Clinical Management of Depression – Summary of RANZCP Guidelines

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In early February 2018, the Australian government published their health spending figures for 2015/2016, which showed that $9 billion was spent on mental health [1]. On average this is $373 per person, and this number has been increasing by 1.4% per annum.

In the context of medical morbidity, depression is a significant contributor to the global burden of disease and is associated not only with an increased health care cost, but more prolonged hospitalisation, poor treatment compliance, and higher rates of morbidity.

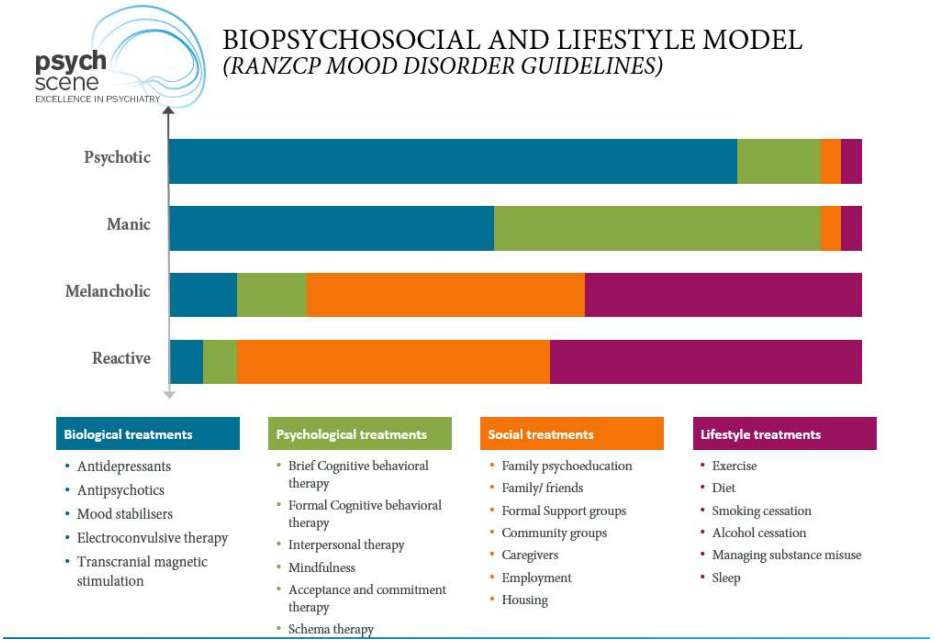
Key facts:

- 1 in 10 patients in primary care present with depressive symptoms
- The lifetime risk of depression is 15%, and 12-month prevalence is 4.1%
- Female to male ratio is 2:1
- 80% of those affected by depression will experience at least 2 episodes of illness in their lifetime
- 54% of individuals recover within 6 months; 70% within one year
- 12-15% fail to recover and develop an unremitting chronic illness

The article is a summary of the RANZCP mood disorder guidelines for depression. The article focuses on management of depression in adults and does not include treatment of special groups such as perinatal, youth, elderly or those with comorbid medical conditions.

CLINICAL MANAGEMENT OF DEPRESSION - RANZCP GUIDELINES

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) Major Depression Guidelines emphasise a *Biopsychosocial Lifestyle Approach (BPSL)*. [2]

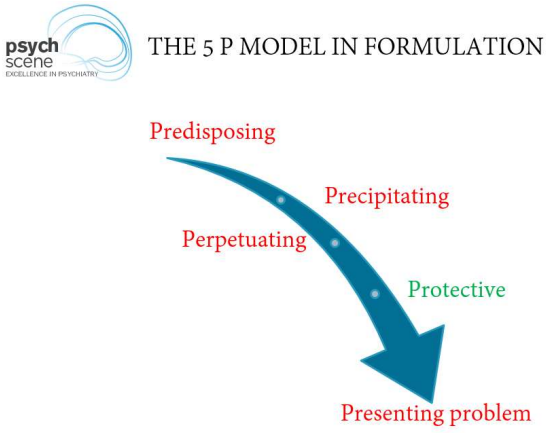


As one can see from the above diagram psychotic depression tends to have greater weighting toward biological factors which is reflected in a greater weight of biological treatments as opposed to reactive depression.

The **BPSL** model forms the framework for the development of a psychiatric formulation which provides a richer understanding of why the patient has developed the illness now.

This model is broader than the traditional biomedical model with treatments tailored to the individual and the subtype of depression.

The BPSL model can be combined with the **5P formulation model** to better understand the genesis of the depressive illness.



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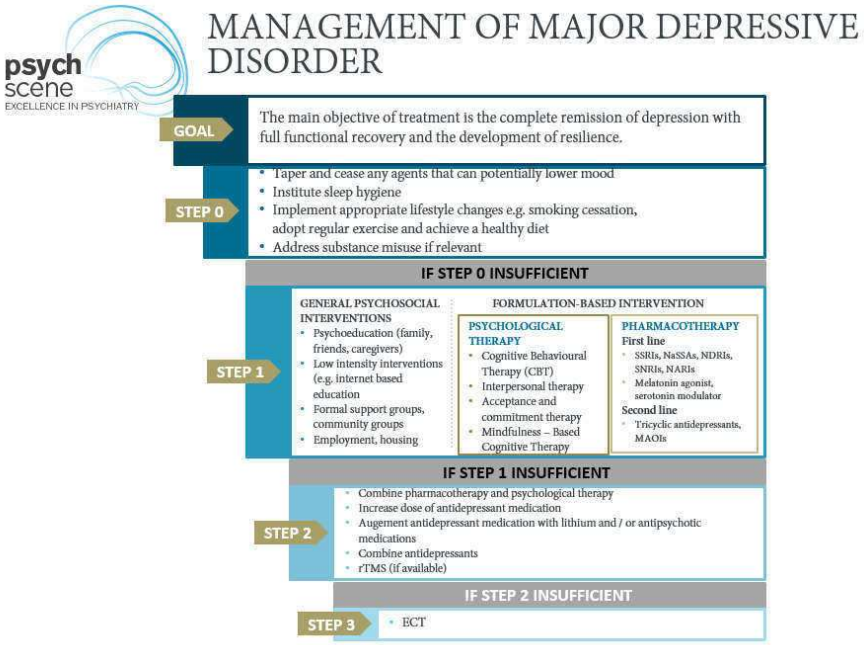
Aims of treatment

- Relieve symptoms
- Reduce the morbidity
- Limit the disability
- Limit self-harm risk or potential risk of fatality.
- Achieve recovery to the premorbid level of functioning with improved health awareness and quality of life

Three phases of treatment

- Acute phase
- Continuation phase
- Recovery phase

GENERAL PRINCIPLES



- Before prescribing medications, primary care physicians and psychiatrists should encourage stress management, a healthy lifestyle (including a balanced diet and exercise) and good sleep hygiene
- For mild-to-moderate depression, psychosocial interventions are indicated as a first-line therapy
- For depression that is moderate-to-severe, pharmacotherapy augmented with psychosocial interventions is the recommended first-line therapy

IMPORTANT POINTS IN THE ASSESSMENT OF DEPRESSION

There a number of factors that determine the course of treatment which is most likely to return the patient to their premorbid functioning with an improved resilience against recurrence.

Firstly, the aetiology of depression needs to be considered by taking a longitudinal life course perspective that views the time of onset, previous episodes of depression, and the presence of dysthymia.

- Evaluation of **comorbid substance abuse** and in particular the relationship of depression with dependence, withdrawal, and abstinence.
- Is the patient taking any **prescribed medications** that are known to cause depression?
- Reviewing whether the patient has any **physical illness** that may have a causative role in the development of depression, or whether there is a co-occurrence due to a shared aetiology
- To carefully consider the relationship between essential aspects such as seasonal affective disorder, peripartum depression, and menstrually related mood disorders with the onset of depression. Learn more about depression in women in https://psychscenehub.com/video/hormones-mental-illness-women-pmdd-depression/
- Clinicians are also required to rule out the presence of **bipolar disorder** at this stage as well by reporting the presence of any hypomanic or manic episodes. Read more about differentiating between unipolar and bipolar depression in https://psychscenehub.com/psychinsights/unipolar-bipolar-disorder-whats-fuss/
- Major depressive disorders (MDD) with **mixed features** is considered to lie along a bipolar trait and is an important differential diagnosis as antidepressants on their own may worsen the condition. Read more about MDD with mixed features in this CPD module in https://psychscenehub.com/psychinsights/major-depressive-disorder-mixed-features-interactive/

Read more about the criteria for depression and the diagnostic interview in https://psychscenehub.com/psychpedia/depression-diagnostic-interviewing/

Learn more about differential diagnosis of depression in https://psychscenehub.com/psychpedia/depression-co-morbidities/

PSYCHOLOGICAL THERAPIES

Symptoms and patient preference should guide psychotherapy choice.

There is a broad range of psychological therapies available in depression:

- Cognitive Behavioural Therapy (CBT)
- Interpersonal Psychotherapy (IPT)
- Non-directive supportive therapy
- Problem-solving therapy
- Behavioural activation therapy
- Self-control therapy
- Short-term psychodynamic therapy
- Mindfulness-based cognitive therapy (MBCT)

- Third wave psychotherapies – Acceptance commitment therapy (ACT), compassionate mind training, functional analytical psychotherapy, extended behavioural activation and meta-cognitive therapy

CBT

- CBT is the most widely researched treatment for depression, and all international guidelines recommend it
- CBT is as effective as antidepressant medication for depression of mild-moderate severity
- May require a patient to be prescribed antidepressants prior because moderate to severe depressive symptoms can hinder therapeutic effect due to poor patient commitment and initiative.
- Involves modifying dysfunctional cognitions that affect emotions and behaviours

Interpersonal psychotherapy

- Focuses on interpersonal factors that may impact the development of depression such as role disputes, loss, role transitions and interpersonal deficits.
- Evidence-based in both acute depression and relapse prevention

Third wave psychotherapies

- Mindfulness-based CBT and acceptance and commitment therapy are recently developed structured therapies. Useful in reducing depressive symptoms and preventing relapse.
- MBCT may be better for patients prone to worry, and ACT may be best for patients needing to accept and adjust to persisting problems.

What does the evidence tell us?

A series of meta-analyses and a network meta-analysis suggest that psychological treatments are equally efficacious in the acute treatment of depression.

There is strong clinical consensus that treatment is best guided by an evidence-based treatment manual, tailored to the individual patient, and with proper attention to the therapeutic relationship.

Psychological therapy should be initiated early in the course of the illness and this can be stand alone (monotherapy). However, if there is minimal response within a reasonable period of time, then pharmacotherapy should be considered. Depending on the severity and symptom profile of the depressed patient, psychological treatment may be best administered after initiating pharmacotherapy, and in thiscontext clinical features such as melancholic features that may predict better response to SSRIs than CBT should be taken into consideration (Simon and Perlis, 2010) (https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2010.09111680)

It is recommended that some form of psychological intervention (at a minimum, psychoeducation) accompany pharmacotherapy whenever possible because sometimes where medications produce response but do not achieve remission, the addition of psychological interventions may enable remission.

Key recommendations

1. Psychological interventions should only be delivered by clinicians trained in the relevant evidence-based approach.
2. Treatment should be guided by a published manual, tailored to the individual, and should pay particular attention to establishing and maintaining the therapeutic alliance.
3. Patients with mild-moderate depression should be offered one of the evidence-based psychotherapies as first-line treatment.
4. Patients with moderate-severe depression should be offered combined pharmacotherapy and psychotherapy as first-line treatment.
5. Patients with chronic depressive disorders should be offered combined psychotherapy and pharmacotherapy as first-line treatment.

PHARMACOTHERAPY

At present, there are no reliable clinical markers for success, and therefore a physician's judgment is required to be evidence-based.

The choice of antidepressant is usually based on:

- illness severity
- the degree of associated impairment
- patient preference
- previous response
- presence of atypical features
- melancholic features
- psychomotor retardation or psychotic features
- a family history of response to treatment
- significant dysfunctional premorbid personality factors (including child abuse history) (reduced response to antidepressant monotherapy alone)
- Psychosocial precipitating factors (reduced response to antidepressant monotherapy alone)

Classification of antidepressants

Antidepressants are classified based on the mechanism of action including:

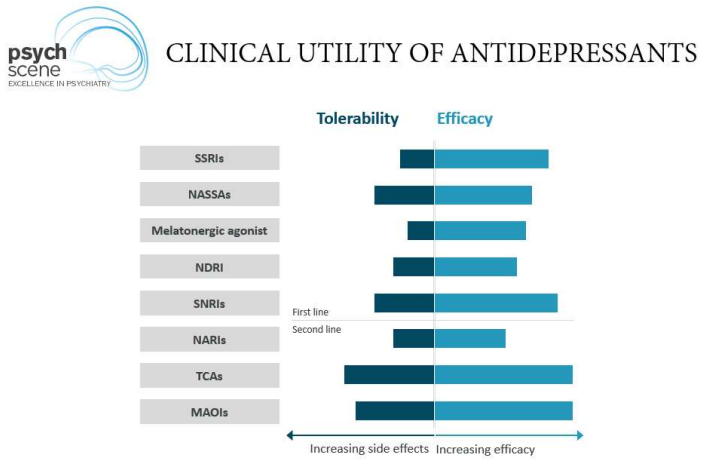
1. **Selective serotonin reuptake inhibitors (SSRIs)** represent the first line of pharmacotherapy as they are considered relatively safe, tolerable and effective. E.g. sertraline, citalopram, escitalopram, fluoxetine, paroxetine, fluvoxamine.
2. **Serotonin-norepinephrine reuptake inhibitors (SNRI's)** e.g. venlafaxine, desvenlafaxine and duloxetine are just as effective but are less well tolerated.
3. **Tricyclic antidepressants (TCA)** (amitryptiline, clomipramine, imipramine) and **monoamine oxidase inhibitors (MAOI)** (phenelzine, tranylcypromine) may have

greater efficacy, but they come with side effects and safety concerns with regarding the potential to overdosing

4. **Melatonergic agonist** – agomelatine
5. **Serotonin modulator** – Vortioxetine
6. **Noradrenaline reuptake inhibitor (NARI)** – Reboxetine
7. **Noradrenaline and dopamine reuptake inhibitor (NDRI)** – Bupropion
8. **Serotonin antagonist and reuptake inhibitor (SARI)** – Trazodone

There is no significant difference in efficacy between the different antidepressants as shown in meta-analyses.

Antidepressants do differ in tolerability which may inform treatment choice.



Malhi, G. S., et al. (2015). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian & New Zealand Journal of Psychiatry, 49*(12), 1087-1206.

TCA's and MAOI's have greater efficacy in melancholic depression, but their use is limited by their side effect profile and risk in overdose. The newer generation antidepressants have a better tolerability profile with SNRI's being more efficacious than SSRI's in melancholic depression.

We covered a summary of mechanisms of actions, side effects and indications for the above classes in https://psychscenehub.com/psychinsights/summary-21-antidepressants-network-metaanalysis/

We also covered the largest network meta-analysis by Cipriani et al. on antidepressants ranking them according to efficacy and acceptability in https://psychscenehub.com/psychinsights/efficacy-acceptability-antidepressants-network-meta-analysis/

Patients who are prescribed an antidepressant should be carefully monitored in the early phase as a **clinical response**—at the therapeutic dose—is usually reported **within two weeks**.

Early follow-ups also allow detection of treatment-emergent suicidality. **Therefore, an adequate antidepressant trial should be a minimum of 3 weeks.**

If an adequate dose has been found effective, remission usually requires six weeks of treatment.

Once a satisfactory therapeutic response has been achieved, antidepressant dosage should remain the same during continuation and maintenance phases of treatment. Maintenance antidepressant treatment should be continued for at least six months and up to one-year particularly if episodes have been recurrent.

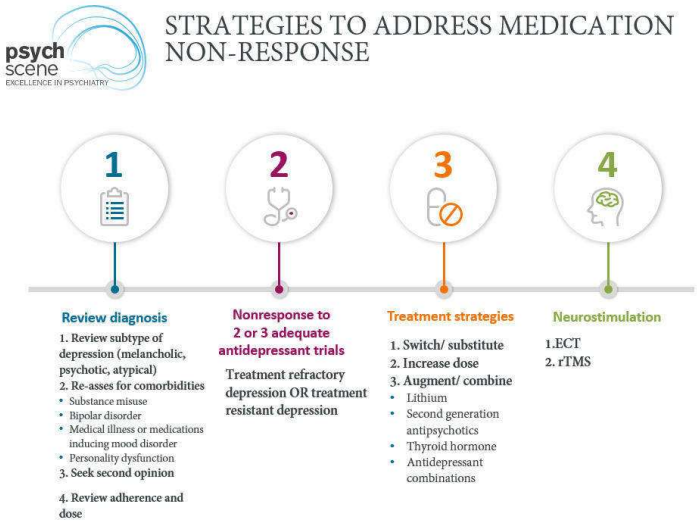
MANAGEMENT OF NON-RESPONSE - TREATMENT OPTIONS

If there is no improvement in symptoms after 3 weeks, reappraisal and adjustment of the pharmacotherapy should be considered as well as patient treatment adherence.

The STAR*D study showed that after four successive trials of antidepressants a cumulative remission rate of 67% was reached, though it may require 2–3 antidepressant trials before complete remission is attained. [3]

Even with switching to an alternative medication or adding an augmenting agent, only 30% of depressed patients achieve a partial response or remain non-responsive (refractory or treatment resistant).

From an economic perspective, a recent US study (see: http://www.psychiatrist.com/JCP/article/Pages/2018/v79n02/17m11725.aspx) showed that treatment resistant depression (TRD) accounts for a large share of the MDD economic burden ($6709 and $9917 higher per patient per year (PPPY) health care costs than non TRD MDD and non-MDD patients respectively with 35.8 work loss days PPPY).



1.Review diagnosis:

- Anxiety and substance misuse is associated with poor response
- Bipolar depression – Approx. 10% of patients with initial unipolar depression will subsequently experience hypomania/mania in the course of their illness. Mixed features also contribute to poor response
- Medical illness

2.Dose increase

- Should be considered if the patient has experienced a partial response to therapy. SSRI's tend to have a flat dose-response curve.
- Some antidepressants such as Venlafaxine have varying plasma levels due to genetic polymorphisms in CYP enzymes. In such cases, pharmacogenomics testing may guide dose increase.

3.Switching and substitution

- If the patient has an unsatisfactory response to a first-line antidepressant, then a second antidepressant (same class or different) can be recommended.
- **When switching there are two considerations** – first the choice of antidepressant and second the strategy of the switch.

*The STAR*D study, an open naturalistic study, showed equivalent remission rates regardless of whether the patient switched from citalopram to bupropion, sertraline or venlafaxine.*

There is randomised controlled evidence for improved outcomes with switching from an SSRI to venlafaxine and mirtazapine, and from a tricyclic to an irreversible MAOI, but the evidence for switching from an SSRI to a TCA is inadequate even though clinical experience and expert opinion supports this strategy particularly in more severe depression (Nierenberg et al., 2007) (http://europepmc.org/abstract/med/17362800)

Three main strategies should be considered when deciding the best way to switch medications. The aim is to minimise any un-medicated interim period and limit the possibility of serotonin syndrome

1. Overlap
2. Taper or stop/start;
3. Washout (safest option but increases chance of worsening depression).

4.Augmentation –

a. **Lithium**

- Effective augmentation agent in combination with SSRI's, TCA's and other antidepressants. Serum levels should be maintained between 0.5-0.8 mmol/l
- Predictors of likely response to lithium augmentation include recurrent major depression with more than 3 recurrences and a family history in first degree relatives of bipolar or unipolar depression

b. **Second generation antipsychotics**

- Effective as augmentation strategies but their use may be limited as they are off-label for depression.
- Adverse effects must be closely monitored, as weight gain, potential metabolic syndrome and extrapyramidal side effects can occur especially in the context of long-term therapy.

c. **Thyroid hormone**

- T3 is beneficial as an augmentation strategy for depression patients with and without subclinical hypothyroidism
- T4 has been less well studied but is also used as an augmentation strategy as t4 is a precursor to T3

d. **Psychostimulants:** There is insufficient evidence to recommend the routine use of **psychostimulants** as an augmentation strategy.

e. **Combining antidepressants**

- Mirtazapine and TCA's with SSRI's are better than SSRI's alone
- Venlafaxine and Mirtazapine used in STAR*D trial

NEUROSTIMULATION

1.Electroconvulsive therapy

First line treatment indications for ECT:

- Severe melancholic depression, especially when the patient is refusing to eat/drink
- High risk of suicide
- High levels of distress
- Psychotic depression or catatonia
- Previous response, patient choice

A large multicentre study of the efficacy of bitemporal ECT showed a remission rate of 95% for completers with psychotic depression.

Second line treatment indications for ECT

- Patients who have not responded to several trials of medication, including for example TCAs, MAOIs

Response to unilateral ECT in patients with non-psychotic depression who have failed one or more medication trials has been shown to be as high as 48%.

A more recent meta-analysis found remission rates with ECT of 48% for medication refractory patients compared to 64.9% for patients who had not received pharmacological treatment prior to ECT. [4]

ECT should not be regarded a treatment of last resort and its administration should be considered on the basis
of individual patient and illness factors.

Memory impairment is the side-effect of most concern to patients. ECT affects both anterograde and retrograde memory. Anterograde memory changes generally return to normal or may be improved compared to pre-ECT levels within 2–4 weeks but retrograde impairment,
which is more likely with bitemporal placement, can persist for prolonged periods.

Ultra-brief pulse width (0.3ms) unilateral ECT and bifrontal ECT is associated with a lower incidence of cognitive effects.

2**. rTMS:**

- Covered in detail with a review of the evidence in a previous article written by one of the authors of the mood disorder guidelines, Prof Paul Fitzgerald at https://psychscenehub.com/psychinsights/transcranial-magnetic-stimulation-for-depression/
- Patients with non-psychotic depression may be treated with rTMS once they have failed one or more trials of standard antidepressant medications and psychological therapies.

Other neurostimulation methods include Deep Brain Stimulation (DBS), Vagus nerve stimulation (VNS), Magnetic seizure therapy (MST) and Transcranial direct current stimulation (tDCS).

COMPLIMENTARY THERAPIES IN DEPRESSION

- **Omega-3 Fatty acids** – as an adjunct
- **St John's wort** – Risk of serotonin syndrome if combined with other antidepressants Caution when co-prescribing with warfarin
- **S-adenosyl-methionine (SAM-e)** – adjunct.
- **Zinc** – adjunct
  - **N-Acetyl Cysteine (NAC)** – Maybe associated with symptom reduction in Major Depression. Learn more about NAC from Prof Michael Berk, an expert advisor for the mood disorder guidelines in https://psychscenehub.com/video/n-acetylcysteine-and-psychiatric-disorders/

- **Multivitamins** – no evidence
- **Folate (including L-Methylfolate)** – as an adjunct

LIFESTYLE INTERVENTIONS

Diet:

There is a strong association between diet quality and depression. Read more about the SMILES trial by Prof Jacka, an expert advisor for the RANZCP mood disorder guidelines at https://psychscenehub.com/psychinsights/diet-new-antidepressant-block/.

Exercise:

Exercise seems to have efficacy as an augmentation strategy in major depression. A possible mechanism appears to involve brain-derived neurotrophic factor (BDNF). [5]

Smoking Cessation:

Smoking is an independent risk factor for mood and anxiety disorders.

A recent systematic review and meta-analysis showed that smoking cessation is associated with reduced depression, anxiety, and stress and improved positive mood and quality of life compared with continuing to smoke. The effect sizes were as large for those with psychiatric disorders as those without and were equal or larger than those of antidepressant treatment for mood and anxiety disorders (Taylor et al., 2014) (https://www.bmj.com/content/348/bmj.g1151).

Sleep:

There is robust evidence for causal (often bidirectional) links between sleep and negative mood, including major depression.

Clinicians should educate patients about sleep hygiene in depression.

CONCLUSION

The aim of the summary is to assist busy clinicians in navigating the complexity of managing depression with the goal of reducing the significant disease burden around the world.

This guideline is best combined with the CPD module on Major Depressive Disorder with mixed features (see: https://psychscenehub.com/psychinsights/major-depressive-disorder-mixed-features-interactive/) which contains mechanisms of actions (MOA's) and side effects of antidepressants and antipsychotics.

A summary of the 21 antidepressants (see: https://psychscenehub.com/psychinsights/summary-21-antidepressants-network-metaanalysis/) covered in this NMA can help in individualising the choice of antidepressant therapy.

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