Depression Update

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Disclosure

- No significant relationships to disclose

Outline

- Overview of depression
- Standard treatment
- Recent treatment options
- New/emerging treatment explorations
- Conclusion
- Please ask questions as we proceed

OVERVIEW OF DEPRESSION

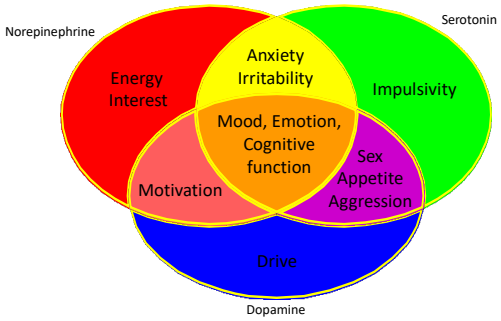
Treatment of depression over time

- In the 5th century B.C., Hippocrates believed that too much "black bile," the humor secreted by the spleen, resulted in melancholia and prescribed lifestyle interventions such as diet, exercise, sleep, bathing and massage and sometimes purges such as vomiting and bloodletting.
- In the Middle Ages depression was thought to be the result of demonic possession. Prayer, exorcism, and burning of witches was the preferred treatment.
- The 17th century featured a return to lifestyle remedies prescribed by the Greeks. The neurologist Thomas Willis wrote that melancholia was a "Distemper of the Brain and Heart." This was a return also to the idea that depression was at least partially biologically mediated.
- Over the next few centuries, various remedies were tried including herbal preparations, hypnotism, opium, and many other with little success.
- Various forms of psychotherapy also gained followings including psychoanalysis in the late 19th century.

Treatment of depression (cont.)

- In 1938, electroconvulsive therapy became the technological solution to depression, but carried with it significant side effects including amnesia.
- By the 1950s the first antidepressant drug, Iproniazid, a monoamine oxidase inhibitor (MAO-I) was being investigated as a treatment for tuberculosis when investigators noted that patients taking the drug were markedly less depressed. A further study showed that in depressed patients the drug was 70% effective, a benchmark that has yet to be surpassed.
- 1957 brought the arrival of another investigational medication for psychosis, imipramine, that worked much better on depression. This was the first medication with the classic 3-ringed structure (tricyclic antidepressants). Many variations on this basic structure were soon to follow.
- We used these medications for years because they empirically worked before investigators found their proposed mechanism of action by modulating one or all of the "Big 3" neurotransmitters involved in depression: dopamine, norepinephrine, and serotonin.
- 1987 saw the arrival of the first selective serotonin reuptake inhibitor, Prozac. While it was no more effective than any previous medication (around 70%), it was much better tolerated and safe in overdose. This led to a revolution in treatment with patients actually taking medication for extended periods and led to adoption of these medications in primary care clinics.
- 2006 was the year of publication of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. A huge collaborative study on the treatment of depression, funded by the National Institute of Mental Health. The focus was on attempting to arrive at the rational treatment of patients with depression with a focus on real world usefulness and guidance if the first line treatment (Citalopram, an SSRI) failed.

The "Big 3" neurotransmitters



Dopamine

- Dopamine seems to modulate pleasure and reward. Targeting this system may effect
  - Mood
  - Cognition
  - Motor function
  - Drive
  - Addiction
  - Aggression
  - Motivation

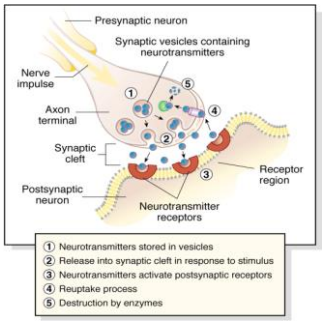
Norepinephrine

- Norepinephrine seems to modulate attention and cognition. Targeting this system may effect
  - Mood
  - Learning and memory
  - Attention and task persistence
  - Hyperactivity
  - Regulation of sleep-wake cycle
  - Regulation of hypothalamic-pituitary axis
  - Regulation of sympathetic nervous system

Serotonin

- Serotonin seems to modulate mood and anxiety. Targeting this system may effect
  - Mood
  - Sleep
  - Anxiety
  - Obsessions and compulsive behavior
  - Cognition
  - Sensory perception
  - Temperature regulation
  - Nociception (e.g., migraine headache)
  - Appetite
  - Sexual behavior

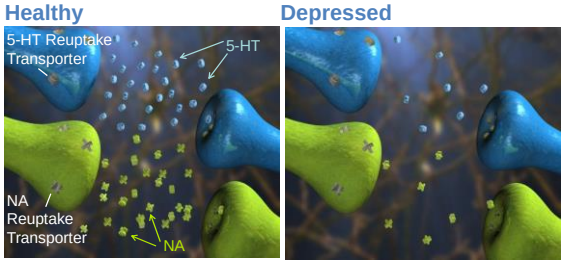
Neurotransmission



Neurotransmission is the process of sending signals from one component of the nervous system to another

5-HT and NA at the Synaptic Level

Healthy **Depressed**



STANDARD TREATMENT

Outline of treatment options

- Start with the SSRI of your choice unless contraindicated.
- If no response, change to a different mechanism of action medication (SNRI, DNRI, atypical antidepressant, tricyclic)
- If partial response, consider augmentation with a second medication (Lithium, second-generation antipsychotic, Loxapine, or triiodothyronine)
- Psychotherapy (especially cognitive-behavioral therapy)
- Electroconvulsive therapy
- Repetitive transcranial magnetic stimulation

Self care and education

- Educate patients and families about the illness, including signs, symptoms, prognosis, time to noticeable improvement, a reasonable treatment course for medication, risk of relapse.
- Suicide risk and safety plan.
- Self care options including diet (the Greeks had a point), keeping to a rigid daily schedule, journaling, cutting back on screen time.
- Exercise works well in randomized trials for mild depression. Group exercise seems more effective than solo effort.
- Basic sleep hygiene, stimulus control (decreasing blue light, no screen time before bed, etc.), and sleep restriction may confer temporary benefit.
- Regularly measure depressive symptoms (use a checklist or screening tool).
- Review and manage side effects.
- Behavioral activation therapy has been shown effective. Therapy targets helping people identify activities that add meaning to their life (reading, volunteering, spending time with friends and family) and encourages them to engage in these activities prior to any improvement in mood symptoms.
- Mindfulness mediation training has been effective for preventing recurrence of depression, particularly by targeting one depressive symptom, rumination. Mindfulness-based cognitive therapy teaches patients to return their attention to the present moment through practices such as mindfulness meditation and yoga. This superior to antidepressants at preventing relapse.

Characteristics of uncomplicated depression

- Depression doesn't always require referral to a behavioral specialist. Consider primary care treatment if patients meet these criteria:
- No suicidal or homicidal ideation or behavior, or ideation that does not pose an imminent risk (passive thoughts that family members would be better off if the patient was dead; or fleeting thoughts of killing oneself, with nonexistent or vague plans to commit suicide and no intent or access to lethal means).
- No psychotic features (paranoia, delusions or hallucinations).
- No significant aggression.
- Intact judgement (the patient or others are not in immanent danger).

Measurement based care

- This is increasingly gaining acceptance in Behavioral Health practices.
- The most common tools used in primary care are the Patient Health Questionnaire 9 item (PHQ-9) for depression and the Mood Disorder Questionnaire (MDQ) for bipolar disorder screening.
- Consider using some type of measurement tool to assess progress in your patients.
- The American Psychiatric Association has a published a host of measures as part of DSM5 and all are online as PDF documents you may use in your practice. Our clinic uses the Level 1 Crosscutting Measure on all appointments to track symptom response to treatment.
- You can access these online at: https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/assessment-measures

PHQ-9 guidelines

- Many offices are using the Patient Health Questionnaire 9 (PHQ-9) for screening of depression. It is a 0-27 point, 9 item test easily self administered. These are our guidelines for interpretation:
- 0 – 4 = no indication of follow-up, repeat PHQ9 as needed or recommended by standard policy.
- 5 – 9 = repeat PHQ9 at next visit.
- 10 – 14 = consider treatment with SSRI or SNRI (only 1 month RX) + 1 month follow-up (recommend 2wk nurse call to check on patient & 1 month face to face encounter) or referral to Behavioral Health for either medication or psychotherapy.
- 15 – 19 = referral to Behavioral Health .
- 20 + = consult with psychiatry and document prior to letting patient leave.
- Question #9 ("Thoughts that you would be better off dead or of hurting yourself in some way") a score of 1 - 3 requires attention. Be sure to address in your chart note as well as with the patient. Ask if weapons are in the home and document.

SSRI salient facts

- Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants.
- Drugs in this class include Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac), Fluvoxamine (Luvox and Luvox CR), Paroxetine (Paxil and Paxil CR), and Sertraline (Zoloft).
- Side effects of SSRIs may include nausea, vomiting, diarrhea, sexual dysfunction, headache, weight gain, anxiety, dizziness, dry mouth, and trouble sleeping.
- Note that use of SSRIs with nonsteroidal analgesics (Aspirin, Ibuprofen, Naproxen, etc.) and blood thinners such as Warfarin (Coumadin) may increase the risk of bleeding.
- Serotonin syndrome is a serious medical condition that can occur when taking SSRIs alone or in combination with other serotonin active medications (Meperidine (Demerol) or Tramadol (Ultram), St. John's wort, and triptans to name a few). Stimulants can also increase the risk including cocaine. Symptoms may include anxiety, restlessness, sweating, muscle spasms, shaking, fever, rapid heartbeat, vomiting, and diarrhea.
- All antidepressants may increase the risk of suicidal thoughts or behavior in children, adolescents, and young adults (18 to 24 years of age).
- Rapid discontinuation of SSRIs may lead to discontinuation syndrome including fever, sweating, nausea, dizziness, insomnia or vivid dreams, and sensations of electric shocks ("brain zaps").

SNRI salient facts

- Serotonin-Norepinephrine Reuptake inhibitors (SNRIs) include Desvenlafaxine (Pristiq), Duloxetine (Cymbalta), Venlafaxine (Effexor and Effexor XR), Milnacipran (Savella), and Levomilnacipran (Fetzima).
- Side effects include nausea, dizziness, and sweating. SNRIs, particularly Duloxetine, Venlafaxine, and Desvenlafaxine may cause sexual dysfunction. Other side effects include tiredness, constipation, insomnia, anxiety, headache, and loss of appetite. Levomilnacipran particularly may cause urinary retention.
- All antidepressants may increase the risk of suicidal thoughts or behavior in children, adolescents, and young adults (18 to 24 years of age).
- Duloxetine and Milnacipran should not be used in patients with uncontrolled narrow angle or angle-closure glaucoma.
- Rapid discontinuation of SNRIs may lead to discontinuation syndrome including fever, sweating, nausea, dizziness, insomnia or vivid dreams, and sensations of electric shocks ("brain zaps"). This may be worse than SSRIs.

Atypical antidepressant salient facts

- Atypical antidepressants do not fit into any of the other classes of antidepressants but all have some effect on one or more of the "Big 3" neurotransmitters.
- Atypical antidepressants include Bupropion (Wellbutrin), Mirtazapine (Remeron), Nefazodone (Serzone), Trazodone (Desyrel, Oleptro), Vilazodone (Viibryd), and Vortioxetine (Trintellix).
- More information will follow on some of these medications, but side effects vary by drug.
- Mirtazapine and trazodone cause drowsiness and are usually taken at bedtime. The sedation from Mirtazapine is usually inversely related to dose.
- Bupropion is weight neutral and is used with Naltrexone in the weight loss combination drug Contrave. It also has minimal sexual dysfunction.
- Vilazodone and Vortioxetine are not associated with significant weight gain or sexual dysfunction.
- Mirtazapine and Trazodone may rarely cause QT prolongation.
- Trazodone may cause priapism, painful and prolonged erection in males.
- Nefazodone may cause hepatotoxicity by inhibiting bile acid metabolism. It is best to avoid this medication for patients with liver/gallbladder issues.
- Suicidal thoughts or behavior: All antidepressants may increase the risk of suicidal thoughts or behavior in children, adolescents, and young adults (18 to 24 years of age).
- Bupropion can lower the seizure threshold and should be avoided in patients with epilepsy, eating disorders, substance use.

Tricyclic salient facts

- Tricyclic antidepressants (TCAs) are equally effective (70%) with other medications, but their use has declined due to increased side effects and lethality in overdose. TCAs block reuptake of serotonin and norepinephrine to greater or lesser degrees depending on the drug. They also inhibit muscarinic M1, histamine H1, and alpha-adrenergic receptors.
- TCAs include Amitriptyline (Elavil), Desipramine (Norpramin), Doxepine (Sinequan), Imipramine (Tofranil), Nortriptyline (Pamelor), Amoxapine (Asendin), Clomipramine (Anafranil), Maprotiline (Ludiomil), Trimipramine (Surmontil), and Protriptyline (Vivactil).
- TCA side effects include dry mouth, constipation, blurred vision, urinary retention, dizziness, tachycardia, weight gain, cognitive impairment, tachycardia.
- TCAs act like class A1 antiarrhythmics, and in overdose can cause cardiotoxicty. EKG monitoring is recommended at initiation of therapy and with dose changes.
- Suicidal thoughts or behavior: All antidepressants may increase the risk of suicidal thoughts or behavior in children, adolescents, and young adults (18 to 24 years of age).

MAOI salient facts

- Monoamine oxidase inhibitors (MAOIs) inhibit the activity of monoamine oxidase, an enzyme that breaks down norepinephrine, serotonin, and dopamine in the brain and other parts of the body. MAOIs are equally effective as the other agents (70%) but their use has declined due to side effects and dosing difficulties.
- Some evidence suggests that patients with "atypical" major depression (hypersomnia, hyperphagia, rejection sensitivity, heavy or leaden feelings in limbs, and/or mood brightens in response to positive events) may respond preferentially to this class of drug.
- MAOIs include Phenelzine (Nardil), Selegiline (Emsam), and Tranylcypromine (Parnate).
- Side effects include postural hypotension, weight gain, and sexual side effects.
- Tyramine-induced hypertensive crisis: taking MAOIs with consumption of tyramine-containing foods or beverages may cause dangerous elevations in blood pressure. Foods to be avoided include wine, aged cheese, sauerkraut, cured meats, draft beer, soy products, and others.
- Suicidal thoughts or behavior: All antidepressants may increase the risk of suicidal thoughts or behavior in children, adolescents, and young adults (18 to 24 years of age).

ECT salient facts

- Electroconvulsive Therapy (ECT) is superior to pharmacotherapy for unipolar major depression, with response rates approaching 90% in some studies.
- ECT has a significant public stigma that may prevent acceptance by patients and there are organized groups (such as the Citizen's Commission on Human Rights funded by the Church of Scientology) that encourage lawsuits particularly around the use of ECT.
- ECT may still be associated with significant memory impairment both for the time surrounding the procedures and some retrograde amnesia.
- ECT also has logistical constraints preventing compliance for some patients and some studies show a high relapse rate after remission.

Switching antidepressants

- When a patient fails a reasonable trial of an antidepressant (12 weeks at a therapeutic dose), switching agents is preferred as the next step.
- Cross-tapering may be indicated, but may increase the risk of side effects. Conversely immediate discontinuation of the existing agent may minimize drug-drug interactions, but may lead to discontinuation syndrome.
- There is some data to suggest for treatment resistant depression, augmentation is superior to switching if the patient is noting even a minimal response to the existing antidepressant, but this in controversial.

Augmentation strategies

- If a patient is noting some benefit from the existing agent ("better" but not "well"), consider augmentation.
- Always be aware that augmentation raises the risk of drug-drug interactions (with the exception of psychotherapy).
- In general, it is better to choose a complementary augmentation agent with a separate mechanism of action.
- Several standard options are available for augmentation.

Psychotherapy

- Patients with major depression who are treatment resistant benefit from adding psychotherapy to drug treatment.
- Cognitive Behavioral Therapy (CBT) has been the most extensively studied modality and has the support of multiple randomized trials.
- There are also studies of Mindfulness Based Cognitive Therapy (MBCT) for depression and it has been shown particularly effective for preventing relapse.

Lithium

- Lithium has been used as an augmentation agent for treatment resistant depression since the 1960s.
- Many patients respond well to subtherapeutic doses (as low as 150-300mg/day) and at these doses it is generally well tolerated.
- There is data showing Lithium's benefit in reducing the risk of suicide.
- Lithium occurs naturally in the drinking water in many areas of the planet and these areas have lower rates of depression, suicide, and violent crime.

Thyroid hormone

- Thyroid hormone (Triiodothyronine or Liothyronine [Cytomel]) has also been used as an augmentation strategy for treatment resistant depression since the 1960s.
- This may be particularly beneficial for patients with depression featuring significant psychomotor retardation, hypersomnia, and anhedonia.
- Response generally takes days to weeks.
- The dose for augmentation is typically 25-50mcg dosed once daily.

Second-generation antipsychotic

- Adding any antipsychotic to antidepressant therapy may convert a partial responder into a full responder and this has been know for decades.
- In recent years, multiple second-generation antipsychotic have pursued studies and gained approval as augmentation agents to add to an existing antidepressant for patients with treatment resistant depression.
- While any antipsychotic may theoretically work, only a few have FDA indication for this purpose.
- Indicated medications are Aripiprazole (Abilify), Brexpiprazole (Rexulti), Olanzapine (in combination with Fluoxetine [Prozac] as Symbyax), and Quetiapine (Seroquel).
- Be aware and discuss with patients potential side effects including akathesia, acute dystonic reactions, tardive dyskinesia (rare), and metabolic side effects.

RECENT TREATMENT OPTIONS

Trazodone XR (Oleptro)

- 5-HT2A receptor antagonism and weak serotonin reuptake inhibition.
- Indicated for MDD.
- 24-hour slow release version of generic Trazodone.
- May be less sedating than regular release Trazodone.
- Start at 150mg/day, may need 300mg/day.

Vilazodone (Viibryd)

- Serotonin reuptake inhibiton and 5-HT1A receptor partial agonist.
- Indicated for MDD.
- Nausea, diarrhea, and headaches are the main side effects.
- Very low rate of sexual dysfunction.
- May confer better anxiolytic effects.
- Taken without food (350 calories or more) decreases absorption but up to 40%.
- May be activating.
- Start low at 10mg. Some patients may improve at 10-20mg, safety data up to 80mg.

Vortioxetine (Trintellix/Brintellix)

- Serotonin reuptake inhibition, weak norepinephrine reuptake inhibition, additional effects on 5-HT1A (agonist), 5-HT1B (partial agonist), 5-HT1D (antagonist), 5-HT3 (antagonist), and 5-HT7 (antagonist).
- Indicated for MDD, good data on cognitive impairment in the elderly.
- Nausea, diarrhea, headache are the predominant side effects.
- Has a 66 hour half life-may be dosed QOD initially?
- 5-HT7 activity may confer cognitive benefit.
- Lower incidence of sexual dysfunction compared to SSRIs.
- Start low, 5mg/day with a target for most people of 20mg/day.

Levomilnacipran (Fetzima)

- Norepinephrine/Serotonin reuptake inhibitor (2:1) at all doses.
- Indicated for MDD.
- Is also an NMDA receptor antagonist at high concentrations.
- Initial side effects include nausea, dizziness, sweating, insomnia, increased heart rate and blood pressure.
- May also cause dose dependent urinary hesitancy, erectile dysfunction and delayed ejaculation in males, and palpitations.
- Start low at 20mg, studied up to 120mg/day.

Brexipiprazole (Rexulti)

- D2 and D3 partial agonist, also multiple serotonin effects: 5-HT1A (partial agonist), 5-HT2A/5-HT2B/5-HT7 (antagonist).
- Indicated for adjunctive therapy for MDD.
- May improve cognition via 5-HT7.
- Atypical antipsychotic, monitor for movement disorders, low incidence of metabolic side effects.
- Start at 0.5mg/day, target dose 2mg/day along with their existing antidepressant.

NEW/EMERGING TREATMENT EXPLORATIONS

Melatonin and depression

- In 2009, the drug Agomelatine (Valdoxan) was approved in Europe to treat major depressive disorder.
- It has a unique mechanism of action by targeting the melatonin system in the brain. It is the first melatonergic antidepressant.
- Similar to its precursor, serotonin, melatonin seems to be involved in regulating circadian rhythms and sleep, it's involvement in mood regulation is under investigation.
- U.S clinical trials are in progress.

Inflammation and depression

- There is some evidence that depressive symptoms respond to therapies to modulate inflammation. There is also some data to show that inflammation may adversely impact neurotransmitter performance.
- In 2016, Celecoxib, an anti-inflammatory was given to patients in a double blind study to investigate augmentation of Escitalopram (Lexapro).
- At studies end, the placebo group showed a 45% response to antidepressant alone with a 10% remission rate. In comparison the combination group showed a 78% response with 63% in remission.
- It seems suggested from this study that addressing inflammation may augment or enhance patient's response to standard antidepressant therapy.

Proteins and depression

- For people suffering from depression response to treatment takes weeks (2-4 weeks for initial response) despite the fact that physiological action of antidepressants is rapid (hours) after initiation of treatment.
- There have been numerous mechanisms proposed to explain this from down regulation of post-synaptic receptors to changes in gene expression.
- Research has identified a protein (p11) that is strongly expressed in one particular neuronal subclass in the hippocampus, the cholecystokinin (CCK) cells. These small neurons play a key role in balancing the excitation and inhibition of the network, and they have a much higher number of receptors to serotonin than the other neurons of the hippocampus. Serotonin normally inhibits CCK neurons, leading to well balanced activity in the hippocampus. Artificially inhibiting CCK results in the same anti-depressant effects of SSRIs, suggesting that these cells may be a promising target for the development of fast acting antidepressant drugs.
- In addition, acute and chronic treatment with SSRIs had strikingly different effects on this system. Serotonin activates different receptors depending on the length of treatment, and long-term treatment reorganizes neural activity, which short term treatment does not.
- Researchers in Finland found another protein, Jun N-terminal kinases (or JNK), is responsible for moderating neurogenesis in the hippocampus, and so seems directly linked to anxious and depressive behavior.
- Inhibition of this protein led to markedly lower anxiety levels and more neurogenesis in animal models.
- A separate study postulated JNK inhibition as possibly helpful for "inflammatory, vascular, neurodegenerative, metabolic and oncological diseases in humans," and protein targets for new medications may be the wave of the future.

The Glutamate System and Depression

- Scientists have investigated the role of the glutamate system in depression. Glutamate is abundant in the brain and is one of the most common neurotransmitters. It's involved in memory, learning and cognition.
- Some research has implicated the dysfunction of the glutamate system in medical conditions, such as Huntington's chorea and epilepsy, and psychological disorders, such as schizophrenia and anxiety disorders.
- Several studies have examined targeting a specific type of glutamate receptor in the CNS, NMDA with antidepressant effects.
- Studies have explored Ketamine, an NMDA antagonist, in treating treatment-resistant depression and acute suicidal ideation. Ketamine has a long history in analgesia and anesthesiology.
- Ketamine appears to have rapid antidepressant effects, present within hours and there is some evidence of a rapid response to suicidal ideation. Unfortunately, its effects only last 7-10 days. Current studies are using ketamine as an IV infusion in hospitalized patients.
- There are two drugs, one from Allergan (Rapastinel [rapid IV]) and one from Johnson & Johnson (Esketamine [nasal]), that work similarly to ketamine and are in late-stage clinical trials. As of now, ketamine is not FDA-approved for depression. So far, clinical trials on ketamine for depression have been few and small, and there is no real placebo control as patients know if they are getting an IV of saline or Ketamine (hallucinogenic).
- Ketamine is also a drug of abuse, known by such street names as "Special K." It induces trance-like or hallucination states. It also has addiction potential.
- Riluzole (Rilutek) is an FDA-approved drug that treats amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease and targets a different part of the glutamate system. There is one small study that augmented an existing antidepressant with Riluzole which showed some promise, but this has not been replicated and this is not FDA indicated for this purpose.

Opioid Receptors and depression

- Recent research has shown that combining Buprenorphine (Subutex) and Naltrexone can have antidepressant effects in mice.
- British researchers are working with a new drug (BU10119) that selectively antagonizes kappa opioid receptors. This has already shown effects in animal models and it seems targeting kappa opioid receptors confers antidepressant effects.
- There are currently no medications indicated for use in depressed patients, but Naltrexone blocks kappa receptors in addition to mu opioid receptors and by itself may confer some antidepressant efficacy.

Conclusion

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