With the pandemic continuing to evolve, it will be critical to keep on answering key questions about the role of SSRIs in the treatment of acute COVID-19 illness. What is the best dose and timing of fluvoxamine, and how effective is it in combination with other treatments against COVID-19 (such as monoclonal antibodies)? Is fluoxetine, which has lower S1R affinity compared to fluvoxamine but has shown promise in preclinical and observational studies, also an effective treatment, considering that it is more widely available and easier to use? And what are the best treatments for neuropsychiatric manifestations of long COVID, and in which patients?

Given that many psychotropics are now appreciated to have widespread molecular, cellular and physiological effects, including anti-inflammatory, neuroprotective and cardioprotective, and antiproliferative, we can expect that lessons learned in testing these medications for COVID-19 will be important for other drug repurposing efforts, ranging from infectious and inflammatory diseases, to neurodegenerative diseases such as Alzheimer's disease, and cancer[9].

Eric J. Lenze[1], Angela M. Reiersen[1], Paramala J. Santosh[2]
[1]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA; [2]Department of Child and Adolescent Psychiatry, King's College London, London, UK

1. Sukhatme VP, Reiersen AM, Vayttaden SJ et al. Front Pharmacol 2021;12:652688.
2. Lenze EJ, Mattar C, Zorumski CF et al. JAMA 2020;324:2292-300.
3. Reis G, Dos Santos Moreira-Silva EA, Medeiros Silva DC et al. Lancet Glob Health 2022;10:e42-51.
4. Hoertel N, Sanchez-Rico M, Gulbins E et al. Clin Pharmacol Ther 2021;110:1498-511.
5. Clelland CL, Ramiah K, Steinberg L et al. BJPsych Open 2021;8:e6.
6. Oskotsky T, Maric I, Tang A et al. JAMA Netw Open 2021;4:e2133090.
7. Davis HE, Assaf GS, McCorkell L et al. EClinicalMedicine 2021;38:101019.
8. Boldrini M, Canoll PD, Klein RS. JAMA Psychiatry 2021;78:682-3.
9. Nykamp MJ, Zorumski CF, Reiersen AM et al. Pharmacopsychiatry 2022;55:24-9.

DOI:10.1002/wps.20983

Empirical severity benchmarks for obsessive-compulsive disorder across the lifespan

Obsessive-compulsive disorder (OCD) is characterized by time-consuming obsessions and compulsions that cause distress and impairment[1]. It can affect people of all ages and has a lifetime prevalence of 1-2%[2,3]. The severity of OCD is assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[4,5]. Despite extensive use of this scale for several decades, there is still uncertainty about what constitutes subclinical, mild, moderate and severe OCD.

To our knowledge, only two previous studies have attempted to calculate Y-BOCS severity benchmarks[6,7], yielding inconsistent results. Both studies were underpowered, as they included a small number of individuals in the lower and higher severity ends of the distribution, and only recruited participants from a single country or single age group.

To provide definitive severity benchmarks for OCD that can be used across the lifespan and different cultures, large multinational samples are required. Empirically supported severity benchmarks would facilitate clinical decision making, trial design, and communication between professionals, the patient community and policy makers.

The OCD Severity Benchmark Consortium collected Y-BOCS data from 5,140 individuals with a lifetime diagnosis of OCD from Sweden, Brazil, South Africa, US and India (47/53% male/female, 21/79% children/adults, age range: 5-82 years). Data were collected as part of various research projects; each of the individual studies was approved by the local ethical review board, and all participants provided written informed consent (or assent if under the age of 18) for participation.

Data from four countries were used for model development (Sweden, N=1,697; Brazil, N=936; South Africa, N=552; US, N=599; total N=3,784). Data from India (N=1,356) were used for external model validation. Experienced clinicians administered the child or adult versions of the Y-BOCS, and the Clinical Global Impression-Severity (CGI-S) scale, which constituted the benchmark measure in this study. The CGI-S is a single-item measure (score range: 1-7) of global disorder severity (in this case, OCD) that synthesizes all available information about the patient, including but not limited to current symptoms, impairment and general function[8].

An ordinal logistic regression model was trained in 80% of the data from the four countries used for model development (training dataset, N=3,027) and accuracy of the best severity benchmarks was separately evaluated in the remaining 20% of these data (holdout dataset, N=757) and in the external dataset from India. To compensate for the unevenly distributed severity classes during model development, oversampling was performed by drawing 2,500 samples, with replacement, from each severity class.

A large proportion of all participants in the training and holdout datasets were classified as having moderately severe OCD (CGI-S score of 4 or 5; N=2,577, 68.1%). The next most common severity class was mild OCD (CGI-S score of 3; N=580, 15.3%), followed by severe OCD (CGI-S score of 6 or 7; N=408, 10.8%), and subclinical OCD (CGI-S score of 1 or 2; N=219, 5.8%). In the external Indian dataset, moderately severe OCD was most common (N=502, 37.0%), followed by severe OCD (N=352, 26.0%), mild OCD (N=341, 25.1%), and subclinical OCD (N=161, 11.9%).

Spearman's rho indicated that severity class and Y-BOCS severity correlated moderately to strongly ($r=.61$, $p<0.00001$). An ordinal regression model with severity class as the dependent

variable and Y-BOCS score as the independent variable was statistically significant ($p<0.00001$), and the Nagelkerke's pseudo R^2 estimate of the model indicated that variation in Y-BOCS severity accounted for 47.9% of the variation in the CGI-S severity classification.

Using the training dataset, the ordinal regression model indicated that subclinical OCD corresponded to scores of 0-13 points on the Y-BOCS, mild OCD to 14-21 points, moderate OCD to 22-29 points, and severe OCD to 30-40 points. These benchmarks classified individuals in the holdout and external datasets with modest accuracy (holdout: 57%, external: 55%). When we allowed the severity levels to overlap three points, accuracy increased to 79% in both datasets. This indicates that roughly half of misclassifications appeared around the breakpoints, which is expected since OCD severity is a dimensional construct[9].

A Y-BOCS score of 14 points separated clinical from subclinical individuals with excellent sensitivity (holdout: 94%, external: 91%) and adequate specificity (62% and 78%, respectively). The positive predictive value (PPV), or proportion of participants classified as having clinical OCD who truly had clinical OCD, was excellent in both the holdout (98%) and the external (99%) datasets. The negative predictive value (NPV), or proportion of participants classified as having subclinical OCD that truly had subclinical OCD, was lower (40% and 28%, respectively).

Interestingly, 14 is two points lower than the 16 points that are typically used as inclusion criteria for entry in most clinical trials of OCD. To the best of our knowledge, the 16-point cut-off used in clinical trials is arbitrary and could be revised in light of the current findings.

A Y-BOCS score of 30 points separated severe from non-severe OCD with adequate sensitivity (holdout: 70%, external: 82%), good specificity (89% and 84%), a low PPV (43% and 49%), and a high NPV (96% and 96%). Thus, a score of 30 may work best to screen out individuals with severe OCD rather than identifying a pure group above a certain severity level. Therefore, decisions to ration access to certain intensive specialist treatments to individuals with Y-BOCS scores above 30 should be questioned.

Largely consistent classification performance (total accuracy, sensitivity, specificity, PPV and NPV) of the general benchmarks was found across countries, genders and age groups, and overall benchmarks were similar in accuracy to subgroup-derived benchmarks (i.e., benchmarks that were based on only subgroups of the training dataset). This indicates that the provided benchmarks are largely invariant across national settings and individuals, and can therefore be used globally and across the lifespan.

In summary, we provide the field with empirically derived Y-BOCS severity benchmarks across the lifespan which will be useful in research and clinical settings (subclinical OCD: 0-13 points; mild OCD: 14-21 points; moderate OCD: 22-29 points; severe OCD: 30-40 points).

However, due to the modest accuracy of the classifications, we caution against the exclusive use of these benchmarks to guide important clinical decisions regarding individual patients, such as offering access to specialist treatment. Other relevant variables should be used, together with Y-BOCS scores, to guide clinical decision making and resource allocation, such as duration of the disorder, time without adequate treatment, psychiatric and somatic comorbidities, family accommodation, socioeconomic circumstances, and personal treatment history.

Matti Cervin[1], OCD Severity Benchmark Consortium, David Mataix-Cols[2,3]

[1]Department of Clinical Sciences Lund, Lund University, Lund, Sweden; [2]Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden; [3]Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden

Further information on this study can be found at https://osf.io/yu3xd/. The OCD Severity Benchmark Consortium includes, in addition to the authors, S.S. Arumugham (India), C. Lochner (South Africa), O. Cervin (Sweden), J.J. Crowley (US and Sweden), M.C. do Rosário (Brazil), T.S. Jaisoorya (India), M.C. Batistuzzo (Brazil), J. Wallert (Sweden), M.A. de Mathis (Brazil), S. Balachander (India), W.K. Goodman (US), D.L.C. Costa (Brazil), E. de Schipper (Sweden), S. Wilhelm (US), A. Palo (US), J.C. Narayanaswamy (India), R.G. Shavitt (Brazil), Y.A. Ferrão (Brazil), Y. Omar (US), J. Boberg (Sweden), T.K. Murphy (US), A. Tendler (US and Israel), E. Ivanova (Sweden), S.C. Schneider (US), D.A. Geller (US), C. Rück (Sweden), D.J. Stein (South Africa), E.C. Miguel (Brazil), E.A. Storch (US) and Y.C.J. Reddy (India).

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Arlington: American Psychiatric Association, 2013.
2. Fawcett EJ, Power H, Fawcett JM. J Clin Psychiatry 2020;81:19r13085.
3. Ruscio AM, Stein DJ, Chiu WT et al. Mol Psychiatry 2010;15:53-63.
4. Scahill L, Riddle MA, McSwiggin-Hardin M et al. J Am Acad Child Adolesc Psychiatry 1997;36:844-52.
5. Goodman W, Price L, Rasmussen S et al. Arch Gen Psychiatry 1989;46:1006-11.
6. Storch EA, De Nadai AS, Do Rosário MC et al. Compr Psychiatry 2015;63:30-5.
7. Lewin AB, Piacentini J, De Nadai AS et al. Psychol Assess 2014;26:679.
8. National Insitute of Mental Health. ECDEU assessment manual for psychopharmacology. Washington: US Department of Health, Education, and Welfare, 1976.
9. Fullana MA, Mataix-Cols D, Caspi A et al. Am J Psychiatry 2009;166:329-36.

DOI:10.1002/wps.20984

Twelve rather than three waves of cognitive behavior therapy allow a personalized treatment

The expression "third-wave cognitive behavior therapy (CBT)" has become a trade mark. It has been argued that it represents a new "process-based therapy", which targets the relationship of the client to his/her own experiences in a transdiagnostic approach[1]. However, a look at both history and present practice suggests that modern CBT encompasses at least a dozen "waves", or basic theoretical concepts and treatment approaches. We summarize them herein.

First wave: classical learning theory. The development of CBT started with classical learning theory, including conditioning, habituation and systematic desensitization[2]. Since then, dozens of technical variations of "exposure treatments" have been developed