematic review (*continued*)

Study	Year	Domain	Baseline N	Mean age	Gold standard	Transdiagnostic construct	Transdiagnostic type	Mansell criteria
Norton ⁶⁶	2012	Treatment	87	33	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Hoiles et al ⁹⁵	2012	C&P processes	224	31	NA	Cognitive model for eating disorder	A-diagnostic	No
Farchione et al ⁶⁷	2012	Treatment	37	29	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Conway et al ⁷⁹	2012	C&P processes	815	15	DSM-IV	Internalizing and externalizing factors	Across diagnoses, across spectra	No
Bilek & Ehrenreich-May ⁴⁴	2012	Treatment	22	10	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Innis et al ⁹⁶	2009	Neuroscience	135	28	DSM-IV	Homocysteine remethylation	Within the same diagnosis	No
Hagenaars et al ¹²³	2009	C&P processes	252	29	DSM-IV	Trauma and panic memories	Across diagnoses, within spectrum and non-clinical samples	No
Fairburn et al ⁶⁸	2009	Treatment	154	26	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No
Bentall et al ¹⁰⁰	2009	C&P processes	237	53	DSM-IV, ICD-10	Paranoia, cognitive performance and depressive style	Across diagnoses, across spectra and non-clinical samples	Yes
Norton et al ⁴⁶	2008	Treatment	54	32	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
Norton ⁴⁵	2008	Treatment	52	33	DSM-IV	Group cognitive behavioral therapy	Across diagnoses, within spectrum	No
McFarlane et al ⁸⁰	2008	Prediction	58	30	DSM-IV	Predictors of relapse	Across diagnoses, within spectrum	No
Corcoran et al ¹²⁴	2008	C&P processes	148	38	DSM-IV	Theory of mind and jumping to conclusions	Across diagnoses, across spectra and non-clinical samples	No
Brown et al ⁹⁷	2008	C&P processes	38	20	NA	Measure of mundane meaning	A-diagnostic	No
Bentall et al ⁹⁸	2008	C&P processes	148	38	DSM-IV	Negative self-esteem and negative expectations	Across diagnoses, across spectra and non-clinical samples	Yes
Wade et al ⁸¹	2006	C&P processes	1,002	35	DSM-IV	Dimensional model of eating disorders	Across diagnoses, across spectra and non-clinical samples	No
Norton et al ¹¹	2004	treatment	23	>19	DSM-IV	Cognitive behavioral therapy	Across diagnoses, within spectrum	No

C&P processes – cognition and psychological processes, CAARMS – Comprehensive Assessment of At Risk Mental State, RDoC – Research Domain Criteria, NA – not available

their primary outcome measure, which may be suggestive of suboptimal study quality. There was also a high variability in the number of primary outcome measures, ranging from one⁴⁸ to thirteen⁸¹ (median: two measures) per study.

Definition of the transdiagnostic approach

The exact definition of the transdiagnostic construct per study is provided in Table 1. Only a minority of constructs

(36%) involved multiple processes^{28,37,38,48,55,59,70,72,75-77,79,80,85,87,91,92,96,98,100,103,106,110,111,113,114,116,119-121,123-132}. Most studies (81%) were descriptive in nature. Mechanistic constructs were more infrequent (19%)^{28,32,38,48,50-53,58,70,83,103,112-118,131,133}, and causal transdiagnostic constructs were hardly ever reported (7%)^{24,48,50-53,58,115} and only during the most recent years (2017-2018).

The transdiagnostic construct was demonstrated across all clinical conditions investigated only in a minority (34%) of studies^{24,27,30,32,38,42,43,45,47,50,52,53,57,58,60-63,65,71,80,83,89,96,98,109-}

113,115,117,118,123,128-130,133. It was demonstrated in a median of three conditions and one spectrum. Several studies did not clarify at all whether the construct was present in the conditions investigated. Overall, no clear universal transdiagnostic construct that could be valid across all mental disorders and diagnostic spectra was identified.

The statistical methods used to test the impact of the transdiagnostic construct encompassed analysis of variance/covariance, correlations, regressions and general linear models, mixed effect models, moderation and mediation analysis, principal component analysis, structural equation modelling, network analysis, and machine learning.

Less than half (44%) of the studies^{27,33,38,58,60,61,65,72-75,77,79-81,83,84,89,93,98,100,101,103,105,107-109,111-121,123-133} performed a statistical comparative assessment of the transdiagnostic approach versus a specific-diagnostic approach. This problem was particularly relevant for interventional studies, half of which lacked a comparative specific-diagnostic group. Overall, only 16% of them^{27,33,38,58,60,61,65,83} performed a statistical comparative assessment. Some of these studies acknowledged that reliable conclusions regarding the diagnostic specificity of the findings could not be drawn^{34,64}. However, other interventional studies lacking both a control group and statistical comparative assessment eventually (over)stated that the transdiagnostic cognitive behavioral treatment was effective in improving outcomes⁴⁰ or that it was more effective than the specific-diagnostic approach²⁹. When comparative analyses were available, they generally indicated similar effects of the transdiagnostic vs. the specific-diagnostic intervention^{58,60,61,83}.

The qualitative appraisal of the transdiagnostic vs. specific-diagnostic effects – when available – revealed further inconsistencies. For example, some predictive modelling studies indicated that the transdiagnostic approach was only able to explain an additional 1% of the variance¹⁰⁹. Other studies acknowledged that the observed transdiagnostic effects were small in magnitude, but at the same time suggested developing transdiagnostic clinical interventions¹³¹.

In general, neuroscientific studies provided better descriptions of these effects. For example, one of them concluded that the transdiagnostic biotypes identified specific, coherent associations between symptoms, behavior, brain function, and real-world function that cut across DSM-IV defined diagnoses¹¹¹. Other neuroscientific studies demonstrated shared neurobiological mechanisms across current categories of mental disorders^{108,112,113,115,117} or both specific and transdiagnostic effects across mental disorders^{74,116,129}.

Quality assessment

A substantial proportion of studies (40%)^{23,28-30,37,40,47,67,69-71,73,75,78,80,82-88,93,96-98,100,104-109,113-118,120,124,126,128,130} did not acknowledge an *a priori* protocol. There were very few studies reporting industry involvement (4%)^{52,57,103,110,111}. Transdiagnostic findings were hardly ever externally replicated, with

the exception of four studies (4%)^{73,85,93,111}. Other methodological weaknesses involved the use of clinical prediction methods (i.e., stepwise selection methods) that produce biased models^{109,82}, in particular in small databases^{131,120,80}. The use of small samples⁸⁰ also led to underpowered analyses across diagnostic subgroups¹³³.

Some studies interpreted overfitted and not externally replicated models to favor transdiagnostic over disorder-specific approaches⁷⁶. Other studies conducted a large number of comparative analyses without controlling for multiple comparisons¹⁰⁶. One study stated that participants were randomized, but eventually allocated them to a single treatment arm³⁸. Another study re-analyzed data from three previously published interventional studies that adopted different designs, without clarifying how the final database was amalgamated⁴⁷.

Literature analysis

Mansell's transdiagnostic criteria

Only three studies (3%)^{98,100,117} met Mansell's transdiagnostic criteria. The most frequently unmet requirement was the demonstration of the transdiagnostic construct across all conditions investigated by the study.

Type of transdiagnostic approach

The majority of studies (82 out of 111, 74%) (Table 1) endorsed an across-diagnoses approach. Of them, 33 (40%) were conducted within the same diagnostic spectrum (three of which also included a non-clinical sample) and 49 (60%) were across different diagnostic spectra (22 of which also included a non-clinical sample) (Table 1). Only three studies (3%)^{111,126,130} endorsed a beyond-diagnoses approach. They were also the most methodologically sophisticated.

For most of these across/beyond-diagnoses studies, the transdiagnostic approach was intertwined in the baseline recruitment of participants with different diagnoses. However, two studies (2%) defined their transdiagnostic approach through the inclusion of different diagnostic outcomes, as opposed to different patient groups at baseline (these studies were termed "transdiagnostic outcomes")^{75,77}. Two other studies (2%)^{24,51} defined their transdiagnostic approach as the overlap between physical (gastrointestinal, headache) and mental health (anxiety and depression) symptoms (these studies were termed "across physical and mental health diagnoses").

Despite their self-proclaimed transdiagnostic status, the remaining 22 studies (20%) were actually not transdiagnostic at all.

Eight studies (7%)^{70,78,82,85,87,92,95,97} did not consider any ICD/DSM diagnostic information as gold standard nor defined any new diagnostic construct. These were usually population-based studies which adopted a continuum rather than a categorical measurement of psychopathology, the results of which were

completely unrelatable to any existing ICD/DSM category. Therefore, these studies were termed as being “a-diagnostic” rather than transdiagnostic.

Five studies (5%)^{29,86,88,90,91} confounded symptoms and disorders. These studies explored only DSM or ICD-related symptoms without any clear reference to diagnostic categories of mental disorders, and were therefore defined as “across symptoms”.

Nine studies (8%)^{50,59-63,96,109,110} were defined as “within the same diagnosis”. Six of them investigated comorbid disorders in addition to a single primary disorder: comorbid depression, generalized anxiety disorder and social anxiety disorder in addition to panic disorder⁶⁰; comorbid depression, generalized anxiety disorder and panic disorder in addition to social anxiety disorder⁶¹; comorbid generalized anxiety disorder, panic disorder and social anxiety disorder in addition to major depressive disorder⁶²; comorbid major depressive disorder, social anxiety disorder and panic disorder in addition to generalized anxiety disorder⁶³; comorbid panic disorder, social anxiety disorder and generalized anxiety disorder in addition to major depression⁵⁰; and multiple mental disorders in addition to binge eating disorder⁵⁹. Another study investigated comorbid depressive and anxiety symptoms (but not disorders) in patients with post-traumatic stress disorder¹¹⁰.

Two further studies used the investigated different subtypes (restricting type and binge eating type) of the same disorder (DSM-IV anorexia nervosa)⁹⁶ or different clinical states of the same disorder (never depressed, past depression, current depression)¹⁰⁹.

Bibliometric analysis

Figure 3 illustrates the network of specific mental disorders that have been investigated by transdiagnostic research to date. A predominant focus on anxiety and depressive disorders is evident.

DISCUSSION

To the best of our knowledge, this is the most comprehensive review systematically appraising transdiagnostic research in psychiatry. The empirical analysis revealed that the transdiagnostic literature is heterogeneous and intrinsically incoherent. The bibliometric analysis showed that, to date, transdiagnostic research has focused on a limited number of mental disorders. The conceptual analysis leveraged these findings to demonstrate that, at present, transdiagnostic research does not represent a credible paradigm shift that can impact the classification of or clinical care for mental disorders.

This systematic review provides several lines of evidence showing that transdiagnostic approaches in psychiatry are heterogeneous. For example, only three studies out of 111 qualified as being truly transdiagnostic, according to established criteria²¹. This empirical test demonstrates that the transdiagnostic designation is applied in a loose and unstandardized way, encompassing a number of different and often conflicting conceptualizations.



Figure 3 Network map of specific mental disorders analyzed by transdiagnostic research in psychiatry to date. Each node indicates a specific mental disorder, with the node’s size reflecting how many different connections with other nodes were present. The thickness of the edges reflects the number of connections between a pair of nodes/mental disorders.

Paradoxically, some of these approaches were intrinsically incoherent and incompatible with a transdiagnostic framework, because they investigated symptoms and not disorders (across-symptoms), a single disorder (within-disorder) or, to the extreme, reported no diagnostic information at all (a-diagnostic).

Furthermore, transdiagnostic studies were often characterized by methodological weaknesses. For example, the exact ICD/DSM types of mental disorders were frequently poorly defined, raising the question of how the researchers could legitimately challenge the boundaries of mental disorders, if these were not even accurately determined. In addition, the boundaries between primary and comorbid disorders in transdiagnostic literature have often been blurred. Arguably, transdiagnostic approaches have been more heterogeneous, incoherent and paid less attention to the problem of comorbidities than the DSM/ICD diagnoses that were criticized for the very same problems.

The other key methodological caveat was that transdiagnostic studies often tested several outcomes, enhancing the likelihood of type I error from data fishing expeditions. This problem was amplified by the use of arbitrary cut-offs to measure symptom severity¹³⁴, a general lack of external replication studies, and by overenthusiastic interpretations of the results. In line with these arguments, there were only a few methodologically sound studies which have been able to identify robust mechanistic transdiagnostic constructs that were causally related with the outcome of interest.

Consistent with the above limitations, most transdiagnostic studies (excluding those not properly transdiagnostic, as noted above) limited their analyses to the search for shared features across a certain set of mental disorders (across-diagnoses). However, the bibliometric analysis revealed that these studies remained almost entirely confined within the restricted original area of interest of transdiagnostic research: anxiety and depressive disorders.

No universal transdiagnostic process has been identified, and the extent to which transdiagnostic approaches could pragmatically benefit other mental disorders and diagnostic spectra is undetermined. In fact, only a few transdiagnostic studies have eventually tested new classification systems, beyond the existing gold standard (beyond-diagnoses).

To date, the contribution of transdiagnostic literature to the development and validation of an alternative classification system, which has genuine clinical value – and which is not a

“fudge”¹³⁵ – has been negligible. Notably, transdiagnostic approaches have not replaced classification systems in any other branches of clinical medicine. On the contrary, continuous (transdiagnostic) and categorical (specific-diagnostic) dimensions frequently co-exist in organic medicine (e.g., vascular surgery)¹³⁶, as well as in psychiatry (e.g., the new DSM-5 dimensional approach to personality disorders¹³⁷). In reality, transdiagnostic studies have also produced evidence to support the existence of diagnostic categories^{130,138}.

It is thus apparent that future extensive research in this field is greatly needed, in particular beyond-diagnoses studies that include several diagnostic spectra. However, a key prerequisite would be to overcome the empirical weaknesses of current transdiagnostic research. To facilitate this outcome, we propose in Table 2 some pragmatic “TRANSD”iagnostic guidelines. We hope these guidelines will improve the consistency and quality of the next generation of transdiagnostic research.

Transdiagnostic research is also affected by some significant conceptual weaknesses. First, it is less innovative than it often proclaims. The fundamental argument for transdiagnostic approaches is that diagnostic categories (mostly anxiety, depressive and eating disorders) are not discrete entities, because there are shared features cutting across them. However, twenty-four years ago, when the DSM-IV was released, an official disclaimer was added to its forefront: “there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders”¹³⁹.

It has to be considered that current polythetic (i.e., based on a list of symptoms and signs believed to be characteristic¹⁴⁰) diagnostic categories originate in prototypical descriptions containing a core structure (gestalt) of the disorder and its polysymptomatic manifestations. Accordingly, the boundaries of mental disorders, as illustrated in Figure 1, are dotted, not solid. Unfortunately, psychiatric knowledge has overlooked these issues and, over the ensuing two decades, the abstract (rather than physical) nature of DSM-IV categories¹⁴¹ has been reified to the point that they are often seen as real ontological entities, discrete and demarcated from each other by distinct boundaries.

During this process, the symptoms shared by two or several mental disorders tended to be omitted from the diagnostic lists, in order to strengthen the clinical distinctiveness of the categories¹⁴⁰. Therefore, transdiagnostic research represents more of a rediscovery of what has been forgotten from proto-

Table 2 “TRANSD”iagnostic research recommendations in psychiatry

Transparent definition of the gold standard (ICD, DSM, other), including specific diagnostic types, official codes, primary vs. secondary diagnoses, diagnostic assessment interviews.
Report the primary outcome of the study, the study design and the definition of the transdiagnostic construct in the abstract and main text.
Appraise the conceptual framework/approach of the transdiagnostic approach: across-diagnoses, beyond-diagnoses, other (explain).
Numerate the diagnostic categories, spectra and non-clinical samples in which the transdiagnostic construct is being tested and then validated.
Show the degree of improvement of the transdiagnostic approach against the specific diagnostic approach through specific comparative analyses.
Demonstrate the generalizability of the transdiagnostic construct through external validation studies.

typical descriptions as well as the consequence of the diagnostic reification. In fact, it would make no sense to challenge the diagnostic boundaries without assuming that these do exist on some ontological level.

Second, transdiagnostic approaches are largely based on an epistemological error, which triggers an illusion of continuity¹⁴². The devaluation¹⁴³ and simplification of psychopathological phenomena – introduced by recent versions of the DSM and ICD – to brief, ordinary, non-technical lay language descriptions, has converted complex symptoms and psychic phenomena into phenomenological primitives or homogeneous elementals¹⁴⁰. For example, there is only one kind of depressive state, one kind of anxiety, one kind of delusion, and it is assumed that all of these states share the same phenomenological structure when they are observed in different mental disorders¹⁴⁰. Consequently, mental disorders, solely constituted by aggregates of such elementals, lose their characteristic salience, and their clinical boundaries become blurred¹⁴⁰.

An illustrative example is provided by the use of self-report psychometric scales that – not surprisingly – are frequently adopted in transdiagnostic research in order to reduce psychopathology to elementals. Some studies measured the severity of “a specific symptom of depression”⁷⁸ in children through self-reported lay statements such as “I am sad once in a while”, “I am sad many times” and “I am sad all the time”⁷⁸. The trivialization of the contextual significance of these statements¹⁴⁴ (there are potentially infinite reasons why one could feel sad), is associated with the deprivation of any phenomenological framework (e.g., subjective appraisal of sadness, level of insight, presence of existential despair, perception of time)^{145,146}. Such a simplification process transforms these statements into self-contained atomic symptoms¹⁴⁷, which become highly blurred and aspecific, in contrast with the claim of the authors that they are specific symptoms. This point is empirically confirmed by the fact that transdiagnostic literature frequently confounded the measurement of psychometric items in non-clinical samples with clinical symptoms and/or established mental disorders.

Third, the highest interest and biggest clinical contribution of transdiagnostic research has been in the development of emotion-focused cognitive behavioral therapy (CBT) protocols (e.g., the Unified Protocol⁵⁸) for anxiety disorders. A recent meta-analysis indicated that these transdiagnostic treatments lack clinical superiority compared to diagnostic-specific treatments¹⁴⁸.

Although these results and the Unified Protocol are presented as a breakthrough, they are again more like a rediscovery. In fact, psychotherapy was broadly transdiagnostic, driven by a psychoanalytical focus on core emotional issues (termed neurotic conflicts) until 1980, when the DSM-III initiated a gradual splitting of psychopathology into psychiatric categories¹⁴⁹. This led to an outpouring of CBT diagnosis-specific protocols, which have allowed CBT to balkanize and dominate the psychotherapeutic landscape for over two decades¹⁴⁹. In this context, some authors have interpreted the Unified Protocol as

the end of the CBT-centric dominion and as the resurgence of psychodynamic psychotherapies¹⁴⁹.

This review has some limitations. Because of the intrinsic heterogeneity in the design, methodology and topic covered, we were unable to perform quantitative analyses. However, our main aim was to provide an extensive, detailed snapshot of transdiagnostic research and not to produce summary estimates. Furthermore, there are most probably other studies that have implicitly employed transdiagnostic approaches which have not been included in this review. However, to deconstruct the core characteristics of transdiagnostic research, we selectively focused on those studies that have explicitly acknowledged transdiagnostic approaches as their core distinctive features in their titles.

In conclusion, transdiagnostic research in psychiatry has, to date, been overenthusiastic and undercritical, heterogeneous, intrinsically incoherent and predominantly focused on a limited subset of mental disorders. It is grounded more in re-discoveries than true innovations, and it is demonstrably affected by conceptual biases. Medicine has always worked by a gradual evolutionary evidence-based process and, before rejecting time-tested and progressively refined concepts that are rooted in clinical tradition^{5,102}, a reliable and valid alternative is needed¹⁵⁰.

To date, transdiagnostic approaches have not delivered the substantial empirical clinical “meat”¹³⁵ required for them to represent a credible paradigm shift⁵. The risk of an acritical endorsement of transdiagnostic approaches would be to throw the baby out with the bathwater¹⁵¹ and be lost in a controversial¹⁰² *mare magnum* of diagnostic uncertainty that may be deleterious for patients and clinicians⁵.

Transdiagnostic research has promised (too) much to psychiatry. It is hoped that this review will guide the next generation of transdiagnostic research to complement, refine and improve – less likely to replace^{5,136} – the way we currently classify and treat mental disorders.

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