

THE IMPACT OF THE PSYCHOPHARMACOLOGICAL  
REVOLUTION ON PSYCHIATRY

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Oral Drug Treatment of Acute Major Psychiatric Disorders

I well remember a group of students making rounds with me in 1952 at the Verdun Protestant Hospital (now Douglas Hospital) in Montreal. We were looking at two young schizophrenic patients gesturing excitedly toward the ceiling from where they were hearing frightening voices. One of the students asked softly "will we ever get a pill to help these people?" I smiled patronizingly and replied that, unfortunately, it would never be as simple as "just a pill".

One year later we started our first clinical trial of chlorpromazine with 75 schizophrenic patients. Within days, some of the patients had stopped hallucinating and within two weeks, a few were in remission and ready to leave the hospital. I assumed we were seeing a series of flukes - perhaps resulting from a strange chance selection in the sample. It seemed almost as improbable as winning \$1 million twice in a lottery.

Much as I wanted to believe what I was seeing, I didn't. For two years, even in my correspondence with other clinicians in the states working with the phenothiazines, neither I nor they dared to attribute specific antipsychotic effects to these drugs. We thought it might be a peculiar modification of some sedating and inhibiting action, but we did not label the drugs antipsychotic. In 1956, when I was addressing the Canadian Medical Association I introduced the term antipsychotic apologetically, and more as a metaphor than a designation.

Just to remind you, here was the backdrop in the early 1950's - one generation ago:

We had Kraepelin's and Bleuler's guides to diagnosis of major psychiatric disorders, the psychoses. We had insulin coma and electroconvulsive shock therapies for major psychiatric illness, and we had psychoanalysis and some derivative psychotherapy for the treatment of the neuroses. Drug therapy consisted of paraldehyde and the barbiturates to quell agitation and aggression. The trouble with the shock therapies was that they often worked dramatically for a few weeks, and then the patients - 70-80% of them - relapsed and had to be rehospitalized. Besides, these treatments were very invasive, cumbersome and often hazardous. Psychiatric research was carried out with Rorschach cards and MMPI questionnaires.

All of the mental hospitals were overcrowded, and living conditions for the patients were often shameful. The outlook then was that 60-70% of all schizophrenic patients would, once hospitalized, never live in the community again.

But we finally did recognize the fact that we had a simple pill for the treatment of acute schizophrenic symptoms. And, later in the 1950's, we had other pills as well - the tricyclics and MAO inhibitors - to effectively deal with depressive disorders. The psychiatrist - and the General Practitioner - quite suddenly had the means to treat patients in the office or the patient's home.

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Oral Drug Treatment of Chronic Major Psychiatric Disorders

It didn't even cross our minds that the new drugs might help the chronic back-ward patients - those who had not responded to insulin coma and ECT - to leave the hospital. However, we put a number of these "hopeless" patients on chlorpromazine for its symptomatic, sedative effect and to our amazement, some of them actually went into remission. Again, it took us at least two years to accept the fact that at least some chronic schizophrenic patients were remitting with phenothiazines.

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Maintenance Drug Treatment

None of us was so euphoric as to think we had a cure for schizophrenia or depression. We remembered all too well what had happened to Von Meduna in Hungary who enthusiastically reported 90% recoveries with metrazole convulsive therapy for his schizophrenic patients, but who discovered that most of these had relapsed by the time his paper was published in the late 1930's. And so it was with our sample. Typically, we were stopping drug treatment shortly after the patient became asymptomatic - much as if we had been using an antibiotic for an infection. Not surprisingly, 70-80% of our schizophrenics and many of our depressed patients relapsed within a year.

We wondered: might there be such a thing as long-term, perhaps indefinite, protective maintenance treatment - a real secondary prevention of major mental illness? It seemed too much of a long shot that these patients might be protected against recurrences by continued administration of the new drug. There

was no choice but to try it. And, to our delight, it worked. It was the first time in the long history of mental illness that maintenance pharmacotherapy was successfully carried out. That was the real breakthrough.

We still did not know what complications might develop with long-term treatment - new side effects, perhaps later development of tolerance and resistance to the drugs, or how patients and families would accept the idea of continued use of drugs when they were feeling fine. How long would they accept the known side effects? A few years later - in the 1960's - lithium, for the maintenance treatment of bipolar disorder, would present the same set of promises and problems.

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A New Phenomenon: Drug Induced Extrapyrarnidal Syndrome

Two or three months after we started patients on chlorpromazine I remember standing on the ward with a neurologist colleague and watching three patients who walked with a shuffling gait, did not swing their arms and had mask-like faces. We wondered about these peculiar side effects and agreed that these symptoms looked very much like Parkinsonism. But there was a problem: Nobody had ever been able to produce Parkinsonism experimentally with any substance, in animals or humans. It was known only in its idiopathic form. It took us another week until we finally were sure we had seen, for the first time, drug-induced extrapyramidal symptoms. Other investigators also made the same discovery. Clinicians had done what experimental neuroscientists had been unable to do. Drugs were soon developed

to effectively suppress these Parkinsonian side effects and treatment of the extrapyramidal symptoms became part of all antipsychotic pharmacotherapy.

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### Clinical Trial Methodology: Placebo Control

An avalanche of new psychotropic drugs started to appear in the late 50's and early 60's. It was evident that our primitive, early open trial procedure of chlorpromazine would be utterly inadequate to test all these new drugs in any valid fashion. Our first trial with chlorpromazine had been conducted with 75 patients simultaneously, using no written protocol, no stated criteria for selecting the patient sample, no placebo or other controls, no government permission (not required then) and - it seems incredible today - no informed consent from the patients or their families. We also had no financial assistance from the pharmaceutical company, no grant from the government or any other private agency. The work was simply folded into our other clinical routines. Clearly, a new methodology had to be devised - which soon grew into considerable complexity, involving careful design of every study, random selection, diagnostic criteria, placebo control, and sophisticated statistical evaluations.

National and international conferences were scheduled for comparision and further fine tuning of the various research methods and procedures being used in different research centers. We hardly realized that the new scientific discipline psychopharmacology was being born.

Many of us veterans balked <sup>at first</sup> at the placebo requirement,

feeling that our clinical savvy allowed us to account for placebo effects without having them concretely introduced. We also disliked being compelled to permit outside statisticians to infiltrate our cliquish clinical teams.

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### A New Concept: Informed Consent

Medical ethics did not exist as a special discipline at the time. We had only the Hippocratic oath to guide us. Virtually nobody was looking over our shoulders. Then the thalidomide disaster obliged governments all over the world to become involved in the regulation of clinical drug trials.

Added to the horrors of human experimentation in Hitler's concentration camps, this disaster created a public awareness and reaction to the risks of human experimentation, leading to the Nuremberg Laws - then the Helsinki Conference - in covering experimentation with human subjects.

The US Food and Drug Administration required informed consent - to the point when patients had to be told that they might be getting either a placebo or an active new drug. Many of us thought then that this spelled doom for future clinical drug trials. Fortunately, and to our surprise, we were wrong. Even under the new rules, many patients did consent to participation in placebo-controlled trials. Needless to say, the real meaning and implications of informed consent continue to be debated today in and outside the courts.

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Pharmacodynamic Theories: The Door to Neuroscience

Epistemologically speaking, at this point we had the psychiatric cart before the horse. We had new drugs that effectively suppressed psychotic and affective symptoms. But their action mechanism remained a complete mystery. The first opening for a theoretical understanding came with Brodie's discovery at the NIMH that reserpine depleted presynaptic neurons of their biogenic amines - more specifically, noradrenaline and serotonin. Reserpine also produced a depression-like syndrome in animals and a real depression in about 10% of human patients to whom it was given for the treatment of hypertension. This led to the theory that a deficiency of biogenic amines might be a factor in the etiology of depressive disorders. It could now be understood why MAOI's, which increased the availability of biogenic amines at the synaptic cleft, relieved depression. But not until the Nobel laureate Axelrod and others had shown that the tricyclics inhibited the reuptake of biogenic amines into the neuron did we begin to get the first explanation for the action of these antidepressants. The action mechanism of the antipsychotics was not understood for 10 years - when Carlsson and Lindquist discovered, in 1963, that all substances with antipsychotic action shared one common property: they all blocked dopaminergic neurons. Thus, the dopamine theory of schizophrenia was born. While it does not tell us the cause of schizophrenia, it at least establishes a testable hypothesis on the final common path of its pathophysiology. The simple explanation that too little or too much of a monoamine in the synaptic cleft is the cause of depression, no longer suffices



today. The complicated interactions of many systems - receptors on cell membranes, neurohormones, neuropeptides and other modulators - are necessarily involved today in any attempts to explain the action of psychotropic drugs.

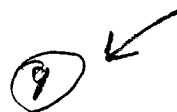
The antipsychotic and antidepressant drugs, in fact, served as the "Rosetta stone" for the hieroglyphs of mental disease symptoms and opened new avenues for the development of modern neuroscience.



#### A New Disease - Tardive Dyskinesia

The first ugly gremlin to appear out of the Pandora's box came about a decade after the first use of the new antipsychotics, when we discovered that they had created a new disease - tardive dyskinesia. This extrapyramidal complication of long-term antipsychotic therapy affects about 15-20% of all patients. There is no known treatment for it, and it is in many cases irreversible.

Today, one of the clinician's major challenges is how to weigh the cost/benefit ratio of prolonged pharmacotherapy in schizophrenia. Should we obtain informed consent from the patient, the family, or both, for maintenance treatment and, if so, when? How can we protect ourselves against malpractice suits?



#### Pathomorphosis

The introduction of effective psychoactive drugs has changed the phenomenology of mental disease. Few of today's psychiatrists have any real first-hand knowledge of the

stuporous, posturing catatonics who had to be tube-fed, the emaciated, mute, chronic depressed individuals who sat for years in the back-wards of the mental hospitals, the deteriorated hebephrenics smearing feces and grinning fatuously. Only textbooks, and a few historical films, have preserved these grotesque fossils of our psychiatric past.

Pathomorphosis is the term some authors have applied to the changing face of schizophrenia which today expresses itself in more subdued, less florid symptomatology, than in the past. We see today more of the negative schizophrenic symptoms which do not respond to drug therapy than positive symptoms which are effectively suppressed by neuroleptics.

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### Business Explosion in Psychopharmaceutics

Psychopharmaceutics, an industry of little economic consequence previously, quite suddenly mushroomed into a multibillion dollar business - world wide. The big companies all scrambled for part of the action and developed an endless list of me-too drugs, each variety claiming to be a little different and a little better than the other - although there was not much solid evidence for most of these competitive claims. Small companies lobbied for legislative changes that would allow them to muscle in on the profits of the big companies through licenses to produce generic drugs before patents ran out. Now before the Canadian legislature are proposals to revise current patent laws permitting the big companies to reembark on expensive research ventures which they had abandoned, when the smaller

companies were legally permitted to produce and sell drugs at low cost in the absence of patent protection.

Drug advertising has become slick, almost hypnotically seductive, and for many physicians, unfortunately, the main source of pharmacological information.



### The Drug Scene

Another monster that emerged from the Pandora's box was an offshoot of the suddenly increased awareness of the great power of drugs. The monster was two-faced. The emergence of street drugs for recreational purposes and the overdependence on prescribed tranquilizers. Morphine and cocaine addicts had been with us for a long time. A few people - mostly artists, poets and musicians - had experimented with marijuana, and American Indians were using mescaline and psilocybin. But now worldwide epidemics of drug abuse broke out: amphetamines in Japan, marijuana and LSD in North America and an endless chain of street drugs such as PCP (phencyclidine or "angel dust"), "designer drugs" which recently produced the awful consequences of MPTP, the synthetic Demerol derivative that froze its young victims in terminal Parkinson's disease. Cocaine is the latest scourge - the recreational drug of the rich.

Street drugs have become a lucrative new focus of organized international crime and consumes an ever increasing amount of law enforcement time and money.

Introduction of the benzodiazepines in the 1960's seemed at first to be the fulfillment of an old medical dream: a nontoxic sedative and tranquilizing drug.

But the public soon came to believe that drugs could be a quick fix for just about any ailment or stress - even the stresses inherent in normal daily existence, necessary for the exercise of one's coping capacities.

True, nobody could kill themselves with librium or valium, but within a few years we discovered that these drugs, not unlike barbiturates, also produced tolerance and, not infrequently, led to psychological and physical dependence and resulted in withdrawal symptoms upon discontinuation. Also, quite a lot of prescription tranquilizers found their way into the streets.

Many unsuspecting physicians had been overprescribing benzodiazepines, until some unpleasant facts were revealed during the last decade. In the early 1970's a survey showed that one out of six people in the North American adult population was using tranquilizers. Even though virtually all physicians responded to the problem by prescribing more carefully and rationally, we still have many "old" patients who continue to be dependent on these drugs, and some well may stay dependent on them for years to come.

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#### Antidrug Backlash

The destructive aspects of the drug scene and the often questionable tactics of the pharmaceutical industry, as well as the oversell by some members of the psychiatric community and the disenchantment of the legislators and other budgeteers, led to an antidrug backlash in the 1970's.

Not only were illegitimate uses of drugs denounced, but also

legitimate uses and prescribers were implicated. Physicians put away their prescription pads, and probably many patients with genuine need of tranquilizers, sedatives or drugs for insomnia, were scared away from even reasonable, limited use of such drugs.

Recent epidemiological studies, as well as some of today's most knowledgeable observers, indicate that today psychoactive drugs are actually underprescribed, in view of the need for treatment of diagnosed psychiatric disorders.

The patient who is suffering from symptoms which are quite treatable by tranquilizers is being told - by physicians, self help groups, friends and the media - that he should instead try jogging or relaxation exercises or meditating or a diet change or Yoga or just personal ego power, to solve his problems. If he cannot manage any of these alternatives, and feels too guilty to take tranquilizers, he finds himself lodged between a rock and a hard place.

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### The Renaissance of Psychiatric Diagnosis

The fact that there suddenly were new drugs that could deal effectively with previously untreatable mental illness but also had side effects and potential toxicity, made it imperative to take a new look at psychiatric diagnosis.

One long-standing nosological controversy had already been swept aside by the new drugs. There had been two schools in established psychiatry - one claiming that psychoses and other emotional and mental disorders were different categories, and the other claiming that the disorders simply represented different degrees of severity on a continuum. The two schools had been

referred to as the gradualists and the separatists. If psychoses were only to be regarded as more intense disturbances than the neuroses, their treatment would simply call for larger doses of those drugs that were effective in the treatment of neurotic anxiety, i.e. the anxiolytic sedatives. This is not so. Only the antipsychotic (neuroleptic) drugs have a quasi-specific antipsychotic action. A relatively small dose of an antipsychotic is usually much more effective in the treatment of a psychotic condition than a very large dose of an anxiolytic sedative. Psychoses do belong in a different category from neurotic, emotional maladjustments.

Because there is today a multitude of antipsychotic, antidepressant and anxiolytic drugs, and because we are now aware that neither schizophrenia, nor depression, nor anxiety are unitary concepts, it is obvious that we need to find the right specific drug for the right specific subgroup of schizophrenia, depression or anxiety. A great deal of effort has gone into the construction of better diagnostic instruments in the form of structured interviews, questionnaires, personality inventories and rating scales. The search for the elusive will-o-the-wisp of a biological marker continues unabated. DSM III has introduced an updated, operationally defined, neo-Kraepelinian system which has been eagerly received throughout North America and in many other parts of the world - too eagerly for my own liking, although I do admit it is useful as a diagnostic primer and middle ground.

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An Administrative Nightmare: The Revolving Door Patient

The new drugs have made it possible to discharge patients early from the hospital. They also have given us a means of maintaining a patient in the community by protecting him against frequent relapses - provided he follows instructions and complies with the prescribed drug therapy. However, many patients do not comply - some because they do not like the drugs' side effects, some because they simply forget to take the drug and some because they, or their families, do not believe that they need drug treatment. I think there are even some who do not take the drugs because - consciously or unconsciously - they want to come back to the hospital. The result is the administrative nightmare of the "revolving door patient" who may enter and leave the hospital several times a month.

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The Young, Aggressive, Chronic Patient

There have always been young chronic mental patients. But before the advent of the new drugs they were institutionalized, quiet and even docile. Today, many young chronic mental patients are out in the community. They are a new and growing problem in psychiatry - a third monster unleashed by the advances in psychopharmacology. They do not comply with prescribed treatment but demand social, clinical and related services of their own choosing. They are all street-wise and frequently sell their prescription drugs. Many of them are tough, delinquent and aggressive, and many are into street drugs. So far neither psychiatry nor any other sector of society has any handle on them. They are a new and growing problem in psychiatry - a third

monster unleashed by the advances in psychopharmacology.

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Social Curse: The Derelicts of Deinstitutionalization

We never even imagined the extent of another social consequence brought about by the psychopharmacological revolution. Deinstitutionalization, the buzz-word of the 60's, has resulted in many parts of the world in a growing army of homeless bag-ladies and other derelicts on the streets. It is estimated that 40% of the 300,000 homeless in the streets of North American cities - some 120,000 individuals - are mentally disturbed - i.e. psychotic, alcoholic, drug abusers, former mental hospital patients and others who should be, but cannot be admitted to mental hospitals because of the new "progressive" admissions policies.

Within the overall poverty population, these derelicts are the poorest and most vulnerable of all. Most are unemployed and unemployable. Many are at a loss to find even the well-worn paths in the labyrinth of welfare benefits. Of the poor, they are the "untouchables" of our caste system - the most disdained and rejected by the communities in which they are wondering today.

We are seeing now a scramble for alternatives, novel living arrangements and supportive services for these people. But there is no prospect of any near term achievement of that goal.

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Dehumanization of Psychiatry?

In this era of uncertainty of almost everything, medical



students and psychiatric residents are groping for the security blanket of "real science" - hard biological facts and rigorous scientific methodology. They are demanding - and getting - that orientation in their curricula. They are dazzled by multimillion dollar instrumentation which produces fascinating images of the living brain, and they fully expect to see these images translated soon into psychological understanding. They are hailing the new orientation of DSM III, with its operationally defined concepts, as a long-awaited breakthrough in clarity. They welcome the high reliability of this new diagnostic tool. They applaud the psychopharmacological revolution for all the scientific innovations that will put psychiatry, they think, on an equal footing with the other branches of medicine as being "really scientific".

*Some of us* I am afraid that the students are as oversold on science as ~~we~~ were on miracle drugs at the outset of this revolution. I am worried about the self-assuredness - even smugness - with which medical students arrive at the wrong diagnosis by checking off DSM criteria in cookbook fashion. [ + + + + - - ]

A good psychiatrist today still needs - as much as ever - a high tolerance for uncertainty and deviation from supposed norms, standards of reliability and uniformity; an intense personal commitment; the courage to commit himself, if necessary, to diagnostic and therapeutic decisions without the backing of statistics and controlled experiments.

A good psychiatrist today must recognize and respect the ever-changing, always unique, utterly human aspects of the individual - sick or well - which can be grasped only through

empathy and knowledgeable intuition, and through continued close personal contact with people and problems - not electronic instruments. These were, of course, our original, if inadequate, tools.

The Janus - faced term psychopharmacology comprises the two approaches to the psychiatric patient today - the psychological and the biological - both of them necessary but neither of them sufficient in themselves. Before the advent of psychopharmacology and the dramatic growth of the neurosciences, we were restricted by default to the psychological approach. Are we now risking abandonment of a truly integrated approach in favor of the apparently easier, strictly scientific approach? Are we alienating ourselves from the living patient?

Recent studies have demonstrated that antidepressant drug therapy is more effective if it is combined with psychotherapy, and the most dramatic new progress in the treatment of chronic schizophrenia has been seen when family therapy was added to pharmacotherapy the patients were receiving.

I believe we in the psychiatric community have, for the time being, shot our wad so far as the neurosciences are concerned. Sure, we opened the door for them, but we should now leave the next round of research and development to the neuroscientists and industry, and concentrate our energies on exploiting the full potential of today's rich enough therapeutic armamentarium.