

Relishing the Past and Welcoming the Future: Examining Psychiatry's Recent and Future Breakthroughs

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THE PAST

Selective Serotonin Reuptake Inhibitors

Charles L. Raison, MD

“Listening to Prozac”

Two weeks after starting Prozac, Tess appeared at the office to say she was no longer feeling weary....She looked different, at once more relaxed and energetic—more available—than I had seen her...she laughed more frequently, and the quality of her laughter was different, no longer measured but lively, even teasing.

With this new demeanor came a new social life, one that did not unfold slowly, as a result of a struggle to integrate disparate parts of the self, but seemed, rather, to appear instantly and full-blown...Low self-worth, competitiveness, jealousy, poor interpersonal skills, shyness, fear of intimacy—the usual causes of social awkwardness—are so deeply ingrained and so difficult to influence that ordinarily change comes gradually if at all. But Tess blossomed all at once.

Kramer PD. *Listening to Prozac*. New York, NY: Viking Books; 1993.

“Listening to Prozac”

Tess's work, too, became more satisfying. She responded without defensiveness in the face of adamant union leaders, felt stable inside herself...she said the medication had lent her a surety of judgment; she no longer tortured herself over whether she was being too demanding or too lenient....Tess's management style changed. She was less conciliatory, firmer, unafraid of confrontation...she was given a pay raise, a sign that others noticed her new effectiveness.

There is no unhappy ending to this story...the patient recovers and pays no price for the recovery... Tess did go off the medication, after about nine months, and she continued to do well. She was, she reported, not quite so sharp of thought, so energetic, so free of care as she had been on the medication, but neither was she driven by guilt and obligation. She was altogether cooler, better controlled, less sensible of the weight of the world than she had been.

Kramer PD. *Listening to Prozac*. New York, NY: Viking Books; 1993.

THE PAST

The Quiet Revolution – Rise of the Atypicals

Rakesh Jain, MD, MPH

Since 1991, Atypicals Have Been a Major Presence in Global Psychiatry



Indications

Schizophrenia

Major depression augmentation

Irritability associated with autism

Schizoaffective disorder

Bipolar disorder – mania

Bipolar disorder – mixed

“Off-label” uses

- Dementia related psychosis
- Refractory anxiety disorder
- Insomnia

Consider This – to Appreciate Atypicals Unusually Broad Reach –

- Majority of Mood Stabilizers are atypicals
- EVERY approved Major Depression augmentation medication is an atypical
- EVERY Bipolar Depression medication is an atypical

Yet – There is a Problem in Paradise

- Weight gain
- Metabolic insult
- Neuroleptic malignant syndrome (NMS)
- Tardive dyskinesia (TD)

These are all significant risks and affects millions of people. Newer atypicals are attempting to reduce some of this side-effect burden

Morrison P, et al. *Int J Ment Health Nurs*. 2015;24(3):253-261.

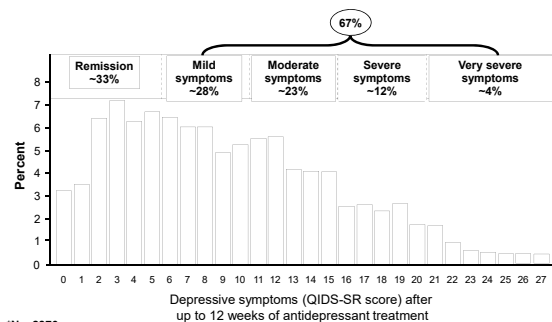
In Conclusion: Atypicals Are a True Revolution and Here to Stay

- Less metabolically impactful Atypicals have been developed and more are coming
- Atypicals are being studied and marching into uncharted territories
 - Dementia related agitation
 - Negative symptoms
 - Cognitive symptoms of depression

THE PAST STAR*D and Its Aftermath

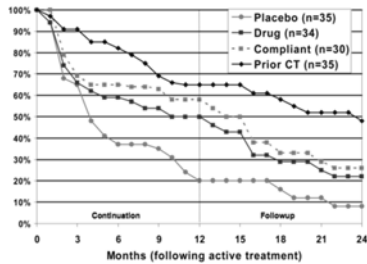
Charles L. Raison, MD

SSRI Results in the Real World



*N = 2876.
QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-report.
Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

Going the Distance ... or Not



CT = cognitive therapy.
DeRubeis RJ, et al. *Nat Rev Neurosci*. 2008;9(10):788-796.

“Listening to Prozac”

An indication of the power of medication to reshape a person's identity is contained in the sentence Tess used when, *eight months after first stopping Prozac*, she said... “I am not myself.”

When I asked her to expand on what she meant, Tess said she no longer felt like herself when certain aspects of her ailment—lack of confidence, feelings of vulnerability—returned even to a small degree. Off medication, she was aware that, if she returned to the old inhibited state, she might need Prozac in order to “feel herself.” In that sense, she might have a lifelong relationship to medication, whether or not she was currently taking it.

Who was I to withhold from her the boundaries of science? Tess responded again as she had hoped she would, with renewed confidence, self-assurance, and social comfort

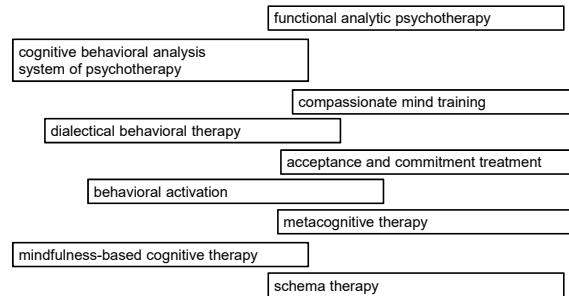
Kramer PD. *Listening to Prozac*. New York, NY: Viking Books; 1993.

THE PAST

Rise of the Third Generation of Psychotherapies

Rakesh Jain, MD, MPH

Here Are Some of the Third Generation Psychotherapies of the Last 3 Decades



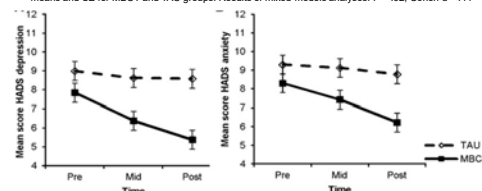
Hunot V, et al. *Cochrane Database Syst Rev*. 2013;(10):CD008704. *Ost LG. Behav Res Ther*. 2006;46(3):296-321.

Some Reasons Why They Are Popular and Will Get More Popular with Time

- They are effective
- They are time limited
- They often blend Western and Eastern philosophies
- They have good patient acceptance
- Their efficacy data looks good

Data on Third Wave Psychotherapies Generally Positive – MBCT as an Example

Left: Effect of MBCT on depressive symptoms. Data are presented as means and SE for MBCT and TAU groups. Results of mixed-models analyses: $P < .01$, Cohen $d = .52$. Right: Effect of MBCT on anxiety symptoms. Data are presented as means and SE for MBCT and TAU groups. Results of mixed-models analyses: $P = .02$, Cohen $d = .44$



Compared with TAU, MBCT resulted in a reduction of emotional distress and an increase in health-related quality of life in diabetic patients who had lower levels of emotional well-being

MBCT $n = 70$; TAU $n = 69$.
HADS = Hospital Anxiety and Depression Scale; MBCT = mindfulness-based cognitive therapy; TAU = treatment as usual.
van Son J, et al. *Diabetes Care*. 2013;36(4):823-830.

There Are Challenges to Wide Adoption of Third Generation Psychotherapies

- Not enough well-trained clinicians are out there
- Not enough trained clinicians / therapists in midsize to small communities
- Insurance coverage is spotty
- Prescriber attention is excessively focused on the “shiny penny” (the neurobiological revolution, the next great medication, income generation pressures, etc.)

In Conclusion

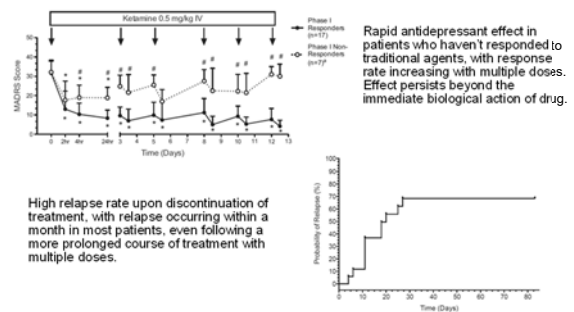
- Even expert psycho-pharmacologists appreciate the limits of biologically delivered treatments and embrace psychotherapies
- Third wave psychotherapies are making great strides as both augmentation and stand alone treatment

THE PAST

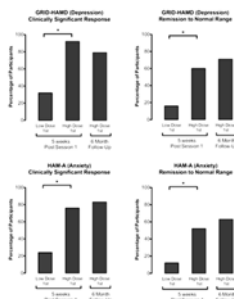
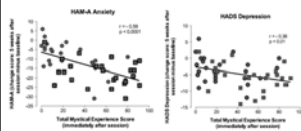
Ketamine and Psychedelics as One Set of Keys to the Future

Charles L. Raison, MD

What Ketamine Does ... and Doesn't Do



An Ancient Practice for the Modern World?



HAM-A = Hamilton Rating Scale for Anxiety; HAMD = Hamilton Rating Scale for Depression. Griffiths RR, et al. *J Psychopharmacol*. 2016;30(12):1181-1197.

THE PAST

Peering into the Previously Unseen Void – The Remarkable Revolution in Brain Imaging Techniques

Rakesh Jain, MD, MPH

List the Various Imaging Studies

CT scan

MRI

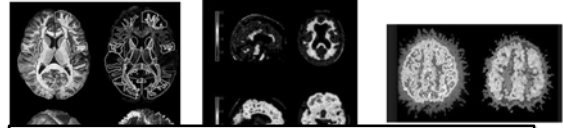
SPECT

fMRI

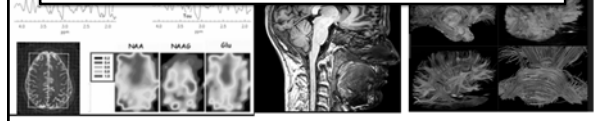
PET

MRS

Diffusion Tensor Imaging



All of these techniques help us peer into the previously unknown void of Brain / Mind / Normal Functioning / Disease Process



What This Revolution in Imaging Has Done for Us

- Helped us better understand mechanisms of illnesses
- Helped us better understand our therapies
- It will help us personalize Psychiatry

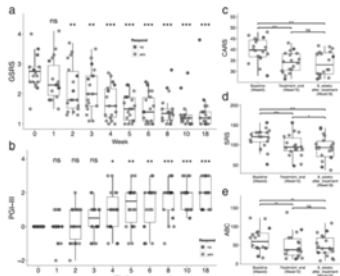
THE FUTURE

Human Microbial Interactions

Charles L. Raison, MD

Microbiota Transplant in Autism

- 18 patients with autism spectrum disorders, aged 7 to 16 years, underwent antibiotic cleansing of the gut followed by prolonged transplant of standardized human microbiota
- This treatment significantly improved both gastrointestinal and behavioral symptoms



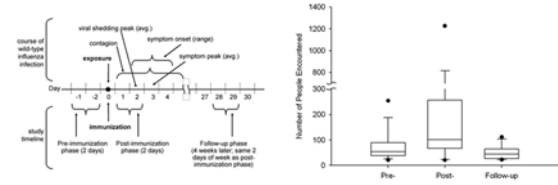
ABC = Aberrant Behavior Checklist; CARS = Childhood Autism Rating Scale; GRS = Gastrointestinal Symptom Rating Scale; PGI-III = Parent Global Impressions-III; SRS = Social Responsiveness Scale. Kang DW, et al. *Microbiome*. 2017;5(1):10.

Sociality before Sickness: Who (or What) Benefits Most from Positive Social Connections?



Reiber C, et al. *Ann Epidemiol*. 2010;20(10):729-733.

Sociality before Sickness: Who (or What) Benefits Most from Positive Social Connections?



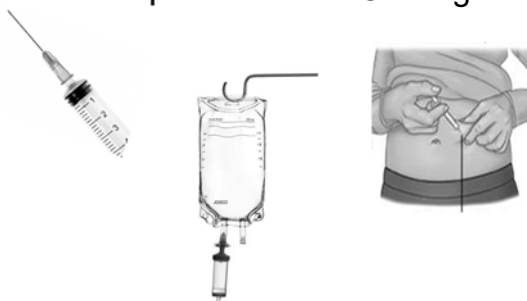
In individuals receiving an influenza vaccine, social contacts were significantly increased in the 48 hours after the injection when compared to either pre-injection or follow-up periods. Importantly, the period when sociality was maximally increased following vaccine coincides with the period of greatest virus shedding, and hence infectivity, during naturalistic influenza infection.

Reiber C, et al. *Ann Epidemiol.* 2010;20(10):729-733.

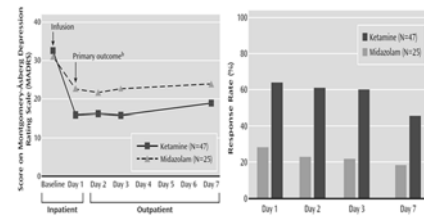
THE FUTURE Novel Mechanism, Parenterally Administered Antidepressants Revolution is Coming ...

Rakesh Jain, MD, MPH

Parenterally Administered Antidepressants Are Coming



Rapid Antidepressant Effects of IV Ketamine Compared to Psychoactive Control



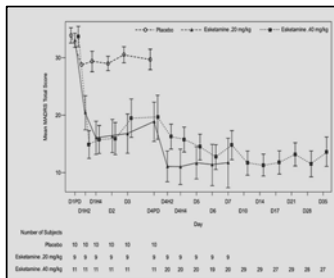
Ketamine dose = .5 mg/kg.

*Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group ($P \leq .002$).

MADRS = Montgomery-Asberg Depression Rating Scale.
Murrough JW, et al. *Am J Psychiatry.* 2013;170(10):1134-1142.

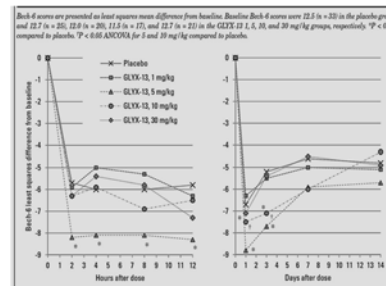
Esketamine in Treatment Refractory Depression – Evidence for Rapid Onset

This multicenter, randomized, placebo-controlled trial was conducted in 30 patients with treatment-resistant depression. Patients were randomly assigned 1:1:1 to receive an IV infusion of .20 mg/kg or .40 mg/kg esketamine or placebo over 40 minutes on day 1. The primary end point was change in MADRS total score from day 1 (baseline) to day 2. Non-responders who received placebo on day 1 were randomly assigned again 1:1 to IV esketamine .20 mg/kg or .40 mg/kg on day 4. Secondary efficacy and safety measures were also evaluated.



Singh JB, et al. *Biol Psychiatry.* 2016;80(6):424-431.

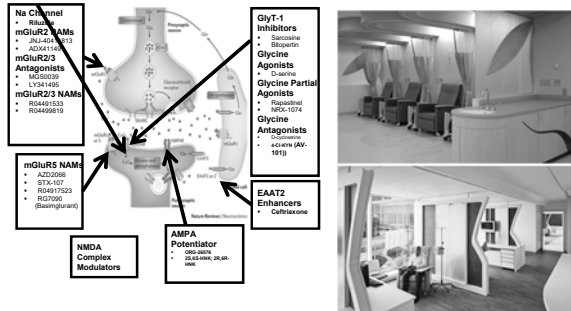
Rapastinel – Glycine Agonist at the NMDA Receptor



MADRS = N-methyl-D-aspartate.
Preskorn S, et al. *J Psychiatr Pract.* 2015;21(2):140-149.

Double-blind, randomized, placebo-controlled study, a single IV dose of GLYX-13 (1, 5, 10, or 30 mg/kg) or placebo was administered to 116 participants with major depressive disorder who had not benefited from a trial of at least 1 biogenic amine antidepressant during the current episode.

And this is just the beginning ... Many, Many More Parenterally Administered Drugs are on the way ...



Park M, et al. *Curr Behav Neurosci Rep.* 2015;2(4):198-208.

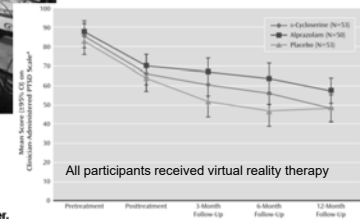
THE FUTURE Computer-Brain Interfaces: Rise of the Cyborgs

Charles L. Raison, MD

"Most of the complexity of a human neuron is devoted to maintaining its life-support functions, not its information-processing capabilities. Ultimately, we will be able to port our mental processes to a more suitable computational substrate. Then our minds won't have to stay so small.... Our human intelligence is based on computational processes that we are learning to understand. We will ultimately multiply our intellectual powers by applying and extending the methods of human intelligence using the vastly greater capacity of non-biological computation."

Kurzweil R. *The Singularity Is Near: When Humans Transcend Biology*, New York, NY: Penguin Books; 2005.

Virtual Reality Therapy for PTSD



PTSD = posttraumatic stress disorder. Rothbaum BO, et al. *Am J Psychiatry*. 2014;171(6):640-648. Levy CE, et al. *Am J Phys Med Rehabil*. 2015;34(4):e31-e32.

But Maybe We Are Only Scratching the Surface:
Good Luck Not Believing What Virtual Reality Tells You

www.youtube.com/watch?v=I3V8zeSijUU. Accessed July 10, 2017.

And What Will Be Possible When
Computers Can Read Our Minds?

<http://spectrum.ieee.org/tech-talk/robotics/medical-robots/monkeys-navigate-wheelchair-with-their-thoughts>. Accessed July 10, 2017.

A DARPA spokesperson told Fusion that “brain-neural interfaces” have not been implanted in soldiers, though researchers have already begun testing such devices by temporarily implanting electrical arrays into the brains of volunteers undergoing surgery for other neurological issues. Defense One, an online magazine that covers the military, reported last year on DARPA’s work on brain chips to treat PTSD, and said that DARPA was not yet in the testing phase. When DARPA launched its RAM (Restoring Active Memory) program last year, it projected it would be about 4 years until researchers were implanting permanent chips in humans.

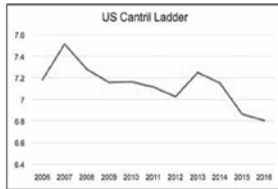
DARPA = Defense Advanced Research Projects Agency. Brown KV. September 28, 2015. <http://fusion.kinja.com/darpa-is-testing-implanting-chips-in-soldiers-brains-1793851273>. Accessed July 10, 2017.

THE FUTURE Rise of Mental Wellness in Psychiatry

Rakesh Jain, MD, MPH

American Happiness – On a Slide

US Happiness Score, 2006–2016



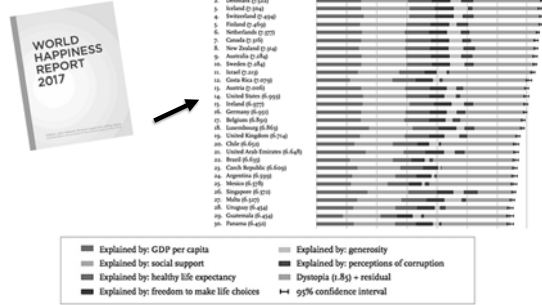
Source: Gallup International Cantril ladder

The United States showed less social support, less sense of personal freedom, lower donations, and more perceived corruption of government and business

The central paradox of the modern American economy, as identified by is this: income per person has increased roughly 3 x since 1960, but measured happiness has not risen. The situation has gotten worse in recent years: per capita GDP is still rising, but happiness is now actually falling.

Helliwell J, et al (Eds). *WORLD HAPPINESS REPORT 2017*. <http://worldhappiness.report/wp-content/uploads/sites/2/2017/03/HR17-Ch1.pdf>. Accessed July 10, 2017.

World Happiness Ranking: 2014–2016



Helliwell J, et al (Eds). *WORLD HAPPINESS REPORT 2017*. <http://worldhappiness.report/wp-content/uploads/sites/2/2017/03/HR17-Ch1.pdf>. Accessed July 10, 2017.

Some Countries Are Making Wellness a Priority...

Gross National Happiness (GNH) is a development philosophy as well as an index that is used to measure the collective happiness in a nation. The concept is indigenous to the country of Bhutan, and was enshrined in the country’s 2008 constitution which states that “the State shall strive to promote those conditions that will enable the pursuit of Gross National Happiness.”



Rise of Global Wellness Focus

United Arab Emirates (UAE)
2016. Creates a Cabinet level position –
Minister of Happiness



UAE’s minister of happiness insists her job is no laughing matter



