MEDICAL BITS FROM YOUR DOCTOR

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""Sadness flies away on the wings of Time".

Jean de La Fontaine

"Sadness is but a wall between two gardens".

Kahlil Gibran

1 – Medical News
"Tripledemic".

2 – YOUR HEALTH
DEPRESSION I & II

3- Debunking Myths: Less is More

"The Happiness of your Life depends upon de Quality of your Thoughts". Marcus Aurelius

Medical News

As you are all very well aware, as the weather gets colder and our human activities move indoors, circulation of respiratory viruses increases and infections tick upwards. Not only Influenza, Respiratory Syncytial Virus (RSV), parainfluenza, metapneumovirus, rhinoviruses and of course, SARS CoV2 – COVID all become a threat to our health and comfort.

You continue to read about the "Tripledemic" (RSV, Flu, Covid) and the excessive utilization of urgent care and OTC remedies to quell symptoms. But after almost 3 years since the beginning of the great pandemic of the new millennium, we are all ready to "move on". Fortunately, the virus is cooperating and while it is likely to remain "endemic" as previously reported, major disruptions are not anticipated.

Several strains are vying to become the dominant virus, but they all belong to the same Omicron family tree and therefore, there is no new "wave" developing as we experienced when the new Delta and then the Omicron variants appeared. Most Americans have a combination of natural and vaccine-induced immunity, prompting new CDC recommendations:

- If you are healthy and tested positive (regardless of vaccination status) you should isolate for 5 days only.
- Once isolation completed, wear a high-quality mask through Day 10.
- If you test negative on two rapid antigen (Ag) tests, stop wearing mask.
- Avoid visiting older and immunocompromised hosts for 10 days.

Pandemics tend to fade away and become endemic in places with low vaccination rates with intermittent flare-ups. This time around, we have learned that despite high levels of vaccination and natural immunity, the excessive infectivity of these viruses, frequent mutations, waning antibody titers induced by vaccination, periodic increases in viral activity and infection have become the norm. The BA.5 omicron subvariant surged in the summer and is still responsible for almost ½ of the infections, but BQ.1 and BQ1.1

are multiplying rapidly leading to rising infections, hospitalizations and deaths. Almost 500 fellow citizens are reported to be dying from COVID and associated complications daily.

We have discussed the reasons why a “zero” Covid policy is only possible under an authoritarian government and doomed to fail. As distant observers, we can surmise that over the past four decades, many Chinese people accepted limits to their political and social freedoms in exchange for economic stability and prosperity. Now it appears that bargain is in jeopardy. The government touted the early success of lockdown policies The poor long-term consequences are now becoming obvious, as the population is under-vaccinated, the shots deployed have lower efficacy and the elderly are poorly protected. If social restrictions were lifted, public health modeling suggests ICU-bed demands would swell to 7x the current existing capacity. Thus, the central government faces a difficult dilemma of appeasing the social demands for more freedom and eliminating the “Zero Covid” policy versus risking a serious epidemic as we approach the Northern Winter.

Once again, democracies can be messy and disorderly, but that independent “fresh air” is essential for creative solutions, despite the high human toll incurred (with > 1 million lives lost in the US and approaching 30 million worldwide).

For those of you who like to get more details about our multiple pandemic response shortfalls and missteps, you may want to read the recently released “Senate Report” which summarizes the problems with data collection, insufficient testing capacity, inadequate funding, supply chain problems, overlapping responsibilities and gaps in all branches of government, starting at the very top of the White House. When a president is a science denier and undermines the public health authorities, you can only expect dismal results.

For additional COVID-19 DATA, check our Bits or these sites:

- HERE: new cases, hospitalizations and deaths.
- HERE, you can find all the COVID-19 STATS and more.
- The Coronavirus Vaccine Tracker from the NYT is an excellent resource.
- Nature.
- Vaccine information.

COVID-19 Q & A: Please, refer to prior Bits.

- **Should we get a 3rd booster – 5th shot this winter? YES.**
  - Since protection against disease continues to decrease after 4-6 months (mucosal protection is mediated by virus-specific neutralizing antibodies), best to obtain another shot. Hopefully, most of you are already immunized.
  - 4 vaccine-doses improved short term protection compared to 3 doses and decreases symptomatic disease, severe illness and hospitalizations.

- A recent study from Qatar in 2.3 million people confirms findings and 5 shots against these more infectious variants are likely to be more effective.
- Mild disease or asymptomatic infection should not be considered "breakthrough" infection after vaccination. They should be expected.
- **Particularly if > 65 yo or with comorbid conditions, best to plan on a 5th shot.**
- Risk/Benefit marginal for 15 to 30-year-old men (higher risk of pericarditis and myocarditis after vaccination).

- **Is infection inevitable?**
  - During the course of a pandemic, infection is almost inevitable, unless you take draconian measures that will negatively impact your quality of life.
- **Is the risk of complications reduced with repeat infection?**
  - Yes. Vaccines, boosters and natural infection augment our immunity and reduce the odds of developing complications and "long-covid".
- **Will the Pandemic come to an end soon?**
  - As mentioned above, there is no "end of a pandemic". But we will reach a point (arguably, almost there in the Western world) when the virus will no longer disrupts our daily lives, hospitals are not challenged by the pandemic and those vulnerable can access effective treatments.

VACCINES AND "BROAD SPECTRUM SHOTS"

As of late November 2022, almost 16 billion Covid-19 Vaccine doses been administered worldwide and the WHO estimates that 75% of the world population has now been vaccinated.

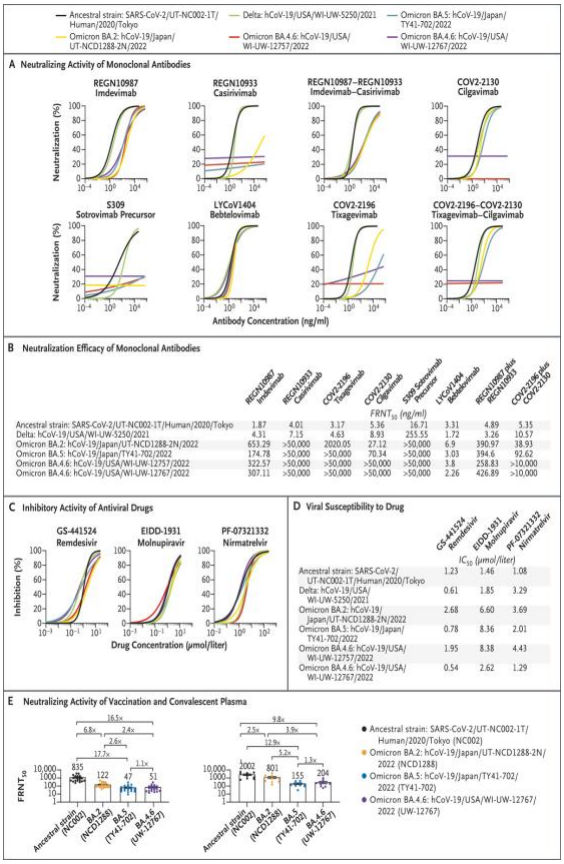
A few months ago, we briefly discussed the international effort to develop a "Universal Coronavirus" vaccine or a "broad-spectrum" vaccine that may provide wide protection against several coronaviruses, including yet-unidentified strains. The huge diversity of bat coronaviruses, their proximity to humans and the high mutability of the spike gene essential for immune recognition, have prompted a large collaborative international effort to develop "pan-coronaviruses shots.

An ongoing cloud computing infrastructure called Serratus is enabling and accelerating the analysis of millions of novel RNA viruses which can point to the origin and evolution of new dangerous viruses and improve our surveillance for mitigation of future pandemics. These new broad vaccines in development display different viral antigens in diverse manners, such as Ferritin and Mosaic Nanoparticles and Chimeric Spikes, among others.

COVID-19 TREATMENTS

- **Paxlovid** (Nirmatrelvir+Ritonavir) prevents admissions / deaths
  - Oral combination antiviral, blocks a protease (3CL) enzyme essential for viral replication.
  - Effective against all variants
  - Symptomatic, unvaccinated and high-risk Covid + adults were given Paxlovid or placebo twice daily x 5 days within 3 days of symptom onset.
  - Paxlovid: 5/697 hospitalized (0.72%) and 0 died.
  - Placebo: 44/682 hospitalized (6.45%) and 9 died (1.32%).
  - Similar if initiated first 5 days.
  - 10-fold decrease in viral load at day 5 relative to placebo and therefore anticipated to decrease infectivity.
  - A longer course may be necessary to prevent "Paxlovid Rebound".
  - Most common side-effect: transient change in taste perception 5%.
  - Safe. Check here for common drug-drug interaction.
  - And check here to locate pharmacies with stock.

Antiviral Efficacy and Antibody Response in Vitro against Omicron variants.



Shown is the neutralizing activity (Panel A) and efficacy (Panel B) of monoclonal antibodies and the inhibitory activity (Panel C) and efficacy (Panel D) of antiviral drugs against omicron subvariants. GS-441524 (the main metabolite of remdesivir) and EIDD-1931 (the active form of molnupiravir) are RNA-dependent RNA polymerase inhibitors. PF-07321332 (nirmatrelvir) is an Mpro inhibitor.

E Takashita et al. N Engl J Med 2022;387:2094-2097.

COVID-19 Monoclonal Antibodies

Monoclonal antibodies are expensive engineered human monoclonal antibodies specific against the Spike protein of SARS-CoV2 and have been investigated to prevent progression of mild-moderate Covid-19 infection in ambulatory, **UNVACCINATED patients (post-exposure prophylaxis) and for pre-exposure prevention in patients with moderate to severe immunocompromise, unable to**

mount a good response to vaccination. Since Paxlovid is now available, the use of these agents is anticipated to decrease. There are many formulations.

- **Sotrovimab**, neutralizes most sarbecoviruses is effective against Omicron and the 500 mg may be administered as an infusion or intramuscular but Bebtelovimab recommended as first line.
- **Tixagevimab / Cilgavimab (Evusheld)** is effective for pre-exposure prophylaxis in moderately to severely immunocompromised hosts unable to mount a good response to vaccination and not a substitute to vaccination.
  - 300/300 mg IM injections every 3-6 months**.**

COVID-19 - PROVEN THERAPY

NIH has a wonderful resource summarizing the evidence in their NIH Covid-Treatment Guidelines (now > 400 pages). Another review: Open Critical Care. In summary:

- Use **Dexamethasone** at 6 mg daily for 10 days after diagnosis of COVID-related pneumonitis / pneumonia
- **Remdesivir**: marginal benefit. Early oral formulation may be beneficial**.**
- In hospitalized patients, use IV **Tocilizumab**. If not available, **Baricitinib**.
- **Ivermectin**. NO EVIDENCE. Do not use. Now we know that it may be beneficial in lower- and middle-income nations where intestinal parasites are more prevalent. Effective against lice, scabies, filariasis and intestinal parasites!
- **Convalescent plasma** – Ab from previously infected patients: No benefit.
- **Plasma exchange** – plasmapheresis. No benefit, costly and invasive.
- **Colchicine**. Insufficient evidence. Do not use
- **Interleukin 1 – 6 inhibitors**. Insufficient evidence. Do not use.
- **Janus Kinase Inhibitor Baricitinib**. Possibly beneficial in the right setting.
- **Anticoagulants**. Only in prophylactic doses.
- **Supplements**: Vitamin D, C, Zinc. No benefit.
- **High-Flow O2** in severe Covid-19 reduces intubation and time to recovery.

YOUR HEALTH: DEPRESSION

As you well know, our life journey is short and plagued by myriad challenges that conspire against our sense of well-being and as you suspect, most “psychiatric care” is delivered at home and in primary care settings. Given the high prevalence and bad consequences of untreated depression, we decided to review “the basics”. Moreover, it seems that social media, the uncertainties induced by the Pandemic, domestic and international political unrest, autocrats and their wars (necessary condition for most conflicts), migrations, etc. have heightened human vulnerabilities and led to a spike in Psychological and Psychiatric care throughout the world

Depression is estimated to be the third leading cause of disability worldwide and in the US, the estimated lifetime risk of a major depressive episode approaches 30% and suicide – one of its consequences- has been increasing and is now the 10th leading cause of death.

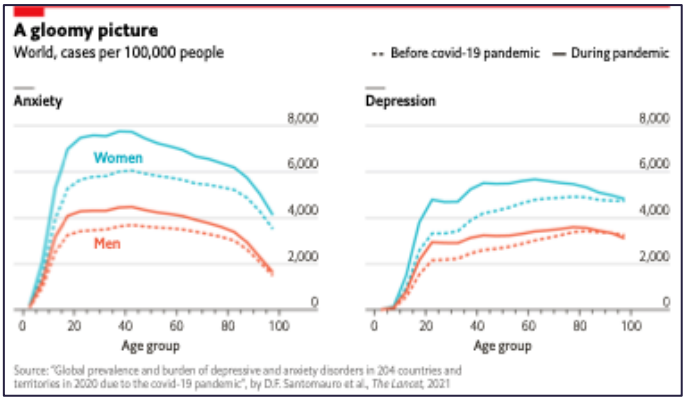
The Winter Holidays, Winter Solstice, Saturnalia or Christmas (Christ's Mass) can be happy times but also quite difficult for many. As you may know, the upcoming "Holidays" are likely a progressive evolution of pagan customs and rituals merging those of early Romans and Mithraism – the Iranian mystery God Mithra. Curiously, according to ancient legend Mithra's birth on December 25th of a virgin, was witnessed by shepherds and Magi and eventually raised the dead, healed the sick and cast out our demons, finally returning to the heavens at the Spring equinox after having a last supper with his twelve disciples – the 12 signs of the Zodiac – and eating bread marked with a cross – Universal sign of the Sun. Fortunately for us, such fecund Mythology has provided rich material for artists throughout the centuries and an explosion at the Renaissance that has enriched and colored our human experience!

We should be aware that for many of our fellow humans this season can be particularly difficult, as it may remind them of loved ones no longer present and may exacerbate loneliness and anguish.

We all think that we are "experts" at recognizing depression and "the blues". But it is not always straight forward and we may be remiss to accept that it could be affecting our own performance.

Depression is a mood disorder characterized by the inability to experience pleasure (anhedonia) and the persistent feeling of sadness with associated impaired daily functioning.

Global costs are staggering, it is the leading cause of disability and productivity loss and the economic costs are expected to double by 2030. But analysis identify a return of $4 for every buck spent on depression care. In the US, the prevalence ranges from 5-10% but in certain settings is much higher and only about half of depressed people receive adequate treatment. It is easy to understand how depression impacts most other medical conditions (the reverse is also true) and it is the leading risk factor for suicide, which has risen by almost 40% in the last two decades.



Risk Factors

- Alcohol dependence
- Childhood trauma
- Chronic medical conditions
- Female sex
- Low socioeconomic status
- Older age
- Personal or family history of depression
- Recent childbirth
- Recent stressful events

Here the diagnostic criteria for Major Depressive Disorders – DSM-5.

The US Preventive Services Task Force recommends screening all adults annually, with particular attention to pregnant and postpartum women, older adults and adolescents. Also, those presenting with unexplained somatic symptoms, chronic pain, anxiety, substance misuse or nonresponse to effective treatments for medical conditions.

The real “pathophysiologic” cause of major depression is a “mystery” and until recently, no biological markers were available. Last year, a group of researchers from Indiana University found 13 RNA markers that not only diagnose depression but also predict who will go on to develop bipolar disease, who is likely to be hospitalized and which drugs are most likely to be effective. Six RNA’s were good predictors of depression, another 6 anticipated depression and mania and one predicted mania.

There are several tools for screening, but these two simple questions have a sensitivity of 86% and specificity of almost 80% in primary care settings.

PHQ–2 Screen for Depression

Questions:

- “Over the past 2 weeks, have you felt down, depressed, hopeless?”
- “Over the past 2 weeks, have you felt little interest or pleasure in doing things?”

Scoring: 0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day

Total score = sum of 2 item scores

A score of 2 should prompt this next questionnaire. A score of > 10 is diagnostic and provides a severity rating. Major depression can be identified by duration (>two weeks, most of the day)

Table 2. **Patient Health Questionnaire–9***

Over the past 2 weeks, how often have you been bothered by any of the following problems? (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day)

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people have noticed, or the opposite (i.e., being so fidgety or restless that you have been moving around a lot more than usual)
9. Thoughts that you would be better off dead or hurting yourself in some way
10. If you have checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

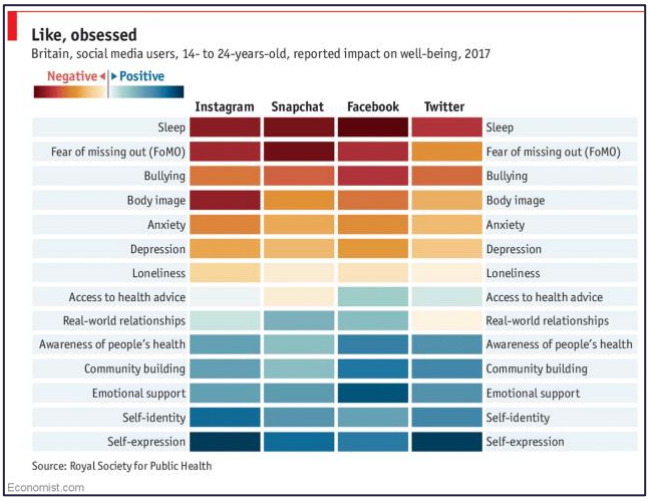
symptoms and degree of distress and functional impairment (unable to provide basic self-care may require hospitalization and psychiatric consultation).

More than 40,000 people die by suicide annually in the US (or 1 every 12 minutes). Mental health and addiction disorders are strong risk factors and prior attempts are the best predictors of completion. Unfortunately, most people who die by suicide have seen a physician in recent months.

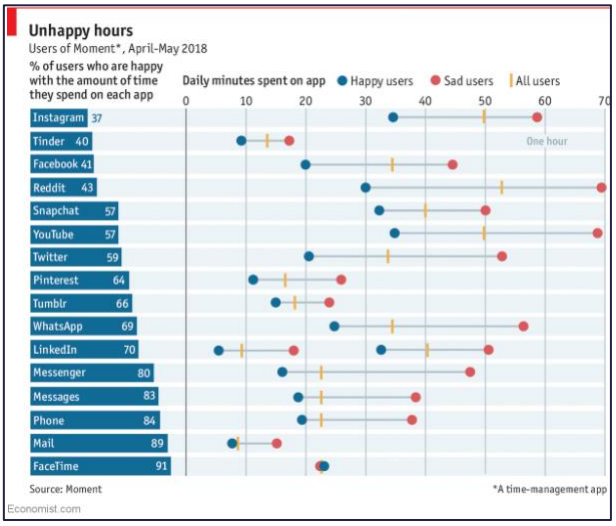
In patients at risk, it is best to ask them directly about suicidal thoughts, intent and/or plans. More than 50% of men “succeed” with firearms.

Psychiatric consultation may be necessary, particularly when other conditions present, such as severe anxiety, psychosis, mania, hypomania or substance misuse.

According to several surveys conducted in Europe and the US, those aged 14-24 believe that social media enhanced self-expression and community building but worsened anxiety, depression, sleep deprivation, exposure to bullying and heightened worries about body image and "fear of missing out".



Another survey that tracked 5300 Americans found that an increase in Facebook activity was associated with a future decrease in reported mental health. The "happiness" rate was much higher for FaceTime (91%) and phone calls (84%). As reported by The Economist, **real conversations and gossip are "hard to beat"!** And another survey last year in more than 2000 adults in the US found that less than ½ of men were satisfied with how many friends they had and 15% said they had no close friends at all – a fivefold increase since 1990 and men were less likely than women to rely on friends for emotional support or to share personal feelings. Thus, men crave deep personal relationships but have more trouble "opening up".



I have the frequent pleasure of asking my patients "How are they doing"? and how they feel about getting older. They usually reply "getting old is better than the alternative!"

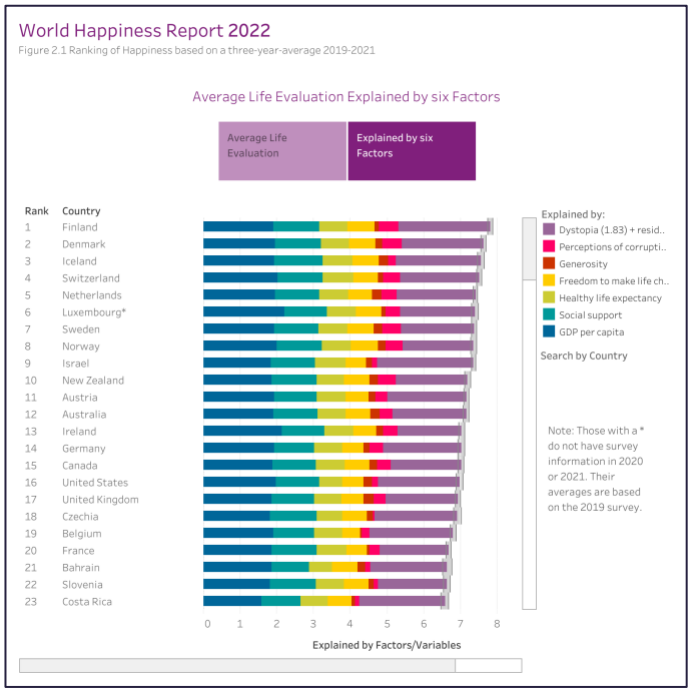
Life is not a long decline from birth towards becoming "fertilizer". As I look at my now young adult children and reflect back on my own life, young adults are quite cheerful. But as we reach the late 30's and early 40's, the levels of "happiness" go down and reach a low usually labeled "the mid-life crisis" around the mid 40's (no wonder divorce rates peak). The surprising and good part is that as we get older and wiser, we become more comfortable within our own skins, we learn who we are, and most importantly who we are not, and despite the gradual loss of our mental sharpness, vitality and great looks; we gain "happiness!". And this "U-bend" in joy is maintained no matter which part of the world is analyzed.

Circumstances also matter. Being married gives a little bump and those with children in the house get a dip. More education does not lift it, when

you control for income. Richer people are a bit more cheerful, but how much is arguable.

It seems that gender, personality, circumstances and age all have significant impacts. Women are slightly happier than men and regression analysis demonstrate that two traits have consequences: Neurotic people tend to be unhappy (think guilt, anger, anxiety and poor emotional intelligence) and extroverted ones are happier which may also help explain some cultural differences. Studies comparing similar groups, found Southern Europeans happier than Northerners and all were happier than the Chinese and Japanese. More extroversion was associated with increased happiness (or lack of honest insight).

You may be familiar with the World Happiness Report. Studies in identical twins reared apart have indicated that 30-40% of the differences in happiness between people is due to genetic differences, making them more or less fortunate. But these and other molecular epigenetic studies seem to confirm that 60-70% of the variance is due to our environmental experiences and that the genetic influences are not fixed from birth but can change in response to our exposures.



Moreover, the majority of the variance is within-country (>80%) rather than between nations and in another study evaluating the overall satisfaction with life in 41 countries only 13% of the variance was explained by between-nation differences.

You realize that happiness and most human traits are influenced by both, genes and environments. But we may be able to use findings from those genetic and social studies to create policies and environments that promote happiness and blooming of our genetic potentials.

We know that freedoms, social networks, vertical integration of families, remaining relevant with a sense of purpose (familial, social, professional or all of them) are important contributors to our “joy” and inner satisfaction and we all realize that taking a pill or psychotherapy is not the answer, but rather the daily construction of a meaningful existence, always attempting to keep our gaze far into the horizon and above human pettiness.

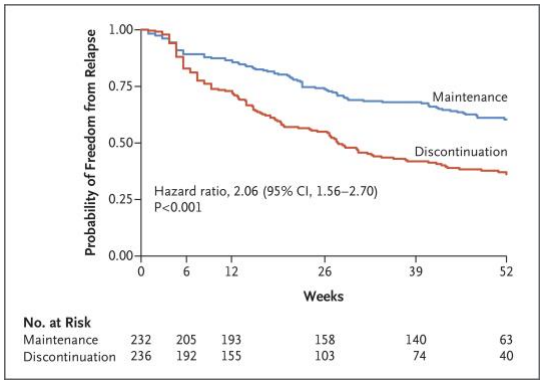
All have heard the mantra “Don’t worry, be happy and take a happy pill! But a recent round-up of studies on depression seem to bust the long-held

hypothesis that a lack of proper amount of the neurotransmitter serotonin is in part responsible for depression. A recent large study by Dr. Moncrieff of University College, London this past July, ignited a debate on the benefits of Selective Serotonin Receptor Inhibitors (SSRI's), as they concluded that there is no proven link between a lack or deficit of serotonin and depression, possibly undoing a long-held framework of research in neurobiology.

And another study analyzing 232 randomized, double blind, placebo-controlled trials of drug monotherapy for major depression submitted to the FDA between 1979 and 2016 found that only 15% of participants had a substantial effect beyond that caused by the "placebo" effect (proven to be approximately 30% in multiple studies).

Therefore, DON'T WORRY, BE HAPPY AND DO NOT TAKE A PILL"?

It appears that life is never quite that simple.



Multiple studies have shown benefit from SSRI's. And a recent study in patients who felt well enough to discontinue antidepressants, those who stopped medications had a much higher risk of relapse after 1 year of follow up, indicating a real and sustained benefit from treatment.

DEPRESSION TREATMENT

Initial treatment of depression may include a non-pharmacologic approach with psychotherapy (cognitive behavioral therapy – CBT- and interpersonal therapy – IPT- are the best studied) complementary, alternative and exercise therapies but also medications. The choice is driven by severity, patient preference, presence of comorbid conditions and it is an ongoing dialogue.

For further extensive reading check these sites.

The general consensus is to recommend psychotherapy as initial treatment for mild depression with symptom monitoring and consideration to medications if response is inadequate. Data provide support for cognitive behavioral therapy, interpersonal therapy and behavioral activation as first-line for mild to moderate depression. Psychotherapy / medications or both for moderate depression. Consultation with a psychiatrist should be obtained for patients with severe depression and urgently in those with psychosis or suicidal thoughts.

The American College of Physicians (ACP) and the American Psychiatry Association (APA) updated their guidelines to recommend CBT or second-generation antidepressants as initial treatment of moderate to severe Major Depressive disorders after discussion of risks, benefits, costs and patient preferences after extensive systematic review of the literature.

Psychotherapy is effective for almost 50% of patients. No significant difference in response rate comparing CBT, behavioral activation, supportive counseling or psychodynamic therapy. If substantial improvement is not realized within 6 weeks, medications or psychiatric consultation should be considered.

For mild to moderate depression, the initial agents (based on side-effect profile and efficacy) are fluoxetine, citalopram or escitalopram. If progress is inadequate, consideration of sertraline, venlafaxine or bupropion. The response rate varies from 50-65% and a recent meta-analysis of more than 500 studies showed that some antidepressants (amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine and vortioxetine) were more effective than alternatives. Vilazodone and levomilncipran appear promising as well.

Table 2. First-Line Antidepressant Medications for Major Depressive Disorder.*

LT Park, CA Zarate Jr. N Engl J Med 2019;380:559-568.

Drug Class and Agent	Dose	Adverse Effects	Clinical Considerations	Indications
SSRIs†				
Fluoxetine	20–80 mg/day	Gastrointestinal and sexual side effects, agitation	Long-acting active metabolites decrease risk of discontinuation syndrome‡; 1-wk washout required when switching to another SSRI or SNRI; increased risk of drug interactions	Major depressive disorder; also FDA-approved for PMDD, OCD, bulimia, panic disorder
Sertraline	50–200 mg/day	Gastrointestinal and sexual side effects, headache; generally acceptable side-effect profile	Risk of sexual side effects higher than with other SSRIs and SNRIs	Major depressive disorder; also FDA-approved for PMDD, OCD, panic disorder, PTSD, social anxiety
Paroxetine	10–60 mg/day	Anticholinergic effects (weight gain, sedation, constipation), gastrointestinal and sexual side effects	Risk of discontinuation syndrome‡ may require slower taper; controlled-release formulation may decrease risk of discontinuation syndrome; increased risk of drug interactions; consider for patients with coexisting depression and anxiety	Major depressive disorder; also FDA-approved for PMDD, OCD, panic disorder, social anxiety, generalized anxiety disorder, PTSD
Fluvoxamine	50–300 mg/day	Anticholinergic effects (weight gain, sedation, constipation), gastrointestinal and sexual side effects, anorexia, insomnia; poor side-effect profile	May have fewer associated sexual side effects than other SSRIs and SNRIs; consider for patients with coexisting depression and anxiety; increased risk of drug interactions	FDA-approved only for OCD; off-label use for major depressive disorder
Citalopram	10–40 mg/day	Gastrointestinal and sexual side effects, sedation; acceptable side-effect profile	Black-box warning regarding doses >40 mg because of QT prolongation	Major depressive disorder; off-label use for anxiety disorders
Escitalopram	5–20 mg/day	Gastrointestinal and sexual side effects	May be associated with a lower risk of headache, dizziness, sedation, and gastrointestinal side effects than other SSRIs and SNRIs; S-enantiomer of citalopram	Major depressive disorder; also FDA-approved for generalized anxiety disorder
SNRIs				
Venlafaxine	37.5–225 mg/day (extended-release formulation) or twice daily (immediate-release formulation, sustained-release formulation)	Agitation, insomnia, tremor, hypertension, tachycardia, sweating, gastrointestinal and sexual side effects, headache, discontinuation syndrome‡	Risk of discontinuation syndrome‡ may require slower taper; extended-release formulation may decrease risk of discontinuation syndrome; may increase energy; may help with anergia or attentional symptoms; risk of death from overdose greater than with other first-line agents	Major depressive disorder; also FDA-approved for generalized anxiety disorder, social anxiety, panic disorder, neuropathic pain
Desvenlafaxine	50–100 mg/day	Agitation, insomnia, tremor, hypertension, tachycardia, sweating, discontinuation syndrome‡	Primary active metabolite of venlafaxine; risk of discontinuation syndrome‡; extended-release formulation may reduce risk of discontinuation syndrome; may increase energy; may help with anergia or attentional symptoms; may need to adjust dose in patients with renal insufficiency	Major depressive disorder; off-label use for anxiety disorders
Duloxetine	60 mg total/day, administered once or twice daily	Agitation, insomnia, tremor, hypertension, tachycardia, sweating	May increase energy; may help with anergia or attentional symptoms; consider for patients with coexisting pain conditions	Major depressive disorder; also FDA-approved for generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain
Other agents				
Levomilnacipran	20–120 mg/day	Agitation, sweating, hypertension, tachycardia, palpitations, dysuria	L-enantiomer of milnacipran; may increase energy; may help with anergia or attentional symptoms; fewer gastrointestinal side effects, weight gain, sedation, and sexual dysfunction than SSRIs and SNRIs	Major depressive disorder
Bupropion	50–450 mg/day (extended-release formulation) or twice daily (immediate-release formulation, sustained-release formulation)	Tachycardia, agitation, insomnia, seizures	Consider in combination with SSRI or SNRI; sustained-release and extended-release formulations allow for less frequent dosing and may increase adherence than immediate-release formulation‡; may help with anergia or attentional symptoms; 0.4% increased risk of seizure at approved doses; contraindications include seizure disorder, bulimia or anorexia, alcohol or benzodiazepine withdrawal; not associated with sexual dysfunction	Major depressive disorder; also FDA-approved as aid to smoking cessation; extended-release formulation indicated for prophylaxis of seasonal depression; may be helpful for ADHD, attention problems, or anergia symptoms
Mirtazapine	15–45 mg/day	Sedation, increased appetite, weight gain	Consider in combination with SSRI or SNRI; consider for patients with coexisting depression and anxiety; lower dose may be more sedating; consider bedtime administration if insomnia or low appetite are present; should not be used if weight gain is an issue; associated with less sexual dysfunction than SSRIs or SNRIs and may aid in SSRI-induced sexual dysfunction	Major depressive disorder; off-label use for anxiety disorders
Vilazodone	10–40 mg/day	Gastrointestinal side effects, insomnia	Associated with less sexual dysfunction than SSRIs and SNRIs; should be taken with food	Major depressive disorder
Vortioxetine	10–20 mg/day	Gastrointestinal and sexual side effects, dry mouth	Effective in patients with cognitive dysfunction from major depressive disorder	Major depressive disorder, cognitive impairment (may improve processing speed)
Agomelatine	25–50 mg/day	Headache, gastrointestinal side effects, fatigue, back pain, anxiety, abnormal dreams, weight gain	May help to normalize sleep cycle (melatonin agonist); increased risk (1–3%) of transaminitis; liver function should be checked at baseline, at adjustment of dose (at 3, 6, 12, and 24 wk), and thereafter when clinically indicated	Major depressive disorder; not available in United States

* ADHD denotes attention deficit–hyperactivity disorder, FDA Food and Drug Administration, OCD obsessive–compulsive disorder, PMDD premenstrual dysphoric disorder, PTSD post-traumatic stress disorder, SNRI serotonin–norepinephrine-reuptake inhibitor, and SSRI selective serotonin reuptake inhibitor.

† SSRIs may increase the risk of bleeding and should be used with caution in combination with nonsteroidal antiinflammatory drugs, aspirin, or other anticoagulants, or in patients who are at risk for bleeding.

‡ The discontinuation syndrome may involve flulike symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal.

Selection should also take into account the side-effect profile and the patients' symptoms and additional conditions.

There are areas of uncertainty, such as the use of functional MRI, genetic risk profile, pharmacogenomics testing and biomarkers.

Again, these simple questions may assist identifying those in need of help.

A Patient Health Questionnaire 2

Over the past 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3

B Ask Suicide-Screening Questions

LT Park, CA Zarate Jr. N Engl J Med 2019;380:559-568.

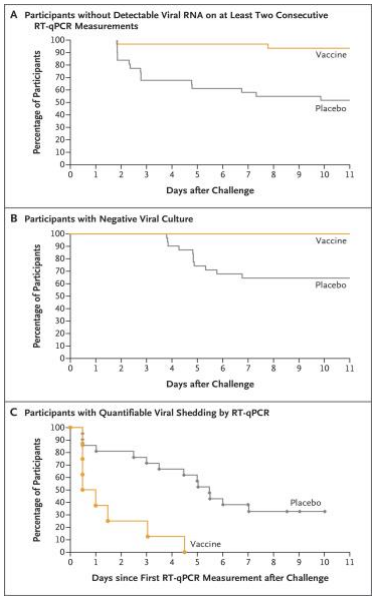
1. In the past few weeks, have you wished you were dead? ☐ ☐
2. In the past few weeks, have you felt that you or your family would be better off if you were dead? ☐ ☐
3. In the past week, have you been having thoughts about killing yourself? ☐ ☐
4. Have you ever tried to kill yourself? ☐ ☐
   If yes, how?_____ When?_____
5. Are you having thoughts of killing yourself right now? ☐ ☐
   If yes, please describe:_____

There are multiple other subjects worth exploring beyond this basic review: The use of Ketamine for refractory depression, combination drugs, electroconvulsive therapy, vagus-nerve stimulation, transcranial magnetic stimulate, intranasal esketamine and other forms of treatment, many approved by the FDA for use in Depression. There are many fronts of active investigation with the use of psychedelics and hallucinogens to combat depression as well.

But as you all know, we live in an imperfect world and to be happy and make the best of our short "one-way" journey, it is best to be realistic about the imperfections we can change and those we cannot, and even better to spend more time and energy looking within than out! And no… it's not necessary to see a therapist as a badge of honor to demonstrate your commitment to self-improvement as is becoming more common among young adults.

Try promoting Freudenfreude and kicking Schadenfreude into the ditch! Enhance positive empathy and joy for others' success! Dr. Chambliss guide.

Other significant medical news



B Schmoele-Thoma et al. N Engl J Med 2022;386:2377-2386.

RSV vaccine for adults likely to be approved by the Spring of 2023 as recent studies demonstrated adequate efficacy.

And if you are one of the 58% of Americans who consumes vitamins, minerals, botanicals, live microorganisms, dietary supplements (spending about 55 Billion in 2020) to prevent or treat various real or (mostly) imaginary ailments and "conditions" (infections of all sorts, memory loss, lack of energy, heart disease, aging, degenerative bone disease, etc.) you may want to read the Dietary Supplement Listing Act of 2022 and will realize why it's always best to "keep it simple" and if not proven, do not use it.

If you have 10 minutes, enjoy this time-lapse of the Entire Universe.
If you have another 10 minutes, read Dr. Fauci's reflections.
If you have 6 more minutes, the massive expanse of our Universe and the magnificent insignificance of humans will delight you.
You will not be able to watch these two videos without smiling.
If you have 7 minutes daily, you can start to improve your fitness right now with the Scientific 7- Minute Workout. Get the app on your phone!
11 more minutes will get you in shape!
For core strength, try this 9-minute routine!

AND START EXPLORING AND PRACTICING MINDFULNESS! It will also help you lower your blood pressure and levels of stress. It will raise pain threshold and your overall sense of well-being.
THERE ARE MULTIPLE RESOURCES ON THE WEB.

Let's all remember that the only certainty in life, is death and the only fountains of youth proven by science and experience are love, exercise, laughter, humor and a positive attitude!

Happy Holidays!

OFFICE UPDATES

- Olivia Dragovits (oliviad@chevychasepulmonary.com) replaced Simran Singh in July, as she pursues her medical degree in Buffalo. She is most competent, efficient, sensitive and ready to help you!
- Samantha Morales will continue to assist you until this coming summer, when she will follow her Medical School dream and already has several acceptances.
- Nicole Loy and Jonathan Sir are excellent and will continue to assist with your office needs as they continue to work towards Medical School
- We are lucky to have Andrew Fookes and Nicholes Rhinesmith who are assisting as Respiratory Technicians and all office needs as they also work towards their medical school acceptance.
- Dr. Shahzad Ahmad has joined us from Stanford University and is proving to be a great addition to our practice.
- I will be away for a few days from January 11-17th catching some turns on the slopes with my family, but never too far from email. My partners will cover emergencies in my absence as usual.

Wishing you Happy Holidays and a Sunny Winter!

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