The curious incident of the neuroleptic prescription

Amy Du Beau, PhD **April 2020**

Satirical exposé exploring neuroleptic action at the neuronal and neurochemical level with emphasis on the efficacy of off-label prescribing and diagnostic criteria.

Contents

Neuroarchitecture of psychosis

Your brain is a complex circuitry of approximately 86 billion neurons, each projecting axons and dendrites to proximal (nearby) and distal (far away) regions. Neurons are not created equally. Rather, each serves a specialized function. For those with thought disorders (psychosis), the culprit seems to be malfunctioning neurons specifically in striatal regions within the brain's evolutionarily ancient limbic system. Only neurons in these regions need to be treated, which means that the majority of neurons throughout the central nervous system (brain and spinal cord) are otherwise healthy. Refer to Figure 1.

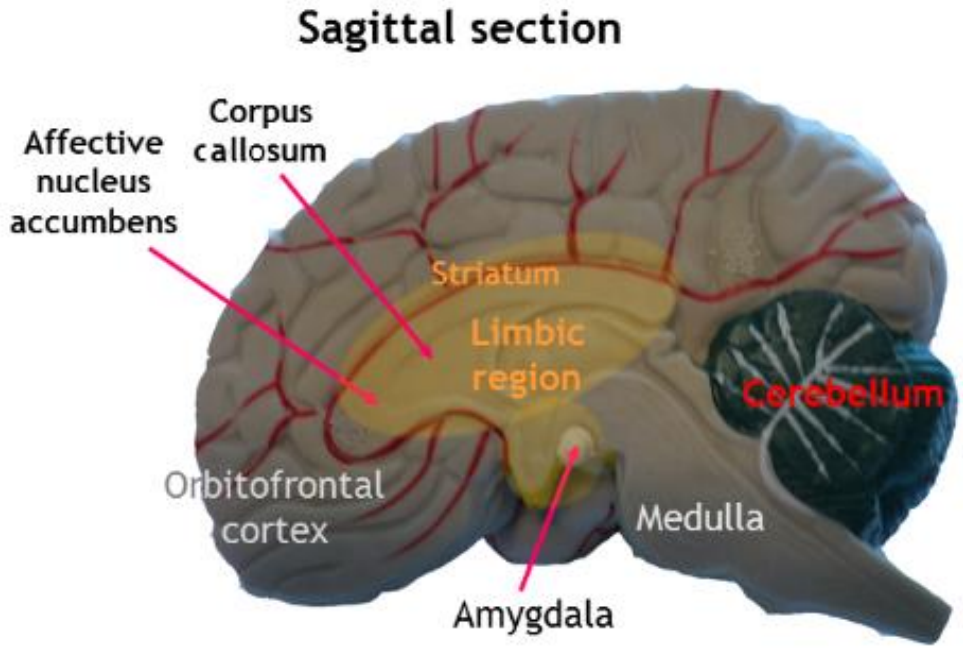

Figure 1 | Brain regions associated with psychosis

Sagittal (cross) section of the human brain showing limbic/striatal regions (yellow shading). Monoamines arise from midbrain regions. The corpus callosum divides the brain into left and right hemispheres, and the affective nucleus accumbens is associated with the dopaminergic reward circuit. Other brain regions shown for context. Figure adapted from Du Beau (2018).

Psychosis

Psychosis is an episodic symptom marked by incoherent, disorganized thought incongruent with reality. Psychotic motifs include hallucinations (auditory, visual or sensory) and delusions (paranoia, grandiosity or religiosity). Psychiatric disorders that entail persistent and recurring psychosis are schizophrenia (inclusive of schizoaffective disorder), bipolar disorder and sometimes major depression.

Anybody can experience dissociative states of psychosis. For instance, prolonged sleep deprivation will invariably induce psychosis. Related, acute bouts of grief, extreme emotional duress, illicit drug use, sensory deprivation, running a fever, even hypnogogic states such as daydreaming can temporarily induce psychosis.

- Factoid: Poltergeist activity is oftentimes attributed to prolonged exposure to low-level household carbon monoxide (CO) (Grant, 2015). CO exposure can induce hallucinations, inclusive of a physiological sense of doom (heart palpitations, anxiety and flushing). In lieu of recruiting a ghostbuster, exorcist or psychiatrist, just check your CO detector. But back to the story.

Neurochemistry, transmission and dosing of neuroleptics

Neuroleptics are psychoactive drugs belonging to the class of major tranquilizers, prescribed to treat psychosis. Zyprexa (olanzapine) is a popular neuroleptic developed and marketed by the pharmaceutical company Eli Lilly (Lilly). Refer to Figure 2. How do neuroleptics work in the brain?

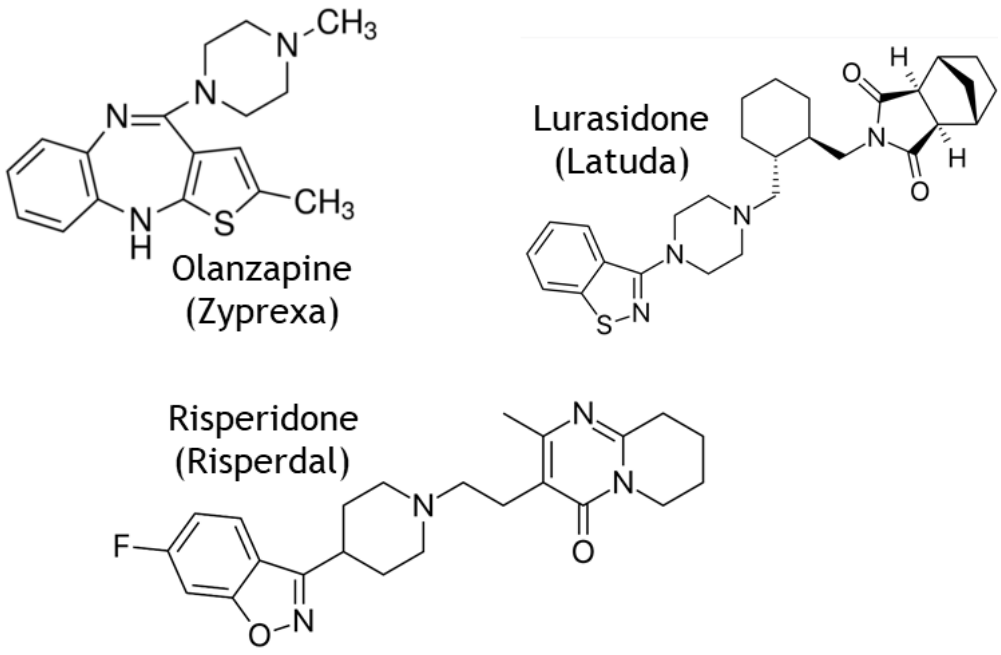

Figure 2 | Neuroleptic structures

Neuroleptics (antipsychotics) belong to the class of major tranquilizers with similar psychoactive actions. Chemical structures of exemplary neuroleptics are shown in this figure. Zyprexa and Risperdal are popularly prescribed for schizophrenia and Latuda is commonly used to treat bipolar disorder and major depression.

Neurons in your brain talk to each other using the language of neurotransmission. Neuroleptics work by blocking monoaminergic (catecholaminergic) receptors in the brain. By design, neurons each have specialized receptors on their surface membranes activated by various neurochemicals such as monoamines – imagine them like little electrical outlets. Monoamines (dopamine, serotonin and noradrenaline (aka norepinephrine)) are readily convertible chemicals that transmit signals between neurons by plugging in to these receptors, switching them off and on.

Monoamines are associated with mood. Dopamine regulates emotion, motivation and reward whereas serotonin is generally associated with pleasure. Monoamines change the relative contribution of other neurotransmitters in your central nervous system, both excitatory (glutamate and histamine) and inhibitory (glycine and GABA). That is, monoamines are like the lubricant 'WD-40' of your brain. Refer to Figure 3.

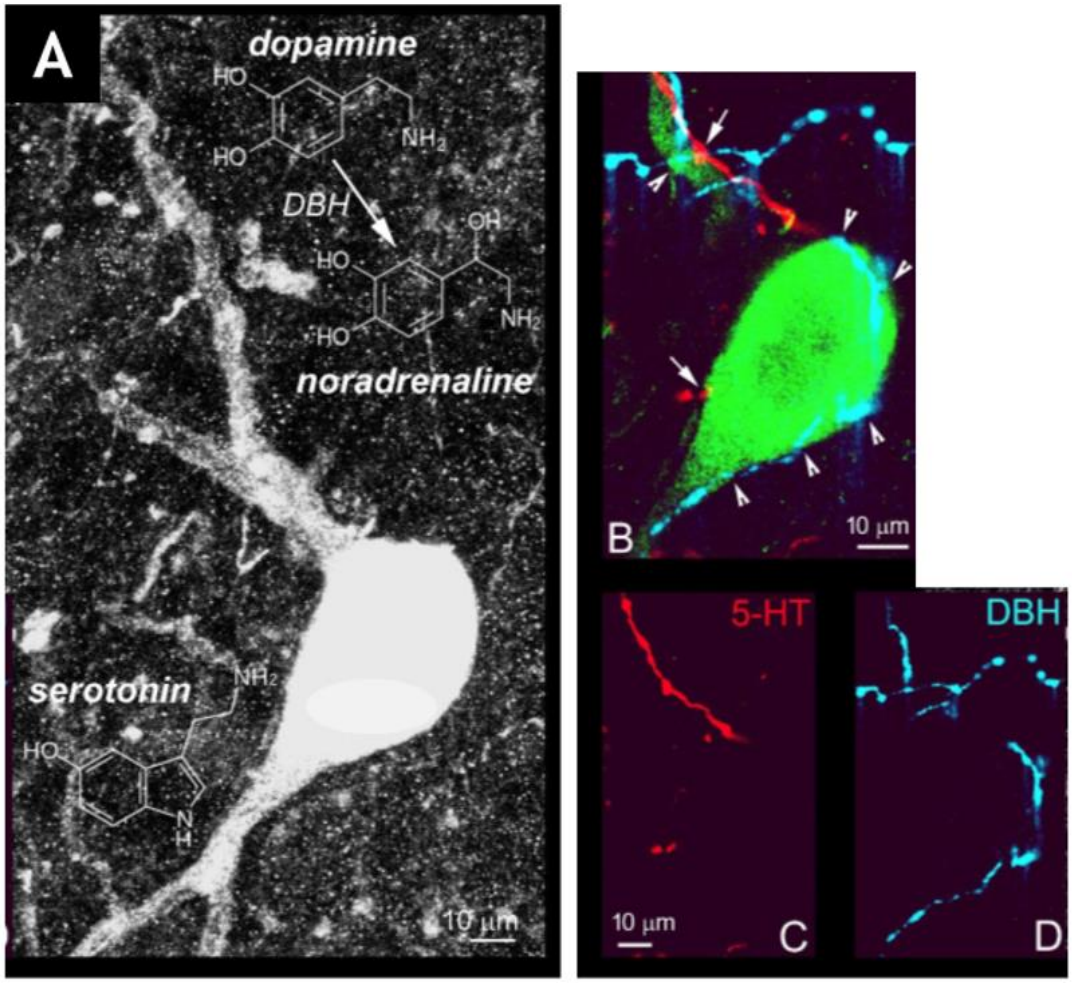

Figure 3 | Monoamines in the central nervous system

My confocal microscopy image showing (A) Monoamines in the central nervous system. (B) Serotonin (5-HT, red) and dopamine (DBH, blue) modulating a neuron (green). (C) Serotonin (5-HT). (D) Dopamine (DBH). µm = micrometers. Figure by Du Beau.

There is no evidence that the schizophrenic or bipolar brain has too much dopamine. Rather, dopamine specifically in limbic/striatal regions of the thought disordered brain is misallocated. Too much dopamine may be sequestered by limbic/striatal neural receptors, disproportionately leaving too little between neurons, thus hampering cross-talk between neurons. While neuroleptics do target limbic/striatal regions, the salient issue is that these agents block neural receptors throughout the entire central nervous system indiscriminately and unnecessarily. Yes, the whole enchilada.

The usual dosing for Zyprexa is 5 to 20 milligrams once daily administered orally. Psychiatrists notoriously advise that their patients take neuroleptics for the rest of their life, even if psychotic symptoms may be fleeting. Heavy emphasis on the consequences if their patients do not comply. Further, institutionalized or hospitalized patients may be forcibly drugged against their will (Gottstein, 2020).

To compound neuroleptics' 'sledgehammer' approach, neurons are very adept at growing new receptors to compensate for those that are blocked. Psychotic symptoms then rebound with a vengeance. As per psychiatric protocol, dosage of the neuroleptic are then increased accordingly - if the treatment is unsuccessful, just add more. Now the vulnerable patient really is incapacitated, complacent and permanently mentally ill. Snowball effect.

- As a quick fix, acute psychotic episodes can often be squelched with a big dose of the common over-the-counter anti-histamine allergy medicine Benadryl, aka diphenhydramine (50+ milligrams), although certainly no cure! Benadryl works by blocking histamine, an excitatory neurochemical. By the same token, pretty much any sedating drug will work, such as benzodiazepines like Ativan, which is an especially fast-acting titration. But back to the story.

Alternate applications for neuroleptics: off-label prescribing

Neuroleptics are broadly used to treat other conditions too, a practice referred to as 'off-label' prescribing (e.g., Gottstein, 2020; Eisenberg, 2012). Conditions that may be treated with neuroleptics include mood disorders (depression) that do not respond robustly to selective serotonin reuptake or monoamine oxidase inhibitor drugs, autism, Asperger's syndrome, post-traumatic stress, traumatic brain injury, dementia, obsessive compulsion, anxiety, personality disorders, substance abuse, insomnia, Tourette's syndrome, geriatric conditions, extreme nausea, migraines, epilepsy, criminal behavior, attention deficit disorder and even just delinquent naughtiness in children and teens.

The outstanding problem is that these various disparate conditions, each with very different etiologies, do not necessarily entail psychotic symptoms and/or dopaminergic dysfunction at all. Throwing the proverbial dart at the open Diagnostic and Statistical

Manual of Mental Health book, yes? Indeed, dopaminergic inhibition is contra-indicated in many of these conditions. So what motivates psychiatrists to off-label prescribe neuroleptics in these cases?

Lilly, cognizant of Zyprexa's side effects, marketed off-labelling, incentivizing psychiatrists to prescribe (Gottstein, 2020). If you are wondering, psychiatrists earn approximately $270,000 and upwards annually (online source: ZipRecruiter). Presenting a conflict of interest, psychiatrists can earn cushy kick-backs from pharmaceutical companies rivaling their annual income (online source: ProPublica). Ruh-roh.

Psychosis is a transitory symptom. Those with schizophrenia and bipolar disorder are not psychotic 24/7/365, but rather experience episodic states of psychosis. Neuroleptic drug action is continuous, however. Pharmacologically, do the psychokinetics of neuroleptics match intended therapeutic goals? Let us consider the ubiquitous scientific concepts of accuracy and precision.

Accuracy versus precision

'Accuracy' refers to how close the given acting agent is to the intended target. In this case, let us imagine any given neuroleptic is the agent and aberrant neural receptors are the target. Alternatively, 'precision' refers to how close the acting agents are to each other. Such agents may totally miss the target, but they are precisely clustered. For effective utility, any given pharmaceutical agent must be both precise and accurate. However, neuroleptics are neither accurate nor precise. Refer to the Figure 4.

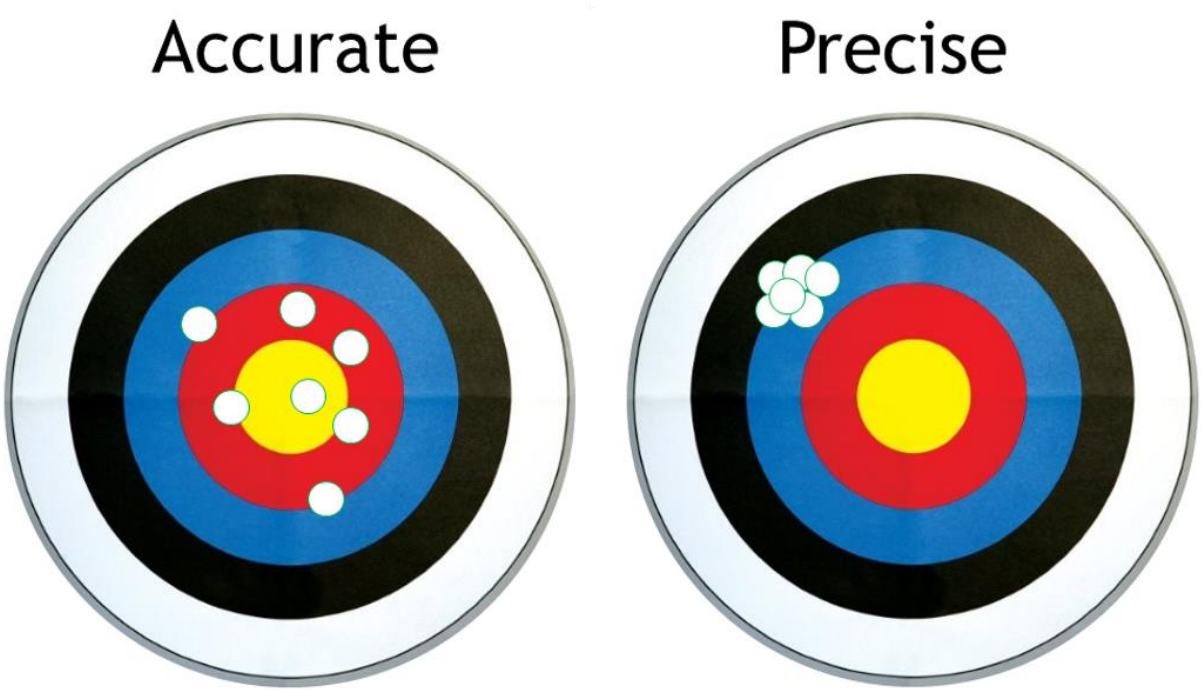

Figure 4 | Accuracy versus precision

Let the center yellow ranging to red bullseyes represent the limbic/striatal neural target and the white dots represent the neuroleptic agents. Accurate (left): Agents are accurately targeting their intended neural ranges, but lacking precision. Precise (right): Agents are precise, but miss their target. Image by Du Beau.

Toxicity

Tinkering with neurotransmission may have deleterious side effects (e.g., Gottstein, 2020; Boushra & Nagalli, 2020). Indeed, the daunting toxic side effects of neuroleptics include the following non-exhaustive list:

- Metabolic disorders such as obesity and diabetes which may result in complications such as limb amputation and blindness. Psychiatric patients treated with neuroleptics will invariably gain weight, a lot of weight.

- Decrease in white blood cell count, rendering a greater risk of serious systemic infection.

- Neuroleptic malignant syndrome is potentially fatal. Related, Tardive Dyskinesia (TD) and related dystonias evidenced by involuntary spastic repetitive muscle movements that range from embarrassing to downright disfiguring. TD is virtually permanent and irreversible.

- Malaise, apathetic complacency and oversleeping that is a sequela of chronic sedation, thus curtailing the patient's capacity to successfully hold down any job, go to school, take care of children or safely drive, etc.

- Hormonal imbalances resulting in sexual dysfunction and gynecomastia (breast development in men) and lactation in the absence of pregnancy.

Diagnostics

To preface, as a forensic neuroscientist with an analytical laboratory background, operating based on evidentiary data informs my decisions. Scientific methodologies quantify evidence that is verifiable and repeatable. So inferring pivotal conclusions with gravitas about nuanced human psychology makes me cringe.

Psychiatrists may refer their patients to clinical psychologists for a formal diagnosis to help determine the course of treatment. Self-reporting tests such as the Minnesota Multiphasic Personality Inventory (MMPI) can help guide the clinician. To titillate my readers, let us sample a few representative questions from the 567 total yes/no MMPI questions:

- I would like to be a florist.

- I gossip a little at times.

- I do not have a great fear of snakes.

- I like mechanical magazines.

- I am always disgusted with the law when a criminal is freed through the arguments of a smart lawyer.

    - Author's note: an Eli Lilly executive wistfully answers '*No – I'm ok with it*' to this loaded MMPI question.

Ad nauseam. Onto the Rorschach inkblot test, premised on the concept of pareidolia, the perceptual tendency to assign meaning to ambiguous stimuli, such as seeing clouds shaped like hippopotamus, Jesus Christ on toast, etc., ostensibly determining your mental and emotional functioning and personality. As an exercise, let us look at three representative inkblots together. Refer to Figure 5.

Figure 5 | Rorschach inkblots

Examples of Rorschach inkblots, online source.

Can you guess? The problem is that there really are wrong answers to such diagnostic tests. Human behavior is dynamic and responses to such queries is variable depending on external circumstances, environment, mood, being hangry, etc. and the very hortative nature of clinical practice. There is naturally a great deal of behavioral variability between people, so diagnostic errors happen inevitably. In this author's opinion, these baseless tests are pseudoscience. Psychological examinations are necessarily subjectively interpretative, relying on your clinician's supercalifragilistic powers of intuition.

Ethics, the law and new directions

Attorney Jim Gottstein's groundbreaking book, *The Zyprexa Papers* (2020), explicitly reveals the profound harm caused by neuroleptics. Given the grievous effects of neuroleptics, weighing all prognostic options, psychiatrists ought to justify prescribing neuroleptics, reserving their use for the most intractable psychotic disorders, yes? Psychiatrists uphold the Hippocratic Oath as per their medical training: to practice ethically without maleficence and 'do no harm.'

The evidence against neuroleptics is irrefutably mounting, impervious to gaslighting by the pharmaceutical industry incentivizing prescribing psychiatrists. Lilly would not have

subjugated the damning Zyprexa Papers unless they knew the coveted scientific reality were so very powerfully persuasive. When challenged, Lilly defended Zyprexa with vigor.

The denouement to Gottstein's lawsuit against Lilly? By January 2009, nakedly exposed and exhausting their defensive 'smoke and mirrors' bravado, Lilly conceded, paying 1.4+ billion dollars to resolve off-label promotion of Zyprexa. Lilly's settlement was the largest individual corporate criminal fine in history. In sum, hold onto scientific evidence, the truth, and never let go! Refer to Figure 6.

Figure 6 | Ruby slippers

Image courtesy of *The Wizard of Oz*, online source.

To aptly quote Glinda the Good Witch of the North's sage advice to Dorothy when threatened by the Wicked Witch of the West, "*Keep tight inside those ruby slippers. Their magic must be very powerful, or she wouldn't want them so badly.*"

Developing novel therapeutics to treat thought disorders is long overdue. Rather than pridefully defending agents that do not work, let us learn from such mistakes, moving forward with curiosity, compassion, bravery and 'fresh eyes' to find better solutions. Refer to Addendum.

About the author

I am an independent consultant, a neuroscientist (PhD) and criminal behavioral profiler (D-ABP) with expertise in bloodstain pattern analysis.

Disclaimer

I am the sole author of this report and declare no conflict of interest. All contents referenced from this document must be cited directly to me. Questions and comments are welcome. AD

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Addendum

Modern research addressing alternatives to neuroleptic drugs must be equivocally considered, revising existing therapeutic applications accordingly. The following lists are by no means inclusive, but rather suggestive of possible options.

Sleep and circadian rhythm aberrations are evidenced in major psychiatric conditions such as schizophrenia and bipolar disorder, inclusive of treatments involving altering photoperiodicity. E.g.,

Pritchett D., Wulff K., Oliver P.L. *et al*. (2012) Evaluating the links between schizophrenia and sleep and circadian rhythm disruption. *J Neural Transm*. 119. Pgs. 1061-1075. doi.org/10.1007/s00702-012-0817-8

Harvey, A. (2008). Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. APA. doi.org/10.1176/appi.ajp.2008.0810098

Caliyurt, O. (2017). Role of chronobiology as a transdisciplinary field of research: Its application in treating mood disorders. *Balkan Med J*. 34(6). Pgs. 514-521.

Kaladchibachi, S., Fernandez, F. (2018) Precision light for the treatment of psychiatric disorders. *Neural Plast*. doi: 10.1155/2018/5868570

Sikoglu, E.M., Liso Navarro, A.A., Starr, D. (2015) Vitamin D3 supplemental treatment for mania in youth with bipolar spectrum disorders. *J Child Adolesc Psychopharmacol*. 25(5). Pgs. 415-424. doi: 10.1089/cap.2014.0110

Bauer, M., Glenn, T., Alda, M. *et al*. (2012) Impact of sunlight on the age of onset of bipolar disorder. *Bipolar Disord*. 14(6). doi: 10.1111/j.1399-5618.2012.01025.x

Lamont, E., Coutu, D.L., Cermakian, N. (2010). Circadian rhythms and clock genes in psychotic disorders. *Israel J of Psy*. Jerusalem. 47(1). Pgs. 27-35.

Saccadic eye movement may be applied to treat major psychiatric disorders. Such applications have made great strides in ameliorating post-traumatic stress already. E.g.,

Bittencourt J., Velasques, B., Teixeira, S. *et al*. (2013). Saccadic eye movement applications for psychiatric disorders. *Neuropsychiatr Dis Treat*. 9. Pgs. 1393-1409. doi. 10.2147/NDT.S45931

Exercise therapy including yoga for psychiatric conditions may particularly help reduce negative symptoms of schizophrenia and increase self-control, esteem and sociability. The role of exercise in mood disorders and related neuropathic pain (fibromyalgia) have been promising. E.g.,

Gorczynski, P., Faulkner, G. (2010). Exercise therapy for schizophrenia. *Cochrane Database of Systematic Reviews*. 5. doi 10.1002/14651858.CD004412.pub2.

Lang, D. (2018). Brain health and exercise in schizophrenia. ClinicalTrials.gov Identifier: NCT01392885