What do clinicians treat: diagnoses or symptoms? The incremental validity of a symptom-based, dimensional characterization of emotional disorders in predicting medication prescription patterns

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Monika A Waszczuk[1], Mark Zimmerman[2], Camilo Ruggero[3], Kaiqiao Li[1], Annmarie MacNamara[4], Anna Weinberg[5], Greg Hajcak[6], David Watson[7] and Roman Kotov[1]

[1] Department of Psychiatry, Stony Brook University, Stony Brook, NY, USA

[2] Department of Psychiatry and Human Behavior, Brown Medical School, and Department of Psychiatry, Rhode Island Hospital, Providence, RI, USA

[3] Department of Psychology, University of North Texas, Denton, TX, USA

[4] Department of Psychology, Texas A&M University, College Station, TX, USA

[5]Department of Psychology, McGill University, Montreal, Canada

[6] Department of Psychology, Stony Brook University, Stony Brook, NY, USA

[7] Department of Psychology, University of Notre Dame, Notre Dame, IN, USA

Corresponding author: Roman Kotov, Department of Psychiatry, Stony Brook University, Room 060H, Health Sciences Center, Stony Brook, New York 11794-8790, Phone: 631-638-192, Fax: 631-638-1935, Email: roman.kotov@stonybrook.edu

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Abstract

Background: Although practice guidelines are based on disorders specified in diagnostic manuals, such as the DSM, practitioners appear to follow symptoms when making treatment decisions. Psychiatric medication is generally prescribed in a transdiagnostic manner, further highlighting how symptoms, not diagnoses, often guide clinical practice. A quantitative approach to nosology promises to provide better guidance as it describes psychopathology dimensionally and its organization reflects patterns of covariation among symptoms.

Aim: To investigate whether a quantitative classification of emotional disorders can account for naturalistic medication prescription patterns better than traditional diagnoses.

Methods: Symptom dimensions and DSM diagnoses of emotional disorders, as well as prescribed medications, were assessed using interviews in a psychiatric outpatient sample (N= 318, mean age 42.5 years old, 59% female, 81% Caucasian).

Results: Each diagnosis was associated with prescription of multiple medication classes, and most medications were associated with multiple disorders. This was largely due to heterogeneity of clinical diagnoses, with narrow, homogenous dimensions underpinning diagnoses showing different medication profiles. Symptom dimensions predicted medication prescription better than DSM diagnoses, irrespective of whether this was examined broadly across all conditions, or focused on a specific disorder and medication indicated for it.

Conclusions: Psychiatric medication was prescribed in line with symptoms rather than DSM diagnoses. A quantitative approach to nosology may better reflect treatment planning and be a more effective guide to pharmacotherapy than traditional diagnoses. This adds to a diverse body of evidence about superiority of the quantitative system in practical applications and highlights its potential to improve psychiatric care.

Keywords: Diagnosis; Internalizing; Pharmacology, Treatment planning

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1. Introduction

Pharmacotherapy is a leading treatment option for a range of psychiatric illnesses [1, 2]. The standard of psychiatric care is for clinicians to treat patients based on diagnosis assigned in accordance with diagnostic manuals such as the DSM [3]. Medications are approved by government agencies such as the Food and Drug Administration for the treatment of disorders defined according to these manuals, and practice guidelines published by professional organizations also target these diagnoses [4, 5]. However, evidence suggests that clinicians do not necessarily use or closely adhere to practice guidelines when making diagnoses and treatment decisions [6-9]. Furthermore, studies found that practitioners view symptoms as more informative than the DSM diagnoses during treatment selection [10-13].

One reason why symptoms are considered useful in clinical practice is that pharmacotherapy is transdiagnostic, with medications being effective across different disorders that share common symptoms [12-16]. This is consistent with many medications receiving regulatory approval for the treatment of multiple disorders. For example, selective serotonin reuptake inhibitors were originally regarded as antidepressants, but subsequently were found to be efficacious in treating anxiety disorders and are increasingly used in eating disorders [1, 17]. Similarly, a recent study found that a substantial proportion of patients with anxiety disorders are prescribed antipsychotics [16]. A second reason for considering symptoms in clinical practice is that diagnoses are heterogeneous and disorders can have rather different presentations. There is emerging evidence that practitioners tailor treatment to how a disorder is manifested. For example, depressed patients presenting with largely somatic and pain symptoms are less likely to be treated with antidepressants, as compared to patients who present with cognitive symptoms of depression

[18, 19]. Thus, practitioners often prescribe medication based either on target transdiagnostic symptoms, or individual homogenous symptoms within diagnoses, rather than specific diagnoses.

The DSM and other traditional psychiatric classification systems offer a limited guide to care and do not align with clinical practice and transdiagnostic or symptom-specific treatments. These limitations may be due to these systems lumping patients with very different presentations under the same diagnostic label, being unable to account for complex patterns of comorbidity regularly seen in clinical settings, and missing crucial information about subthreshold symptoms and illness severity [11, 20-24]. Quantitative classifications, such as the Hierarchical Taxonomy Of Psychopathology (HiTOP), have emerged as an alternative to traditional taxonomy that can overcome these limitations, [25]. HiTOP and other quantitative systems can inform intervention research and clinical practice better than traditional taxonomies because they describe psychopathology dimensionally, thereby accounting for illness severity; are organized based on the covariation among symptoms, placing patients with different symptom profiles on different dimensions; and are structured hierarchically, grouping dimensions that co-vary together in larger spectra, which can summarize information about commonalities in treatment response among its constituent conditions [25]. As such, a quantitative nosology might reflect clinical reality better than traditional diagnostic classification. In fact, we have previously demonstrated that symptom dimensions provided almost twice as much information about patients' global functioning than DSM diagnoses [26].

It is unclear, however, whether the HiTOP can account for practitioners' prescription of psychiatric medication in the community. The current study used a large, outpatient sample to investigate whether a quantitative description of disorders would be more informative about medication prescription patterns than traditional diagnoses. We focused on emotional disorders, which consist of a cluster of closely related conditions, including depressive, bipolar and anxiety disorders as well as post-traumatic stress disorder (PTSD) and obsessive–compulsive disorder (OCD) [27-29]. First, we describe the pattern of associations between dimensional symptoms, traditional diagnoses and medication classes. Second, we compared the incremental validity of each classification system in predicting medication prescriptions, using aggregate

information on all emotional psychopathology, thus making no assumption about how medication is prescribed, as well as targeting an individual disorder and a medication specifically indicated for it. In line with the emerging evidence, we hypothesized that symptoms would provide more information about clinicians' medication prescriptions than traditional diagnoses both when looking broadly at prescriptions across all emotional psychopathology, and when medication is matched to the disorder.

2. Methods

2.1. Sample

To encourage a range of severity and diagnoses, participants were recruited from a variety of outpatient sources, including outpatient Psychology and Psychiatry clinics at a public university, local community mental health centers, assisted-living facilities and community programs for the mentally ill, oversampling for OCD and bipolar disorder. There were no other inclusion and exclusion criteria and participants were not selected based on any medication use information. The patient sample size was N=318: 59% female, 81% Caucasian, ranging in age from 18 to 78 years (mean=42.50, SD=13.26). Further details on this sample can be found elsewhere [30]. The study was approved annually by institutional review boards of respective data collection sites and all participants provided written informed consent.

2.2. Measures

Participants completed a revised version of the Interview for Mood and Anxiety Symptoms (IMAS) [26, 31]. The IMAS assesses all DSM-IV and ICD-10 emotional disorder symptoms, as well as items tapping other manifestations of internalizing psychopathology, such as hopelessness and self-harm, in the past month, and does not permit skip-outs. As such, the IMAS contains the most complete set of emotional disorder symptoms of all existing measures and is a quantitative representation of the internalizing domain as recommended by the HiTOP consortium [25]. Each IMAS item was scored by extensively trained lay interviewers on using a 3-point rating scale (*absent*, *subthreshold*, *above threshold*). The item-level inter-

rater reliability (ICC) was excellent (ICC=.90-1.00 (CI: .78-1.00))[1]. The interview allows dimensional scoring of 31 empirical dimensions (homogenous components) underpinning nine DSM-IV emotional disorders plus irritability [26]; these are listed in Table 1. Prior work in the present sample has shown that IMAS components are psychometrically sound and are closely related to corresponding diagnoses [26].

The Structured Clinical Interview for DSM-IV (SCID) [32] was used to assess current DSM-IV Axis I diagnoses. The SCID was administered by five extensively trained master's-level clinicians closely supervised by a licensed clinical psychologist (R.K.). The hierarchical exclusion rules were applied when making diagnoses. The inter-rater reliability based on a subsample of 21 patients was high (K=.70-1.00). Diagnoses used in the current study and their prevalence rates are presented in Table 2a.

Participants were asked to bring their medication bottles or a list of medication to the session, and interviewers recorded medication prescriptions. Medications were not prescribed as part of the current study, and were prescribed by a community provider unrelated to the study. Medications that the patient was using at the time of the interview was coded into one of seven medication classes. Specific medications that were grouped to create medication classes are listed in Table S1. Classes and their frequency of use in the sample are presented in Table 2b.

2.3. Analytic approach

Associations between the IMAS components and DSM-IV diagnoses (SCID), and the medication classes, were examined by calculating polyserial and tetrachoric correlations. The incremental ability of the IMAS

[1] Raters in the reliability substudy were 33 random rater pairs (each interview was blindly rated twice by the primary and secondary rater at different sites, with 18 different raters in total). We investigated specific values rater assigned, thus our reliability analyses used a two-way random with absolute agreement model, and item-level estimates for a single measure are reported.

dimensions and SCID diagnoses to explain medication prescription was evaluated using logistic regression models. Each medication class was a separate outcome. For each medication class, first the SCID diagnoses were included as a predictor, and the incremental validity of including the IMAS dimensional scores as a predictor was tested. Second, the IMAS scores were included as a predictor, and the incremental validity of including the SCID diagnoses as a predictor was tested.

We compared the two approaches to diagnosis in two ways: omnibus and targeted analyses. Omnibus analyses compared all SCID diagnoses and all 31 IMAS components. As such, omnibus analyses were agnostic to practice guidelines, capturing broad links between diagnoses, symptoms and medication classes. Next, in order to directly reflect matches indicated by practice guidelines, such as the American Psychiatric Association [5], targeted analyses only considered one disorder at a time, so that for each medication they compared a relevant SCID diagnosis with IMAS components of this same disorder (e.g. antidepressant prescription was predicted by all components constituting the IMAS depression modules versus diagnosis of current unipolar depression on the SCID). Significant p-values, adjusted for a number of predictors in each block, indicate that including the second predictor significantly improved prediction of medication prescription over and above the first predictor, indicating incremental validity of the second predictor. To illustrate and compare effect sizes, we calculated areas under the curve (AUC) of receiver operating characteristics curve for first predictor, as well as the increment in effect size of adding the second predictor (ΔAUC). All analyses were conducted in SPSS version 22 and SAS version 9.4.

3. Results

Descriptive statistics for IMAS components indicated that outpatients reported a wide range of emotional disorder symptoms (Table 1). Table 2a reports SCID diagnoses: unipolar depression was the most prevalent diagnosis (35%), followed by specific phobia (32%) and GAD (28%), with all disorders showing high enough prevalence to be analyzed reliably (>10%). Antidepressants were the most frequent form of

pharmacotherapy (67% prevalence rate), and under half of the sample was prescribed anxiolytics and antipsychotics (41% and 38%, respectively) (Table 2b).

Overall, associations between diagnoses and medication prescription were modest (Table 3), with the largest association found for bipolar disorder and mood stabilizers (r=.41), which indicates that mood stabilizers were prescribed primarily, but not exclusively, for bipolar disorder. Individual IMAS components often were associated with different medications than the corresponding SCID diagnosis. For example, unipolar depression diagnosis was significantly associated with the prescription of anxiolytics (r=.24) and hypnotics (r=.32), but some IMAS depression components (e.g. dysphoria, anhedonia) were only associated with anxiolytics, as well as antidepressants, while other components (e.g. insomnia) were associated with the hypnotics. Conversely, PTSD diagnosis did not show significant associations with any medication class, but individual IMAS PTSD components were associated with a range of medications: anticonvulsants (e.g., avoidance, r=.18), antidepressants (e.g., numbing, r=.16), anxiolytics (e.g., intrusions, r=.18) and mood stabilizers (hyperarousal, r=.20). Analogous findings were observed for agoraphobia, social anxiety and OCD diagnoses, which did not correlate with any medication classes, while individual, corresponding IMAS components showed associations with various medications. Furthermore, panic disorder diagnosis on the SCID was associated only with anxiolytics (r=.33), which parallels the IMAS physical component of panic (r=.15 with anxiolytics), however the IMAS psychological component of panic was additionally associated with anticonvulsant and antidepressant prescription (r=.19 and .18, respectively). Specific phobia diagnosis was significantly associated with anticonvulsants prescription (r=.26), but each IMAS specific phobia component showed more extensive associations beyond anticonvulsants. Finally, bipolar diagnosis was associated with four medication classes: anticonvulsants (r=.40), antidepressants (r=.30), mood stabilizers (r=.41) and neuroleptics (r=.37), but each of the IMAS components showed different relations with these four medications. For example, none were significantly associated with antidepressants, while overactive cognition was associated with anxiolytics prescription (r=.15). Regardless of whether a diagnostic or dimensional analysis was used, results showed that most

psychiatric medications were prescribed in transdiagnostic manner, linking to more than one diagnosis or homogenous symptom component.

In the omnibus analyses, the IMAS components jointly were better at explaining medication prescription than all SCID diagnoses combined (Table 4). Specifically, the addition of the 31 IMAS components provided significant incremental information about the prescription of antidepressants, mood stabilizers, neuroleptics and stimulants, over and above the prediction contributed by the SCID diagnoses. In contrast, the SCID diagnoses only predicted anticonvulsants and hypnotics over and above the prediction made by the IMAS components. On average across all medications, IMAS components increased prediction above SCID by ΔAUC=.14 (SD=.05, range=.08-.24), while SCID diagnoses increased predictions above IMAS by ΔAUC=.04 (SD=.04, range=.01-.12).

Similarly, in the targeted analyses, when focusing on matching disorders and medication classes, the IMAS components again predicted medication prescription better than the corresponding SCID diagnoses (Table 5). Specifically, the addition of the IMAS components provided significant incremental information over and above the prediction from the corresponding SCID diagnoses in the prescription of antidepressants in depression, social anxiety and OCD; anxiolytics in GAD, agoraphobia and specific phobia; hypnotics in GAD; and mood stabilizers in mania. Conversely, SCID diagnoses predicted medication prescription over and above the corresponding IMAS diagnoses in just three cases: antidepressants in GAD; anxiolytics in panic disorder; and hypnotics in depression. On average across all disorder-medication class pairs, IMAS components increased prediction above SCID diagnoses by ΔAUC=.08 (SD=.03, range=.04-.13), while SCID diagnoses increased prediction above IMAS by ΔAUC=.01 (SD=.01, range=.00-.03).

4. Discussion

The current study is the first to empirically investigate whether medication prescription is more closely associated with DSM diagnoses or dimensions of quantitative nosology, indicating that the latter aligns

better with clinical treatment planning. We found that homogenous symptoms that constitute emotional disorders often show differential and specific associations with medication prescription relative to the diagnosis as a whole. Moreover, dimensional approach based on symptom components more often was better at explaining prescribing practices than diagnoses. Thus, quantitative classification appears to better reflect current treatment practices and may prove to be a more effective guide to pharmacotherapy than traditional diagnoses, although this promise has to be verified in future research. Taken together, the current analyses indicate that providers tend to prescribe medications in line with symptoms rather than based on diagnoses.

Diagnoses were frequently associated with prescription of multiple medication classes. This complexity was likely driven in part by the heterogeneity of these diagnoses, as symptoms underpinning diagnoses tended to show different medication profiles. For example, the physical component of panic was associated only with anxiolytics prescription, probably because this medication targets physiological fear responses related to the bodily symptoms that characterize panic attacks. Conversely, the psychological component of panic was additionally associated with anticonvulsant and antidepressant prescription, as these medications are more likely to alter a patient's mood and processing biases associated with panic disorder, such as worries about future panic attacks and maladaptive beliefs about their consequences. Furthermore, most of the examined medications were transdiagnostic, as they were associated with symptoms of different disorders. This is in line with the view that psychopharmacology is transdiagnostic and medications operate broadly on a number of disorders [12-16]. It also reflects the realities of everyday clinical practice as reported by providers [6-9]. Medication use was only moderately associated with diagnoses and symptoms, most likely due to medication efficacy, other available treatments such as psychotherapy, and imperfect compliance.

We found that symptoms predicted medication prescription better than DSM diagnoses, irrespective of whether we looked broadly across all conditions, or focused on a specific disorder and medication indicated for it. The only notable exception was SCID contribution to predicting hypnotic medication prescriptions,

possibly because hypnotics are generally used to treat insomnia symptoms in more severe and impaired patients [33-35], which might not be captured as well by the IMAS. Nonetheless, overall results demonstrate the incremental predictive power of components against a clinical diagnostic interview, providing novel evidence that homogeneous components are better concurrent predictors of pharmacotherapy than categorical diagnoses. These results reinforce our previous findings that IMAS components provided almost twice as much information on patients' global functioning as DSM diagnoses [26]. These results were particularly impressive given that impairment is explicitly included in diagnoses but not in the IMAS components. Taken together, the emerging evidence suggests that quantitative dimensions are more informative about patients than are traditional diagnoses.

These results were obtained using dimensional components that were empirically derived using a bottom-up approach, from a very comprehensive pool of individual signs and symptoms of emotional disorders captured by the IMAS. The current analyses inform the ongoing debate between categorical and dimensional approaches to psychiatric classification [25, 36-42], supporting quantitative nosologies, including the HiTOP [25]. They can be modelled with tools such as the IMAS, which aim to identify transdiagnostic and psychometrically sound symptom dimensions, which in turn can provide a systematic list of targets for pharmacotherapy. Growing evidence indicates that quantitative nosology may be a more valid description of psychopathology with regard to genetic and environmental risk factors, neural abnormalities, illness course, and functional impairment [25]; in particular the present study suggests that it also may be informative in understanding patterns of treatment provision. The advantage of hierarchical approaches is that they resolve problems of heterogeneity and comorbidity, allowing to focus on symptoms within, as well as across, diagnostic boundaries, providing a guide for clinician's assessment approaches and consequently medication prescriptions that reflect the empirical organization of psychopathology [43]. From a treatment development perspective, this can be informative for developing and delivering treatment across diagnostic boundaries, as illustrated by transdiagnostic cognitive therapies [44, 45]. Specifically, the

current results illustrate that community psychiatrists already prescribe medication in this way rather than following diagnostic categories.

4.1. Limitations

Strengths of the current study include a comprehensive, dimensional interview measure that was used alongside a structured diagnostic interview to understand medication prescription patterns, in a large outpatient sample. However, two limitations are notable. First, we did not assess symptoms and diagnoses at treatment entry, or for how long patients were using the prescribed medications, as the sample was composed of already established patients. Thus, study assessments may reflect symptoms that are refractory to treatment. Such symptoms are fairly common, as internalizing psychopathology often is chronic and recurrent, with many patients not responding to medication [46, 47]. Importantly, any treatment effects would decrease symptoms and thus weaken the link between medication prescription and symptom/current diagnosis, but the associations that we observed emerged despite treatment effects. The current study is the first to explore the link between different symptoms versus diagnoses and medication prescription, and future studies should build on this effort by assessing patients at first contact with services.

Second, the current study focused only on internalizing psychopathology related to emotional disorders. It is possible that certain medications have been prescribed for other psychiatric problems, e.g. anticonvulsants for comorbid psychotic disorders. However, this would have weakened the explanatory ability of the IMAS, and as such it is even more impressive how informative the measure was, despite being limited to emotional disorders. Nevertheless, future research should focus on a wider range of symptoms as well as medication classes to investigate this issue further.

Finally, we were not able to study practitioners' decision-making directly, therefore cannot determine whether they consciously disregarded diagnoses and evaluated symptom profiles instead, or identified most important and impairing symptoms as part of the standard diagnostic assessment, and matched these

symptoms to the most optimal medication class. Future research should explore processes underpinning practitioners' decision-making.

4.2. Conclusions

The current study demonstrated that psychiatric medication is prescribed according to individual symptoms comprising disorders rather than according to DSM diagnoses, raising concerns about the clinical utility of traditional diagnoses. In contrast, a quantitative approach to nosology was able to explain medication prescription much better. This adds to a diverse body of evidence about superiority of a quantitative system in practical applications and highlights its potential to improve psychiatric care.

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Tables

Table 1 – Descriptive statistics of IMAS components

Module	Component	Range	Mean	SD	α
Depression	Dysphoria	0-10	4.81	3.54	.79
	Anhedonia	0-12	6.51	4.18	.81
	Lassitude	0-10	6.12	3.67	.84
	Suicidality	0-8	2.01	2.18	.64
	Agitation	0-10	4.15	3.46	.78
	Retardation	0-10	2.60	2.91	.72
	Appetite loss	0-6	2.89	2.46	.78
	Insomnia	0-8	4.40	2.96	.75
GAD	Total	0-18	9.34	5.77	.84
PTSD	Intrusions	0-8	5.13	2.70	.74
	Avoidance	0-6	3.02	2.39	.74
	Hyperarousal	0-12	5.01	4.01	.80
	Numbing	0-6	2.46	2.30	.76
	Dissociation	0-6	1.13	1.59	.58
Panic	Physical	0-18	7.90	5.27	.79
	Psychological	0-14	3.80	3.73	.73
Social anxiety	Interactive	0-6	2.21	2.11	.70
	Performance	0-12	5.23	3.80	.80
Agoraphobia	Public	0-12	3.46	3.65	.83
	Enclosure	0-12	4.25	3.75	.79
Specific phobia	Animal	0-6	1.58	2.00	.71
	Situational	0-6	2.47	2.09	.62
	Blood	0-8	1.49	2.02	.63
OCD	Cleaning	0-10	1.15	2.37	.82
	Ritual	0-12	1.61	2.90	.82
	Checking	0-8	2.27	2.90	.84
Mania	Euphoric activation	0-12	1.89	3.01	.79
	Hyperactive cognition	0-8	2.98	2.91	.80
	Reckless overconfidence	0-8	0.63	1.51	.69
Obsessions	Total	0-12	3.06	3.28	.74
Irritability	Total	0-12	5.42	4.48	.87

Note: SD – standard deviation; α – Cronbach alpha; GAD – generalized anxiety disorder; PTSD – posttraumatic stress disorder; OCD – obsessive compulsive disorder

Table 2 – Prevalence of SCID diagnoses and medication prescription

		N	%
(a) SCID diagnosis	Unipolar depression	110	35
	GAD	89	28
	PTSD	52	16
	Panic disorder	82	26
	Social anxiety	79	25
	Agoraphobia	69	22
	Specific phobia	103	32
	OCD	42	13
	Bipolar disorder	51	16
(b) Medications	Anticonvulsants	70	22
	Antidepressants	212	67
	Anxiolytics	129	41
	Hypnotics	24	08
	Mood stabilizers	65	21
	Neuroleptics	120	38
	Stimulants	27	09

Note: GAD – generalized anxiety disorder; PTSD – posttraumatic stress disorder; OCD – obsessive compulsive disorder.

Unipolar depression consists of major depressive disorder and dysthymia.

Both diagnoses and medications are dichotomous variables, scored as 0 (absent) versus 1 (present).

Specific medications that constitute medication classes are listed in Table S1.

Additional diagnoses in this sample were substance use disorder (N=62, 20%) and psychosis (N=34, 11%).

Table 3 – Correlations between medication classes and SCID diagnoses and IMAS components.

		Anticonvulsants	Antidepressants	Anxiolytics	Hypnotics	Mood stabilizers	Neuroleptics	Stimulants
SCID diagnosis								
Unipolar depression		-.16	.13	.26	.32	-.24	-.15	-.08
GAD		.16	.25	.23	.31	.06	-.02	.29
PTSD		.22	.08	-.04	-.09	.18	.04	.05
Panic disorder		.00	.11	.33	-.01	.04	-.03	.06
Social anxiety		.12	-.02	.02	-.24	.10	.18	.02
Agoraphobia		.13	.00	.19	-.02	.14	.08	-.14
Specific phobia		.26	.03	.09	.19	.15	.11	.07
OCD		.04	.21	.18	-.02	.02	.15	.04
Bipolar disorder		.40	.30	.04	.17	.41	.37	.13
IMAS module	**IMAS component**							
Depression	Dysphoria	.14	.22	.15	.05	.06	-.01	-.01
	Anhedonia	.02	.24	.20	.09	-.09	.10	-.08
	Lassitude	.05	.31	.23	.17	-.07	-.01	.04
	Suicidality	.08	.11	.14	.12	.10	-.02	-.03
	Agitation	.14	.08	.07	.10	.13	.20	.15
	Retardation	.06	.19	.09	.10	-.04	.00	.04
	Appetite loss	.11	.20	.05	.21	.02	.11	.22
	Insomnia	.07	.07	.10	.24	-.01	.15	.01
GAD	GAD	.17	.18	.21	.28	.11	.11	.07
PTSD	Intrusions	.20	.19	.18	.02	.16	.14	.01
	Avoidance	.18	.10	.06	.05	.11	.06	-.09
	Hyperarousal	.25	.17	.15	.17	.20	.11	-.03
	Numbing	.04	.16	.09	.09	.00	.10	-.15
	Dissociation	.13	.12	.06	.14	.07	.11	.14
Panic disorder	Physical	.11	.18	.15	.14	.07	.03	.01
	Psychological	.19	.18	.15	.13	.14	.12	.00
Social anxiety	Interactive	.25	.18	.12	.13	.17	.22	.03
	Performance	.17	.17	.18	.11	.18	.13	-.02
Agoraphobia	Public	.21	.13	.21	.11	.18	.20	-.21
	Enclosure	.11	.14	.21	.11	.06	.16	-.01
Specific phobia	Animal	.26	.15	.15	.15	.19	.28	-.06
	Situational	.21	.10	.18	.12	.15	.17	-.15
	Blood	.15	-.02	-.04	.05	.17	.12	-.27
OCD	Cleaning	.15	.05	.17	.04	.11	.14	-.20
	Ritual	.09	.27	.16	.08	.05	.24	.05
	Checking	.09	.17	.19	.05	.09	.12	.08
Bipolar disorder (mania)	Euphoric activation	.22	.09	.00	.07	.26	.21	-.03
	Hyperactive cognition	.19	.10	.15	.19	.21	.10	.06
	Reckless overconfidence	.28	.03	-.03	.10	.27	.20	.00
Obsessions	Obsessions	.21	.17	.08	.03	.24	.10	-.05
Irritability	Irritability	.13	.03	.15	.07	.14	.03	.07

Note: GAD – generalized anxiety disorder; PTSD – posttraumatic stress disorder; OCD – obsessive compulsive disorder. Significant correlations at $p<.05$ are shaded

Table 4 – Predicting medication classes from total IMAS scores and total number of SCID diagnoses

Medication	Predictor 1	AUC	Predictor 2	ΔAUC	-2[L0-L1]	DF	p-value
Anticonvulsants	SCID	.695	IMAS	.115	39.03	31	.153
	IMAS	.765	SCID	.045	17.87	9	**.037**
Antidepressants	SCID	.651	IMAS	.134	49.86	31	**.017**
	IMAS	.755	SCID	.030	16.89	9	.050
Anxiolytics	SCID	.658	IMAS	.098	37.05	31	.210
	IMAS	.739	SCID	.017	12.22	9	.201
Hypnotics	SCID	.780	IMAS	.084	21.63	31	.894
	IMAS	.745	SCID	.119	26.91	9	**.001**
Mood stabilizers	SCID	.651	IMAS	.164	46.27	31	**.038**
	IMAS	.789	SCID	.026	14.38	9	.109
Neuroleptics	SCID	.647	IMAS	.129	55.74	31	**.004**
	IMAS	.766	SCID	.010	10.83	9	.288
Stimulants	SCID	.648	IMAS	.243	48.60	31	**.023**
	IMAS	.860	SCID	.031	11.10	9	.269

Note: AUC-area under the ROC curve for Predictor 1; ΔAUC –difference between areas under the ROC curve for Predictors 1 vs Predictors 1 and 2 jointly; 2[L0-L1] – difference in -2 log likelihood

P-value is adjusted to the number of predictors used per block.

Table 5 – Predicting medication classes from IMAS and SCID – analyses focused on matching disorders and medication classes.

Disorder	Medication	Predictor 1	AUC	Predictor 2	ΔAUC	-2[L0-L1]	DF	p-value
Depression	Antidepressants	SCID	.537	IMAS	.131	19.720	8	**.011**
		IMAS	.667	SCID	.001	.273	1	.601
	Hypnotics	SCID	.628	IMAS	.073	8.568	8	.380
		IMAS	.688	SCID	.013	4.804	1	**.028**
GAD	Antidepressants	SCID	.573	IMAS	.036	3.32	1	.068
		IMAS	.589	SCID	.020	4.59	1	**.032**
	Anxiolytics	SCID	.562	IMAS	.048	5.42	1	**.020**
		IMAS	.593	SCID	.017	2.63	1	.105
	Hypnotics	SCID	.619	IMAS	.067	4.06	1	**.044**
		IMAS	.655	SCID	.031	2.89	1	.089
PTSD	Antidepressants	SCID	.514	IMAS	.102	9.99	5	.076
		IMAS	.613	SCID	.003	.14	1	.708
	Anxiolytics	SCID	.513	IMAS	.087	8.67	5	.123
		IMAS	.584	SCID	.016	1.98	1	.160
	Hypnotics	SCID	.524	IMAS	.087	4.41	5	.492
		IMAS	.588	SCID	.023	1.23	1	.267
Panic disorder	Anxiolytics	SCID	.585	IMAS	.037	2.15	2	.341
		IMAS	.589	SCID	.033	6.86	1	**.009**
Social anxiety	Antidepressants	SCID	.504	IMAS	.103	8.36	2	**.015**
		IMAS	.592	SCID	.015	1.39	1	.239
Agoraphobia	Antidepressants	SCID	.501	IMAS	.094	5.70	2	.058
		IMAS	.584	SCID	.011	1.31	1	.253
	Anxiolytics	SCID	.547	IMAS	.068	8.48	2	**.014**
		IMAS	.614	SCID	.001	.16	1	.689
Specific phobia	Antidepressants	SCID	.506	IMAS	.090	7.37	3	.061
		IMAS	.595	SCID	.001	.49	1	.483
	Anxiolytics	SCID	.525	IMAS	.101	11.63	3	**.009**
		IMAS	.627	SCID	.000	.17	1	.677
OCD	Antidepressants	SCID	.535	IMAS	.074	10.70	3	**.013**
		IMAS	.607	SCID	.002	.38	1	.538
Mania	Mood stabilizers	SCID	.570	IMAS	.093	10.52	3	**.015**
		IMAS	.644	SCID	.019	3.16	1	.075

Note: AUC-area under the ROC curve for Predictor 1; ΔAUC –difference between areas under the ROC curve for Predictors 1 vs Predictors 1 and 2 jointly; 2[L0-L1] – difference in -2 log likelihood; GAD – generalized anxiety disorder; PTSD – posttraumatic stress disorder; OCD – obsessive compulsive disorder.

For each disorder module, a corresponding SCID diagnosis, and all corresponding IMAS components (see Table 1), were included in the analysis. For example, for depression module analyses, unipolar depression was included as SCID block, and all IMAS depression components were included in the IMAS lock: dysphoria, anhedonia, lassitude, suicidality, agitation, retardation, appetite loss and insomnia. The number of IMAS components is reflected in the DF value, and p-value is adjusted to the number of predictors used per block.

The matching between medication classes and disorders reflects recommendations from practice guidelines [5].

Supplementary Materials

Table S1 – Specific medications that constitute medication classes.

Medication class	Generic drug name
Anxiolytics	Droperidol
	Chlordiazepoxide
	Diazepam
	Oxazepam
	Meprobamate
	Chlordiazepoxide
	Clidinium bromide with librium
	Hydroxyzine hydrochloride
	Hydroxyzine pamoate
	Lorazepam
	Alprazolam
	Clorazepate dipotassium
	Buspirone
	Halazepam
	Chlormezanone
Anticonvulsants	Carbamazepine
	Clonazepam
	Phenytoin sodium
	Valproate sodium
	Divalproex sodium
	Valproic acid
	Gabapentin
	Tiagabine
	Topiramate
	Oxcarbazepine
	Lamotrigine
	Methsuximide
	Fosphenytoin sodium
	Felbamate
	Cyclobenzaprine
	Mephenytoin
	Phensuximide
	Primidone
	Ethotoin
	Trimethadione
	Ethosuximide
	Zonisamide

	Levetiracetam
Antidepressants	Imipramine hydrochloride
	Imipramine pamoate
	Amitriptyline
	Nortriptyline hydrochloride
	Desipramine hydrochloride
	Doxepin hydrochloride
	Clomipramine hydrochloride
	Phenelzine sulfate
	Anti-depressant, not specified
	Paroxetine
	Maprotiline hydrochloride
	Trazodone hydrochloride
	Amoxapine
	Tranylcypromine sulfate
	Isocarboxazid
	Trimipramine maleate
	Protriptyline hydrochloride
	Fluoxetine hydrochloride
	Bupropion hydrochloride
	Bupropion
	Sertraline hydrochloride
	Venlafaxine
	Fluvoxamine maleate
	Nefazodone
	Mirtazapine
	Citalopram
	Duloxetine
	Escitalopram oxalate
	Pristiq
Hypnotics	Triazolam
	Temazepam
	Chloral hydrate
	Flurazepam hydrochloride
	Phenobarbital sodium
	Diphenhydramine
	Zolpidem tartrate
	Amobarbital sodium
	Eszopiclone
	Zaleplon
	Ramelteon
	Quazepam

	Doxylamine succinate
	Ethchlorvynol
	Estazolam
	Midazolam hydrochloride
	Clonidine
Mood stabilizers	Lithium carbonate
	Lithium
	Carbamazepine
	Valproate sodium
	Divalproex sodium
	Valproic acid
	Oxcarbazepine
	Lamotrigine
Neuroleptics	Chlorpromazine
	Trifluoperazine
	Perphenazine
	Fluphenazine
	Fluphenazine decanoate
	Thioridazine
	Prochlorperazine
	Molindone
	Mesoridazine
	Acetophenazine
	Triflupromazine
	Phenothiazine
	Chlorprothixene
	Thiothixene
	Haloperidol
	Anti-psychotic, not specified
	Loxapine
	Haloperidol
	Pimozide
	Clozapine
	Risperidone
	Olanzapine
	Quetiapine
	Ziprasidone
Stimulants	Methylphenidate
	Amphet asp/amphet/d-amphet
	Amphetamine sulfate
	Fenfluramine hydrochloride

Dexfenfluramine
Modafinil
Atomoxetine
Phentermine hydrochloride
Pemoline
D-amphetamine sulfate
Dimethylaminoethanol
Methamphetamine
D-amphetamine sulfate
Diethylpropion hydrochloride
Phentermine hydrochloride
Phentermine resin
Phentermine hydrochloride
Diethylpropion hydrochloride
Mazindol
Phentermine hydrochloride
Diethylpropion hydrochloride
Phentermine hydrochloride
Methylphenidate