Neuropsychiatric Disease and Treatment

Dovepress

open access to scientific and medical research

Open Access Full Text Article

EXPERT OPINION

A Southeast Asia Consensus on the Definition and Management of Treatment-Resistant Depression

Phern Chern Tor[1], Nurmiati Amir[2], Johnson Fam[3], Roger Ho[3], Pichai Ittasakul[4], Margarita M Maramis[5], Benita Ponio[6], Dharmawan Ardi Purnama[7], Wanida Rattanasumawong[8], Elizabeth Rondain[9], Ahmad Hatim Bin Sulaiman[10], Kannokarn Wiroteurairuang[11], Kok Yoon Chee[12]

[1]Department of Mood and Anxiety, Institute of Mental Health, Singapore; [2]Department of Psychiatry, Cipto Mangunkusumo Hospital, Jakarta Pusat, Indonesia; [3]Department of Psychological Medicine, National University Hospital, Singapore; [4]Department of Psychiatry, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [5]Department of Psychiatry, Dr. Soetomo General Academic Hospital-Faculty of Medicine, Airlangga University, Surabaya, Indonesia; [6]Department of Psychiatry, Metro Psych Facility, Manila, Philippines; [7]Dr Soeharto Heerdjan Jakarta Mental Hospital, Jakarta, Indonesia; [8]Department of Psychiatry, Phramongkutklao Hospital, Bangkok, Thailand; [9]Department of Psychiatry, Makati Medical Center, Makati City, Philippines; [10]Department of Psychological Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [11]Prasrimahabodhi Psychiatric Hospital, Ubon Ratchathani, Thailand; [12]Department of Psychiatry, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Correspondence: Ahmad Hatim Bin Sulaiman, Department of Psychological Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, 50603, Malaysia, Email hatim@um.edu.my

Introduction: Despite the abundance of literature on treatment-resistant depression (TRD), there is no universally accepted definition of TRD and available treatment pathways for the management of TRD vary across the Southeast Asia (SEA) region, highlighting the need for a uniform definition and treatment principles to optimize the management TRD in SEA.

Methods: Following a thematic literature review and pre-meeting survey, a SEA expert panel comprising 13 psychiatrists with clinical experience in managing patients with TRD convened and utilized the RAND/UCLA Appropriateness Method to develop consensus-based recommendations on the appropriate definition of TRD and principles for its management.

Results: The expert panel agreed that "pharmacotherapy-resistant depression" (PRD) is a more suitable term for TRD and defined it as "failure of two drug treatments of adequate doses, for 4–8 weeks duration with adequate adherence, during a major depressive episode". A stepwise treatment approach should be employed for the management of PRD – treatment strategies can include maximizing dose, switching to a different class, and augmenting or combining treatments. Non-pharmacological treatments, such as electroconvulsive therapy and repetitive transcranial magnetic stimulation, are also appropriate options for patients with PRD.

Conclusion: These consensus recommendations on the operational definition of PRD and treatment principles for its management can be adapted to local contexts in the SEA countries but should not replace clinical judgement. Individual circumstances and benefit-risk balance should be carefully considered while determining the most appropriate treatment option for patients with PRD.

Keywords: depression, pharmacotherapy, major depressive disorder, anti-depressive agents, depressive disorder – treatment resistant

Introduction

Depressive disorders, like major depressive disorder (MDD) and dysthymia, are among the leading causes of non-fatal health loss worldwide.[1] MDD is associated with significant individual, societal and economic burden.[2] While pharmacological therapy with antidepressants (AD) is a well-established and effective treatment for MDD, 30–60% of patients with MDD do not respond adequately to the initial AD treatment[3] and an estimated 40% of patients do not respond to two consecutive AD therapies.[4]

Treatment-resistant depression (TRD) is associated with a poorer quality of life and health status, decrease in productivity, higher suicide risk, increase in hospitalization rates, and higher healthcare costs.[5–7] Several risk factors

Received: 1 July 2022
Accepted: 28 October 2022
Published: 22 November 2022

have been associated with TRD, including comorbidities (anxiety and personality disorders), suicide risk, episode severity, episode recurrence, number of hospitalizations, early onset, and non-response at first treatment.[5,8] The reported worldwide prevalence of TRD varies widely from 11% to 50%; this inconsistency may be attributed to varying definitions of TRD used in the different studies and potential under-reporting of cases of TRD.[9–13]

Although many definitions for TRD have been proposed, there is a lack of a uniformly accepted clinical definition.[3,14] A commonly used definition of TRD is 'failure of two consecutive adequate AD trials'.[3,15] A recently published Asia Pacific consensus defined TRD as "failure of ≥2 AD therapies given at adequate doses, for 6–8 weeks during a major depressive episode",[12] while a French consensus defined TRD as the "failure of two AD of adequate dose and duration (optimal duration of 4–6 weeks when target dose is achieved)".[2]

In the absence of a TRD-focused treatment guideline, recommendations for the management of TRD are typically included in guidelines for the management of MDD in adults.[16–19] In Southeast Asia (SEA), only a few country-specific clinical practice guidelines provide recommendations for the management of patients with TRD.[20–22] In these guidelines, however, TRD is variably defined and the treatment pathway for the management of TRD varies. Furthermore, SEA is a vastly diverse region, and healthcare systems (including psychiatry) across SEA are highly heterogeneous,[23] rendering direct application of an international guideline to various country-specific settings difficult. Therefore, there is a need for a regional consensus that provides a uniform definition and treatment principles that can be easily adapted to various countries in the SEA region to optimize the management of patients with TRD. We aim to provide consensus-based recommendations on the definition and management of TRD in adults, which can be adapted to local contexts and implemented in clinical practice by specialists in SEA.

Methods

This consensus was developed by an expert panel comprising 13 purposefully sampled national psychiatrists from SEA, including Indonesia, Malaysia, Philippines, Singapore and Thailand. All experts work in a university or tertiary medical/psychiatric institution, are key members in relevant academic or professional associations, participated in research in mood disorders or have extensive clinical experience in psychiatry in mood disorders, and have relevant experience in the management of patients with TRD.

The SEA expert panel convened in November 2019 in Singapore to discuss and develop a SEA-specific consensus on the definition and management of TRD that can support psychiatrists across SEA in making informed clinical decisions.

Prior to the consensus meeting, a thematic literature review of TRD publications in SEA, including the definition, management and treatment guidelines of TRD, as well as available international guidelines of TRD was conducted, and the available data was summarized. A pre-meeting survey was then distributed to the expert panel to gain insights on practice patterns in their respective countries. Based on the available evidence from the literature review and pre-meeting survey responses, a definition of TRD and 27 clinical scenarios in the management of TRD were drafted for the consensus development (Figure 1). The thematic literature review, pre-meeting survey and clinical scenarios were developed by an independent medical communications agency (Healthy Thinking Group Asia), following initial inputs from the lead author.

The RAND/UCLA Appropriateness Method was used to obtain consensus. This method incorporates evidence from the literature as well as expert clinical opinions and has been used widely for the development of guidelines.[24] The panel convened to discuss the draft definition and clinical scenarios at the consensus meeting. The panel independently and confidentially rated the appropriateness of each clinical scenario based on a 1 to 9 Likert scale in two rounds of voting. After each round of voting, discrepancies in the ratings were identified. "Disagreement" was defined as one-third or more of the panelists rating a scenario in the lowest 3 points of the appropriateness scale (score 1, 2 or 3) and one-third or more of the panelists rating the same scenario in the highest 3 points of the appropriateness scale (score 7, 8 or 9). In the absence of "disagreement", a rating with a median score of 7 to 9 was considered "appropriate", 4 to 6 was "equivocal" and 1 to 3 was "not appropriate". After the first round of voting, the panel discussed their individual views on the appropriateness of each clinical scenario before proceeding to the second and final round of voting. Following the consensus meeting, clinical scenarios rated as "appropriate"

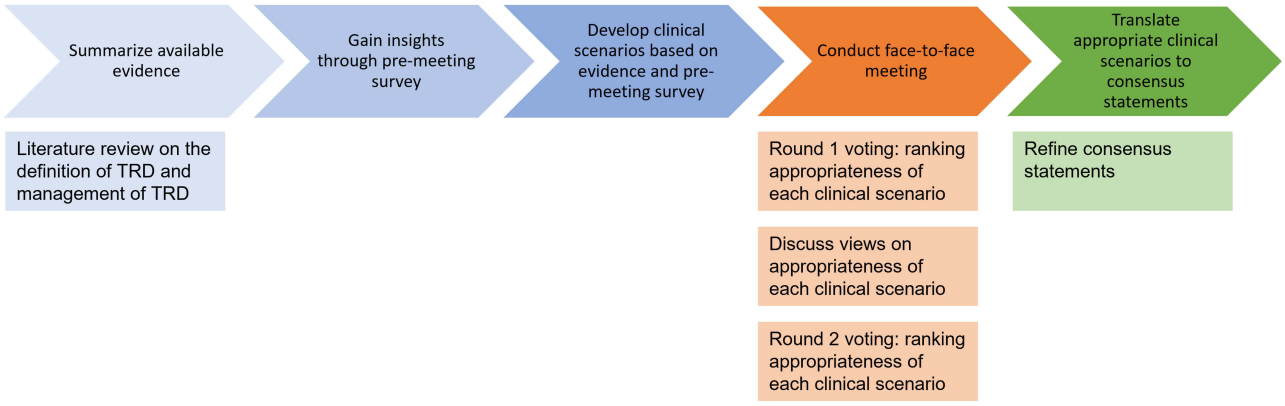

Figure 1 RAND/UCLA method for achieving consensus.

were translated into consensus statements which were subsequently refined by the expert panel. A treatment pathway based on the "appropriate" clinical scenarios was also drafted.

Results

Definition of TRD in Clinical Practice

The expert panel deliberated on the need to clarify that TRD refers specifically to resistance to pharmacological treatments only. It was agreed that "pharmacotherapy-resistant depression" (PRD) is a more suitable term compared with TRD and will be used henceforth when referring to the consensus and opinions from the SEA expert panel.

Based on the consensus, the panel agreed on the operating definition of PRD in clinical practice as the failure of two drug treatments of adequate dose, for 4–8 weeks duration with adequate adherence, during a major depressive episode.

Treatment Options for PRD in Adults

Twenty clinical scenarios in the management of PRD in adults were rated "appropriate" (Table 1).

Four clinical scenarios were rated "inappropriate" – switching treatment to another drug within the same class was considered as "inappropriate" in 1) an adult patient who has no response to two successive oral AD monotherapies of adequate dosage, duration and adherence; 2) an adult patient with PRD who has partial response to an AD monotherapy of adequate dose, duration and adherence; and 3) special situations where an adult patient is suicidal or when rapid response is needed. Additionally, the use of psychotherapy in adult patients who are suicidal or require rapid response was also rated as "inappropriate".

Two clinical scenarios were classified "equivocal" by the expert panel members due to uncertainties regarding 1) the use of psychotherapy in an adult patient who has no response to two successive oral AD monotherapies of adequate dosage, duration and adherence, and 2) the use of repetitive transcranial magnetic stimulation (rTMS) in special situations where a patient is suicidal or when rapid response is needed.

Panel members "disagreed" on the use of electroconvulsive therapy (ECT) in an adult patient with PRD who has partial response to an AD monotherapy with adequate dose, duration and adherence.

Treatment Pathway for MDD and PRD in Adults

The expert panel also proposed a simplified treatment pathway to support the treatment of MDD in adults, including the treatment of PRD (Figure 2).

- The first step in the proposed treatment approach for MDD is to initiate an AD monotherapy with monitoring for 4–8 weeks; if required, the treatment dose can be escalated or maximized.

Table 1 Consensus Statements on the Appropriate Management of MDD and PRD; in the Absence of Disagreement, Median Score of 7–9 is Appropriate, 4–6 is Equivocal and 1–3 is Not Appropriate

Indication	Ratings
If an adult patient with MDD has partial response to the initial AD monotherapy of adequate dose, duration and adherence,	
1. Increase the dose of the initial AD monotherapy to the maximum recommended dose as tolerated by the patient	Appropriate
2. Switch to another drug within the same class	Not appropriate
3. Switch to another class of treatment	Appropriate
4. Add another AD with different mechanism of action than that of the original AD	Appropriate
5. Use augmenting agents that have sufficient clinical evidence (eg, lithium, atypical antipsychotics, etc.)	Appropriate
6. Use psychotherapy	Appropriate
7. Use rTMS	Appropriate
8. Use ECT	Disagreement
If an adult patient under the age of 65 has a depressive unipolar episode with no significant organic or psychiatric history and has no response to two successive oral AD monotherapies with adequate dose, duration and adherence (defined as PRD),	
9. increase the dose of the second AD monotherapy to the maximum recommended dose as tolerated by the patient	Appropriate
10. Switch to another drug within the same class	Not appropriate
11. switch to another class of treatment	Appropriate
12. add another AD with different mechanism of action than that of the original AD	Appropriate
13. use augmenting agents that have sufficient clinical evidence (eg, lithium, atypical antipsychotics, etc.)	Appropriate
14. use rTMS	Appropriate
15. use ECT	Appropriate
16. use intranasal esketamine, in conjunction with a new oral AD*	Appropriate
17. use of psychotherapy	Equivocal
In special situations where a patient with MDD is suicidal or when rapid response to treatment is needed, it is appropriate to: 18. increase the dose of the initial AD monotherapy to the maximum recommended dose as tolerated by the patient	Appropriate
19. switch to another drug within the same class	Not appropriate
20. switch to another class of treatment	Appropriate
21. add another AD with different mechanism of action than that of the original AD	Appropriate
22. use augmenting agents that have sufficient clinical evidence (eg, lithium, atypical antipsychotics, etc.)	Appropriate
23. use psychotherapy	Not appropriate
24. use ECT	Appropriate
25. use intranasal esketamine, in conjunction with a new oral AD*	Appropriate
26. use of rTMS	Equivocal
If the patient with PRD has started intranasal esketamine, in conjunction with a new oral AD, and is in stable remission (MADRS score ≤12) at 4 weeks and wishes to reduce the risk of relapse of depressive symptoms,	
27. continue esketamine treatment for at least 6 months*	Appropriate

Note: *Based on FDA-approved indication, use in SEA will depend on local approved indications; AD, antidepressant; ECT, electroconvulsive therapy; MADRS, Montgomery-Asberg Depression Rating Scale; PRD, pharmacotherapy-resistant depression.

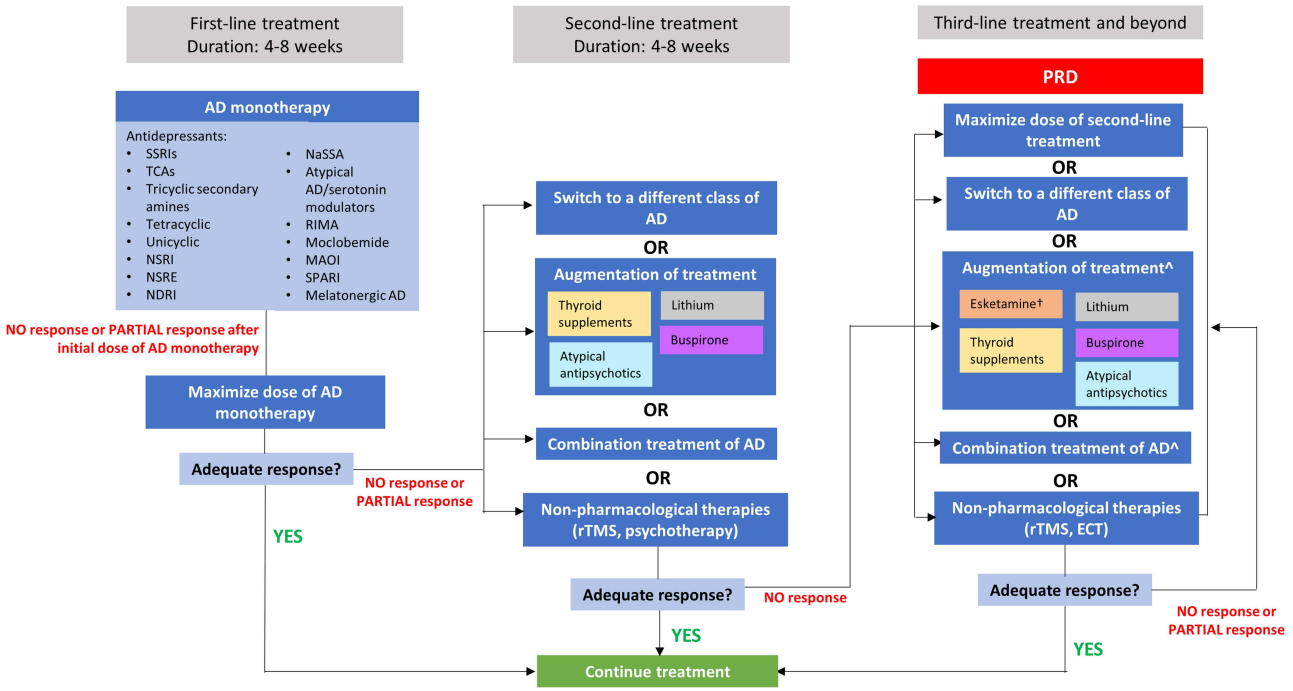

Figure 2 Treatment pathway to guide the management of MDD and PRD in adults in the SEA region. ^Combination or augmentation treatment regimen in the third line should be different from the failed combination or augmentation regimen used in second-line treatment. †Esketamine contraindications based on FDA approval: aneurysm; vascular disease; known history of atrial cerebral hemorrhage; known history of hypersensitivity to esketamine, ketamine or any of the excipients; previous ketamine abuse, bipolar disorder. Use with caution in uncontrolled hypertension.

Abbreviations: AD, antidepressant; ECT, electroconvulsive therapy; MAOI, mono amine oxidase inhibitors; NaSSA, noradrenaline and specific serotonin antidepressants; NDRI, norepinephrine-dopamine reuptake inhibitor; NSRE, norepinephrine serotonin reuptake enhance; NSRI, norepinephrine serotonin reuptake inhibitors; PRD, pharmacotherapy-resistant depression; RIMA, reversible selective mono amine oxidase inhibitors; rTMS, repetitive transcranial magnetic stimulation; SPARI, serotonin partial agonist reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic tertiary amines.

- In case of partial response or non-response after 4–8 weeks of treatment despite maximizing the treatment dose, a second AD monotherapy should be trialed for a further 4–8 weeks with response monitoring; options for second line treatment include switching to a different class of ADs, augmenting or combining treatment modalities.
- Upon failure of second line of treatment following 4–8 weeks of monitoring despite adequate dose and adherence (defined as PRD), a third-line treatment should be offered; treatment options for PRD include maximizing the dose, switching to a different class, augmenting or combining treatment modalities. Combination or augmentation treatment regimen in the third line should be different from the failed regimen used in the second-line treatment. Based on the available clinical data and FDA approval, the panel considered that esketamine, an augmenting agent, could be a potential third-line option for the treatment of PRD.
- Non-pharmacological treatment options can be considered during the second-line treatment of MDD, and PRD.

Re-assessment of treatment response during treatment is essential to optimize management. A shorter follow-up schedule after treatment initiation is recommended for special populations, such as patients with recurrent episodes, patients with severe depression, patients with physical or psychiatric comorbidities (eg, personality disorder, dual diagnosis, anxiety disorder, etc.), elderly patients, patients who are pregnant, or patients at risk for substance abuse. Treatment response should be assessed and next steps decided by the clinician after careful consideration of risks and benefits. Clinical scales (eg, CGI scale, PHQ-9) provide clinicians with additional support when assessing treatment response.

Discussion

Although a wide variety of pharmacological therapies are currently available for the management of MDD, many patients do not show improvement with adequate doses of ADs given for adequate durations, leading to TRD. However, there has

been no universal definition of TRD despite the abundance of literature on TRD. Indeed, a systematic review identified 155 definitions for TRD in the literature.[25] These variations in the definition renders evidence synthesis and translation of research findings into daily clinical practice challenging.[14] It may also affect the design of clinical trials or observational studies whose outcomes are crucial for improving TRD treatment.[14]

To establish a uniform definition and management principles for patients with TRD in SEA, the expert panel employed the RAND/UCLA Appropriateness Method to achieve consensus. This method has been widely used for the development of guidelines involving medical and surgical procedures,[24] but its use in a psychiatric setting is limited. Recently, the French Association for Biological Psychiatry and Neuropsychopharmacology and the foundation FondaMental published clinical guidelines for the management of TRD utilizing the RAND/UCLA Appropriateness method.[2] Compared with the Delphi consensus method, the authors considered this method capable of detecting agreement without trying to promote consensus, while also potentially minimizing differences between clinical opinions.[2]

Building upon the commonly used definition of TRD, the expert panel has developed a common operating definition for TRD that can potentially be utilized in clinical practice across the SEA region – the failure of two drug treatments of adequate dose, for 4–8 weeks duration, with adequate adherence, during a major depressive episode. Importantly, as TRD refers to failure of two drug treatments, the term PRD may better reflect this definition by specifying the failure to pharmacological agents only. Recently published consensus/clinical guidelines have recommended a treatment duration of either 4–6 weeks or 6–8 weeks as adequate for defining TRD,[2,12] while the expert panel consider 4–8 weeks as a more appropriate duration. The clinical experiences from SEA suggest that treatment response or lack thereof usually becomes apparent in 4 weeks of treatment, and it may be inappropriate to wait for 6 weeks in these patients.

Approaches to pharmacological management of TRD include 1) increasing or maximizing the AD dose, 2) switching to another AD (within the same class or from a different class), 3) combining two ADs, 4) augmenting ADs with other agents, and 5) using non-pharmacological treatments (psychotherapy, brain stimulation).[3] However, treatment outcomes for TRD depend on various factors, including clinical features (eg, duration of episode, time to AD response), psychosocial elements (eg, age, age at first treatment, duration of illness, suicidality, education level), environmental stress and stressful life events (eg, childhood maltreatment, job loss, psychological trauma, loss of a loved one), and psychiatric (eg, anxiety, social phobia, post-traumatic stress disorder) and physical comorbidities (eg, cardiovascular disease, diabetes); and genetic factors.[26]

Dose escalation has been a standard practice and may be a useful initial strategy for patients with MDD with partial response, but evidence also suggests that the benefit of increasing treatment dose depends on the class of AD. For example, tricyclic antidepressants have an established strong relationship between dose and clinical response, but this is not true for selective serotonin reuptake inhibitors.[27] When dose escalation fails, switching ADs within the same class or to a different class is typically employed. Several reviews have reported comparable outcomes between switching AD within the same class and switching to a different class of AD,[28–30] but a meta-analysis showed that switching to a different class of AD results in significant, albeit modest, higher remission rates compared with switching within the same class of AD.[31] This is indeed recommended in local guidelines as well[22] and reflects the clinical experiences of the SEA expert panel – most patients gain benefit from switching to another class of AD. Drugs of the same class have a similar mechanism of action and failure to one class of drug may require a switch to a drug with a different mechanism of action involving a different neurotransmitter pathway. Patients also may not wish to take a different AD from a same class to which they have previously failed to respond. As such, switching to another class of AD is an appropriate next strategy for patients with TRD who failed two consecutive AD monotherapies despite adequate dose, duration and adherence. To switch ADs, one of three strategies can be employed – concurrent switch, where the dose of both medications is changed simultaneously; overlapping switch, where the current medication is continued at the original dose while the dose of the second medication is increased to optimal level; and sequential switch, where the dose of the current medication is titrated downward until interruption and the new medication is then introduced.[32] The efficacy of augmentation in managing TRD, especially with atypical antipsychotics and lithium, are well established, and this strategy has been frequently used in routine clinical care.[3] Evidence for combination strategy (addition of at least another AD, usually from a different class) is limited and has contradicting findings,[33] but it is a widely used strategy in routine clinical practice.[2,3] Both augmentation and combination strategies offer similar advantages in maintaining the

initial improvements and producing a rapid response but carry the risk of increased side effects due to drug–drug interactions;[33] these side effects may be difficult to manage because identification of the AD leading to the side effects is not a straightforward process. Tapering down medications in combination regimens can also be difficult to achieve. Patients already on multiple drugs for their comorbid medical conditions may be reluctant to add several more medications to manage their mood. Additionally, ensuring treatment adherence is more challenging with combination therapy than monotherapy. With combination therapy, patients may need to take medications several times in a day and this may increase the likelihood of patients forgetting to take the required doses, leading to poor adherence and hence outcomes. Comparative data across these pharmacotherapy strategies are scarce, therefore clinicians must ultimately determine the appropriate treatment strategy based on individual circumstances of the patient, and careful consideration of the risk-benefit balance.

Non-pharmacological approaches, including brain stimulation techniques and psychotherapy, can also support the management of TRD. The expert panel believe that non-pharmacological approaches can be used at any point during the treatment of MDD and TRD.

ECT has demonstrated a good efficacy and safety profile and is indicated for severe major depression, mania, schizophrenia and catatonia, but it is associated with concerns about cognitive impairment and the informed consent process; as such, its use has mainly been reserved for situations where AD is unable to adequately treat severe depression.[34] Increasing evidence also suggests rTMS to be a useful adjunctive modality with AD in treating TRD.[35] Several systematic reviews and meta-analyses have demonstrated the beneficial effect of rTMS in improving depressive symptoms in patients with TRD, with or without AD.[36–38] Furthermore, the reported adverse effect discontinuation rate of rTMS was only 4.5% in contrast to 25.1% discontinuation rate for AD.[39,40] Compared with rTMS, ECT has been shown to be more effective in the treatment of depression.[41–43] However, patients receiving ECT may experience more cognitive side effects compared with those receiving rTMS.[41] Additionally, combination of ECT and AD may also increase the incidence of memory deterioration compared with ECT alone.[44] Guidelines have recommended ECT as a first-line treatment for MDD in urgent and emergency situations, such as high risk of suicide and extreme levels of distress;[19,45] it can also be considered for the prevention of relapse as monotherapy or in combination with AD.[2] In line with this, the expert panel recommends the use of ECT in patients with MDD who are suicidal or require rapid response. However, there was disagreement among the panel members regarding the use of ECT in patients with MDD with partial response to pharmacological treatment – while some of the panel members consider ECT as an appropriate adjunctive therapy for partial responders due to its proven efficacy, some consider it inappropriate for patients who have had a meaningful albeit partial response to treatment. In this case, further optimization of pharmacological treatment is warranted based on efficacy and cost-effectiveness considerations. Furthermore, based on the available evidence, the expert panel recommends the use of rTMS in partial responders and in patients with PRD but indicates uncertainty regarding its use in special situations where a patient is suicidal or requires rapid response. Sparse evidence suggests that rTMS may be useful in reducing suicide risk,[46,47] and hence its use in patients with suicidal risk in the SEA is limited. While rTMS is a viable treatment option in this patient population, further real-world studies are warranted to demonstrate the effectiveness of rTMS.

Psychotherapy has a slower onset of action,[48] but a recent Cochrane review concluded that there is moderate-quality evidence showing that psychotherapy as an adjunctive treatment to AD is beneficial for improving response and remission rates in the short term for patients with TRD.[49] There is, however, no evidence of benefit for switching to a psychotherapy alone compared with continuing an AD regimen.[49] As such, the expert panel considers the use of psychotherapy in patients with MDD with partial response to pharmacological treatment as appropriate. However, psychotherapy is not appropriate for patients who are suicidal or require rapid response because of the slower onset of action of psychotherapy. Furthermore, evidence supporting the efficacy of psychotherapy in patients with suicidal risk are scarce. The SEA expert panel indicates uncertainty regarding the use of psychotherapy in patients with PRD based on their clinical experiences – patients with PRD typically have severe depression; they may not be able to focus and participate actively in the process of psychotherapy due to a lack of ability to concentrate and control their cognitive distortion. Furthermore, there is a lack of standardized certification for psychotherapy and qualified psychotherapists or

clinical psychologists in the SEA region. Local guidelines also do not recommend adjunctive psychotherapy in the management of patients with TRD due to limited evidence.[22]

Recently, the US Food and Drug Administration and the European Medicines Agency approved esketamine nasal spray, in conjunction with an oral AD, for TRD in adults.[50,51] Esketamine is the S-enantiomer of ketamine that significantly reduces symptoms of depression in TRD with an acceptable safety profile.[52] Reported side effects of esketamine are typically mild and transient.[53,54] Furthermore, esketamine has a rapid onset of action and maintains treatment response with continued use.[53,54] However, it is important to note that there are safety concerns over sedation and dissociation, and a potential for misuse and abuse of esketamine. Therefore, it can only be prescribed and administered by certified healthcare providers in certified centers where patients can be monitored for adverse events for at least 2 hours after treatment initiation.[50] Data from long-term follow-up studies will further provide insights on safety issues and long-term use of esketamine. Regardless, esketamine may be a useful addition to the limited treatment armamentarium of TRD. At the time of the consensus meeting, esketamine in Asia was only approved and available in South Korea.[55] However, it is now approved and available in Singapore,[56] Malaysia,[57] the Philippines,[58] and Indonesia.[59] Based on the available clinical data and the FDA label, esketamine should be used with caution in patients with an increased risk of substance use disorders and all exclusions listed in the FDA approval for esketamine should be considered as exclusions for the use of esketamine in the SEA as well. Personality disorders should not be considered an exclusion for the use of esketamine; in these patients, the clinician's judgement should guide the use of esketamine.

Our consensus on the pharmacological treatment strategies for patients with MDD and TRD is generally consistent with existing guidelines.[2,17–19] However, our consensus does not provide specific recommendations on dosing and agents, as availability and accessibility of treatment agents vary across the SEA region. Instead, we provide a treatment pathway summarizing the appropriate treatment options for the management of patients with MDD and TRD (Figure 2). Our consensus on the non-pharmacological treatment strategies is also aligned with the clinical guidelines by Bennabi et al[2] brain stimulation techniques (ie, rTMS and ECT) are reserved for patients with treatment resistance, while various types of psychotherapy are recommended for those with MDD.

While cost is an important factor in deciding treatment option for patients, the RAND/UCLA Appropriateness Method focuses on the effectiveness of a procedure and does not take cost implication into account.[60] We also recognize that the adaptation of the proposed definition and treatment principles of PRD in clinical practice will be influenced by various local contexts in the SEA region, including differences in healthcare system and resources, the availability and accessibility of treatment options, and financial constraints and reimbursement system. By and large, psychiatry services are available in all large hospitals or medical centers across the SEA region, and thus the implementation of our proposed treatment principles can be applied to both inpatient and outpatient settings. These principles can be implemented in smaller clinics as well, but this may be limited by manpower and logistics constraints in monitoring patients and patients may need to be referred to larger centers. In private settings, patients can be monitored for treatment response more frequently, so the treatment timeline can be adjusted to a shorter duration. However, time and manpower restrictions in public settings may render a shorter follow-up interval difficult. Trained medical officers, nurses or junior doctors should be allowed to carry out treatment monitoring with supervision by the lead psychiatrist to circumvent issues related to time and manpower limitations. As such, our proposed principles and treatment pathway for the management of MDD and PRD in the SEA region are evidence- and experience-based, and incorporate all available treatments, including newer treatment options like rTMS and esketamine; these principles provide a pragmatic definition and clear management guidance for PRD, and can be broadly applied over the entire SEA region. In the absence of a regional treatment guideline for PRD that can be employed across this widely heterogenous region, the principles and pathway we propose will support treatment decisions for PRD across SEA regardless of clinical settings.

Conclusion

To optimize the management of patients with PRD in the SEA region, we have developed a consensus on the operating definition and treatment principles of PRD that can be adapted according to various local contexts in the SEA countries. This expert consensus is not a prescriptive guideline and should not replace clinical judgement. Individual circumstances and benefit-risk balance should be carefully considered in determining the most appropriate treatment option for patients with PRD.

Ethics Approval

There were no human subjects involved, and there is no human material or identifiable data in the manuscript. As such, institutional review board or ethics committee approval was not deemed necessary.

Acknowledgment

The authors thank Yulyana of In Vivo Communications (Asia) Pte Ltd for the provision of medical writing assistance in the preparation of this manuscript; funding for this assistance was provided by Johnson and Johnson Pte Ltd. The authors also acknowledge the support from the Healthy Thinking Group Asia in performing the literature review and developing the pre-meeting survey and clinical scenarios for discussion.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors received honoraria and travel support from Johnson & Johnson Pte Ltd to attend and participate at the consensus meeting. Pichai Ittasakul has received salary support from Mahidol University, Bangkok, Thailand, lecture honoraria from Janssen, Servier, AstraZeneca, Novartis, Pfizer, Sumitomo Dainippon Pharma. Ahmad Hatim Sulaiman has received honoraria as speaker for Johnson & Johnson, participated and received grants for clinical trial for Johnson & Johnson. Kok Yoon Chee has received honoraria as speakers for Johnson & Johnson, Lundbeck, Novartis and Pfizer; participated and received investigator fees for clinical trial for Johnson & Johnson. Phern Chern Tor, Benita Ponio, Dharmawan Ardi Purnama, Johnson Fam, Elizabeth Rondain, Nurmiati Amir, Roger Ho Chun Man, Wanida Rattanasumawong, Kannokarn Wiroteurairuang and Esketamine is marketed by Janssen, a Johnson & Johnson company. The authors report no other conflicts of interest in this work.

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collabolators. Global, regional and national incidence, prevalence, and years lived with disability for 354 disease and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1789–1858. doi:10.1016/S0140-6736(18)32279-7
2. Bennabi D, Charpeaud T, Yrondi A, et al. Clinical guidelines for the management of treatment-resistant depression: french recommendations from experts, the French Association for biological psychiatry and neuropsychopharmacology and the foundation fondaMental. *BMC Psychiatry*. 2019;19(1):262. doi:10.1186/s12888-019-2237-x
3. Dold M, Kasper S. Evidence-based pharmacotherapy of treatment-resistant unipolar depression. *Int J Psychiatry Clin Pract*. 2017;21(1):13–23. doi:10.1080/13651501.2016.1248852
4. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905–1917. doi:10.1176/ajp.2006.163.11.1905
5. Bergfeld IO, Mantione M, Figee M, Schuurman PR, Lok A, Denys D. Treatment-resistant depression and suicidality. *J Affect Disord*. 2018;235:362–367. doi:10.1016/j.jad.2018.04.016
6. Johnston KM, Powell LC, Anderson IM, Szabo S, Cline S. The burden of treatment-resistant depression: a systematic review of the economic and quality of life literature. *J Affect Disord*. 2019;242:195–210. doi:10.1016/j.jad.2018.06.045
7. Klug J, Yu F, Chang C, et al. Estimating the economic burden of treatment resistant depression in Taiwan using the NHIRD. *Value Health*. 2016;19:A840–1.
8. Souery D, Oswald P, Massat I, et al. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry*. 2007;68(7):1062–1070. doi:10.4088/jcp.v68n0713
9. Kubitz N, Vossen C, Papadimitropoulou K, Karabis A. The prevalence and disease burden of treatment-resistant depression – a systematic review of the literature. *Value Health*. 2014;17:A455–6.
10. Mahlich J, Tsukazawa S, Wiegand F. Estimating prevalence and healthcare utilization for treatment-resistant depression in Japan: a retrospective claims database study. *Drugs Real World Outcomes*. 2018;5(1):35–43. doi:10.1007/s40801-017-0126-5
11. Fife D, Feng Y, Wang M, et al. Epidemiology of pharmaceutically treated depression and treatment resistant depression in Taiwan. *Psychiatry Res*. 2017;252:277–283. doi:10.1016/j.psychres.2017.03.006
12. Ng CH, Kato T, Han C, et al. Definition of treatment-resistant depression – Asia Pacific perspectives. *J Affect Disord*. 2019;245:626–636. doi:10.1016/j.jad.2018.11.038

13. Fife D, Reps J, Cepeda MS, Stang P, Blacketer M, Singh J. Treatment resistant depression incidence estimates from studies of health insurance databases depend strongly on the details of the operating definition. *Heliyon*. 2018;4(7):e00707. doi:10.1016/j.heliyon.2018.e00707
14. Gaynes BN, Lux L, Gartlehner G, et al. Defining treatment-resistant depression. *Depress Anxiety*. 2020;37(2):134–145. doi:10.1002/da.22968
15. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of treatment-resistant depression: challenges and strategies. *Neuropsychiatr Dis Treat*. 2020;16:221–234. doi:10.2147/NDT.S198774
16. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Moller HJ; World Federation of Societies of Biological Psychiatry, Task Force on Unipolar Depressive Disorders. 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 (5):334–385. doi:10.3109/15622975.2013.804195
17. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Moon 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(9):540–560. doi:10.1177/ 0706743716659417
18. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry*. 2015;49(12):1087–1206. doi:10.1177/0004867415617657
19. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol*. 2015;29(5):459–525. doi:10.1177/0269881115581093
20. Thailand Ministry of Public Health. Clinical practice guideline of major depressive disorder for general practitioner: CPG-MDD-GP; 2010. Available from: http://www.thaidepression.com/www/news54/CPG-MDD-GP.pdf. Accessed March 16, 2020.
21. Philippine Psychiatric Association. Consensus treatment guidelines on major depressive disorder in adults; 2017.
22. Malaysia Ministry of Health. Clinical Practice Guidelines – management of major depressive disorder (second edition); 2019. Available from: http://www.moh.gov.my/moh/resources/Penerbitan/CPG/1)_CPG_Management_Major_Depressive_Disorder_(Second_Edition).pdf. Accessed March 16, 2020.
23. Chongsuvivatwong V, Phua KH, Yap MT, et al. Health and health-care systems in Southeast Asia: diversity and transitions. *Lancet*. 2011;377 (9793):429–437.
24. Nair R, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic criteria and guideline development. *Semin Arthritis Rheum*. 2011;41(2):95–105. doi:10.1016/j.semarthrit.2010.12.001
25. Brown S, Rittenbach K, Cheung S, McKean G, MacMaster FP, Clement F. Current and common definitions of treatment-resistant depression: findings from a systematic review and qualitative interviews. *Can J Psychiatry*. 2019;64(6):380–387. doi:10.1177/0706743719828965
26. Kraus C, Kadriu B, Lanzenberger R, Zarate CA Jr, Kasper S. Prognosis and improved outcomes in major depression: a review. *Transl Psychiatry*. 2019;9(1):127. doi:10.1038/s41398-019-0460-3
27. Philip MS, Carpenter LL, Tyrka AR, Price LH. Pharmacologic approaches to treatment resistant depression: a re-examination for the modern era. *Expert Opin Pharmacother*. 2010;11(5):709–722. doi:10.1517/14656561003614781
28. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354:1231–1242. doi:10.1056/NEJMoa052963
29. Schosser A, Serretti A, Souery D, et al. European Group for the Study of Resistant Depression (GSRD)--where have we gone so far: review of clinical and genetic findings. *Eur Neuropsychopharmacol*. 2012;22:453–468. doi:10.1016/j.euroneuro.2012.02.006
30. Bschor T, Baethge C. No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy. *Acta Psychiatr Scand*. 2010;121:174–179. doi:10.1111/j.1600-0447.2009.01458.x
31. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry*. 2008;63(7):699–704. doi:10.1016/j.biopsych.2007.08.010
32. Malhi GS, Hitching R, Berk M, Boyce P, Porter R, Fritz K. Pharmacological management of unipolar depression. *Acta Psychiatr Scand Suppl*. 2013;443:6–23. doi:10.1111/acps.12122
33. Tundo A, de Filippis R, Proietti L. Pharmacologic approaches to treatment resistant depression: evidences and personal experience. *World J Psychiatry*. 2015;5(3):330–341. doi:10.5498/wjp.v5.i3.330
34. Kellner CH, Greenberg RM, Murrough JW, Bryson EO, Briggs MC, Pasculli RM. ECT in treatment-resistant depression. *Am J Psychiatry*. 2012;169(12):1238–1244. doi:10.1176/appi.ajp.2012.12050648
35. Somani A, Kar SK. Efficacy of repetitive transcranial magnetic stimulation in treatment-resistant depression: the evidence thus far. *Gen Psychiatr*. 2019;32(4):e100074. doi:10.1136/gpsych-2019-100074
36. Gaynes BN, Lloyd SW, Lux L, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2014;75(5):477–89;quiz 489. doi:10.4088/JCP.13r08815
37. Wei Y, Zhu J, Pan S, Su H, Li H, Wang J. Meta-analysis of the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *Shanghai Arch Psychiatry*. 2017;29(6):328–342. doi:10.11919/j.issn.1002-0829.217106
38. Health Quality Ontario. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis of randomized controlled trials. *Ont Health Technol Assess Ser*. 2016;16(5):1–66.
39. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746–758.
40. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure and during reintroduction treatment. *J Clin Psychiatry*. 2008;69(2):222–232. doi:10.1016/S0140-6736(09)60046-5
41. Hansen PE, Ravnkilde B, Videbech P, et al. Low-frequency repetitive transcranial magnetic stimulation inferior to electroconvulsive therapy in treating depression. *J ECT*. 2011;27(1):26–32. doi:10.1097/YCT.0b013e3181d77645
42. Berlim MT, Van den Eynde F, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. *Depress Anxiety*. 2013;30 (7):614–623. doi:10.1002/da.22060
43. Ren J, Li H, Palaniyappan L, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;51:181–189. doi:10.1016/j.pnpbp.2014.02.004

44. Song GM, Tian X, Shuai T, et al. Treatment of adults with treatment-resistant depression: electroconvulsive therapy plus antidepressant or electroconvulsive therapy alone? Evidence from an indirect comparison meta-analysis. *Medicine*. 2015;94(26):e1052. doi:10.1097/MD.0000000000001052
45. Milev RV, Giacobbe P, Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. *Can J Psychiatry*. 2016;61(9):561–575. doi:10.1177/0706743716660033
46. Abdelnaim MA, Langguth B, Deppe M, et al. Anti-suicidal efficacy of repetitive transcranial magnetic stimulation in depressive patients: a retrospective analysis of a large sample. *Front Psychiatry*. 2020;10:929. doi:10.3389/fpsyt.2019.00929
47. Desmyter S, Duprat R, Baeken C, Van Autreve S, Audenaert K, van Heeringen K. Accelerated intermittent theta burst stimulation for suicide risk in therapy-resistant depressed patients: a randomized, sham-controlled trials. *Front Hum Neurosci*. 2016;10:480. doi:10.3389/fnhum.2016.00480
48. Weissman MM, Markowitz JC. The future of psychotherapies for mood disorders. *World Psychiatry*. 2003;2(1):9–13.
49. Ijaz S, Davies P, Williams CJ, Kessler D, Lewis G, Wiles N. Psychological therapies for treatment-resistant depression in adults. *Cochrane Database Syst Rev*. 2018;5:CD010558. doi:10.1002/14651858.CD010558.pub2
50. United States Food and Drug Administration. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic; 2019. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified. Accessed February 17, 2020.
51. European Medicines Agency. Spravato; 2019. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/spravato. Accessed February 17, 2020.
52. Bozymski KM, Crouse EL, Titus-Lay EN, Ott CA, Nofziger JL, Kirkwood CK. Esketamine: a novel option for treatment-resistant depression. *Ann Pharmacother*. 2020;54(6):567–576. doi:10.1177/1060028019892644
53. Bahr R, Lopez A, Rey JA. Intranasal Esketamine (Spravato^{TM}) for use in treatment-resistant depression in conjunction with an oral antidepressant. *Pharm Ther*. 2019;44(6):340–375.
54. Kryst J, Kawalec P, Pilc A. Efficacy and safety of intranasal esketamine for the treatment of major depressive disorder. *Expert Opin Pharmacother*. 2020;21(1):9–20. doi:10.1080/14656566.2019.1683161
55. Ministry of Food and Drug Safety, South Korea. Integrated pharmaceutical information system. Spravato nasal spray (esketamine hydrochloride); 2020. Available from https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetail?itemSeq=202004585. Accessed July 14, 2020.
56. Health Sciences Authority, Singapore. Healthcare professional guide for SPRAVATO® (esketamine) nasal spray; 2021. Available from: https://www.hsa.gov.sg/docs/default-source/hprg-vcb/pem-pmg-pac/spravato-pem_version2_08122021.pdf. Accessed November 10, 2022.
57. Ministry of Health, Malaysia. Horizon scanning report, intranasal esketamine; 2019. Available from: https://www.moh.gov.my/index.php/database_stores/attach_download/561/41. Accessed November 10, 2022.
58. Food and Drug Administration, Philippines. Esketamine; 2021 Available from: https://verification.fda.gov.ph/drug_productslist.php?cmd=search&t=drug_products&psearch=spravato&psearchtype=. Accessed November 10, 2022.
59. Indonesian Food and Drug Supervisory Agency. Esketamine; 2021. Available from: https://cekbpom.pom.go.id//home/produk/n1rjqvhpj0f51249qe2151ctm4/all/row/10/page/1/order/4/DESC/search/5/esketamine. Accessed November 10, 2022.
60. Fitch K, Bernstein SJ, Aguilar MD, et al. The RAND/UCLA appropriateness methos user's manual; 2001. Available from: https://www.rand.org/pubs/monograph_reports/MR1269.html. Accessed July 14, 2020.