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‘What Doctors May Not
Tell You About
Psychiatric Drugs’

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Dr. Jackson, a Board certified psychiatrist, is a 1996 graduate of the University of Colorado School of Medicine. She holds degrees in biology and political science, as well as a Master's degree in Public Administration. Dr. Jackson completed her psychiatric internship and residency in the U.S. Navy, with subsequent assignment to Bethesda Naval Hospital as a staff physician. Since transitioning out of the military in spring 2002, Dr. Jackson has lectured widely in Europe and the United States, speaking about "The Unintended Consequences of Developing Biotechnologies"; "The History and Philosophy of Attention Deficit Disorder"; "Drug-Induced Psychiatric Emergencies"; and "The Limitations of Biological Psychiatry". She has spoken at international conferences featuring highly respected clinicians, such as Dr. David Healy (The Antidepressant Era and The Creation of Psychopharmacology); Dr. David Stein (Ritalin Is Not The Answer); and Dr. Bertram Karon (Psychotherapy of Schizophrenia: The Treatment of Choice). Dr. Jackson is currently working as a Locum Tenens psychiatrist, based in North Carolina.

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For those who aren't familiar with anti-psychotic medications, three of the short-term effects include Parkinsonian symptoms; a sometimes lethal condition called Neuroleptic Malignant Syndrome; and the third is called NIDS (Neuroleptic Induced Deficit Syndrome). I don't imagine many people have heard about this last one. Does anybody know what that is (some response from crowd)? Great, there are some well-informed people here. NIDS was never a part of my training, so that's great.

Other bodily effects; I swear to God it seems that many doctors forget that there is something attached from here down (points to base of neck downwards). I'm a psychiatrist, I know, but some physicians seem to only think these pills effect everything from the neck up, and they forget that when they give the medications there is an entire human body that may be feeling unanticipated effects of these medications. I'm going to be speaking about NIDS in much more detail as it's something that very few people are ever told about, and the advertisement for this lecture is "What Doctors May **Not** Tell You About Psychiatric Drugs" so I'm not going to spend much time on Neuroleptic Malignant Syndrome. I hope to God that your doctors are telling you about that, although I think most times they don't because they don't want to panic people.

With regards to the antidepressant medications: many people may not also realise that many individuals who receive serotonergic antidepressants, such as Prozac (Fluoxetine), Seroxat (Paroxetine) Zoloft or Lustral (sertraline) and many more; all of these are in the family of serotonergic anti-depressants. Many patients who take these drugs also develop Parkinsonian side effects. What many people might **not** have been told by their doctors about antidepressants is that just as there is a Neuroleptic Malignant Syndrome with antipsychotic medicines, there's a baby version of this: patients who take Prozac or Zoloft might experience something called Serotonin Syndrome. It's almost like Neuroleptic Malignant Syndrome but it's not quite as severe, and does not appear to cause death.

Violence and suicide: these are possible drug reactions that a doctor is not typically going to tell patients about. If you take Prozac and Luvox (Faverin = fluvoxamine) it might make you more prone to suicide. Maybe you saw the programme on BBC called "Secrets of Seroxat". It's a very important topic right now in the United States, as it has been here in the U.K, looking at the potential for serotonergic and other anti depressants to actually contribute to violence or suicide in some individuals who receive these medications. It's probably not a high percent of people, but when you think about how many people are receiving these medicines it turns out to be a large number of individuals who have been affected.

The Brain

The brain is very complex, often it seems to me that people may not realise what's in the brain, or doctors may sometimes not say to a patient what they need to. One of the things that doctors probably seldom tell their patients (if they refresh their own memories) is what is in the brain and what is the target of these medications. The brain consists of over 100 billion neurons. Each one of these cells makes a thousand to ten thousand connections with other cells. When we think about what's actually going on inside the human brain, things are quickly getting out of hand - very complex. There are also other kinds of cells that are called glia, or support cells, and there are five to ten times as many glia as there are neurons. The only thing that the drug companies talk about is the neuron, but it is important to realize that medications also affect the glial cells. This is another thing that people don't hear about.

The most important thing of all is realise that there is a very special barrier called the Blood Brain Barrier. It prevents most things that we eat, or most toxins that we are exposed to, from actually passing through the blood into the brain tissue. When a medication is made, scientists manipulate that molecule so that it can get through this barrier. This is a very interesting thing to think about - what it means to actually be introducing something into the body, which goes around the natural barrier or avoids the natural defences of the brain.

Now, if you're in my country, one of the things that happens is that there are commercials on television right now, and some people think the brain's very simple because of these commercials. I'm not sure if you folks have ever seen ads like this in your newspapers or journals (**APPENDIX A**), some of you may have. This one was an advertisement that appeared on television in the United States. It's an ad for Zoloft /Lustral (sertraline), which is one of the serotonergic antidepressants. The ad comes on TV and says, "Normally, serotonin gets released by nerve A and comes across this little gap and hits this second cell and this is healthy." This represents a serotonin balance. If you're feeling too anxious or too depressed then you have a chemical imbalance. These little bubbles represent serotonin, one of the many chemicals in the human brain. So they say take Zoloft, which works on the receptors on this first cell, and what happens is that serotonin gets rebalanced and you end up with more serotonin. I'm actually using a lot more words and saying this in a lot more complex fashion than the TV commercial but this is about as much as doctors communicate to a patient, 'Just take this pill and this imbalance here will suddenly get filled up and your serotonin levels will go back to normal'. It's sort of like filling your gas tank, just go to the petrol station and fill up. What the doctor's not telling you is just how complex the brain is. How many of you know people taking these medications or have been on them yourself? Have you actually had a doctor tell you **where** in the brain the drug is working? I see a lot of heads shaking. I have never met a doctor who has been able to answer, "Gee Doc, tell me where in the brain this medicine's gonna hit me?"

And they really don't have a clue, because they really don't think about it that much. I hope this is as scary for you as it is for me! What happens with serotonin and these drugs is that they go all over the brain. It becomes very difficult to tease apart where they go. This is especially true of serotonin. I just wanted to show you this advertisement as a reminder for you to ask your doctor, or to show to your friends so they can go and ask their doctor where in the brain this medicine is working.

What we do know about medications comes mostly from animal studies. And only somewhat from studies in humans. Everything gets explained to medical students and other trainees on a very tiny level – at the molecular level. But it's very seldom that you'll meet a physician who knows how to take the molecular level and now expand it and put it into the context of a whole human body. What typically is presented in the commercials and the textbooks is a cellular description. And they never go beyond that. They never say, "here's the part of the brain and here's how this is going to make a person feel and why." It's just a molecular description. So part of my research has been always trying to take it up to the next step or the larger level.

I've seen some things on the Internet where they show Earth from outer space and they keep coming down by powers of ten. They go right down into the leaf of the tree, and they go inside the leaf until they go way down into the nucleus of the leaf's cell and it's almost like that in psychiatry! Many times, doctors are stuck inside the cells inside the leaf - they don't quite know how to come back up and see the tree. So what I'm trying to do here is to come back up and see the whole tree or encourage you to do that, although possibly there are people here who are already doing that.

Inside the body there are (in the brain) nerve cells called neurons. The neurons have a nerve cell body which is sort of the business end of things when it comes to the functioning of the cell. Inside the cell body lies the nucleus which contains the cell's DNA. The DNA is responsible for reproducing the proteins and enzymes that the cell needs for survival, or which the cell uses for communicating with other neurons. So, what happens is that neurotransmitters get made in the cell body - then sent down a long connection (axon) which is like a highway, until they reach the business end of the neuron. The business end, in terms of medications, is typically what the commercials and television tells you about. This is the nerve terminal.

The nerve terminal is the region of the neuron where neurotransmitters get released. That's basically what a neuron does -- it makes things and releases them: kind of like writing a letter and sending it in the mail. The business of neurons is to generate mail and then send it on to a recipient. And so that's what these medications do. They're either decreasing the transmission of messages, or increasing the transmission of messages.

Another thing I'd like to mention is this (**APPENDIX B**) partial listing of some of the chemicals that the brain uses to deliver messages. This is a list of about 60 different chemicals, but for all we know there may be hundreds more that have not yet been identified. Now, medications that are used most often in psychiatry only address or target five of these chemicals. So the next time the patient says 'doctor what is this drug doing?' and he or she's says 'well this is only working on serotonin' - well that's a lot of nonsense because we really don't have doctors or scientists who are studying the ripple effects (of drugs). When you block dopamine receptors what about leu-enkephalin, gastrin, and CCK (cholecystokinin)?

What you need to realise is that when neuroscientists devote their lifetime to the study of these chemicals they literally study just one of these chemicals. One chemical may be their entire life's work. So these are wonderful people who are doing wonderful research but it's very difficult to find people who know how to put these things together, which is really what a human being is - a very complex system, where all these chemicals impact each other (at the same time).

Now people say, 'Geez Doc, so what's happening in this nerve ending?' This is the nerve terminal, which is the focus of attention for psychiatrists. A message comes from the first cell, (you remember what I said about writing a letter, and the nerve tries to send the letter across this space, like putting a letter in a post box). If it's successful it's going to find a recipient, which will be another cell, another neuron, and the cell that receives the letters has to have a mail-drop. The mail-drops are called receptors. They sit on that cell and they wait for a letter to come, waiting for a transmitter. They wait for some chemical to come and hit the receptor. What happens inside the body is a response (and this really is the gist of my lecture, is for you to be thinking and to encourage your physicians, or physicians you know, to be thinking about how the body

compensates for, or responds to the medication.) What appears to be the case is that whenever you start turning off the flow of letters, you begin diminishing the (net) rate of chemical transmissions in the brain. Guess what? You remember the Newton quote at the start; 'For every action, there is an equal and opposite reaction' (**APPENDIX C**). Well, in the human brain, it seems that "For every action, there is an unequal and sometimes unpredictable reaction." (**APPENDIX D**) When you begin decreasing the flow of (neuro) transmission, the number of receptors changes- it goes up.

This is a very important thing to understand; it explains why some people get withdrawal or discontinuation syndromes when they stop taking their medication or when their medication is lowered in dose. It also explains why some people may become more sensitive to side effects over time, because now there are more receptors there, waiting for the chemical. This idea of receptor change is something that is very important and something that very few physicians share with their patients.

Alternatively, what could happen is that the person who is taking the medication experiences an increase in the flow of messages - the neurotransmitters could actually get revved up. Dopamine or serotonin could really get revved up, and guess what? The body reacts to that. And when the flow of transmissions gets revved up, the number of receptors usually goes down. This may be an explanation for why some people go back to their doctor and say, "I'm not feeling good. I've been on this medicine for six weeks, and I felt pretty good for the first six weeks but now, either they gave me a bad dose at the pharmacy, or it was a bad lot, but the medicine is just not cutting it anymore". So this idea of down-regulation – when receptors disappear or stop responding – this is something that can result in people saying that the medicine has worn off. With an anti-depressant, for instance, some people refer to this phenomenon as Prozac "poop-out". It means, basically, that tolerance develops to the effects of a drug. This is precisely what happens to some people who drink alcohol and they eventually find that they can drink more and more, because their receptors keep going down and down. And then psychiatrists always blame the patient (for Prozac poop-out). I said this the other day at a lecture, and I think one of the psychiatrists in the audience almost had a seizure! I kept saying they always blame the patient and he said, "You mean the underlying disease?" and I said "yes, like I said they always blame the patient!" Many doctors, in my experience, have been extremely reluctant to give credit to their clients or their patients. They seem to feel they are a different species and that it 'couldn't happen to me'. We're all human, we're all capable of psychosis and depression, we all could go there.

So, with receptor change, the evidence is based on animal and human studies.

Another aspect of medications which doctors frequently don't share with patients is the fact that there are many types of receptors. Some physicians may be asked by a patient: "how will this medicine affect my brain?" and they will say something about the dopamine (D2) receptor. At least, I imagine some doctors have said that. What they're probably not telling you is that there are five types of dopamine receptors. And when it comes to serotonin receptors, there are fifteen different types. For a doctor to very simplistically say the drug will only block the dopamine 2 receptor, he should hopefully be thinking about the other four receptors being blocked, as well. Many doctors have a very simplistic understanding of just what these drugs are doing to other kinds of receptors, even when it's the same molecule involved. And this will become important as we move to some of the side effects.

Antipsychotics and the Major Dopamine Circuits of the Brain

Next, we're going to focus on antipsychotic medications. If we have time, we're going to talk about the chemicals that the anti-depressant medications effect. In a way it's a bit artificial to suggest that medication only affects one chemical at a time, because there are always ripple effects. But when it comes to the kinds of receptors that the medications given for psychosis are most likely to affect directly, then that chemical is called dopamine. Dopamine is found in the brain in three

major circuits. (There are many different circuits for these.) Some people would classify four major circuits.

When it comes to understanding the effects of the antipsychotic medications in the brain, it is actually very important for you to understand that these drugs are impacting 4 separate highways or pathways in your brain. Dopamine gets made by very specific neurons within the brain. One section of these neurons is found in the midbrain, in a zone called the ventral tegmentum. So, when a drug is given that blocks dopamine, it's blocking the functions of these ventral tegmental cells. These are midbrain cells – also known as “meso” for middle, or midbrain (**APPENDIX E**). These cells have many connections and communicate to the frontal cortex of the brain. Hence, this is called the **meso-cortical** circuit of the brain.

There's also a connection from the midbrain that goes into the emotional parts of the brain, such as the cingulate gyrus, and into the hippocampus and into other regions associated with the emotions. This circuit from the midbrain to the limbic regions is called **meso-limbic**. This is a key target for the antipsychotic medications in terms blocking a hallucination of a delusion - because neuroscientists (at least currently) believe that this circuit is an important region of the brain for those symptoms.

Next, there is another circuit which physicians seldom speak about - called the **tuberoinfundibular**. It's probably such a long word that this is why the doctors don't often say it! What it means is that there's another place in the brain that makes dopamine - the hypothalamus - and this is probably the most critical section of the human brain for the control of metabolism. The hypothalamus is located under (hypo) the thalamus. It releases many hormones that communicate with the pituitary gland. This is why patients who are on anti-psychotic medications end up with elevations in prolactin. Male patients can develop enlarged breast tissue, if you're a woman you might start to secrete milk, probably have your periods stop. And individuals (particularly females) who stay on these medicines long term may actually develop osteoporosis. That is a long term side effect (of the elevated prolactin.)

And there is some concern that if prolactin remains elevated throughout the life span; a patient may be at increased risk for heart disease or breast cancer. In sum, there are serious effects associated with anti-psychotic drugs that are related to these other circuits, which doctors seldom tell their patients about.

And finally, there's a fourth circuit. Hopefully this is something all patients have been told about when it comes to anti-psychotics. This pathway involves the movement centre of the human brain. This is called the **nigrostriatal** pathway. This is another location in the brain where dopamine is made and released. Dopamine gets made inside cells of a brain region called the substantia nigra (The cells are named for the way they appear - especially under the microscope. They look black due to the fact that they contain pigment. Hence, they are called nigral cells). Substantia nigra cells send dopamine from the midbrain into other brain regions: most importantly, the basal ganglia. These latter structures include: the caudate, the putamen, the globus pallidus and the subthalamic nucleus.

The bottom line is that the doctor should have told you that if you are taking anti-psychotic medication, the drug will block receptors in the substantia nigra (and the striatum) and turn off the flow of dopamine into the caudate and putamen. This is why many people develop the symptoms of Parkinson's disease from these medications. They'll get tired; they might start moving more slowly, and if they stay on these medications for a very long time there's a 5% risk per year of developing an irreversible condition known as tardive dyskinesia. But hopefully doctors who give these medications are warning their patients about these disorders.

So, what about the newer medicines? Well, the jury is still out about whether these medications will cause Tardive Dyskinesia because these medications haven't been out long enough to know. It took doctors fourteen years to acknowledge Tardive Dyskinesia after the first generation of neuroleptics was created. So far, it appears to be true that fewer patients develop Parkinsonian side effects, depending on the dose of these new medicines. Interestingly what many doctors don't tell their patients about Risperdal (risperidone) as that it seems to be the only one of the newer drugs that causes a prolonged elevation of prolactin.

I promised that I'd talk about a few things you probably had **not** heard before and one of the important things from my perspective is a condition called Neuroleptic Induced Deficit Syndrome (NIDS). In 1994 a concerned group of psychiatrists, psychologists and social workers convened in Stockholm, Sweden to discuss the cognitive side effects of the anti-psychotic medications. They heard from speakers who believed that over time, the anti-psychotic medications in many individuals were leading to cognitive deficits; slower processing time, some memory loss, difficulties with attention and concentration, and overall slowness. They proposed to do some more study on this phenomenon. To give you a description of NIDS, the word derives from the word "Neuroleptic". "Neuroleptic" wasn't in Webster's Dictionary. It was created in 1950's by one of the first inventors (pioneers) of the anti-psychotic medications, Jean Delay. He gave birth to this name, "Neuro" and "Leptic" which meant to; "Seize the neuron". And here's what he said the new medications appeared to do. He stated that a neuroleptic effect was present when the following features were observed:

1. Psychomotor Retardation – motor slowing, body not moving so well
2. Emotional indifference - not being emotionally responsive / not caring
3. Reduced initiative – not showing interest in initiating activity
4. Slowing of thought

These were all seen as desirable outcomes of these medications when they were first discovered and used in the 1950's.

Now, a more recent dictionary definition (from Dorland's Medical Dictionary) refers to a neuroleptic as follows:

"This refers to effects on cognition and behaviour of anti-psychotic drugs, which produce a state of apathy, lack of initiative, limited range of emotion, and in psychotic patients they cause a reduction in confusion and agitation and a normalisation of motor activity."

Neuroleptics -- which almost all of us learned to mean the anti-psychotic medications or at least the first generation of anti-psychotics -- were at the time of their very discovery **known** to create cognitive limitations. It was these limitations which the doctors in Sweden were meeting to discuss.

Now, not everyone is going to experience NIDS, but what I encourage providers and system users to think about is how their own experience with these medications may have reflected some of these symptoms – including change in emotional awareness, sense of aliveness, and in the speed, and clarity of thought. Many people who have taken these medications describe the experience as feeling like a zombie. The graph(**APPENDIX F**) shows that as the dose of the medication increases, and more time elapses, it appears to be the case that the effects change – from sedative effects, into anti-psychotic effects, and possibly into other less desirable side effects; akathisia, emotional parkinsonism (emotional blunting) and on into some other unwanted side effects.

Here's one important one: **neuroleptic dysphoria**. These doctors in Sweden were concerned that at high enough doses over a long period of time, many of these anti-psychotic medications were making people become quite depressed. So they were concerned enough to have a

conference. This was the graph of how they conceptualised NIDS. They wanted to know: what would this look like if the person you were seeing was actually developing this condition? How would you know if the problem was there? And they said that a graph of the severity of undesired cognitive effects could be useful. This is really a description on why the newer medicines were desired.

With the older drugs especially (and with the newer drugs to a certain extent) the first symptoms that might be present, in terms of apathy, emotional indifference, motor slowing or slow mentation were attributed to the underlying condition of the patient. As the medications were introduced, some people actually demonstrated an improvement in the symptoms but then what seemed to be the case over time is that with treatment the improvement that was there seemed to go away, or only reached a certain point and then plateaued (levelled off). That is what they interpreted as a part of NIDS.

There were many studies about NIDS. One of them (**APPENDIX G**) tracked symptoms over time, and it appeared to be the case that many of the negative symptoms which doctors had easily confused with schizophrenia worsened as medication dose increased. The lower doses of Haldol (see diagram...) in this case were 10 milligram and 5 mg., the higher dose of Haldol was 20mg. Over four weeks of treatment the cognitive improvement went from about 2 in the negative direction, which meant the improvement deteriorated with the higher dose of Haldol. That's because once the higher dose is there for a while, the negative cognitive effects of Haldol take over. So patients can actually begin to look worse cognitively. This research group saw this and it concerned them.

This is the part of the brain we will focus on next: **the Basal Ganglia (APPENDIX H)**. There are deep structures in the human brain that control motor movement, and I mentioned before the nigrostriatal circuit, which includes the substantia nigra, the caudate, the putamen, the globus pallidus and the subthalamic nucleus. All of these parts of the brain work with each other to control our movement. And if you have too much movement that is bad. If you have too little movement, that's also a problem. So these are the parts of the brain we are talking about. Interestingly, when people have the dopamine receptors blocked in this part of the brain it turns out now that research has demonstrated that the basal ganglia are also involved in implicit memory: the memory that involves things like opening the door to your house, riding a bicycle, etc.

This is important, because it means that drugs are affecting functions (cognitive effects) which have not historically been linked to these brain regions. Usually, we think of movement abnormalities in these circuits. Parkinson's disease - this is a map or a schematic of what happens to people who get Parkinson's disease. People typically develop this as they get older. Julia Child, a very famous cook over in the US and the actor Michael J Fox are both famous victims of severe Parkinson's disease.

If you have ever seen Michael J Fox interviewed it is almost painful to watch, as there is so much movement, he's hyper kinetic now. But these are what doctors frequently don't tell their patients about, or perhaps they think it doesn't happen so often. A lot of people are affected by these conditions. About 40-50% (or more) experience Parkinsonian symptoms. So this makes you wonder - tell your doctor that you're worried about these movements. Ask "will I get them? Why won't I get them or why will I get them?" When you take a dopamine blocking drug, remember what happens at the nerve ending, Dopamine gets released; it's a message that gets sent away. When it gets released it's looking for a mail drop (a receptor on another cell). And there are many kinds of dopamine receptors, but when you start blocking these dopamine receptors in certain parts of the brain, you start eliminating the capacity of the human body to move normally.

In Parkinson's disease people lose these dopamine cells in the substantia nigra. With anti-psychotic medication, we're not killing off those cells but we are modulating how they function and this happens in a fairly high rate of patients. This is all happening in the short term.

The long term situation is equally concerning. When I was working on my most recent job in the prison system, I had many psychotic patients or people labelled with psychosis. They had been on anti-psychotic medications for many years. At least a third, probably more like 50%, of my caseload had developed tardive dyskinesia. These were patients who could not control the movement of their arms and hands; they could not control the movements of their face, their head, the puckering of their lips. The published rate for tardive dyskinesia among people who stay on the older drugs is approximately 3-5% per year - if you stay on these medications, for ten years, the risk of developing TD is 50%. Now a lot of people say that's not so bad, that's a good trade off for psychosis and I'd rather have the movement disorder than psychosis.

That's a decision that many people may choose to make, but I am hoping that their doctors at least fully explain to them the risk that occurs and how that risk doesn't go away over time – rather, it actually increases.

Causes of Tardive Dyskinesia

So, what in the world causes this tardive dyskinesia? This is the great mystery. Even fifty years after the invention of these drugs, doctors still don't really know yet what causes tardive dyskinesia. There are many theories: one of the theories is that the number of dopamine receptors increases, so some people believe that tardive dyskinesia begins to emerge when those dopamine receptors begin to increase in number. Another possible theory is that the acetylcholine (important motor control neuron also) neurons begin to drop away. So, there are many theories about how long term changes might occur.

There are a couple of other things I didn't tell you about (related to TD). Largely in animal studies, researchers have demonstrated that as anti-psychotic medications are given over time they decrease the firing-rate of dopamine cells. The firing-rate of dopamine cells actually goes down. In the 1800's/1900's the neurologists were having a big debate. They asked whether or not brain function should be explained primarily in terms of electricity or chemicals. It was called the "sparks versus the soups"! There were some people who wanted to focus on the electrical aspect of brain function, and there were other people who thought the emphasis should be upon the chemical. In a way, the soups won: we have been living in the chemical era for the past fifty years – largely due to the way that debate was won, many years ago. It is possible, though, that we are just beginning to break out of that tradition now, as people are talking about transcranial magnet stimulation therapy.

The electrophysiologists have always been interested in electrical activity but what's important to recognise is the fact that when the cells in the brain are working, the events are always a combination (synthesis) of electrical AND chemical activities. It's like a carburettor in a car – it needs to fire, in order to turn over the engine. One of the theories about the cause of TD is that the cell firing rate diminishes to the point where cells are not firing as they should be.

Now a fourth possible mechanism for tardive dyskinesia (or for other delayed or long term effects) has to do with proteins that are inside the cells which received dopamine. You remember we said the first cell is sending the message, and that the cell it is connecting with (the mailbox) is waiting to get the dopamine. What happens next is very complex. Once a medication hits the receptor on the second cell, all kinds of things are going to happen inside that cell. What appears to be the case is that many times, certain proteins get turned on inside the second cell. These proteins can hang around – they don't go away. For example, one of these proteins which is thought to hang around for a long period of time is called delta c-fos, Delta c-fos is thought to stick around inside neurons, where it may contribute to symptoms of addiction even months or years later. Have you ever heard about heroin addicts walking by a (shooting) gallery, and they start sweating or having other physical reactions? One of the explanations may be that the transduction proteins, like c-fos, have been revved up by previous drug use.

And what's interesting is that Haldol also induces delta c-fos, so, it's possible that some people who develop tardive dyskinesia have this transduction protein waiting in the brain until the right moment arrives, and it shifts into gear resulting in these movement disorders. Back to the heroin: we believe there is a thought process going on that activates the addiction / cravings. By walking by a shooting gallery, or by watching a TV show or movie that shows someone using a drug, the memory of having used the heroin before can turn on this c-fos protein in the brain. It is possible that TD results from a similar process of delayed activation.

Other Tardive Phenomena

Just about everybody I went to school with understood about tardive dyskinesia - this long term side effect of an undesired movement disorder. But how many of you know about **tardive dysmentia**? What about **tardive psychosis**? Well, there are some people here who are very well informed. Doctors did not know or did not think about Tardive Dyskinesia until 1964 – a full fourteen years after the neuroleptics first appeared. It took them all that time to figure out it was a medication effect. They tried to blame it on the patients and the only reason that they stopped blaming it on the patient was because, in the UK, you had the few remaining asylums in the world that weren't quickly jumping to use the anti-psychotic drugs. One of the doctors who studied the long term effects of the new drugs was George Crane (you can read about him in a book by Sheldon Gelman - he's actually an attorney who developed an interest in psychiatric history, and he wrote a book called "Medicating Schizophrenia".) Gelman tells the story of how tardive dyskinesia was discovered.

At first, psychiatrists blamed TD on schizophrenia. Then, Crane figured out that people in British hospitals who had not received the new drugs did not develop high rates of tardive dyskinesia. In the 1970's a physician in Montreal named Guy Chouinard had the audacity to propose the possibility that the same mechanism which causes the long term motor side effects of neuroleptics might also cause psychotic relapse. According to this theory, it might be possible for neuroleptics to induce a delayed-onset psychosis which might be long-lasting. Chouinard named this condition tardive psychosis. Now, nobody will really research this. Nobody will really give this any research attention, for the very reason that tardive psychosis implies that, since the 1950s, psychiatrists have been administering drugs which promote the continuation of the very symptoms which they are supposed to treat. So, it's been very difficult to find people who will take this concept seriously.

Now, the best way to actually investigate the existence of tardive psychosis is to compare catamnestic studies. Catamnestic refers to long-term or natural lifespan. What happens if you have a person who is diagnosed with psychosis at age 22, but who does not receive neuroleptics. You then compare this person to a group of people diagnosed with psychosis at age 22 who do receive neuroleptics. Some of these studies have been conducted; it appears to be the case that people who are not given dopamine blocking drugs, or who receive them on a limited basis, often have very favourable long-term outcomes. Some of these studies have been conducted by Luc Chompi in Switzerland. Journalist and author Robert Whittaker, from America, has written about the World Health Organisation and IPSOS studies that tracked natural outcomes of psychosis in countries that used no drugs, versus those that relied heavily upon neuroleptics. Long term outcomes favoured the patients without neuroleptics.

So, the best thing we can do at this point in time is to guess that tardive psychosis is a real event. But why wouldn't it be a real event? If we know that tardive dyskinesia occurs, perhaps because receptors are changing (up-regulating) then why would that only occur in one part of the human brain? Why would it not be the case that these receptors might also up-regulate in the limbic system, or in the frontal lobes?

People have been concerned about other parts of the brain in which tardive phenomena might occur. In the 1980's an article was published in *Acta Psychiatrica Scandinavica*, which is a Scandinavian psychiatric journal. In the mid-1980's in the *Schizophrenia Bulletin* (an American

publication) ran a series of articles in the 1980's which also explored other types of tardive phenomena. These articles concerned the frontal lobes -- the front part of the brain. The researchers proposed that there might be two syndromes that emerged over the long term. One was called **tardive dementia**, meaning that for some individuals the long-term use of the neuroleptics might contribute to a frontal lobe syndrome, or a dementia, if you will, resulting in a depressive condition similar to NIDS. In some individuals, it seemed that long term treatment with neuroleptics was more likely to affect emotional centres in the human brain, such as the right hemisphere or orbito-medial aspects of the frontal lobes. Patients exposed to neuroleptics were noted to develop dramatic or euphoric mood swings (changing from a purely schizophrenic picture, to a manic or schizoaffective picture over time). This was called **tardive dysmentia**.

Auto-Receptors in the Brain: Do We Know What They Do?

The final thing about anti-psychotics that you probably don't hear about is auto-receptors. These are not the receptors on a vehicle! Rather, auto-receptors are located on the cell bodies and nerve terminals of the neurons which make transmitters, such as dopamine and serotonin. The human brain needs to know when it is time to turn off certain cell functions. This is actually a picture of a serotonin cell (see diagram) but we'll pretend it is a dopamine cell, since I'm talking about anti-psychotics. What happens when your body begins making these chemicals is that sites of the brain which make the chemicals wait for a signal to tell them that they've made enough or too much of a neurotransmitter. If the brain perceives that there is too much dopamine in circulation, it gets a message (via a feedback loop – see this collateral highway) which comes back around to the cell body or nerve terminal - telling the cell to stop. It does this by way of the auto-receptors. Auto-receptors for dopamine are located in several regions of the brain: the hypothalamus, the midbrain, and the substantia nigra.

Neuroscientists are unsure about the existence or function of auto-receptors in the frontal lobes. For instance, this may be why Risperdal and the newer drugs have slightly different effects upon cognitive functions. What appears to be the case is that auto-receptors can work to slow down the production and release of neurotransmitters. If auto-receptors, like other dopamine receptors, down-regulate or change over time, they can exert important effects upon neurotransmission (for good or bad). The only point here is that the long term effects of the drugs, old and new, are very complicated and still not well understood.

Neuroleptic Discontinuation Syndromes: mistaking withdrawal as relapse

The last topic I want to leave you with is **Neuroleptic Discontinuation Syndrome**. Now, I said I'd talk about anti-depressants if I had time (I won't have time). You can imagine the same thing, I am going to talk about next in terms of anti-depressant medications, too (just slightly different processes). Once a medication has been in the brain for a while, when you lower the dose or, especially, when you take the medication away quickly - there is going to be a reaction to that change. If you remember Jackson's First Law of Biopsychiatry, "For every action, there is an unequal and frequently unpredictable reaction." How many of you have been told by doctors, or know of a patient whose doctor has said that they are going to start this medicine but beware of Neuroleptic Discontinuation Syndrome? I have **never** known a doctor to say this.

There's a very important article by Richard Tranter and David Healy in The Journal of Psychopharmacology (1988) about neuroleptic discontinuation syndrome and the history of this phenomenon. What they wanted to know was the following: if a person were admitted into the hospital and then enrolled in a drug trial, the person would be abruptly withdrawn from previous medication prior to starting the experimental (new) treatment. Patients of this kind might demonstrate exacerbations of psychosis. Tranter and Healy wondered about the cause of this kind of psychosis – should symptoms be attributed to an underlying disease/illness or should symptoms be considered as a reaction to the removal of previous therapy?

So, that's a question you might think would be impossible to figure out. A psychotic person gets put on medication, runs out of medication, and then becomes delusional or hallucinates. Guess where they end up? Back in the hospital or sectioned again, and the doctors are quick to say that the problem is a schizophrenic **relapse**. My concern is that many times the doctors don't think to ask when a patient last took his or her antipsychotic medication. A discontinuation syndrome can sometimes last for weeks or months - some people have said they can last as long as six months.

You remember all these proteins that are in the cells. We just don't know if it's a receptor change or if it's a protein change that is responsible for the recurrence of symptoms. There are many people who have been told that they can never come off medication because the schizophrenia will come back. They may not be having schizophrenia relapses at all – instead, they may be having a drug discontinuation syndrome. Imagine what would happen if the journals and the textbooks were to re-write the history of schizophrenia since 1954 – studying very carefully how many patients had been told that they were withdrawing from drugs rather than relapsing – what a very different picture would emerge.

Another reason why this is an important concept is because of the study design used to approve new medications. In most drug trials, they invite all the patients into the new study – let's say it is "Drug Jackson". For two weeks, no one in the study can take ANY medication. Two weeks later, half of the patients will be put into the group that will take Drug Jackson, and the other half will receive nothing but a sugar pill. Four weeks later, the researchers will ask: who seems better? The patients who received Drug Jackson, or the patients who received the sugar pills? But the problem with these studies is the first two weeks. Remember those first two weeks when nobody could take any medications? Guess what was happening to some people? Those who had previously received medications may have gone into abrupt withdrawal. This is why so many studies make the new drugs (in this case, Drug Jackson) look so good - because no one is paying attention to the fact that many of the patients who are in the placebo group (the sugar pills) are in withdrawal. They have been withdrawn abruptly from their neuroleptics (or from their antidepressants).

This is a problem that you cannot get the drug industry, the MHRA or the Committee of Safety in Medicine, to acknowledge or correct. This is part of the reason that they've been able to approve Risperdal, Zyprexa and a lot of other new medications - because the flawed study designs make the new drugs look better than placebo or other treatments. Take Haldol vs. Zyprexa, for example: the researchers took Haldol patients off of their drugs, and placed some of them onto Zyprexa, and some of them onto placebo. So, who looked better? People having their dopamine receptors blocked by Zyprexa or people who were thrown into a continuous withdrawal from Haldol? Of course, all the published studies you will see are Haldol and Zyprexa or Zyprexa and Placebo, and in every one of them, the researchers have ignored the effects of withdrawal symptoms due to the placebo washout period. This is a trick that drug companies do for every single psychiatric drug.

Neuroleptic Discontinuation Syndrome; how in the world did we figure out this was for real? How could we really prove that it was taking the drugs **away** from the psychosis and not the schizophrenia which was the cause of returning symptoms? Curiously there's been a good way to show this, and this is mentioned in the Healy and Tranter article in the Journal of Psychopharmacology from 1988. What they found, first of all, is that there are other medications in medicine that block dopamine receptors. These are anti-nausea medications which help prevent human beings from throwing up. Some of these drugs include metaclopramide (Reglan) and prochlorperazine (Compazine). Like neuroleptics, these drugs block dopamine receptors in the brain. This is a typical case report from a gastroenterologist:

"Mrs Brown comes into my office she's got intractable vomiting so I gave her Reglan. She comes in three weeks later, complaining of facial tics and she has also had problems with Parkinsonian side effects. I said to Mrs Brown that I want to take her off this medicine and to come back and see me in

two weeks. The next time Mrs B comes back to see me, I ask how Mrs Brown is. She replies that she is a little bit nervous and doesn't know how to say this but she thinks she is beginning to hear things."

So they found that in these anti-nausea patients, who were never psychotic before, the removal of dopamine-blocking medication actually began to cause strange side effects. Now I may be misquoting slightly but in this case the withdrawal effects were typically things like anxiety, agitation, depression, reduced libido, nausea, sweating and changes in concentration and memory. Many times, people who were never psychotic or mentally ill before started to experience psychological symptoms upon the withdrawal of dopamine blocking agents.

This is one historical clue which tells us that Neuroleptic Discontinuation Syndrome is for real. It's not an underlying or pre-existing psychosis, because people who have never been psychotic experience the same kinds of symptoms when dopamine antagonists are stopped.

A second line of evidence (for Neuroleptic Discontinuation Syndrome) comes from Largactil (chlorpromazine) studies. Chlorpromazine (Largactil) was the first anti-psychotic medication invented. Did you know that early on, when they tried to figure out what this drug does, they were testing it as an antibiotic. They wanted to see if it could be used to treat tuberculosis. When they mixed it up in test tubes with tuberculosis (mycobacterium), they thought that the drug limited the growth of the bacterium (It didn't kill them all, but it seemed to slow down the rate of reproduction). The researchers were understandably excited about this, and they decided to test the drug for six months in patients with tuberculosis. Guess how much tuberculosis went away? None! What they did find is when they stopped the chlorpromazine in these patients, many individuals experienced a neuroleptic discontinuation syndrome - very much like what we see when psychiatric patients stop taking, or run out of, their drugs – vomiting, sweating, depression, cognitive and mood swings, or even symptoms of TD.

A third line of evidence for neuroleptic discontinuation syndrome is found in the history of combined therapies. Once upon a time (and we're now living to see this come back again) the drug companies were marketing combination medications. They'd take an anti-depressant and mix it with an anti-psychotic and put it in the same pill. This was done in the 1960's, with a drug called Triptafen - a combination pill containing Elavil (amitriptyline) and Trilafon (perfenazine), so the Elavil was the anti-depressant and the Trilafon was the anti-psychotic. That was given to people just in one pill. There was another pill called Parstelin, which consisted of Parnate (tranylcypromine) and Stelazine (trifluoperazine). What happened when people started coming off of those medications, and they may not have been psychotic patients to begin with – is that they developed hallucinations, headaches, insomnia, anxiety, fatigue, nausea and nightmares.

So, there have been many examples throughout the history of psychiatry where patients who were never psychotic, but who were placed on anti-psychotic drug, came off of that medicine only to become acutely psychotic or acutely agitated. To the extent that psychiatrists themselves frequently have not thought about these syndromes, means that we have, perhaps, misinterpreted many relapses when we should have been thinking about medication withdrawal syndromes. And when you resume treatment with the medicine in these cases, you eclipse the withdrawal syndromes. The patients almost always seem to get better when the drugs are resumed.

(End of formal lecture – beginning of question & answer session)

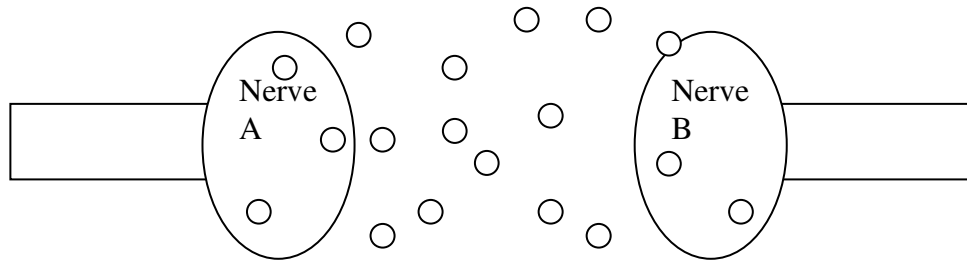
What Your Doctor May NOT Tell You About Psychiatric Drugs – Grace E. Jackson, MD

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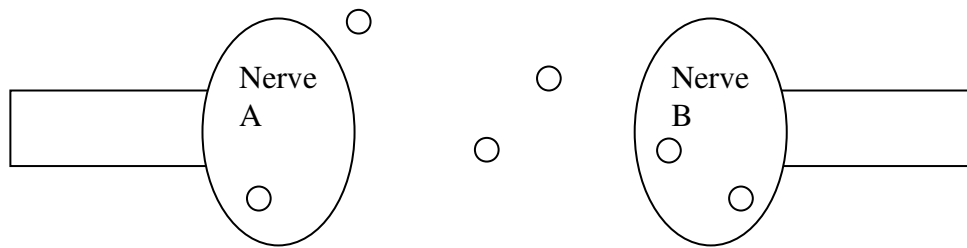
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APPENDIX A

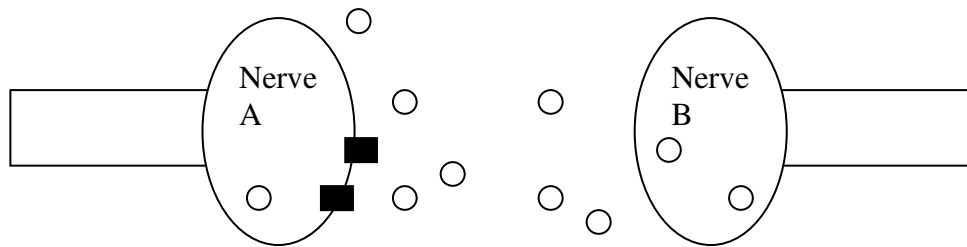
How Zoloft (sertraline HCl) can help



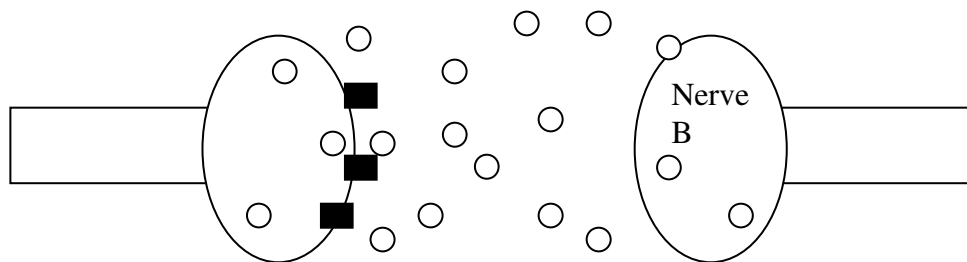
Normally, serotonin is released from one nerve cell and then picked up by the next nerve cell. Some of the serotonin is also taken back up into the first nerve cell.



However, people suffering from panic disorder may have an imbalance of serotonin so the nerve cells cannot communicate properly.



What Zoloft does is block serotonin from going back into the nerve cell that sends the chemical message.



This blocking action by Zoloft helps build up more serotonin between the nerve cells, which in turn may help message transmission return to normal.

APPENDIX B

AMINES	AMINO ACIDS
Serotonin(5HT)	Gamma-aminobutyric acid(GABA)
Dopamine(DA)	Glycine
Norepinephrine(NE)	Glutamic acid(glutamate)
Epinephrine(E)	Aspartic acid(aspartate)
Acetylcholine(Ach)	Gamma-hydroxybutyrate
Tyramine	
Octopamine	GUT HORMONES
Phenylethylamine	Cholecystokinin(CCK)
Tryptamine	Gastrin
Melatonin	Motilin
Histamine	Pancreatic polypeptide
	Secretin
PITUITARY PEPTIDES	Vasoactive intestinal peptide(VIP)
Corticotropin(ACTH)	
Growth hormone(GH)	OPIOID PEPTIDES
Lipotropin	Dynorphin
Alpha-melanocyte-stimulating hormone(alpha-MSH)	Beta-endorphin
Oxytocin	Met-enkephalin
Vasopressin	Leu-enkephalin
Thyroid-stimulating hormone(TSH)	Kyotorphin
Prolactin	
	MISCELLANEOUS PEPTIDES
CIRCULATING HORMONES	Bombesin
Angiotensin	Bradykinin
Calcitonin	Carnosine
Glucagon	Neuropeptide Y
Insulin	Neurotensin
Leptin	Delta sleep factor
Atrial natriuretic factor	Galanin
Estrogens	Oxerlin
Androgens	
Progestins	GASES
Thyroid hormones	Nitric Oxide(NO)
	Carbonmonoxide(CO)
HYPOTHALAMIC-RELEASING HORMONES	
Corticotropin-releasing factor(CRH)	NEUROKININS/TACHYKININS
Gonadotropin-releasing hormone(GnRH)	Substance P
Somatostatin	Neurokinin A
Thyrotropin-releasing hormone(TRH)	Neurokinin B
LIPID NEUROTRANSMITTER	
Anandamide	

Neurotransmitters in brain

APPENDIX C

Sir Isaac Newton



Laws of Motion

First Law

Every object persists in its state of rest or uniform motion in a straight line unless it is compelled to change that state by forces impressed on it.

Second Law

Force is equal to the change in momentum (mV) per change in time (For a constant mass, force equals mass times acceleration. $F = m a$).

Third Law

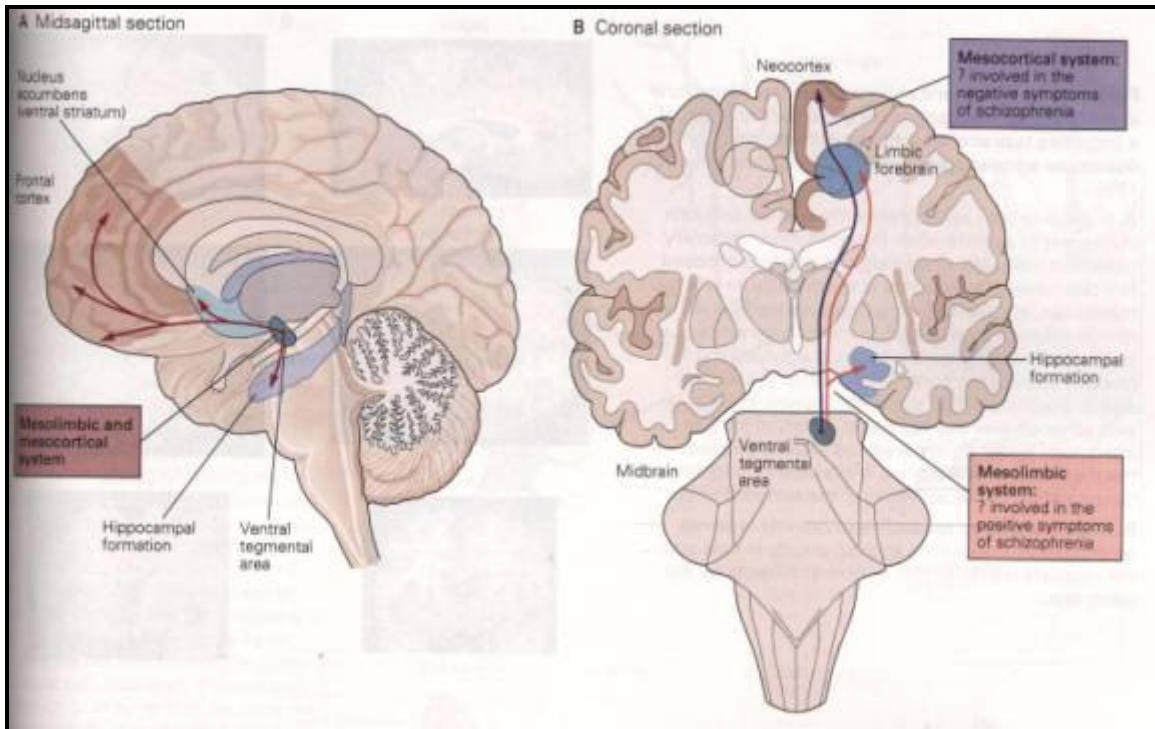
For every action, there is an equal and opposite reaction.

APPENDIX D

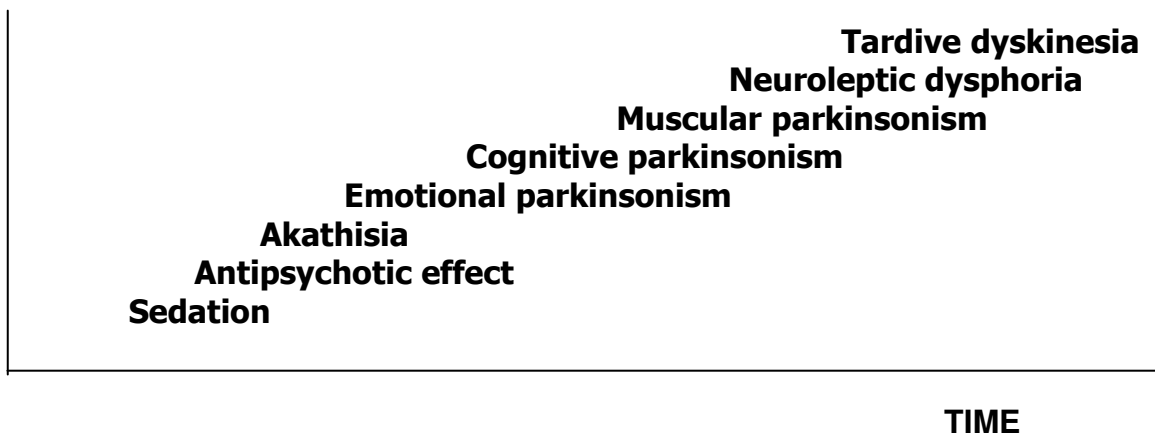
Jackson's Law of Biopsychiatry

“For every action, there is an unequal and frequently unpredictable reaction.”

APPENDIX E

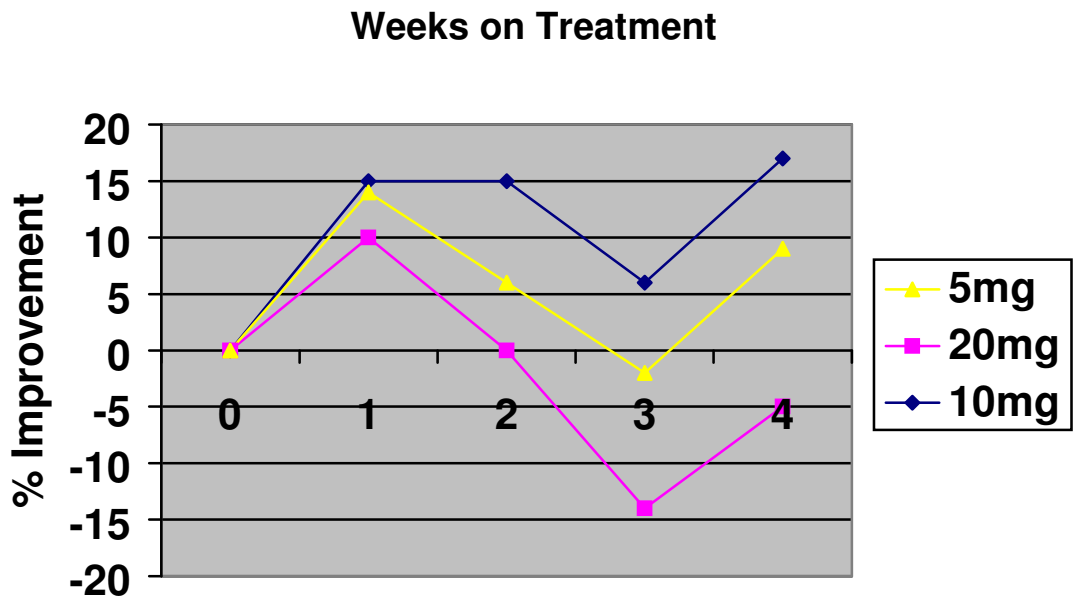


APPENDIX F



A tentative model for the relationship between dose, duration of treatment and side effect profile for classical neuroleptics.

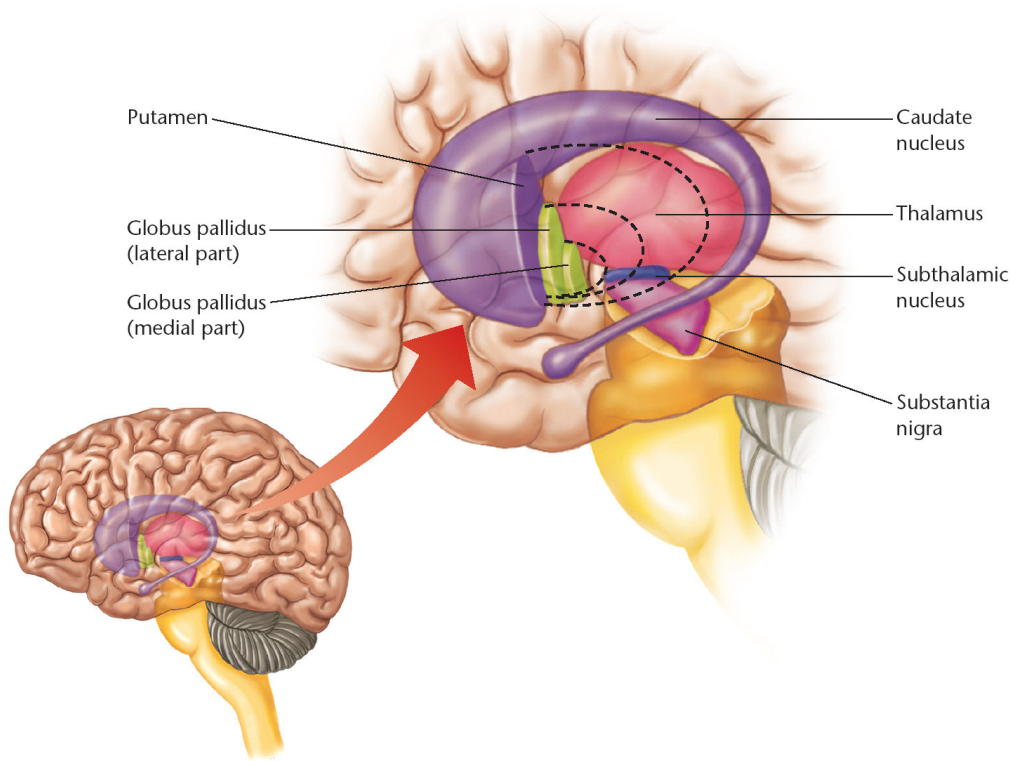
APPENDIX G



Weeks on treatment

NIDS worsening with increased Haldol dose

APPENDIX H



Basal Ganglia