

**Title**

Antidepressant Prescription Patterns and Clinical Correlates within Psychiatry Treatment Settings in Asia: A Cross Sectional REAP Consortium Study (REAP-AD3)

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**Abstract**

Research on Asian Psychotropic prescription study (REAP) is a consortium consisting of psychiatrists, pharmacologists, epidemiologists, and researchers in Asia. Since 2001, REAP has completed four surveys on antipsychotics (schizophrenia) prescription patterns, two on antidepressants (major depression), and one on mood stabilizers (affective disorder). The cumulative research has involved more than 600 psychiatrists, more than 100 psychiatric medical units, and 13,500 patients in the data analysis of REAP. So far, more than 90 research reports have been published in international journals. Major depressive disorder is a common mental disorder that affects approximately 280 million people worldwide. World Health Organization research data have shown that the number of global major depressive illnesses increased from 172 million in 1990 to 258 million in 2017, an increase of nearly 50% during this period. Given the rising incidence of major depressive disorder, it is not surprising that prescription consumption of antidepressants is increasing year by year. With the development of some new antidepressants with different pharmacological mechanisms, clinical prescriptions and treatment models are gradually used in other mental disorders besides major depression. At present, many western countries have conducted relevant research on this issue. In Asia, we hope to understand the changes in the use of antidepressants in these areas through this survey. The results of this study can provide clinicians the information on antidepressant prescription patterns in various countries, and references for policy formulation by competent authorities. Furthermore, as the COVID-19 pandemic is a socially important issue in every country, and Hikikomori, a pathological condition of social withdrawal is getting popular in modern society, related information on study subjects will also be collected.

## Background

Depression is a common mental health disorder and it affects approximately 280 million people in the world (WHO) (2022). The number of incident cases of depression worldwide has been reported to increase from 172 million in 1990 to 258 million in 2017, representing an increase of 49.86% (Liu et al., 2020). Given the increasing rate of depression, it is not surprising that the consumption of antidepressants (ADs) has grown over the years (Lalji et al., 2021, Soleymani et al., 2018, Luo et al., 2020). The patterns of antidepressant use are changing and have been studied in many western countries (Arias et al., 2010, Guaiana et al., 2005, Olie et al., 2002, van Marwijk et al., 2001). It is important to understand the changing patterns of antidepressant use, as it helps shape optimal antidepressant prescription and future policy making.

The Research in East Asia Psychotropic Prescription Patterns on Antidepressants (REAP-AD) had worked collaboratively in 2003 (REAP-AD1) and 2013 (REAP-AD2) to study the prescription patterns of antidepressant in Asia (Uchida et al., 2007, Chee et al., 2015). The REAP-AD studies found that the selective serotonin reuptake inhibitors were the most common antidepressant prescribed in the participating centers and prescription of newer generation antidepressants had increased in 2013 survey; on the contrary, prescription of tricyclic antidepressants had reduced. Concomitant use with other psychotropics (polypharmacy) is another important issue. Compared with the first survey, the second survey showed that among individuals with AD prescriptions, concomitant use of anxiolytics (including sedative-hypnotics) decreased in patients with mood disorders (aOR, 0.34 [0.27-0.42];  $P < 0.001$ ) and anxiety disorders (aOR, 0.43 [0.27-0.67];  $P < 0.001$ ). In contrast, concomitant use of antipsychotics in patients with mood disorders increased (aOR, 1.43 [1.15-1.77];  $P = 0.001$ ), and concomitant use of mood stabilizers in patients with psychotic disorders also increased (aOR, 3.49 [1.50-8.14];  $P = 0.004$ ) (Huang et al., 2018).

Approximately 10 years after the last collaborative study, REAP-AD study group will conduct another study (REAP-AD3) to reexamine the prescription patterns of antidepressants in Asia. With the introduction of newer generation antidepressants, update of antidepressant prescribing guidelines, impact of COVID-19 pandemic and new

clinical conditions, such as Hikikomori, we anticipate a drastic change in the pharmaco-epidemiological patterns of antidepressant prescription over time.

Antidepressants are indicated to treat patients with depression or anxiety (Sabella, 2018, Kennedy et al., 2016, Katzman et al., 2014). Several clinical factors may influence antidepressant selections. For example, the Canadian clinical practice guidelines recommend antidepressants based on severity of illness, presence of anxiety, patient preference and so on (Kennedy et al., 2016). Patient-reported outcome instruments are used for the detection of some mental disorders and assessment of the severity. The Patient Health Questionnaire -9 (PHQ-9) (Villarreal-Zegarra et al., 2019) and Generalized Anxiety Disorder 7 (GAD-7) (Toussaint et al., 2020) are patient-reported outcome instruments to measure depressive and anxiety symptoms. It is useful to understand the associations between antidepressant use and patient-reported symptoms. The consumption of antidepressants has been affected by the coronavirus disease 2019 (COVID-19). There had been a substantial increase in mental health problems worldwide since the occurrence of COVID-19 pandemic (Qiu et al., 2020, Ngoc Cong Duong et al., 2020, Mazza et al., 2020). It has been reported that the prevalence of depression had increased 3-folds in the United States since the emergence of COVID-19 (Ettman et al., 2020). Studies in the United Kingdom have reported that the consumption of antidepressants had also increased during COVID-19 pandemic (Rabeea et al., 2021, Read et al., 2020). One characteristic element of the stressor of COVID-19 pandemic compared with other stressors is fear (Ahorsu et al., 2022, Shigemura et al., 2020, Voitsidis et al., 2021). To measure fear of COVID-19, the Fear of COVID-19 Scale (FCV-19S) has been developed as a brief and valid instrument to capture an individual's fear of COVID-19 (Ahorsu et al., 2022). This scale has been validated in various cultures (Elemo et al., 2020, Martinez-Lorca et al., 2020, Soraci et al., 2020, Alyami et al., 2021, Masuyama et al., 2022, Perz et al., 2022). Based on our knowledge, there is no study exploring the associations between antidepressant prescription and the fear of COVID-19.

Antidepressants may have partial efficacy in treating a clinical condition named Hikikomori (Martinotti et al., 2021). Hikikomori is characterized by marked social isolation in one's home for at least 6 months and significant functional impairment or distress associated with the social isolation (Kato et al., 2020). The 25-item Hikikomori

Questionnaire (HQ-25) was developed as a self-administrated instrument for assessing the symptoms of Hikikomori (Teo et al., 2018). Just recently, one month version of HQ-25 (HQ-25M) has been developed to evaluate hikikomori-like conditions more specifically as a state condition (Kato et al., 2022). Given that Hikikomori is associated with depression (Teo et al., 2020), it is worthwhile to assess Hikikomori symptoms when exploring antidepressant prescription patterns.

### **Aim**

The aims of the REAP-AD3 study are to: (1) assess the trend of prescription patterns of antidepressants in Asia; (2) evaluate the relationship between antidepressant use and clinical correlates including socio-demographic characteristics, depressive and anxiety symptoms. Also an optional study of patient self-rated questionnaires including 1. Patient Health Questionnaire-9 (PHQ-9); 2. Generalized Anxiety Disorder 7 (GAD-7); 3. Fear of COVID-19 Scale (FCV-19S); and 4. One Month Version of Hikikomori Questionnaire (HQ-25) will be implemented.

### **Hypothesis**

Based on limited data in Asia and clinical experience, we hypothesize that the use of antidepressants would be associated with varying diagnoses, differences in types of psychotropic drug-combinations, demographic (such as gender and age) and clinical factors (such as treatment setting, anxiety symptoms, fear of COVID-19 and Hikikomori symptoms).

### **Methods**

This is a cross-sectional survey of antidepressant prescriptions of 000 (target number) patients at 000 (name of your hospital). Within this group, around half of the patients will be recruited from outpatient clinics and the other half from inpatient wards. Overall, the aim is to recruit at least 1600 subjects from the 16 countries for this study. Followings are the participating countries: 1. China 2. Hong Kong 3. Japan 4. Korea 5. Singapore 6. Taiwan 7. India 8. Malaysia 9. Thailand 10. Indonesia 11. Bangladesh 12. Myanmar 13. Pakistan 14. Sri Lanka 15. Vietnam 16. Iran.

Inclusion criteria could be: (1) Patients who are receiving antidepressants (Appendix 1); (2) Aged between 10 and 80; (3) Provision of informed consent.

Exclusion criteria could be: (1) Patient is unable to give informed consent; (2) Patients who are illiterate for optional self-rated questionnaires study.

The potential patients in the inpatient or outpatient settings will be approached and explained about the study. Only the patients who agree to participate and give a written consent will be recruited. Socio-demographic, clinical and prescribing information will be collected through a unified data form adopted across all the sites in the 16 Asian countries.

The study is coordinated by REAP consortium lead collaborators and coordinators. Taipei City Hospital will be in charge of the data collection by internet data key-in system, and Kyushu University run the secretarial affairs. All a memorandum of understanding will be signed before the start of the study. Only de-identified, anonymized data would be shared by all the participating countries via secure web based platform which is hosted by the coordinating site and secretariat at Taipei City Hospital.

## **Data collection**

### Major part of this study (Mandatory)

The following data will be collected by the investigator.

1. Demographic Data form with socio-demographic, clinical and prescription details including birth day, age, sex, body weight, height, current setting, and other treatment (appendix 2).
2. Major psychiatric diagnosis by ICD-10 classification system (appendix 3).
3. Physical comorbidities (appendix 4).
4. Depressive Symptoms by NICE guideline (appendix 5).
5. Additional items for 2023 survey (appendix 6).

### Optional part of this study (The investigator can decide whether or not to join this part of study) (Appendix 7, 1-4).

1. Patient Health Questionnaire-9 (PHQ-9)
2. Generalized Anxiety Disorder 7 (GAD-7)

3. Fear of COVID-19 Scale (FCV-19S)
4. One Month Version of Hikikomori Questionnaire (HQ-25)

### **Data analysis**

Analyses of data will be done using the Statistical Package for Social Sciences (SPSS). Normality of distributions of continuous measures will be checked using Kolmogorov-Smirnov one-sample test. Differences between groups will be tested by ANOVA (t-test) for normally distributed data, non-parametric Mann Whitney U tests for non-normally distributed continuous data and by contingency table for categorical variables. Averages will be reported as means  $\pm$  standard deviation (SD) for continuous variables, risk estimates will be reported as odds ratios (OR) with their 95% confidence interval (CI). Multiple regression analyses are used to examine the association between the relevant variables.

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## Appendix 1. List of Antidepressants

| code | generic name          | code | generic name     | code | generic name  | code | generic name    |
|------|-----------------------|------|------------------|------|---------------|------|-----------------|
| 101  | agomelatine           | 116  | doxepin          | 131  | maprotiline   | 146  | paroxetine      |
| 102  | alaproclate           | 117  | duloxetine       | 132  | medifoxamine  | 147  | phenelzine      |
| 103  | amineptine            | 118  | escitalopram     | 133  | melitracen    | 148  | pivagabine      |
| 104  | amitriptyline         | 119  | etoperidone      | 134  | mianserin     | 149  | protriptyline   |
| 105  | amoxapine             | 120  | fluoxetine       | 135  | milnacipran   | 150  | quinupramine    |
| 106  | bifemelane            | 121  | fluvoxamine      | 136  | minaprine     | 151  | reboxetine      |
| 107  | bupropion             | 122  | gepirone         | 137  | mirtazapine   | 152  | sertraline      |
| 108  | butriptyline          | 123  | Hyperici herba** | 138  | moclobemide   | 153  | tianeptine      |
| 109  | citalopram            | 124  | imipramine oxide | 139  | nefazodone    | 154  | toloxatone      |
| 110  | clomipramine          | 125  | imipramine       | 140  | nialamide     | 155  | tranylcypromine |
| 111  | desipramine           | 126  | iprindole        | 141  | nomifensine   | 156  | trazodone       |
| 112  | desvenlafaxine        | 127  | iproclozide      | 142  | nortriptyline | 157  | trimipramine    |
| 113  | dibenzepin            | 128  | iproniazide      | 143  | opipramol     | 158  | tryptophan      |
| 114  | dimetacrine           | 129  | isocarboxazid    | 144  | oxaflozane    | 159  | venlafaxine     |
| 115  | dosulepin (dothiepin) | 130  | lofepramine      | 145  | oxitriptan    | 160  | vilazodone      |
|      |                       |      |                  |      |               | 161  | viloxazine      |
|      |                       |      |                  |      |               | 162  | zimeldine       |
|      |                       |      |                  |      |               | 163  | desvenlafaxine  |
|      |                       |      |                  |      |               | 164  | esketamine      |
|      |                       |      |                  |      |               | 165  | vortioxetine    |

## Appendix 2. Rating Scales

1. Data form with socio-demographic, clinical and prescription details

### A. Profile of this patient

|     |  |
|-----|--|
| 1.  | <b>Birth Date:</b><br>(day) (month) (year)   |
| 2.  | <b>Age:</b><br><input type="text"/> years  |
| 3.  | <b>Sex:</b><br><input checked="" type="radio"/> 1.Male <input type="radio"/> 2.Female  |
| 3.1 | <b>Body Weight:</b><br><input type="text"/> Kg   |
| 3.2 | <b>Height:</b><br><input type="text"/> Cm  |
| 4.  | <b>Current Setting:</b><br><input checked="" type="radio"/> 1. Outpatient <input type="radio"/> 2. Inpatient <input type="radio"/> 3. Others <input type="text"/>  |
| 5.  | <b>Does the patient receive any ECT, TMS and Other Brain Stimulation Therapies within 6 months?</b><br><input type="radio"/> NO <input type="radio"/> YES<br><input type="checkbox"/> Electroconvulsive Therapy (ECT)<br><input type="checkbox"/> Transcranial Magnetic Stimulation (TMS)<br><input type="checkbox"/> Vagus Nerve Stimulation (VNS)<br><input type="checkbox"/> Deep Brain Stimulation (DBS) |

### Appendix 3. Major psychiatric diagnoses in ICD-10 classification list

| <i>F0</i> | <i>Organic, including symptomatic, mental disorders</i>                             | <i>F1</i> | <i>Mental and behavioral disorders due to psychoactive substance use</i>                                 |
|-----------|---|-----------|--|
| □F00      | Dementia in Alzheimer's Disease   | □F10      | Mental and Behavioral Disorders Due to Use of Alcohol  |
| □F01      | Vascular Dementia   | □F11      | Mental and Behavioral Disorders Due to Use of Opioids  |
| □F02      | Dementia in Other Diseases Classified Elsewhere                                     | □F12      | Mental and Behavioral Disorders Due to Use of Cannabinoids   |
| □F03      | Unspecified Dementia  | □F13      | Mental and Behavioral Disorders Due to Use of Sedatives and Hypnotics                                    |
| □F04      | Organic Amnesic Syndrome, Not included by Alcohol and Other Psychoactive Substances | □F14      | Mental and Behavioral Disorders Due to Use of Cocaine  |
| □F05      | Delirium, Not induced by Alcohol and Other Psychoactive Substances                  | □F15      | Mental and Behavioral Disorders Due to Use of Other Stimulants, including Caffeine                       |
| □F06      | Other Mental Disorders Due to Brain Damage and Dysfunction and Physical Disease     | □F16      | Mental and Behavioral Disorders Due to Use of Hallucinogens  |
| □F07      | Personality and Behavioral Disorders Due to Brain Disease, Damage and Dysfunction   | □F17      | Mental and Behavioral Disorders Due to Use of Tobacco  |
| □F09      | Unspecified Organic or Symptomatic Mental Disorder                                  | □F18      | Mental and Behavioral Disorders Due to Use of Volatile Solvents  |
|           |   | □F19      | Mental and Behavioral Disorders Due to Use of Multiple Drug Use and Use of Other Psychoactive Substances |

| <i>F2</i> | <i>Schizophrenia, schizotypal and delusional disorders</i> | <i>F3</i> | <i>Mood (affective) disorders</i>     |
|-----------|--|-----------|---------------------------------------|
| □F20      | Schizophrenia  | □F30      | Manic Episode                         |
| □F21      | Schizotypal Disorder                                       | □F31      | Bipolar Affective Disorder            |
| □F22      | Persistent Delusional Disorders                            | □F32      | Depressive Episode                    |
| □F23      | Acute and Transient Psychotic Disorders                    | □F33      | Recurrent Depressive Disorder         |
| □F24      | Induced Delusional Disorder                                | □F34      | Persistent Mood (Affective) Disorders |
| □F25      | Schizoaffective Disorders                                  | □F38      | Other Mood (Affective) Disorders      |
| □F28      | Other Nonorganic Psychotic Disorders                       | □F39      | Unspecified Mood (Affective) Disorder |
| □F29      | Unspecified Nonorganic Psychosis                           |           |                                       |

| <i>F4</i> | <i>Neurotic, stress-related and somatoform disorders</i> | <i>F5</i> | <i>Behavioral syndromes associated with physiological disturbance and physical factors</i>      |
|-----------|--|-----------|---|
| □F40      | Phobic Anxiety Disorders                                 | □F50      | Eating Disorders  |
| □F41      | Other Anxiety Disorders                                  | □F51      | Nonorganic Sleep Disorders  |
| □F42      | Obsessive – Compulsive Disorder                          | □F52      | Sexual Dysfunction, Not Caused by Organic Disorder or Disease                                   |
| □F43      | Reaction to Severe Stress, and Adjustment Disorders      | □F53      | Mental and Behavioral Disorders Associated with the Puerperium, Not Elsewhere Classified        |
| □F44      | Dissociative (Conversion) Disorders                      | □F54      | Psychological and Behavioral Factors Associated with Disorders or Diseases Classified Elsewhere |

|                              |  |                              |   |
|------------------------------|--|------------------------------|---|
| <i>F4</i>                    | <i>Neurotic, stress-related and somatoform disorders</i> | <i>F5</i>                    | <i>Behavioral syndromes associated with physiological disturbance and physical factors</i>  |
| <input type="checkbox"/> F45 | Somatoform Disorders                                     | <input type="checkbox"/> F55 | Abuse of Non- Dependence-Producing Substances   |
| <input type="checkbox"/> F48 | Other Neurotic Disorders                                 | <input type="checkbox"/> F59 | Unspecified Behavioral Syndromes Associated with Physical Disturbances and Physical Factors |

|                              |   |                              |                                |
|------------------------------|---|------------------------------|--------------------------------|
| <i>F6</i>                    | <i>Disorders of adult personality and behaviour</i>                                       | <i>F7</i>                    | <i>Mental retardation</i>      |
| <input type="checkbox"/> F60 | Specific Personality Disorders  | <input type="checkbox"/> F70 | Mild Mental Retardation        |
| <input type="checkbox"/> F61 | Mixed and Other Personality Disorders   | <input type="checkbox"/> F71 | Moderate Mental Retardation    |
| <input type="checkbox"/> F62 | Enduring Personality Changes, Not Attributable to Brain Damage and Disease                | <input type="checkbox"/> F72 | Severe Mental Retardation      |
| <input type="checkbox"/> F63 | Habit and Impulse Disorders   | <input type="checkbox"/> F73 | Profound Mental Retardation    |
| <input type="checkbox"/> F64 | Gender Identity Disorders   | <input type="checkbox"/> F78 | Other Mental Retardation       |
| <input type="checkbox"/> F65 | Disorders of Sexual Preference  | <input type="checkbox"/> F79 | Unspecified Mental Retardation |
| <input type="checkbox"/> F66 | Psychological and Behavioral Disorders Associated with Sexual Development and Orientation |                              |                                |
| <input type="checkbox"/> F68 | Other Disorders of Adult Personality Behavior   |                              |                                |
| <input type="checkbox"/> F69 | Unspecified Disorder of Adult Personality and Behavior                                    |                              |                                |

|                              |   |                              |   |
|------------------------------|---|------------------------------|---|
| <i>F8</i>                    | <i>Disorders of psychological development</i>           | <i>F9</i>                    | <i>Behavioral and Emotional disorders with onset usually occurring in childhood and adolescence</i> |
| <input type="checkbox"/> F80 | Specific Developmental Disorders of Speech and Language | <input type="checkbox"/> F90 | Hyperkinetic Disorders  |
| <input type="checkbox"/> F81 | Specific Developmental Disorders of Scholastic Skills   | <input type="checkbox"/> F91 | Conduct Disorders   |
| <input type="checkbox"/> F82 | Specific Developmental Disorders of Motor Function      | <input type="checkbox"/> F92 | Mixed Disorders of Conduct and Emotions   |
| <input type="checkbox"/> F83 | Mixed Specific Developmental Disorders                  | <input type="checkbox"/> F93 | Emotional Disorders with Onset Specific to Childhood  |
| <input type="checkbox"/> F84 | Pervasive Developmental Disorders                       | <input type="checkbox"/> F94 | Disorders of Social Functioning with Onset Specific to Childhood and Adolescence                    |
| <input type="checkbox"/> F88 | Other Disorders of Psychological Development            | <input type="checkbox"/> F95 | Tic Disorders   |
| <input type="checkbox"/> F89 | Unspecified Disorder of Psychological Development       | <input type="checkbox"/> F98 | Other Behavioral and Emotional Disorders with Onset Usually Occurring in Childhood and Adolescence  |
|                              |   | <input type="checkbox"/> F99 | Mental Disorder, Not Otherwise Specified  |

## Appendix 4. Physical comorbidities

| code | Comorbidities (*) <sup>1</sup>   | Quan's ICD-9-CM <sup>2</sup>   | ICD-10  |
|------|--|--|---|
| □01  | Myocardial infarction (1)  | 410.x, 412.x   | I21.x, I22.x, I25.2   |
| □02  | Congestive heart failure (1)   | 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x                                   | I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0  |
| □03  | Peripheral vascular disease (1)  | 093.0, 437.3, 440.x, 441.x, 443.1–443.9, 47.1, 557.1, 557.9, V43.4   | I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9   |
| □04  | Cerebrovascular disease (1)  | 362.34, 430.x–438.x  | G45.x, G46.x, H34.0, I60.x–I69.x  |
| □05  | Dementia (1)   | 290.x, 294.1, 331.2  | F00.x–F03.x, F05.1, G30.x, G31.1  |
| □06  | Chronic pulmonary disease (1)  | 416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8   | I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3   |
| □07  | Rheumatic disease (1)  | 446.5, 710.0–710.4, 714.0–714.2, 714.8, 725.x  | M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0   |
| □08  | Peptic ulcer disease (1)   | 531.x–534.x  | K25.x–K28.x   |
| □09  | Mild liver disease (1)   | 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7                        | B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4  |
| □10  | Diabetes without chronic complication (1)  | 250.0–250.3, 250.8, 250.9  | E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 |
| □11  | Diabetes with chronic complication (2)   | 250.4–250.7  | E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7  |
| □12  | Hemiplegia or paraplegia (2)   | 334.1, 342.x, 343.x, 344.0–344.6, 344.9  | G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9  |
| □13  | Renal disease (2)  | 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x | I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2  |
| □14  | Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin (2) | 140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6   | C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x   |
| □15  | Moderate or severe liver disease (3)   | 456.0–456.2, 572.2–572.8   | I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7   |
| □16  | Metastatic solid tumor (6)   | 196.x–199.x  | C77.x–C80.x   |
| □17  | AIDS/HIV (6)   | 042.x–044.x  | B20.x–B22.x, B24.x  |
| □18  | Others<br>( )  |  |   |

<sup>1</sup> Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chrom Dis.* 1987; 40(5): 373-383.

<sup>2</sup> Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Sunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005; 43: 1130-1139.

## Appendix 5. Depressive Symptoms (NICE guideline)

Please check the targeted depressive symptoms to prescribe antidepressants for this patient (more than one).

- 1. Persistent sadness or low mood
- 2. Loss of interests or pleasure
- 3. Fatigue or low energy
- 4. Disturbed sleep
- 5. Poor concentration or indecisiveness
- 6. Low self-confidence
- 7. Poor or increased appetite
- 8. Suicidal thoughts or acts
- 9. Agitation or slowing of movements
- 10. Guilt or self-blame

**Appendix 6. Additional items for 2023 survey:**  
(Data should be inputted by physician in charge)

F. Pathway: Who/What referred this patient to your hospital/clinic (multiple check is allowed)

- Psychiatrist
- Physicians (not psychiatrists)
- Other medical facility
- Traditional healer
- Religion
- Other nonmedical agency
- Unknown

G. History of COVID-19 (multiple check is allowed)

- COVID-19 confirmed (within 3 months)
- COVID-19 confirmed (not within 3 months)
- Never affected by COVID-19
- Unknown

- Vaccinated for COVID-19 ( at least once)
- Not vaccinated
- Unknown

H. Comorbidity of substance use disorder (multiple check is allowed)

- F 10 Alcohol
- F 11 Opioid
- F 12 Cannabis
- F 13 Sedative and hypnotics
- F 14 Cocaine
- F 15 Caffeine/amphetamine/other stimulants
- F 16 Hallucinogen
- F 17 Tobacco
- F 18 Volatile matter
- F 19 Multiple use
- Others ( )



Appendix 7 (Optional items for 2023 survey)

(Data should be rated by patient)

1. Patient Health Questionnaire-9 (PHQ-9)

**Over the last two weeks, how often have you been bothered by any of the following problems?**

|    |   | Not at all                         | Several days            | More than half the days | Nearly every day        |
|----|---|------------------------------------|-------------------------|-------------------------|-------------------------|
| 1. | Little interest or pleasure in doing things?  | <input checked="" type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 |
| 2. | Feeling down, depressed, or hopeless?   | <input type="radio"/> 0            | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 |
| 3. | Trouble falling or staying asleep, or sleeping too much?  | <input type="radio"/> 0            | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 |
| 4. | Feeling tired or having little energy?  | <input type="radio"/> 0            | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 |
| 5. | Poor appetite or overeating?  | <input type="radio"/> 0            | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 |
| 6. | Feeling bad about yourself - or that you are a failure or have let yourself or your family down?  | <input type="radio"/> 0            | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 |
| 7. | Trouble concentrating on things, such as reading the newspaper or watching television?  | <input type="radio"/> 0            | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 |
| 8. | Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual? | <input type="radio"/> 0            | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 |
| 9. | Thoughts that you would be better off dead, or of hurting yourself in some way?   | <input type="radio"/> 0            | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 |

## 2. Generalized Anxiety Disorder 7 (GAD-7)

Over the last 2 weeks, how often have you been bothered by the following problems?

|    |   | Not at all              | Several days            | More than half<br>the days | Nearly every day        |
|----|---|-------------------------|-------------------------|----------------------------|-------------------------|
| 1. | Feeling nervous, anxious or on edge               | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 |
| 2. | Not being able to stop or control worrying        | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 |
| 3. | Worrying too much about different things          | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 |
| 4. | Trouble relaxing                                  | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 |
| 5. | Being so restless that it is hard to sit still    | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 |
| 6. | Becoming easily annoyed or irritable              | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 |
| 7. | Feeling afraid as if something awful might happen | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 |

### 3. Fear of COVID-19 Scale (FCV-19S)

Please respond to each item by ticking (✓) one of the five (5) responses that reflects how you feel, think, or act toward COVID-19

|  | Strongly disagree       | Disagree                | Neutral                 | Agree                   | Strongly agree          |
|--|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| 1. I am most afraid of Corona  | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 2. It makes me uncomfortable to think about Corona   | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 3. My hands become clammy when I think about Corona  | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 4. I am afraid of losing my life because of Corona   | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 5. When I watch news and stories about Corona on social media, I become nervous or anxious | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 6. I cannot sleep because I'm worrying about getting Corona                                | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 7. My heart races or palpitates when I think about getting Corona                          | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |

#### 4. One Month Version of Hikikomori Questionnaire (HQ-25)

Over the **LAST MONTH**, how accurately do the following statements describe you?

|     |  | Strongly disagree       | Somewhat disagree       | Neither agree nor disagree | Somewhat agree          | Strongly agree          |
|-----|--|-------------------------|-------------------------|----------------------------|-------------------------|-------------------------|
| 1.  | I stay away from other people.   | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 2.  | I spend most of my time at home.   | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 3.  | There really isn't anyone with whom I can discuss matters of importance. | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 4.  | I love meeting new people.   | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 5.  | I shut myself in my room.  | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 6.  | People bother me.  | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 7.  | There are people in my life who try to understand me.                    | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 8.  | I feel uncomfortable around other people.                                | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 9.  | I spend most of my time alone.   | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 10. | I can share my personal thoughts with several people.                    | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 11. | I don't like to be seen by others.                                       | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 12. | I rarely meet people in-person.  | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 13. | It is hard for me to join in on groups.                                  | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 14. | There are few people I can discuss important issues with.                | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 15. | I enjoy being in social situations.                                      | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |

|     |  | Strongly disagree       | Somewhat disagree       | Neither agree nor disagree | Somewhat agree          | Strongly agree          |
|-----|--|-------------------------|-------------------------|----------------------------|-------------------------|-------------------------|
| 16. | I do not live by society's rules and values.                         | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 17. | There really isn't anyone very significant in my life.               | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 18. | I avoid talking with other people.                                   | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 19. | I have little contact with other people talking, writing, and so on. | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 20. | I much prefer to be alone than with others.                          | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 21. | I have someone I can trust with my problems.                         | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 22. | I rarely spend time alone.   | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 23. | I don't enjoy social interactions.                                   | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 24. | I spend very little time interacting with other people.              | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |
| 25. | I strongly prefer to be around other people.                         | <input type="radio"/> 0 | <input type="radio"/> 1 | <input type="radio"/> 2    | <input type="radio"/> 3 | <input type="radio"/> 4 |