The case against antipsychotic drugs: a 50-year record of doing more harm than good ☆

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Summary Although the standard of care in developed countries is to maintain schizophrenia patients on neuroleptics, this practice is not supported by the 50-year research record for the drugs. A critical review reveals that this paradigm of care worsens long-term outcomes, at least in the aggregate, and that 40% or more of all schizophrenia patients would fare better if they were not so medicated. Evidence-based care would require the selective use of antipsychotics, based on two principles: (a) no immediate neuroleptisation of first-episode patients; (b) every patient stabilized on neuroleptics should be given an opportunity to gradually withdraw from them. This model would dramatically increase recovery rates and decrease the percentage of patients who become chronically ill.
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Introduction

The standard of care for schizophrenia calls for patients to be maintained indefinitely on antipsychotic drugs. The evidence for this practice comes from research showing the drugs are effective in treating acute psychotic symptoms and in preventing relapse [1,2]. Historians also argue that the introduction of neuroleptics in the 1950s made it possible to empty the mental hospitals, and that this is further proof of the drugs' merits [3]. Yet, long-term outcomes with schizophrenia remain poor, and may be no better than they were 100 years ago, when water therapies and fresh air were the treatment of the day [4—7].

There is an evident paradox in the research record. The efficacy of neuroleptics appears to be well established, yet there is a lack of evidence showing that these drugs have improved patients' lives over the long-term. That paradox recently stirred an unusual editorial in *Eur. Psychiatry*, which posed this question: "After fifty years of neuroleptic drugs, are we able to answer the following simple question: Are neuroleptics effective in treating schizophrenia?" [8] A close review of the research literature provides a surprising answer. The preponderance of evidence shows that the current standard of care — continual medication therapy for all patients so diagnosed — does more harm than good.

Did neuroleptics enable deinstutionalization?

The belief that the introduction of chlorpromazine, marketed in the US as Thorazine, made it possible to empty state hospitals stems from research by Brill and Patton. In the early 1960s, they reported that the patient census at state mental hospitals in the US declined from 558,600 in 1955 to 528,800 in 1961. Although they did not compare discharge rates for drug-treated versus placebo-treated patients, they nevertheless concluded that neuroleptics must have played a role in the decline since it coincided with their introduction. The fact that the two occurred at the same time was seen as the proof [9,10].

However, there were obvious confounding factors. In the early 1950s, the Council of State Governments in the US urged the federal government to share the fiscal burden of caring for the mentally ill, and proposed that "out-patient clinics should be extended and other community resources developed to care for persons in need of help, but not of hospitalization" [11,12]. As part of this agenda, states began developing community care initiatives, funneling the mentally ill into nursing homes and halfway houses. This change in social policy could easily have been responsible for the slight drop in patient numbers observed by Brill and Patton.

Moreover, there was one state that did compare discharge rates for schizophrenia patients treated with and without drugs, and its results do not support the historical claim made for neuroleptics. In a study of 1413 first-episode male schizophrenics admitted to California hospitals in 1956 and 1957, researchers found that "drug-treated patients tend to have longer periods of hospitalization... furthermore, the hospitals wherein a higher percentage of first-admission schizophrenic patients are treated with these drugs tend to have somewhat higher retention rates for this group as a whole". In short, the California investigators determined that neuroleptics, rather than speed patients' return to the community, apparently *hindered* recovery [13].

The true period of deinstitutionalization in the US was from 1963 to the late 1970s, the exodus of patients driven by social and fiscal policies. In 1963, federal government began picking up some of the costs of care for the mentally ill not in state institutions, and two years later, Medicare and Medicaid legislation increased federal funding for care of mental patients provided they were not housed in state hospitals. Naturally, states responded by discharging their hospital patients to private nursing homes and shelters. In 1972, an amendment to the Social Security act authorized disability payments to the mentally ill, which accelerated the transfer of hospitalized patients into private facilities. As a result of these changes in *fiscal* policies, the number of patients in state mental hospitals dropped from 504,600 to 153,544 over a 15-year period (1963—1978) [14].

Establishing efficacy: the pivotal NIMH trial

The study that is still cited today as proving the efficacy of neuroleptics for curbing acute episodes of schizophrenia was a nine-hospital trial of 344 patients conducted by the National Institute of Mental Health in the early 1960s. At the end of six weeks, 75% of the drug-treated patients were "much improved" or "very much improved" compared to 23% of the placebo patients. The researchers concluded that neuroleptics should no longer be considered mere "tranquilizers" but "antischizophrenic" agents. A magic bullet had apparently been found for this devastating disorder [1].

However, three years later, the NIMH researchers reported on one-year outcomes for the patients. Much to their surprise, they found that "patients who received placebo treatment were less likely to be rehospitalized than those who received any of the three active phenothiazines" [15]. This result raised an unsettling possibility: While the drugs were effective over the short-term, perhaps they made people more biologically vulnerable to psychosis over the long run, and thus the higher rehospitalization rates at the end of one year.

The NIMH withdrawal studies

In the wake of that disturbing report, the NIMH conducted two medication-withdrawal studies. In each one, relapse rates *rose* in correlation with neuroleptic dosage before withdrawal. In the two trials, only 7% of patients who were on placebo relapsed during the following six months. Twenty-three percent of the patients on less than 300 mg of chlorpromazine daily relapsed following drug withdrawal; this rate climbed to 54% for those receiving 300—500 mg and to 65% for patients taking more than 500 mg. The researchers concluded: "Relapse was found to be significantly related to the dose of the tranquilizing medication the patient was receiving before he was put on placebo — the higher the dose, the greater the probability of relapse" [16].

Once more, the results suggested that neuroleptics increased the patients' biological vulnerability to psychosis. Other reports soon deepened this suspicion. Even when patients reliably took their medications, relapse was common, and researchers reported in 1976 that it appeared that "relapse during drug administration is greater in severity than when no drugs are given" [17]. A retrospective study by Bockoven also indicated that the drugs were making patients chronically ill. He reported that 45% of patients treated at Boston Psychopathic Hospital in 1947 with a progressive model of care did not relapse in the five years following discharge, and that 76% were successfully living in the community at the end of that follow-up period. In contrast, only 31% of patients treated in 1967 with neuroleptics at a community health center remained relapse-free over the next five years, and as a group they were much more "socially dependent" — on welfare and

needing other forms of support — than those in the 1947 cohort [18].

Drug treatment versus experimental forms of care

With debate over the merits of neuroleptics rising, the NIMH revisited the question of whether newly admitted schizophrenia patients could be successfully treated without drugs. There were three NIMH-funded studies conducted during the 1970s that examined this possibility, and in each instance, the newly admitted patients treated without drugs did better than those treated in a conventional manner.[1]

In 1977, Carpenter reported that only 35% of the nonmedicated patients in his study relapsed within a year after discharge, compared to 45% of those treated with neuroleptics. The non-medicated patients also suffered less from depression, blunted emotions, and retarded movements [20]. A year later, Rappaport et al. [21] reported that in a trial of 80 young male schizophrenics admitted to a state hospital, only 27% of patients treated without neuroleptics relapsed in the three years following discharge, compared to 62% of the medicated group. The final study came from Mosher, head of schizophrenia research at the NIMH. In 1979, he reported that patients who were treated without neuroleptics in an experimental home staffed by nonprofessionals had lower relapse rates over a two-year period than a control group treated with drugs in a hospital. As in the other studies, Mosher reported that the patients treated without drugs were the better functioning group as well [22,23].

The three studies all pointed to the same conclusion: Exposure to neuroleptics increased the long-term incidence of relapse. Carpenter's group defined the conundrum

> There is no question that, once patients are placed on medication, they are less vulnerable to relapse if maintained on neuroleptics. But what if these patients had never been treated with drugs to begin with?... We raise the possibility that antipsychotic medication may make some schizophrenic patients more vulnerable to future relapse than would be the case in the natural course of the illness [20].

In the late 1970s, two physicians at McGill University in Montreal, Guy Chouinard and Barry Jones, offered a biological explanation for why this was so. The brain responds to neuroleptics — which block 70–90% of all D_2 dopamine receptors in the brain — as though they are a pathological insult. To compensate, dopaminergic brain cells increase the density of their D_2 receptors by 30% or more. The brain is now "supersensitive" to dopamine, and this neurotransmitter is thought to be a mediator of psychosis. The person has become more biologically vulnerable to psychosis and is at particularly high risk of severe relapse should he or she abruptly quit taking the drugs. The two Canadian researchers concluded:

> Neuroleptics can produce a dopamine supersensitivity that leads to both dyskinetic and psychotic symptoms. An implication is that the tendency toward psychotic relapse in a patient who has developed such a supersensitivity is determined by more than just the normal course of the illness... the need for continued neuroleptic treatment may itself be drug induced [24,25].

Together, the various studies painted a compelling picture of how neuroleptics shifted outcomes away from recovery. Bockoven's retrospective and the other experiments all suggested that with minimal or no exposure to neuroleptics, at least 40% of people who suffered a psychotic break and were diagnosed with schizophrenia would not relapse after leaving the hospital, and perhaps as many as 65% would function fairly well over the long-term. However, once first-episode patients were treated with neuroleptics, a different fate awaited them. Their brains would undergo drug-induced changes that would increase their biological vulnerability to psychosis, and this would increase the likelihood that they would become chronically ill.

The world health organization studies

In 1969, the World Health Organization initiated a study to compare outcomes for schizophrenia in "developed" countries with outcomes in "undeveloped" countries. Once again, the results were surprising. Patients in the three poor countries —

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[1] In the early 1960s, May conducted a study that compared five forms of treatment: drug, ECT, psychotherapy, psychotherapy plus drug, and mileu therapy. Over the short-term, the drug-treated patients did best. As a result, it came to be cited as proof that schizophrenia patients could not be treated with psychotherapy. However, the long-term results told a more nuanced story. Fifty-nine percent of patients initially treated with mileu therapy but no drugs were successfully discharged in the initial study period, and this group "functioned over the follow-up (period) at least as well, if not better, than the successes from the other treatments". Thus, the May study suggested that a majority of first-episode patients would fare best over the long-term if initially treated with "mileu therapy" rather than drugs [19].

India, Nigeria and Colombia — were doing dramatically better at two-year and five-year follow-ups than patients in the US and four other developed countries. They were more likely to be fully recovered and faring well in society — "an exceptionally good social outcome characterized these patients", the WHO researchers wrote — and only a small minority had become chronically sick. At five years, about 64% of the patients in the poor countries were asymptomatic and functioning well. In contrast only 18% of patients in the rich countries were in this best-outcomes category. The difference in outcomes was such that the WHO researchers concluded living in a developed nation was a "strong predictor" that a schizophrenic patient would never fully recover [26].

These findings naturally stung psychiatrists in the US and other rich countries. Faced with such dismal results, many argued the WHO study was flawed and that a number of the patients in the poor countries must not have been schizophrenic but ill with a milder form of psychosis. With that criticism in mind, the WHO conducted a study that compared two-year outcomes in 10 countries, and it focused on first-episode schizophrenics all diagnosed by Western criteria. The results were the same. "The findings of a better outcome of patients in developing countries was confirmed", the WHO investigators wrote. In the poor countries, 63% of schizophrenics had good outcomes. Only slightly more than one-third became chronically ill. In the rich countries, the ratio of good-to-bad outcomes was almost precisely the reverse. Only 37% had good outcomes, and the remaining patients did not fare so well [27].

The WHO investigators did not identify a cause for the stark disparity in outcomes. However, they did note there was a difference in the medical care that was provided. Doctors in the poor countries generally did not keep their patients on neuroleptics, while doctors in the rich countries did. In the poor countries, only 16% of the patients were maintained on neuroleptics. In the developed countries, 61% of the patients were kept on such drugs.

Once again, the research record told the same story. In the WHO studies, there was a correlation between use of the medications on a continual basis and poor long-term outcomes.

MRI studies

While most researchers have used MRIs to investigate possible causes of schizophrenia, a small number have employed this technology to study the effects of neuroleptics on the brain. These investigators have found that the drugs cause atrophy of the cerebral cortex and an enlargement of the basal ganglia [28—30]. Moreover, researchers at the University of Pennsylvania reported in 1998 that the drug-induced enlargement of the basal ganglia is "associated with greater severity of both negative and positive symptoms" [31]. In other words, they found that the drugs cause changes in the brain associated with a *worsening* of the very symptoms the drugs are supposed to alleviate.

Relapse studies

As discussed earlier, evidence for the efficacy of neuroleptics is stated to be two-fold. First, the NIMH trial in the 1960s found that neuroleptics are more effective than placebo in curbing acute episodes of psychosis. Second, the drugs have been shown to prevent relapse. In 1995, Gilbert reviewed 66 relapse studies, involving 4365 patients, and summed up the collective evidence: Fifty-three percent of patients withdrawn from neuroleptics relapsed within 10 months, versus 16% of those maintained on the drugs. "The efficacy of these medications in reducing the risk of psychotic relapse has been well documented," she wrote [2].

At first glance, this conclusion seems to contradict the research showing that the drugs made patients chronically ill. There is an answer to this puzzle however, and it is a revealing one. The studies by Rappaport, Mosher and Carpenter involved patients who, at the start of the experiment, were not on neuroleptics but were then treated either with placebo or a neuroleptic. And in those studies, relapse rates were lower for the placebo group. In contrast, the 66 studies reviewed by Gilbert were *drug-withdrawal* studies. In the studies she analyzed, patients who had been stabilized on neuroleptics were divided into two cohorts: One would keep on taking the drugs and the other would not, and the studies reliably found that people withdrawn from their neuroleptics were more likely to become sick again.

Thus, the literature suggests that relapse rates fall into three groups: lowest for those not placed on neuroleptics in the first place, higher for those who take the drugs continuously, and highest of all for those withdrawn from the drugs. Yet even that picture is misleading.

First, for the most part, the drug-withdrawal studies were conducted in a select group of "good responders" to neuroleptics, rather than in the general patient population. In the real world, up

to 30% of hospitalized patients do not respond to neuroleptics. Among those who do and are discharged, more than one-third relapse within the next 12 months and need to be rehospitalized, even though they reliably take their medications. Thus, fewer than 50% of people who suffer a schizophrenic break respond to standard neuroleptics and remain relapse-free for as long as a year, but the relapse studies, to a large degree, were conducted in this group of good responders. In 1998, Hogarty pointed out how this study design led to a mistaken understanding of true relapse rates with antipsychotics: "A reappraisal of the literature suggests a one-year, post-hospital, relapse rate of 40% on medication, and a substantially higher rate among patients who live in stressful environments, rather than earlier estimates of 16%" [32].

At the same time, the relapse studies were designed in ways that exaggerated the risk of relapse in the drug-withdrawn groups. In response to Gilbert, Baldessarini reanalyzed the same 66 studies, only he divided the drug-withdrawn cohort into "abrupt-withdrawal" and "gradual-withdrawal" groups. He determined that the relapse rate in the abruptly withdrawn group was *three times higher* than in the gradual group [33]. In other words, it was the abrupt cessation that caused much of the excess relapse risk. Indeed, in a further review of the relapse literature, Baldessarini found that only one-third of schizophrenia patients gradually withdrawn from their drugs relapsed within six months and that those who reached this six-month point without become sick again had a good chance of remaining well indefinitely. "The later risk of relapsing was remarkably limited," he concluded [34].

The relapse studies are cited to support a paradigm of care that emphasizes continual drug therapy for schizophrenia patients. But upon closer examination, a new picture emerges. The real-world first-year relapse rate for patients maintained on neuroleptics is understood to be 40%, while the rate for patients gradually withdrawn from the drugs is 33%. Thus, once bad trial design is eliminated, the evidence for continual medication disappears. At the same time, evidence appears showing that a majority of patients — two-thirds in the gradual withdrawal studies — can do fairly well without the drugs.

Doing more harm than good

Although this review of neuroleptics may seem surprising, the research record actually is quite consistent. The pivotal NIMH study in the early 1960s found that the drugs had a short-term benefit, but that over the long-term the drug-treated patients had higher relapse rates. Similarly, in his retrospective study, Bockoven found that patients treated with neuroleptics were more likely to become chronically ill. The experiments by Carpenter, Mosher, and Rappaport all showed higher relapse rates for drug-treated patients, and in 1979, Canadian investigators put together a biological explanation for why this would be so. The World Health Organization reported higher recovery rates in poor countries where patients were not regularly maintained on the drugs. Finally, the MRI studies by investigators at the University of Pennsylvania confirmed the problem of drug-induced chronicity in a compelling way. The drug treatment caused a pathological change in the brain associated with a worsening of symptoms — that is a convincing example of cause and effect.

Thus, there is a preponderance of evidence showing that standard neuroleptics, over the long-term, increase the likelihood that a person will become chronically ill. This outcome is particularly problematic when one considers that the drugs also cause a wide range of troubling side effects, including neuroleptic malignant syndrome, Parkinsonian symptoms, and tardive dyskinesia. Patients maintained on standard neuroleptics also have to worry about blindness, fatal blood clots, heat stroke, swollen breasts, leaking breasts, impotence, obesity, sexual dysfunction, blood disorders, painful skin rashes, seizures, diabetes, and early death [35—40].

Once all these factors are considered, it is hard to conclude that standard neuroleptics are therapeutically neutral. Instead, the research record shows harm done, and the record is consistent across nearly 50 years of research. [See "Timeline to Failure" in Appendix A.]

A better model: the selective use of neuroleptics

At the very least, this history argues that the best model of care would involve selective use of neuroleptics. The goal would be to minimize their use. Several investigators in Europe have developed programs based on that goal, and in every instance they have reported good results. In Switzerland, Ciompi established a house modeled on Mosher's Soteria Project, and in 1992 he concluded that first-episode patients treated with no or very low doses of medication "demonstrated

significantly better results" than patients treated conventionally [41]. In Sweden, Cullberg reported that 55% of first-episode patients treated in an experimental program were successfully off neuroleptics at the end of three years, and the others were being maintained on extremely low doses of chlorpromazine. Moreover, patients treated in this manner spent fewer days in the hospital than conventionally treated patients during the follow-up period [42,43]. Lehtinen and his colleagues in Finland now have five-year results from a study that involved treating first-episode patients without neuroleptics for the initial three weeks and then initiating drug treatment only when "absolutely necessary". At the end of five years, 37% of the experimental group had never been exposed to neuroleptics, and 88% had never been rehospitalized during the two-to-five-year follow-up period [44,45].

Those results are much better than any achieved in the US following the standard model of continual medication. Indeed, in his meta-analysis of such experimental studies, John Bola at the University of Southern California concluded that most "show better long-term outcomes for the unmedicated subjects" [23].

The atypicals: dawn of a new era?

Admittedly, the record of poor long-term results reviewed here was produced by standard neuroleptics. The poor outcomes may also reflect prescribing practices in the US that, until the late 1980s, involved putting patients on high dosages. The long-term research record for clozapine and other atypicals like risperidone and olanzapine has yet to be written.

One hopes that these newer drugs will lead to better outcomes, but there are reasons to be skeptical. As is now widely acknowledged, the clinical trials of the atypicals were biased by design against the old ones, and thus there is no compelling evidence that the new ones are truly better [46]. While the risk of tardive dyskinesia may be reduced with the atypicals, they bring their own set of new problems, such as an increased risk of obesity, hyperglycemia, diabetes, and pancreatitis [47—49]. Together, these side effects raise the concern that the atypicals regularly induce metabolic dysfunction of some kind, and thus their long-term use will lead to early death. The atypicals also have been shown to cause an increase in D2 receptors, just like the old ones do, and that is believed to be the mechanism that makes medicated patients more biologically vulnerable to psychosis [50].

Summary

The history of medicine is replete with examples of therapies that were eagerly embraced for a period and then later discarded as harmful. A scientific examination of the evidence is supposed to save us from such folly today. And science has in fact provided research data to guide prescribing practices. The evidence consistently reveals that maintaining all schizophrenia patients on antipsychotics produces poor long-term outcomes, and that there is a large group of patients — at least 40% of all people so diagnosed — who would do better if they were never exposed to neuroleptics, or, in the alternative, were encouraged to gradually withdraw from the drugs. (The percentage of patients diagnosed with schizoaffective disorder, or some milder form of psychosis, that could do well without the drugs is undoubtedly much higher.)

This conclusion is not a new one, either. Nearly 25 years ago, Jonathan Cole, one of the pioneering figures in psychopharmacology, published a paper provocatively titled "Maintenance Antipsychotic Therapy: Is the Cure Worse than the Disease?" After reviewing the research data, he concluded that "an attempt should be made to determine the feasibility of drug discontinuance in every patient" [17]. The evidence supported a standard of care that involved gradual withdrawal. The research record of neuroleptics since that time — most notably the WHO studies and the MRI study by investigators at the University of Pennsylvania — confirms the wisdom of his advice.

Indeed, Harding's long-term study shows that gradual withdrawal is an essential step on the path to full recovery. She found that one-third of the schizophrenia patients on the back wards of a Vermont state hospital in the 1950s were completely recovered thirty years later, and that this group shared one characteristic: all had long since stopped taking neuroleptics [51]. She concluded that it was a "myth" that patients must be on medication all their lives, and that in "reality it may be a small percentage who need medication indefinitely" [52].

Yet, in spite of all this evidence, today there is almost no discussion within psychiatry of adopting practices that would involve using neuroleptics in a selective manner, and that would integrate gradual withdrawal into the standard of care. Instead, psychiatry is moving in the opposite direction and prescribing antipsychotics to an ever larger patient population, including those said simply to be "at risk" of developing schizophrenia. While this expansion of the use of antipsychotics serves obvious financial interests, it is treatment that is certain to harm many.

Appendix A

A timeline for neuroleptics.

Preclinical
1883   Phenothiazines developed as synthetic dyes.
1934   USDA develops phenothiazines as insecticide.
1949   Phenothiazines shown to hinder rope-climbing abilities in rats.
1950   Rhone Poulenc synthesizes chlorpromazine, a phenothiazine, for use as an anesthetic.

Clinical history/standard neuroleptics
1954   Chlorpromazine, marketed in the US as Thorazine, found to induce symptoms of Parkinson's disease.
1955   Chlorpromazine said to induce symptoms similar to encephalitis lethargica.
1959   First reports of permanent motor dysfunction linked to neuroleptics, later named tardive dyskinesia.
1960   French physicians describe a potentially fatal toxic reaction to neuroleptics, later named neuroleptic malignant syndrome.
1962   California Mental Hygiene Department determines that chlorpromazine and other neuroleptics prolong hospitalization.
1963   Six-week NIMH collaborative study concludes that neuroleptics are safe and effective "antischizophrenic" drugs.
1964   Neuroleptics found to impair learning in animals and humans.
1965   One-year followup of NIMH collaborative study finds drug-treated patients more likely than placebo patients to be rehospitalized.
1968   In a drug withdrawal study, the NIMH finds that relapse rates rise in direct relation to dosage. The higher the dosage that patients are on before withdrawal, the higher the relapse rate.
1972   Tardive dyskinesia is said to resemble Huntington's disease, or "postencephalitic brain damage".
1974   Boston researchers report that relapse rates were lower in pre-neuroleptic era, and that drug-treated patients are more likely to be socially dependent.
1977   A NIMH study that randomizes schizophrenia patients into drug and non-drug arms reports that only 35% of the non-medicated patients relapsed within a year after discharge, compared to 45% of those treated with medication.
1978   California investigator Maurice Rappaport reports markedly superior three-year outcomes for patients treated without neuroleptics. Only 27% of the drug-free patients relapsed in the three years following discharge, compared to 62% of the medicated patients.
1978   Canadian researchers describe drug-induced changes in the brain that make a patient more vulnerable to relapse, which they dub "neuroleptic induced supersensitive psychosis".
1978   Neuroleptics found to cause 10% cellular loss in brains of rats.
1979   Prevalence of tardive dyskinesia in drug-treated patients is reported to range from 24% to 56%.
1979   Tardive dyskinesia found to be associated with cognitive impairment.
1979   Loren Mosher, chief of schizophrenia studies at the NIMH, reports superior one-year and two-year outcomes for Soteria patients treated without neuroleptics.
1980   NIMH researchers find an increase in "blunted effect" and "emotional withdrawal" in drug-treated patients who don't relapse, and that neuroleptics do not improve "social and role performance" in non-relapsers.
1982   Anticholinergic medications used to treat Parkinsonian symptoms induced by neuroleptics reported to cause cognitive impairment.
1985   Drug-induced akathisia is linked to suicide.
1985   Case reports link drug-induced akathisia to violent homicides.
1987   Tardive dyskinesia is linked to worsening of negative symptoms, gait difficulties, speech impairment, psychosocial deterioration, and memory deficits. They conclude it may be both a "motor and dementing disorder".
1992   World Health Organization reports that schizophrenia outcomes are much superior in poor countries, where only 16% of patients are kept continuously on neuroleptics. The WHO concludes that living in a developed nation is a "strong predictor" that a patient will never fully recover.

Appendix A (*continued*)

Clinical history/standard neuroleptics

1992   Researchers acknowledge that neuroleptics cause a recognizable pathology, which they name neuroleptic induced deficit syndrome. In addition to Parkinson's, akathisia, blunted emotions and tardive dyskinesia, patients treated with neuroleptics suffer from an increased incidence of blindness, fatal blood clots, arrhythmia, heat stroke, swollen breasts, leaking breasts, impotence, obesity, sexual dysfunction, blood disorders, skin rashes, seizures, and early death.

1994   Neuroleptics found to cause an increase in the volume of the caudate region in the brain.

1994   Harvard investigators report that schizophrenia outcomes in the US appear to have worsened over past 20 years, and are now no better than in first decades of 20th century.

1995   "Real world" relapse rates for schizophrenia patients treated with neuroleptics said to be above 80% in the two years following hospital discharge, which is much higher than in pre-neuroleptic era.

1995   "Quality of life" in drug-treated patients reported to be "very poor".

1998   MRI studies show that neuroleptics cause hypertrophy of the caudate, putamen and thalamus, with the increase "associated with *greater* severity of both negative and positive symptoms".

1998   Neuroleptic use is found to be associated with atrophy of cerebral cortex.

1998   Harvard researchers conclude that "oxidative stress" may be the process by which neuroleptics cause neuronal damage in the brain.

1998   Treatment with two or more neuroleptics is found to increase risk of early death.

2000   Neuroleptics linked to fatal blood clots.

2003   Atypicals linked to an increased risk of obesity, hyperglycemia, diabetes, and pancreatitis.

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