SUPPLEMENTARY MATERIAL 1

Eligibility criteria of the MAKE BETTER project

Inclusion criteria were: i) aged older than 7 years; ii) diagnosed with MDD, dysthymic disorder, or depressive disorder not otherwise specified (NOS), using the Mini-International Neuropsychiatric Interview (MINI),[1] a diagnostic psychiatric interview applying Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria;[2] iii) Hamilton Depression Rating Scale (HAMD)[3] score ≥14; iv) able to complete questionnaires, understand the objective of the study, and sign the informed consent form. Exclusion criteria were: i) an unstable or uncontrolled medical condition; ii) unable to complete the psychiatric assessment or comply with the medication regimen, due to a severe physical illness; iii) current or lifetime DSM-IV diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder NOS, or other psychotic disorder; iv) history of organic psychosis, dementia, epilepsy, or seizure disorder; v) history of anticonvulsant treatment; vi) hospitalization for any psychiatric diagnosis apart from depressive disorder (e.g., alcohol/drug dependence); vii) electroconvulsive therapy received for the current depressive episode; viii) pregnant or breastfeeding. All participants reviewed the consent form and written informed consent was obtained. For participants aged under 16, written consent was obtained from a parent or legal guardian, and written assent was obtained from the participant.

Stepwise pharmacotherapy

Overall treatment steps and strategies are outlined in Supplementary Figure 1. Before treatment commencement, a comprehensive review was made of patients' clinical manifestation (e.g., psychotic or anxiety symptoms), severity of illness, physical comorbidity and medication profile, and history of previous treatments. In the first treatment Step 1, patients received antidepressant treatment, taking into consideration these data and treatment guidelines[4-6] for 3 weeks. Antidepressants used were bupropion, desvenlafaxine, duloxetine, escitaloproam, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. Initial starting doses were determined individually considering patients' age, body weight, and physical comorbidity and drug intake status. At week 1 and week 2 visits, antidepressant dosages were adjusted to optimise therapeutic benefit for each patient. After Step 1 antidepressant monotherapy, next step pharmacotherapy could be administered every 3 weeks during the 12-week treatment period, whenever needed.

At the end of Step 1 (week 3), overall effectiveness and tolerability were reviewed for proceeding with measurement-based next-step treatments. In cases of insufficient improvement (a HAMD score reduction of <30% from the baseline) or intolerable side effects, patients were instructed to choose whether they would prefer to remain in Step 1 monotherapy continuation including dose adjustment or enter into Step 2 strategies with switching, augmentation, or combination treatment. Pros and cons of each strategy were explained, and clinician opinion was provided, taking into considering both the patient's status and treatment guidelines.[4-6] Patients were also allowed to receive next-step treatment, if they were not fully satisfied with their current treatment for any reason and even if they showed sufficient improvement (a HAMD score reduction of ≥30% from the baseline) and absent/tolerable side effects. For determining treatment strategies, each patient's preference was given priority to maximize medication compliance and treatment outcomes.[7] Antidepressants switched or combined were bupropion, desvenlafaxine, duloxetine, escitaloproam, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. Augmented drugs were buspiron, lithium, triiodothyronine, and atypical antipsychotics including aripirprazole, risperidone, olanzapine, quetiapine, and ziprasidone.

At week 6, the same procedure as at week 3 was carried out to decide whether patients would remain in the same treatment steps or enter into further steps. Categories of treatment strategies in Step 3 were as follows: i) switch: antidepressant monotherapy switched from that in Step 2; ii) augmentation: switching augmented drugs from those received in Step 2; iii) combination: switching antidepressants added in Step 2; iv) switch + augmentation: either switching antidepressants at Step 2 and then adding augmentation drugs at Step 3, or adding augmentation drugs at Step 2 and then switching antidepressants at Step 3; v) switch + combination: either switching antidepressants at Step 2 and then combining other antidepressants at Step 3, or combining other antidepressants at Step 2 and then switching the antidepressant used from Step 1; vi) augmentation+combination: adding augmentation drugs at Step 2 and combining antidepressants at Step 3 or vice versa.

At week 9, the same procedure was repeated to decide whether patients would remain in the same treatment steps or enter into further steps. Categories of treatment strategy changes in Step 4 were as follows: i) switch: antidepressant monotherapy switched from Step 3; ii) augmentation: switching augmentation drugs from Step 3; iii) combination: switching antidepressants added in Step 3; iv) switch + augmentation: either twice switching antidepressants and once adding augmentation drugs, or one switch of antidepressant and two changes of augmentation drugs over the 4 steps; v) switch + combination: either twice switching antidepressants used from Step1 and once combining antidepressants, or once switching antidepressants used from Step 1 and twice changing combined drugs over the 4 steps; vi) augmentation + combination: either twice changing augmented drugs and once changing combined antidepressants, or once changing augmented drugs and twice changing combined antidepressants over the 4 steps; vii) switch + augmentation + combination: three strategies used simultaneously at the Step 4 regardless of the order of administered strategies in the previous steps.

Use of any anxiolytics/hypnotics (including alprazolam, bromazepam, clonazepam, clorazepate, diazepam, ethyl loflazepate, flunitrazepam, lorazepam, and zolpidem) was allowed at any of the time points of the study, whether this was to improve efficacy, relieve associated symptoms, or treat side effects.

REFERENCES

1. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33; quiz 34-57.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV) (4th ed). Washington, DC: American Psychiatric Association; 1994.
3. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
4. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry 2013;14:334-385.
5. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2015;49:1087-1206.
6. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can J Psychiatry 2016;61:540-560.
7. Swift JK, Callahan JL. The impact of client treatment preferences on outcome: a meta-analysis. J Clin Psychol 2009;65:368-381.