

The Past, Present, and Future of Schizophrenia Treatment

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ABSTRACT:

Examines the issues around conventional schizophrenia treatment including the problems with side effects and noncompliance, the introduction of newer atypical neuroleptics and their potential for improvement, and issues around pharmaceutical research and public pressures to get new medications approved. Also discusses costs and benefits of atypical neuroleptics in comparison with conventional neuroleptic treatment, as well as problems with doctors' perceptions of patients and how they affect patient compliance and treatment.

INTRODUCTION:

Throughout history, there has been incidence of schizophrenia, roughly one percent of the population, consistently, in every culture (Peuskens, et al, 2001; McWilliam, 2002). It has been called everything from insanity to demonic possession to magical powers, and its patients have been shunned, sheltered, rejected, or revered.

It wasn't until recently that science has been able to find any kind of effective treatment for schizophrenia, and even though now there appears to be some understanding of the etiology, neurobiology, and treatment of it, in each of these areas, all that is still up for debate, and perhaps further research will find that present understanding is either correct or woefully lacking.

One thing that has happened in recent years is that, for better or worse, the schizophrenic has been able to rejoin society. Previous treatment modalities were carried out inside the walls of a mental institution, and families regularly shuttled off their schizophrenic brood to live and die in secrecy. As treatments have improved and media began focusing on abuses within the mental institutions (most notably, Ken Kesey's 1962 book One Flew Over the Cuckoo's Nest, later made into a movie with Jack Nicholson and Louise Fletcher), there was a call to close the institutions and allow treatment to happen at home.

The reality is, however, that society and medicine may not have been ready for such a change, though to be honest, the change forced medicine and society to catch up. Though neuroleptic medicine had begun in the 1950s with chlorpromazine (Thorazine),

haloperidol (Haldol), and clozapine (Clozaril), there had been fatal agranulocytosis associated with clozapine, while chlorpromazine and haloperidol had severe side effect profiles that made socialized life for the schizophrenic a near impossibility. Images of schizophrenics doing the "Thorazine shuffle," struggling slowly down the street, combined with reports and news footage of violent outbursts when they stopped complying with their medical prescriptions led to fear among the general populace and a drive to improve the treatment of schizophrenics and the mentally ill in general.

The 1990's saw first a reintroduction of clozapine with a new understanding of how to prevent agranulocytosis and then, shortly thereafter, some new medications that showed great promise in the treatment of schizophrenia, both in their effectiveness and their side effect profiles. Still, there is good reason to question whether that promise is being fulfilled and if schizophrenics are receiving the best treatments that can be provided.

HISTORY OF OUR UNDERSTANDING OF SCHIZOPHRENIA:

The current belief of the cause of schizophrenia is the dopamine hypothesis, which states that schizophrenia is the result of an overactivity of dopamine systems in the brain (Baumeister & Francis, 2002; Angrist, et al, 2001). This was discovered from a chain of events beginning with the study of Rauwolfia Serpentina, a shrub that has been used as a folk medicine in India for diarrhea, snake bites, and delayed labor. Western researchers found that it could be used in treating insanity with violent maniacal symptoms, as well as lowering blood pressure and sedating in general. Ciba Laboratories

synthesized reserpine from *Rauwolfia Serpentina* and marketed it under the name of Serapsil.

Soon a similarity between chlorpromazine (Thorazine) and reserpine was noted, specifically that both acted as a sedative without hypnotic effects, which differed greatly from the barbiturates largely in use at the time. The term "tranquilizer" was coined to describe this course of action in 1953 (Baumeister & Francis, 2002).

Serotonin was discovered in 1948 and linked to mental illness in 1954 when LSD was found to be a serotonin antagonist. Since LSD appeared to cause insanity, it was reasoned, then insanity was due to a suppression of the action of serotonin, whether caused by drugs or by natural means. At the time, physical evidence was lacking, but this hypothesis was soon supported through sleep studies showing that reserpine potentiated the hypnotic actions of barbiturates and was antagonized by LSD. It was concluded that reserpine thus enhances the actions of serotonin. It was also noted, however, that this action in excess also leads to serotonin depletion, thus limiting the use of reserpine in the treatment of mental illness (Baumeister & Francis, 2002).

What was most significant about this research was that it showed for the first time the role of brain chemistry in behavior. Soon reserpine's effects on other brain chemicals and neurotransmitters were researched, and depletion of catecholamines and norepinephrine was discovered, and that inhibition of monoamine oxidase (MAO) antagonizes the effects of reserpine. It was concluded that reserpine was a nonselective blocker of monoamine storage and that a deficiency, not an excess, of neurotransmitters due to increased metabolism was responsible for reserpine's effects (Baumeister & Francis, 2002).

Dopamine, first discovered in 1910 and soon forgotten about due to its weak sympathomimetic effects, was soon examined for its mediating effects on reserpine. It was soon realized that areas of the brain containing large amounts of dopamine (the corpus stratum, for example) have little norepinephrine, while areas containing large amounts of norepinephrine (such as the medulla oblongata) have little dopamine. Large amounts of dopamine in the corpus stratum led researchers to suggest that dopamine plays a role in the extrapyramidal motor system.

One of reserpine's side effects is pseudoparkinsonism, which can be explained by the depletion of dopamine. L-dopa was found to reverse the effects of reserpine-induced pseudoparkinsonism (as well as true Parkinsonism), leading to advances in the treatment of Parkinson's disease and the realization that Parkinsonism is caused by a depletion of dopamine. Meanwhile, the induction of pseudoparkinsonism showed that reserpine caused a depletion of dopamine.

The antipsychotic effects seen in reserpine and chlorpromazine (which has similar pseudoparkinsonism-inducing effects) were so consistently present with the pseudoparkinsonism that there was assumed to be a connection. Further study showed that while reserpine depletes all the major neurotransmitters, chlorpromazine does not deplete serotonin or the catecholamines, thus limiting its actions to dopamine. Yet there was still an antipsychotic effect and the presence of extrapyramidal symptoms such as pseudoparkinsonism.

All the while, there was a great deal of research going on examining the effects of stimulants on the brain. Originally, it was hypothesized that amphetamines directly stimulate peripheral adrenergic receptors. However, Jacques van Rossum, a Dutch

pharmacologist, discovered that the locomotor stimulant effects of cocaine could be blocked by reserpine, while the effects of amphetamines could not. It was later discovered that amphetamines are chemically similar in structure to dopamine and that chlorpromazine and haloperidol could block their effects, while as mentioned previously, reserpine could not.

In 1966, van Rossum combined his research on amphetamines with the research on reserpine's and chlorpromazine's antipsychotic effect and hypothesized that schizophrenia was due to an excess of dopamine (Baumeister & Francis, 2002). This has since been supported by research showing the causes and effects of amphetamine psychosis (due to amphetamine's effects on dopamine transmission) and that untreated schizophrenics do not suffer from Parkinson's disease--it is generally medically caused in schizophrenics, and those who are treated with atypical antipsychotics do not experience its effects.

However, recent research is now beginning to question the dopamine hypothesis. Schizophrenia is too complex a disease to explain so simply, and indeed, the dopamine hypothesis only accounts for a small amount of the symptomology of the disease--the positive symptoms of hallucinations, delusions, and paranoia (Noorbala, et al, 1999). These symptoms tend to be acute and transient, and are more commonly seen in the earlier stages of schizophrenia, while later stages tend to be dominated by more chronic negative symptoms--cognitive impairment, flattened affect, and motor difficulty, which would indicate possible dopamine depletion.

While early research on schizophrenia focused on amphetamine psychosis, it was soon discovered that there was a drug that was far superior in showing the effects of

schizophrenia--phencyclidine (PCP). Amphetamine psychosis only resembles the positive effects of schizophrenia, and while cocaine psychosis also has some similarities, it carries with it some characteristics of social interaction that are in opposition to schizophrenia. However, phencyclidine psychosis is virtually indistinguishable to schizophrenia in either positive or negative symptomology, and chronic PCP use may lead to conditions resembling chronic schizophrenia, and there is even some evidence that latent schizophrenia may be triggered by PCP use (Murray, 2002).

PCP blocks N-methyl-D-aspartate (NMDA) receptors in the brain from the actions of the neurotransmitter glutamate postsynaptically while preventing the presynaptic release of glutamate. This accounts for the existence of negative symptomology such as flat affect, motor disruption, and cognitive dysfunction. Post-mortem brain research has shown PCP's effects not only on glutamate and dopamine, but also antagonism of GABA and agonism of sigma opiate receptors (Murray, 2002). McWilliams (2002) states that dopamine is responsible for the positive symptoms and some of the negative symptoms, serotonin the mood changes and some negative symptoms, and acetylcholine the cognitive difficulties. Other researchers are examining other broader hypotheses.

There is still a great lack of understanding of exactly what schizophrenia is, however. Amphetamine psychosis may be able to replicate paranoid schizophrenia fairly accurately, and PCP psychosis even more so, but there is still no clear understanding of what constitutes catatonic schizophrenia, what leads some schizophrenics to show certain types of delusions (religious, for example), or most importantly, why an extremely high

percentage (as many as 40%) of schizophrenics are unresponsive to neuroleptic treatment (Peuskens, et al, 2001).

CURRENT TREATMENT MODALITIES:

Virtually all treatment for schizophrenia currently is pharmaceutical. Some schizophrenics receive concurrent counseling, but the vast majority do not, largely because of a lack of funding, largely because schizophrenics tend as a group not to be compliant with more than minimal expectations of treatment.

Funding is a major issue in schizophrenia treatment, and as most schizophrenics are on public assistance and live in public housing, the latest, most promising treatments are often not available to them, as they are also the most expensive.

The conventional neuroleptics chlorpromazine, haloperidol, and related compounds are the general first line of schizophrenia treatment. They are inexpensive, well understood, well researched. It is clearly understood that they do fairly well against positive symptoms of schizophrenia (delusions, hallucinations, etc.) in approximately 60% of patients, but they do little for the negative symptoms (Murray, 2001) and have a side effect profile that is of major concern and frequently leads to noncompliance (at a rate of approximately 7.6% per month) and relapse (at a rate of approximately 3.5% per month; Csernansky & Schuchart, 2002).

The main issue with conventional neuroleptics is that they cause extrapyramidal side effects due to their antagonism and depletion of dopamine. One example is pseudoparkinsonism, or involuntary movements resembling Parkinson's disease. Like

Parkinson's, pseudoparkinsonism is treated with l-dopa, which raises the dopamine level. Another example is tardive dyskinesia, an involuntary movement of the lips and jaws resembling exaggerated chewing. Unfortunately, tardive dyskinesia is a permanent effect in most people who experience it--cessation of neuroleptic medication does not cause a cessation of tardive dyskinesia, and the risk is great, as much as 50% with long term neuroleptic use (Watson, 2003). Considering that current schizophrenia treatment involves lifelong neuroleptic use, approximately half the patients treated with conventional neuroleptics will develop this debilitating and embarrassing disorder.

Cognitive difficulties are the norm with patients treated with conventional neuroleptics. Schizophrenia may cause confusion, mental cloudiness, flat affect, and difficulty concentrating, but neuroleptics may actually make this worse (Rybakowski & Borkowska, 2001). It is not at all uncommon to have a patient complain that he or she feels detached, unable to focus, or sluggish while treated with neuroleptics (Watson, 2003, states that this is the intended effect. He appears to be opposed to the pharmaceutical treatment of schizophrenia).

One interesting effect of all this is that the negative side effects of neuroleptic medication appear to be lessened somewhat by stimulants, and in particular, nicotine. It is estimated that about 90% of all schizophrenics smoke, and the majority of them smoke extremely heavily (2-4 packs daily). Schizophrenics who desire to quit smoking usually find it difficult to impossible to do so, as to quit will bring back, and may even appear to worsen the side effects. Nicotine both raises the dopamine and acetylcholine levels in the brain and speeds the metabolism of neuroleptic medication (thus effectively lessening the dosage), counteracting the negative symptoms.

The therapeutic range of conventional neuroleptics is extremely small, so dosage adjustments are frequently necessary. Approximately 70% of dopamine receptor occupancy is required for the medication to be effective, but at about 80% occupancy, side effects, especially pseudoparkinsonism and other extrapyramidal effects, abound (Csemansky & Schuchart, 2002).

Another major concern with conventional neuroleptics is neuroleptic malignant syndrome (NMS), a life threatening side effect of neuroleptic use. In cases of NMS, patients will show a sudden increase in body temperature, heart rate, and blood pressure. Blood tests will show creatine kinase levels rising to several times above normal. Urinary retention and fecal incontinence may occur, as may full renal failure, and severe muscle rigidity and confusion (Reznik, et al, 2002; Nishioka, et al, 2002). Considering that muscle rigidity and confusion are both normal states for schizophrenics, particularly when treated with conventional neuroleptics, it may be difficult for a layperson or even a non-psychiatric nurse or physician to recognize NMS at first, which considering it is a life threatening emergency, is problematic.

With all these issues, noncompliance is a major problem with conventional neuroleptics. While they handle the frightening acute psychoses well, they make the chronic negative symptoms worse, and as such, patients who are not actively hallucinating will want to stop taking the medication in hopes of stopping the side effects and in a faulty expectation that perhaps they may be cured. With supervision of schizophrenics on an outpatient level at best minimal, there is little assurance that medication compliance will occur, and schizophrenic relapse is a routine fact of life for many.

The newer atypical neuroleptics are appearing to change some of this. Clozapine and its descendants risperidone (Risperdal) and olanzapine (Zyprexa) work through targeting specific dopamine (D2) and serotonin (5HT2A and 5HT2C) receptors rather than simply blocking the effects of all dopamine (Markianos, 2001). The result is that both the positive and negative symptoms are handled effectively, with far fewer side effects in general, and a much lower incidence specifically of extrapyramidal symptoms like pseudoparkinsonism and tardive dyskinesia, and an elevation of mood and mental clarity. In fact, the use of the term "atypical neuroleptic" was coined specifically to refer to the fact that they do not cause typical neuroleptic side effects (Pani & Gessa, 2002).

Risperidone, in particular, has been shown to be effective in treatment of both acute and chronic conditions, and has some possible effectiveness against tardive dyskinesia (Suenaga, et al, 2000). Some patients that show no improvement with conventional neuroleptics have done very well with risperidone or olanzapine (Peuskens, et al, 2001), and those who fail to respond to those medications do well with clozapine (Llorca, et al, 2002). Presently, the primary obstacle to their use appears to be cost--the cost of these newer medications is far greater than the conventional medications, since they are not as of yet available in generic form.

Yet in reality, the cost is not all that different. A lower side effect profile means a greater likelihood of compliance, meaning fewer psychotic episodes and fewer emergency room admissions or mental hospital evaluations. Since these hospital stays are extremely expensive, they offset any difference in medication cost (Csernansky & Schuchart, 2002). Also, many schizophrenics treated with atypical neuroleptics are able

to hold down jobs and thus earn incomes, hold medical insurance, and pay bills, reducing the strain on society. They are also likely to smoke less, reducing healthcare costs further.

Compliance issues have led to the development of "depot" medications, that is, extended release forms of neuroleptics that must be taken by injection every week or two. There has been some concern that the newer atypical neuroleptics, with their shorter half-lives, are not available in depot form, but in fact, in most cases they do not need to be. The primary reason for noncompliance is side effect problems, and they exist far less than conventional neuroleptic side effects. In practice, compliance is much better with the atypical neuroleptics (Peuskens, et al, 2001). To ensure compliance in inpatient settings, an orally disintegrating form of olanzapine is being developed, which will begin dissolving in the mouth immediately and will be fully dissolved within a minute, eliminating the problem of "cheeking" medications (holding them between the cheek and gum, pretending to swallow them, then spitting them out at a later time; Chue, et al, 2002).

ISSUES WITH GENERAL SCHIZOPHRENIA RESEARCH:

Still, there is a great deal of suspicion where schizophrenia treatment is concerned. There is not as of yet a clear understanding of what schizophrenia is and how it works. A large number of patients still do not respond adequately to medication, and many are still on medication that is potentially as harmful as it is helpful.

Societal pressure seems to have played a major role in the development of the atypical neuroleptics, and there is a possibility that it may have also hastened their

approval. Images of John Hinckley, Jr. professing his love for the actress Jodie Foster and how he shot Ronald Reagan (ironically, a champion of the deinstitutionalization of the mentally ill) to impress her helped bring about fear of the mentally ill to society at large. "Not guilty by reason of insanity" was a phrase increasingly heard in news reports of trials, and the actions of unmedicated and non-compliant schizophrenics were becoming commonplace on television news programs. One example of someone previously thought harmless was the man with the rainbow Afro wig who waved "John 3:16" signs at major sporting events to appear on television, and who later held a hotel maid hostage at knifepoint while negotiators attempted to persuade him to surrender.

Clozapine was a previously forgotten medicine that was reintroduced when it was found how to prevent agranulocytosis (Watson, 2003). Risperidone and olanzapine were descendants of clozapine that had no potential for causing agranulocytosis. These medications were introduced quickly in the late 1980's and early 1990's as alternatives to conventional neuroleptics. Yet there is some doubt as to the adequacy of research into these medications.

It is regularly accepted that these medications have a lower chance of causing extrapyramidal symptoms. Yet the research generally compares these medications to haloperidol, which generally has the highest likelihood of causing these symptoms, rather than chlorpromazine, which is more commonly used. Psychiatric research is supposed to occur under a double-blind condition, so that neither patient nor doctor is to know who is getting the experimental treatment and who is getting the control treatment. Yet the sudden occurrence of extrapyramidal effects in the patients receiving haloperidol makes

it immediately clear which is the control group and which is the experimental group (Cohen, 2002).

Patients involved in neuroleptic research have generally been maintained on a psychotropic medication for an extended period of time. In most cases, this has been a conventional neuroleptic. Prior to the research, the patients are taken off the medications for a short period of time before given their experimental or control medications. In the case of a conventional medication, the control group will continue to experience enhanced symptoms resulting from a sudden withdrawal of the medication, and may withdraw from the study due to an inability to deal with increased side effects--they are reported as "noncompliant." The atypical medication group, on the other hand, will experience the sudden side effects, which will then be treated by the atypical neuroleptic (which specifically deals well with those side effects), patients will report feeling better, and the medication will be deemed a success. The time period of the study is short, other medications are not used, and the only condition truly tested is the ability to handle an acute neuroleptic withdrawal symptom (Cohen, 2002).

In reality, schizophrenics are treated with large varieties of medication, a condition never replicated in research (Cohen, 2002). A typical schizophrenic will be on a conventional neuroleptic, a medication to counteract the extrapyramidal effects, another medication to elevate mood, and perhaps another one to clarify thought. He or she will smoke heavily, and will live inside a public housing project, where he or she will do little the entire day.

In a research setting, the schizophrenic will be on a larger, highly monitored dose of a conventional neuroleptic because he or she is in a condition that requires

institutionalization (most research involves captive audiences who participate willingly, but receive some degree of compensation or privilege for participation). The higher dose will ensure greater side effects, as will the lack of other medications, which were stopped in order to ensure the purity of the study. Smoking may or may not be allowed during the study. Sample sizes may be small, and frequently, there is little control group, or patients spend part of the research in the control group and part of it in the experimental group (Cohen, 2002).

The aspect of schizophrenia most closely studied is symptomology, and to a far lesser extent, behavior resulting from psychiatric symptomology (Cohen, 2002). Yet, the most important aspect of a deinstitutionalized schizophrenic's life is the ability to function socially. This aspect is almost never researched.

Research is rarely done on nonmedical treatments of schizophrenia, and perhaps that is appropriate, though perhaps it is not. There is some concern that the atypical neuroleptics may not be safe for long-term use, and some reports that extrapyramidal effects do eventually occur with long-term use. In addition, there is some anecdotal evidence that some schizophrenics have functioned well with episodic treatment of atypical neuroleptics for acute conditions and counseling for the rest of the time.

ISSUES WITH MEDICAL TREATMENT:

One of the other significant problems with the treatment of the schizophrenic has to do with the attitudes and actions of the physician himself/herself. Many people complain about how doctors interact with them and how their thoughts, beliefs, and ideas

are not taken seriously. With schizophrenics, "crazy people," perhaps, this is more so. Doctors frequently do not take the mentally ill seriously at all, considering anything that does not agree with them to be a symptom of the mental illness. A patient does not stop taking a medication because of side effects or because it is ineffective, but because the patient is "noncompliant" (Marland, 1999).

If the patient's feelings, reactions, and emotions are legitimate, then the doctor would be expected to consider them, even if he or she does not honor them (as is often the case with some doctors). But the schizophrenic has the added obstacle of having his feelings, reactions, and emotions considered a symptom of the disease. So long as a physician or psychiatrist treats the patient as a disease and not as a human, the patient is unable to own his or her recovery and is more likely to be noncompliant.

In the case of a patient treated with conventional neuroleptics, it is fairly easy to disregard the patient's feelings. Although the symptoms are clearly seen and can easily be traced to the medication, they can also be seen as part of what it means to be "crazy." Now that atypical neuroleptics make normal functioning a little more possible, doctors may have to reexamine their perspective of these patients, as they will not look the same.

CONCLUSION:

Whether atypical neuroleptics are the magic bullet for treatment of schizophrenia and whether they are safe and effective for long term use remains to be seen. At this point, they appear to be more effective and safer than conventional neuroleptics for management of the condition on an outpatient basis, which is the reality of the situation

today. If nothing else, there is now new research going into the treatment of schizophrenia, which was not the case twenty years ago. The inevitable result of that is that, whether with the current class of atypical neuroleptics, newer medications, or other treatment modalities, there will eventually be a safe and effective way of dealing with schizophrenia.

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