

STANDARD DEVIATIONS: The Other Elephant

Greetings,

I'm going to talk about the elephant in the room.

No, not that elephant.

The other one.

Who says there can only be one elephant??

Clinical depression, aka major depressive disorder, aka depression, is the other pachyderm. We walk around it, talk around it, dance around it, and still can't see it.

But we know it's there.



More than just feeling sad, it's a serious mental health condition that requires understanding and medical care. Because, like any elephant, depression has a pretty big footprint:

- Percent of adults aged 18 and over with regular feelings of depression: 4.7%
- Percent of physician office visits with depression indicated on the medical record: 10.6%
- Percent of emergency department visits with depression indicated on the medical record: 11.2%
- Number of suicide deaths: 47,511 (2019)



- [Suicide deaths per 100,000](#) population: 14.5 (2019)
- More than 19 million U.S. adults—nearly 8%—had at least one major depressive episode in the past year.

What causes depression?

If there's an exact reason, it's still unknown. We don't understand the etiology.

There *seems* to be a genetic component. An affected parent or sibling can triple the odds. The risk goes up when that relative has recurrent depression. But, no single gene has been parsed out; there seem to be combinations of genetic changes that predispose some people to become ill.

And genetics isn't the only cause. Environmental, biological and emotional triggers contribute:

- Trauma. Stress, physical or sexual abuse, financial problems, and sudden loss may lead to depression.
- Life circumstance. Marital concerns or relationships can be triggers.
- Drugs and alcohol. Around 20% of adults with substance use disorder experience depressive episodes.
- Medical status. A history of sleep disturbances, medical illness, chronic pain, anxiety and attention-deficit hyperactivity disorder (ADHD) are associated. The competence of the pituitary gland and the hypothalamus are implicated. Frontal lobe activity changes are seen in depression.

The search for some underlying physiological or psychological culprit has been an unsuccessful attempt to find the mythical elephant's graveyard.

There is no cure for depression.

The good news is that depressive illnesses often respond to treatment.

The bad news is that we have no really good idea about what therapies work, why they work, or on which patients. Based on historical evidence, trial and error, and an emerging body of search and re-search, depression responds to:

- Psychotherapy. Interpersonal, family-focused and cognitive behavioral therapies.
- Exercise. This seems to be helpful as prevention and with mild-to-moderate symptoms.
- Light therapy. Regulation of melatonin with full-spectrum light works in some cases.
- Alternative avenues. Faith, meditation, acupuncture, aroma, and sound therapies are whack-a-mole hammers that have gained attention, when they succeed.
- Brain stimulation. Electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) are invasive procedures used in patients that did not respond to other treatments. The stigma of this therapy is related to the misuse of equipment, incorrect administration, and improperly trained staff dating back nearly eighty years.
- And then there's Medication. Antidepressants, mood-stabilizers, and antipsychotics are drug alternatives that have beneficial and controversial effects.



We've tried to medicate against depression for a couple centuries. In the last seventy years the pharmacology has evolved to a degree where we have some useful drugs; we just don't know what really makes them work. New frontiers point toward novel therapies that defy our social acceptance but may change the treatment landscape.

St John's Wort, (*Hypericum perforatum*), an invasive weed to much of North and South America, has been used in folk medicine over centuries. Does it work? Data suggests that it is better than placebo but not consistent. It's well tolerated but does have side effects (allergy, gastrointestinal issues, and headache). It is a prescription treatment for depression in Germany but simply a nutritional supplement in the US.



{St John's Wort.}

In 1950, an anti-tuberculosis drug caused a stir in mental health. [Isoniazid](#) was found to be not only effective in tuberculosis (it inhibits the formation of the mycobacterial cell wall) but also improved depression. It was the first to be called an antidepressant. Its mode of action is still unclear.

Tricyclic antidepressants (TCA) came along in 1957 (Imipramine) and soon became the choice for treating depression. It was years later that the mechanisms of norepinephrine and serotonin as neurotransmitters were shown to be affected by TCA.



A tidal swell of discoveries occurred once this relation between serotonin and norepinephrine in neural junctions became recognized in mood alteration. The ability to inhibit re-uptake gave these new drugs potent capabilities in affecting depression and stimulation.

The drug therapies in vogue for depression are focused on the neural synapse and modulation of monoamine transportation (serotonin, norepinephrine, and dopamine). The ones that are selective just for serotonin uptake (SSRIs) are effective antidepressants, like Prozac and fluvoxamine. St John's Wort and those earlier anti-tuberculosis agents also act on this process. We just don't fully understand the science.

But the compounds that function as [monoamine transporters](#) (MATs) are varied. From the tricyclics to amphetamines to MDMA ("ecstasy") to cocaine, these drugs act by mopping up neurotransmitters within the synapse. The fact that some are considered treatment for mental disorder and some are "recreational" does not change their pharmacology.

In fact, some new drugs being investigated for their MAT properties are associated with both recreational use as well as accepted medicinal practices. Others are psychoactive drugs that are found in mushrooms.

Ketamine is one. Psilocybin is another.

Next week [Standard Deviations](#) breaks down the emerging information on these new therapies for treating depression.

Depression is a real and debilitating disorder. Alone it kills thousands of people across the country every year, and its affect on the sick is exacerbating a global pandemic. The best drug treatments are acting on the neural junctions and neurotransmitter concentrations. But the underlying cause(s) and the mechanisms of therapies in depression are still enigmas. We are still in a scientific infancy with our understanding and knowledge.

Have a great week and be safe,

Bryan

