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CURRENT OPINION

The Harms of Antipsychotic Drugs: Evidence from Key Studies

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Abstract This safety assessment provides a detailed analysis of key studies and focuses on the six most widely used antipsychotic drugs. Lines of evidence include mechanisms of action, short-term treatment of psychosis, relapse prevention, early intervention in schizophrenia, long-term comparisons between first- and second-generation agents, and flexible treatment algorithms. Despite the diversity of study settings, several common features were seen. All the agents obstruct normal signaling through widely dispersed dopamine D_2 receptors. Treatment failure or psychosis relapse was the most frequent outcome in most key studies, ranging from 38 to 93%. High discontinuation rates caused most trials to fail to demonstrate a substantial treatment benefit, or difference from an active comparator. Assessment of harm to the extrapyramidal motor system was confounded because of extensive neurological impairment from previous antipsychotic drug treatment measured at baseline, abrupt discontinuation effects, and high rates of concomitant medications to manage drug adverse effects. Claims that second-generation antipsychotic drugs have safety advantages over classical neuroleptic drugs and prevent relapse were not supported in these key studies. The extent of injury to and impairment of multiple body systems caused by antipsychotic drugs shows the need for a scientific, clinical, and regulatory reappraisal of the appropriate use of these agents.

Key Points

We conducted a key studies analysis of the safety of the six most widely prescribed antipsychotic drugs in USA: quetiapine, risperidone, aripiprazole, olanzapine, haloperidol, and ziprasidone. Except for haloperidol, all are second-generation antipsychotic drugs.

The key studies examined antipsychotic drugs administered in different settings, such as for the acute treatment of psychosis, long-term treatment comparisons in schizophrenia, and flexible treatment approaches in older patients with varied mental disorders. One endpoint was treatment failure, defined as dropout for any reason from a clinical study while it was ongoing.

Treatment failure was the most frequent outcome across these diverse studies ranging from 38 to 93%. Drug effects for reducing psychosis were small. In these studies, the second-generation antipsychotic drugs did not demonstrate a better safety profile than the first-generation agents.

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1 Introduction

In 2016, the antipsychotic drug class included 57 unique molecular entities, grouped into six subclasses, based primarily on chemical structure [1]. The first antipsychotic, chlorpromazine, was approved in the USA in 1957, and the most recent, brexpiprazole, in 2015. The initial target symptoms for almost all of these agents are the manifestations of acute psychosis, notably hearing voices, hallucinations, delusions, paranoia, and other abnormal behaviors deemed to indicate a loss of touch with reality. With only a few exceptions, the antipsychotic drugs also share a common primary mechanism of action: they are antagonists of dopamine D_2 neuroreceptors [2]. Most antipsychotic drugs marketed since the 1990s also bind variously to other neuroreceptors, including subtypes of serotonin, histamine, α-adrenergic, and muscarinic receptors.

Over the 60 years that antipsychotic drugs have been used in clinical practice, they have been tested, approved, or used off-label for numerous other psychiatric disorders beyond the core indication of treatment for acute exacerbation of schizophrenia or schizoaffective disorder. Most agents in current use are also approved for prevention of relapse in schizophrenia; others have indications for various uses in bipolar disorder, treatment-resistant depression, and behavioral problems in autism. More controversial off-label use includes behavior control in elderly individuals with dementia, in psychosis in individuals with advanced Parkinson's disease, and to suppress conduct disorders in children. Some antipsychotic drugs cause sedation and are used off-label for that purpose. The D_2 receptors also mediate the vomit reflex, and anti-emetic drugs such as metoclopramide antagonize the same receptors as antipsychotic drugs and share many adverse effects.

Two basic strategies are available to provide a thorough assessment of a topic as complex as the harms of antipsychotic drugs. One choice is the comprehensive review, through either a meta-analysis or a systematic literature search using pre-specified review criteria. The strength of this approach is that it requires the investigator to examine and account for all or almost all the relevant scientific evidence. However, a meta-analysis is limited to comparing studies of similar designs, and most rely on the published data, which are often sparse. In addition, the relevant literature is extensive. A MEDLINE search for 'antipsychotic drugs' in June 2016 retrieved 116,046 publications; limiting the search to articles about clinical trials identified 14,445 entries; searching for review articles retrieved 12,916 publications. The alternative approach is to select a series of key studies, focus on the most widely used agents, and examine each key study in depth. The objective is not only to capture reasonable inferences, but also to explore what drug effects different types of scientific experiments could and could not detect. The limitation of this approach is selectivity and potential bias.

Table 1 Leading antipsychotic outpatient prescriptions in the USA, 2015

Drug name	Brand name	Prescriptions	Year approved
Quetiapine	Seroquel	19,788,379	1997
Risperidone	Risperdal	11,924,021	1993
Aripiprazole	Abilify	9,659,745	2002
Olanzapine	Zyprexa	6,605,620	1996
Haloperidol	Haldol	3,331,036	1967
Ziprasidone	Geodon	2,525,986	2001

Prescription data from the IMS Health Incorporated National Prescription Audit

Using the key studies approach, this analysis will examine the evidence from six lines of scientific evidence: (1) mechanisms of action; (2) short-term treatment of psychosis; (3) relapse prevention; (4) early psychosis in schizophrenia; (5) head-to-head comparisons between drugs; and (6) pragmatic treatment comparisons in older patients. For each perspective, we review a key study in depth, discuss strengths and limitations, and characterize exceptions and variations seen in similar studies for other drugs.

Drugs for the key studies analysis were selected on the basis of use in USA in 2015. Although 57 agents were approved globally at some point, current medical practice is dominated by the six drugs shown in Table 1. Note that the number 1 ranked drug, quetiapine, with 19.8 million prescriptions in 2015, accounts for almost twice as many prescriptions as the number 2 ranked drug, risperidone. All the leading agents are off-patent, and all except haloperidol are classified as 'atypical' or second-generation antipsychotic drugs. None were approved in the last 10 years.

2 Mechanisms of Action

Chlorpromazine, the first antipsychotic drug, spread into global clinical practice in the late 1950s based on empirical observations of its behavioral restraint of patients with psychosis [3, 4]. It predated the requirements for randomized clinical trials for regulatory approval, and was widely used before most neuroreceptors were characterized or fully understood. Thus, chlorpromazine and similar early antipsychotic drugs became a primary treatment for acute manifestations of schizophrenia before it was understood how or why these agents worked, or to what extent.

In 2016, the six antipsychotic drugs that are the primary focus of this analysis, and essentially all others as well, are reported to achieve their primary effects on psychosis through one primary mechanism: extensive occupancy and antagonism of the D_2 receptor [5]. The underlying science is extensive and integrated, linking chemical structure and receptor ligands in vitro [6], animal models in vivo [7], and positron emission tomography studies of receptor occupancy in humans [8–10]. The linkage between D_2 receptor antagonism and an effect on psychosis is so consistent that it has spawned a dopamine hypothesis of schizophrenia [11].

Not only were newer antipsychotic drugs designed specifically to bind to D_2 receptors, their molecular development was designed around substantial occupancy. Positron emission tomography studies in small numbers of patients indicated that risperidone at 2–6 mg/day resulted in 66–79% D_2 receptor occupancy; [12] olanzapine at 5–20 mg/day resulted in 43–80% occupancy [10]; and haloperidol 1–5 mg/day resulted in 53–88% receptor occupancy [13]. Then, scientific literature developed and advanced the theory that a therapeutic response might be seen at 65–80% D_2 receptor occupancy but extrapyramidal side effects and other harms began mostly at >80% receptor occupancy [14]. However, the idea that such a narrow band of receptor occupancy could be achieved in humans given the high degree of variation observed in the above studies in human subjects seems difficult to demonstrate. Furthermore, the receptor occupancy studies also show the effect varies directly with dose, and higher doses for some classical neuroleptic drugs, such as haloperidol at 10–12 mg, would result in nearly 100% receptor occupancy.

The drawback of blocking a large majority of D_2 receptors is that this pharmacological action may cause adverse effects in multiple body systems. This occurs because of the wide distribution and multiple functions of the D_2 receptor family [15]. For example, D_2 receptors are distributed through ten different structures in the brain including the striatum, nucleus accumbens, olfactory tubercle, substantia nigra, ventral tegmental area, hypothalamus, amygdala, and hippocampus. From a functional perspective, their role is pivotal in various locomotor functions, notably those mediated through the extrapyramidal motor system. However, other key functions include learning, memory, rewards, attention, impulse control, decision making, sleep, and regulation of food intake. Outside the central nervous system, D_2 receptors mediate prolactin secretion, aldosterone secretion, blood pressure, vasodilation, and gastrointestinal motility. Furthermore, D_2 receptors are embedded in complex signaling networks involving numerous other neurotransmitters and signaling proteins.

For antipsychotic drugs first marketed in the 1990s and later, in vitro and in vivo assays are available to map the effects on multiple neuroreceptors, and most agents were intended to antagonize more than D_2 receptors, most often serotonin (5-HT_2). For example, one in vitro radioreceptor binding study of olanzapine showed high affinity for D_1, D_2, and D_4 receptors, and multiple subtypes of 5-HT, α-adrenergic, histamine, and muscarinic receptors [6].

Insights into the effects of the D_2 receptor blockade could be seen in the early phase I studies of quetiapine to discover basic human pharmacokinetics. The US Food and Drug Administration (FDA) medical reviewer noted "Because healthy volunteers did not tolerate more than very low doses of the compound, pharmacokinetic studies were performed with volunteer schizophrenic patients." [16]. The tolerability problem with quetiapine occurred again 10 years later with the pharmacokinetic testing of the extended-release formulation. The plan was to start healthy volunteers at 150 mg and then titrate upward towards a likely therapeutic range of 400–600 mg/day. The FDA clinical review noted "Quetiapine at 150 mg was clinically intolerable in this sample of normal, healthy subjects." [17]. One problem was syncope and '"syncope-like" events, "resulting in a determination of absolute intolerability." The likely mechanism would be dysregulation of blood pressure and vascular control mediated by D_2 receptors. The next section will examine the effects in humans, beneficial and harmful, when drugs with these mechanisms of action are administered in randomized clinical trials.

3 Short-Term Treatment of Psychosis

The benchmark scientific evidence to establish the benefits of a new drug and assess harms is documented in the phase III randomized clinical trials required for marketing approval; in USA, these studies are called pivotal trials. This analysis will focus on the largest treatment effect reported in a pivotal trial for the most widely used agent, quetiapine, for its core indication for the treatment of acute psychosis in schizophrenia. This 6-week trial, quetiapine study 0013, compared five fixed doses of quetiapine with 12 mg daily of haloperidol, and a placebo group [16]. When quetiapine was being evaluated for market authorization in the mid-1990s, key features of the potential benefits and harms of the drug class were codified into three measurement scales, one scale for benefit and two scales to measure pre-specified harms.

To measure psychosis, the Brief Psychiatric Rating Scale (BPRS) provided 18 items including hostility, hallucinations, and unusual thought content. Each item was scaled from 1 to 7 with 1 being absent and 7 extremely

severe [18]. This scalar variable therefore ranged from 18, which indicated no symptoms in any category, to a maximum of 126. The inclusion criteria for study 0013 required hospitalized patients with BPRS score of >27. Changes in BPRS scores were the primary measure of benefit. A study linking BPRS changes to investigator assessments of improvement concluded that a 22–34% reduction in the BPRS score was "minimal improvement" and a 46–59% reduction was equivalent to "much improved" [19].

By the time quetiapine was being tested for market approval, it was well known that the antipsychotic drug mechanism of action of blocking D_2 receptors could result in substantial interference with the extrapyramidal motor system [3]. It produced symptoms basically similar to Parkinson's disease, a disorder in which dopamine-producing cells are progressively lost. For this trial, the extent of such impairment was measured by the Modified Simpson–Angus Scale (MSAS) [20]. The 10 items on the scale included symptoms such as drooling, tremor, abnormal gait, and various forms of muscle movement rigidity. The MSAS also included an item for akathisia, a symptom involving constant restlessness, agitation, and distress. Each item on the MSAS is scored 0–4 in severity, with a range of scores from 0 to 40. Scores of 12 and above are classified as a severe degree of movement disorder.

The most troubling, potentially disfiguring, and disabling complication of D_2 receptor blockade was the often irreversible involuntary movements called tardive dyskinesia. This adverse effect was assessed with the Abnormal Involuntary Movement Scale (AIMS) [21]. The symptoms include the tongue darting in and out of the mouth, purposeless finger movements, pelvic gyrations, and choreathetoid movements of entire limbs. The AIMS uses seven items, scored from 0 (not present) to 4 (severe). Tardive dyskinesia as a diagnosis was usually defined as at least two items scoring 2 or more, or at least one item scored as 3. An alternative definition is a total score of 3 or more.

Each of these three seemingly simple metrics is nevertheless challenging to interpret. Psychosis is a waxing and waning disorder with periods of improvement and exacerbations. Parkinsonism, the impaired motor control best captured by the Simpson–Angus scale, would typically have an acute onset when treatment begins [11] but might either remit with anti-Parkinson medication, or sometimes improve spontaneously. Tardive dyskinesia is the most complex of the three. A landmark report in 1980 [3] established a central feature of these disfiguring repetitive movements: the damage to motor control gradually increased with continued use and higher doses. Thus, these adverse effects differ from many others in being cumulative and dose dependent, with a prevalence of around 20–50% in non-elderly patients with years of prolonged exposure [3]. While many cases are irreversible and untreatable, in other patients, the dyskinesia gradually resolves on discontinuation of treatment [22]. A dose increase could, in some patients, lessen the symptoms, at least for a time, only to worsen in the long term. In another patient subgroup, tardive dyskinesia is masked during treatment and appears on discontinuation. This variability means that the scalar results of these measures in a clinical trial of antipsychotic drugs need to be interpreted carefully and in context.

The first step in quetiapine study 0013 was a screening evaluation to select patients meeting the study criteria, in particular a substantial degree of psychosis, measured by the BPRS [23]. Then, all psychotropic medication was abruptly discontinued for 7 days, including medications used to treat the adverse effects of prior antipsychotic drug treatment. Patients who improved in the absence of medication (BPRS score decrease of 20% or more) were excluded. Those who could not tolerate the abrupt medication halt were randomized before day 7.

At the end of the screening and washout period, quetiapine study 0013 enrolled 367 hospitalized patients in USA and Canada, and randomized them to one of the five quetiapine fixed doses, haloperidol, or placebo. The plan was to treat them for 6 weeks.

3.1 Study Population

The study population was patients with chronic schizophrenia, most with more than 10 years of previous treatment, and a majority with six or more previous hospitalizations. Only six patients had no previous exposure to antipsychotic drugs. The baseline safety assessment after all psychotropic drugs were discontinued revealed a patient population with severe motor impairment, presumably from previous treatment. On the MSAS, 46.9% showed a "severe degree" of movement disorder, a subset of the broader category of extrapyramidal symptoms (EPS) [24]. In addition, 34.3% had tardive dyskinesia, based on a score of 3 or higher on the AIMS at baseline. Finally, while the 'placebo' arm was a technically accurate description, it does not capture the likely responses of patients who forgo drug treatment entirely. It described a group of patients whose antipsychotic drugs and medication to manage side effects had been abruptly withdrawn.

Treatment failure is a basic and unambiguous measure of drug effect. It is the number and proportion of patients who discontinue medication during the clinical trial for any reason. The standard accounting for patient disposition contains subjective subcategories such as dropout for adverse effects, lack of efficacy, and patient choice. However, the underlying reasons for discontinuation are

likely a variable balance of benefits and harms. Some patients might discontinue a marginally beneficial drug treatment for lack of effect because they found it unpleasant to take, and judged the small benefits not worth it. A drug might produce a marked reduction in psychotic symptoms but leave the patient so impaired the treatment was judged worse than the disorder. Treatment failure can be calculated for most randomized clinical trials of almost any drug therapy, permitting its uniform use in trials with different endpoints and designs. However, in comparing treatment failure rates, attention must be paid to the duration of the study because attrition increases over time.

3.2 Pivotal Study Results

In quetiapine study 0013, treatment failure was the most frequent outcome. Overall, 59.4% of the patient population discontinued treatment before the 6-week final evaluation, even though the patients were hospitalized for at least the first 4 weeks [16], and therefore under close medical supervision. Among treatment failures, 30% discontinued by 2 weeks. For the quetiapine arms, treatment failure ranged from 69.2% for quetiapine 75 mg to 47.1% for 600 mg. Although the best result on the benefit measure for quetiapine was in the 150-mg arm, 56.3% still discontinued treatment.

Interpreting changes in psychosis with the BPRS at 6 weeks is problematical when treatment failure was the outcome for most patients. In this setting, neither of the standard methods of adjustment provides satisfying results. In the last observation carried forward (LOCF) adjustment, the last BPRS score before dropout is used for the 6-week comparison. This means most of the data are not genuine assessments at that point in time and assumes that treatment effects would be unchanged over time. The alternative, observed cases (OC), calculates the change in psychosis score only for those patients remaining on treatment at the trial's last assessment visit. This approach focuses only on empirical data and better captures the full effects of continued treatment. However, it raises questions about whether inferences to a broader population can be drawn, given that the majority of patients were treatment failures. In addition, the benefit of randomization is lost.

In the LOCF analysis, the numerically best result for quetiapine was in the 150-mg dose arm where the mean BPRS scores dropped from baseline 47.2 to 38.2, an 18% relative improvement ($p < 0.01$ vs. placebo). This 18% gain was smaller than the more subjective criterion of "minimal improvement" cited previously, which required a 22–34% relative reduction. The placebo group was largely unchanged, with a 1.7-point mean increase in BPRS scores. Using the OC outcome data, the quetiapine differences with placebo were not statistically significantly different at any dose [24]. With so many dropouts, the original 50-patient trial arms lacked the statistical power to discriminate between treatment groups. However, in numerical terms, the reduction in BPRS scores in all of the treatment arms for OC were more than twice the size of the LOCF results. This captures the phenomenon that mean scores are inevitably higher if they only include the patients who do well. A secondary endpoint was response rate, defined as a 30% improvement in BPRS scores "at any time" during the trial [23]. The best result for quetiapine was a 51% response rate for 300 mg, compared with 35% for the placebo group. The five different fixed doses of quetiapine also permitted assessment of a dose–response curve. In study 0013, no statistically significant dose response was seen for the four higher doses even though the highest dose, 750 mg, was five times higher than the lowest partially effective dose. The exception was the 75-mg dose, which produced changes in BPRS scores similar to the placebo arm.

Changes in the AIMS and MSAS during the trial were variable and hard to interpret given that: (1) a majority were not treated for even 6 weeks; (2) many had a pre-existing impairment; (3) other medications were frequently used to manage EPS; and (4) treating with either of the D_2 blockers might well reduce apparent tardive dyskinesia in the short term [22], especially among those in whom the condition appeared on abrupt treatment discontinuation. The published report abstract declared, "Quetiapine was no different from placebo across the dose range study regarding the incidence of extrapyramidal symptoms …" [23]. This conclusion is not valid because this trial design cannot provide a meaningful assessment of harms to the extrapyramidal motor system.

However, one safety concern detected in study 0013 set quetiapine apart from haloperidol and the placebo arm. Despite the limited period of exposure, quetiapine treatment was associated with rapid and substantial weight gain. In a median exposure of only about 4 weeks, clinically significant weight gain (>7% body weight) occurred in 11–17% of quetiapine patients, compared with 4% with haloperidol, and 6% with placebo.

Thus, study 0013, with a short duration, 59.4% dropout rate, no-dose response curve, and a modest 18% mean relative improvement in psychosis symptoms does not provide convincing evidence of the benefits of quetiapine, or proof of safety in the short-term treatment of exacerbations of schizophrenia. Three other pivotal trials of quetiapine conducted in the same period varied in design but provided similar or less favorable results [24]. Study 008 allowed for dose adjustment of quetiapine in two ranges (up to 250 mg/day or up to 750 mg/day). There was no statistically significant difference from placebo for the low-dose group by either LOCF or OC methods, even

though the largest treatment effect in study 0013 was in the 150-mg dose arm. The high-dose group, however, had a statistically significant benefit by both methods of adjusting for dropouts, and a 21.3% decline in the BPRS score. Treatment failure rates were again 50% or higher. Study 0012 compared twice-daily and three times-daily dosing regimens and had no placebo or active drug controls. Study 006 compared one variable quetiapine dose group and placebo; no statistically significant differences were seen in BPRS scores by either LOCF or OC methods, and treatment failure was similar to that reported in the other studies.

Ten years later, the short-term benefits of quetiapine in psychosis were again assessed in three pivotal trials conducted for marketing approval of an extended-release formulation. While an international 6-week trial (including Greece, Russia, India, and Bulgaria) provided evidence of treatment benefit, both trials conducted in USA and Canada failed to demonstrate a difference from placebo in any extended-release dose regimen tested as well as for the immediate-release active controls [17].

3.3 Results from Modified Designs

The question of whether quetiapine pivotal trials might not have captured the full benefits of treatment because of design limitations is answered in part in the pivotal trials for the newest antipsychotic, brexpiprazole, approved in 2015 [25]. In its mechanism, brexpiprazole resembles aripiprazole in being a partial agonist/antagonist of D_2 receptors, but still blocking normal signaling because of 80–90% receptor occupancy [26].

Three notable methodological differences with the quetiapine trials were identified. The brexpiprazole patient population was highly selected. It was limited to patients who had shown a good response to other antipsychotic drugs in the previous 12 months. In addition, patients with tardive dyskinesia or severe akathisia were excluded as well as anyone newly diagnosed with psychosis. Each treatment arm contained three times as many patients as the pivotal quetiapine trial, or approximately 150. This protected against loss of statistical power because of dropouts. Finally, the LOCF-OC conundrum was resolved through a new statistical approach, the mixed models repeated measures. Like quetiapine studies, the brexpiprazole pivotal trials were 6 weeks in duration and conducted in patients with long-term schizophrenia experiencing an exacerbation that would benefit from hospitalization.

Treatment failure occurred less frequently in the two brexpiprazole pivotal trials for schizophrenia, 29–40% across all treatment arms, compared with greater than 50% in the quetiapine pivotal trials. This could be a result of a more highly selected patient population already proven to respond to antipsychotic drugs, a more tolerable drug, hospitalization for the entire trial period, or some mixture of these factors.

However, the effects of brexpiprazole on psychosis were marginal [27]. Although most efficacy comparisons were statistically significant because of the different design, the changes on the Positive and Negative Symptom Scale (PANSS) measuring psychosis were small. In one trial, the PANSS scores for patients receiving brexpiprazole 2–4 mg only improved by 7% compared with placebo; in the other, by 12%. A more generous benefit measure identified responders, defined as improving 20% or more on the PANSS. Only 14% more patients receiving 2–4 mg responded, compared with placebo (51 vs. 37%). Additionally, the placebo group fared well in these trials. At 6 weeks, 29.9% had improved 50% or more without drug treatment, with a similar percentage difference with the brexpiprazole arms.

One can easily see why clinicians might overestimate the clinical benefits of brexpiprazole based on direct observation of patients. At 6 weeks, 44% of PANSS scores for brexpiprazole patients had improved 50% or more. However, 68% of this apparent benefit was duplicated in the placebo group, which also was not exposed to the harms of antipsychotic drugs.

4 Relapse Prevention

Whatever the results from the short-term treatment of psychosis, many textbooks and guidelines recommend continued treatment to prevent relapse. For example, a review of 66 studies of classical antipsychotic drugs concluded that if therapy were withdrawn, 56% would relapse over a median of 9.7 months, compared with just 16% for those continuing antipsychotic drugs [28]. A psychiatry textbook said 53–72% could be expected to relapse unless treated long term, while 16–23% would still relapse with continued treatment [11]. This review will focus on the relapse study for aripiprazole, the most recently approved of the selected drugs. As with the short-term trials, focusing on the measurement scales and definitions as well as data contribute to a balanced perspective.

The primary endpoint for the aripiprazole relapse trial was to compare the time to failure to maintain a response for a group of initially hospitalized patients, with 861 randomized to aripiprazole, and 433 to haloperidol [29]. The trial failed to show a difference with haloperidol in the time to failure to maintain a response, and therefore received only cursory review and disclosure in the FDA review for approval, which focused on the short-term trials. The FDA also was concerned because the results were from two pooled trials rather than a single study, concluding “There was no question the studies were negative”

[30]. Available data, however, provide insights into drug benefits and harms over longer periods of time.

From initial screening, the aripiprazole relapse trial was designed to select patients likely to do well on antipsychotic drug treatment. As in the quetiapine trials, the patients were selected from those hospitalized with acute exacerbations of schizophrenia after many years of prior exposure to antipsychotic drugs. At screening, investigators included only those with a previous history of responding to antipsychotic drugs. The population studied for relapse was further limited to those who responded to treatment during a 4-week initial hospitalization phase. The extent of psychosis was measured by the PANSS [29], and a response was defined as a 20% decline in PANSS score at any single point in time. While the definition of an initial response was modest, a relapse was defined as a much more severe episode of psychosis, for example, a clinical global impression of 'severely ill' or an adverse event of 'psychosis.'

At the end of the 4-week hospitalization phase, 31% of haloperidol and 28% of aripiprazole patients had already been excluded for failure to respond, intolerability, or other issues. By 52 weeks, a total of 73% of haloperidol patients either did not maintain a response or discontinued treatment, compared with 60% of those on aripiprazole ($p < 0.01$) [30].

A more detailed assessment of harms was complicated. As with quetiapine, the patient population had years of prior exposure to antipsychotic drugs at onset. Baseline evaluations were made after all psychotropic medications had been abruptly withdrawn. In addition, only mean values for the patient populations were reported, an uninterpretable number given how many patients discontinued. Nevertheless, the heavy use of concomitant medications to deal with parkinsonism and other complications make it clear that study patients had experienced extensive impairment of the extrapyramidal motor system. The study reported that 57% of haloperidol patients and 23% of aripiprazole patients received medication for parkinsonism or other EPS [29].

4.1 Other Relapse Studies

A 1-year relapse study of quetiapine also failed to show a difference with haloperidol [16]. However, a risperidone relapse study with a different design and a longer duration (a median of 354 days for risperidone) claimed a relapse benefit [31]. While the published study reported 25.4% relapsed on risperidone compared with 39.9% on haloperidol, treatment failure was again the principal result of antipsychotic drug therapy. At trial conclusion, 69.4% of risperidone patients and 92.6% of haloperidol patients had either relapsed, failed to respond, or discontinued for other reasons.

The impression that most patients will relapse unless treatment continues is not substantiated by these relapse trials, which show that 60–93% of patients randomized will either not show benefit at any point, relapse, or discontinue over approximately 1 year. This review differs from the cited relapse literature in that the outcome event totals include treatment failure and failure to respond.

5 Early Psychosis in Schizophrenia

Because the prevalence of tardive dyskinesia increases with cumulative exposure to D_2 blocking agents, a clearer perspective on harms comes through examining clinical trials in patients with little or no previous exposure. Patients experiencing an early or first episode of psychosis therefore make an ideal target population. A duration of 1 or 2 years would permit not only comparisons of benefits and harms over time, but also between comparator drugs selected. In the late 1990s, an early psychosis study was conducted comparing the second-generation risperidone with the classical neuroleptic haloperidol [32].

This risperidone early psychosis study, conducted in 11 countries, was structurally similar to the relapse studies described previously. The critical difference was to be eligible, patients had to have 12 weeks or less prior exposure to antipsychotic drugs. Another feature was a protocol calling for use of the lowest possible dose of both risperidone and haloperidol. The study was also larger ($n = 555$) and longer (minimum of 2 years) than most relapse studies. The investigators and sponsor Janssen Pharmaceuticals hypothesized that patients getting the second-generation risperidone and low doses would experience less EPS, would therefore be more willing to continue treatment, and as a result experience fewer relapses [32].

The measurement of harms in the early psychosis study provides one of the most unbiased estimates of EPS caused by antipsychotic drugs occupying D_2 receptors for sustained periods of time. At trial endpoint (median exposure 206 days), 8.3% of the risperidone group and 13.4% of haloperidol had tardive dyskinesia ($p = 0.05$). Other adverse effects on the motor system were also illustrated by the extensive medication required to manage the consequences of D_2 blockade (Table 2). The table also makes clear that schizophrenia was being treated not with a single antipsychotic drug but with a cocktail of drugs to treat drug adverse effects, even under the controlled circumstances of a clinical trial.

In this patient population, treatment failure occurred somewhat less frequently than in the relapse studies: 39.3% discontinued, with no statistically significant differences between the first- and second-generation antipsychotic drugs. A large majority in both treatment groups either

Table 2 Concomitant medications, early psychosis study Data from Schooler et al. [32]

Medication	Adverse effect	Risperidone (%)	Haloperidol (%)
Anticholinergic agents	Parkinsonism	41.7	49.5
Benzodiazepines	Agitation, EPS	54.7	61.7
β-Blockers	Akathisia	5.0	10.5

EPS extrapyramidal symptoms

relapsed or failed to respond with a 20% reduction in PANSS, 59% in the risperidone arm, and 67% for haloperidol [32].

In addition, evidence of new adverse effects emerged for risperidone, the second-generation agent. Risperidone patients were more likely to experience abnormal prolactin levels (a sex hormone mediated by the D_2 receptor), and 14 (5%) risperidone patients reported direct effects such as gynecomastia and galactorrhea. Similar events were seen in a single haloperidol patient (0.3%).

The early psychosis trial also provided a fresh perspective on weight gain associated with antipsychotic drugs. Weight gain had been associated with the first antipsychotic drug, chlorpromazine, since the early 1970s [33]. In this study, patients in both groups gained weight steadily throughout the trial, with the risperidone group gaining a mean of 16.5 lb and haloperidol patients, 14.3 lb.

This systematic comparison showed that the extensive adverse effects on the extrapyramidal motor system seen for classical neuroleptic drugs was also occurring with a leading second-generation agent in patients with little previous exposure, and outcomes remained poor with relapses, discontinuation, and failure to demonstrate a benefit. However, a different type of study would be required to provide head-to-head comparisons of the leading second-generation agents.

An open-label, industry-funded European clinical trial in early psychosis illustrated the importance of blinding [34]. It enrolled 498 first-episode psychosis patients and randomized them to open-label treatment comparing haloperidol with four second-generation agents, aripiprazole, olanzapine, quetiapine, and risperidone. In the trial, 72% of the haloperidol group discontinued in a median of 2 weeks. The inference of such rapid dropout is that the older drug was rejected by patients and participating physicians. Discontinuation rates (or treatment failure) were lower (33–53%) in the second-generation drug arms, and the duration of treatment was longer.

6 Antipsychotic Drugs Compared

The Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) was funded by the US National Institutes of Health with the objective of comparing four second-generation antipsychotic drugs in widespread use with a typical first-generation drug, specifically perphenazine [35]. The investigation plan noted, "We hypothesize that treatment with the newer atypical antipsychotic drugs is associated with greater long term effectiveness and tolerability than treatment with perphenazine" [36]. With 1493 patients randomized, it was one of the largest randomized clinical trials of antipsychotic drugs, and with an 18-month duration, one of the longer ones. Investigators were given substantial flexibility in selecting the dose. With no manufacturer involvement in the design, the investigators could avoid allegations that comparator drugs were used sub-optimally. To capture both benefits and harms, the investigators selected treatment failure as the primary endpoint. The study design had two limitations. As with most recent antipsychotic drug trials (except in early psychosis), the patients randomized had extensive prior exposure to other such drugs. The CATIE patient population had been taking antipsychotic drugs for a mean of 14.4 years, and 85% were unemployed, suggesting most were substantially impaired by illness or previous drug treatment. In addition, because prior medications were gradually discontinued, some patients might fare worse than before if randomized to a different, possibly less effective or tolerable medication.

Over the 18-month trial period, treatment failure occurred for 72% of all patients, with few differences among the five study drugs [35]. Olanzapine showed the longest median time to discontinuation (9.2 months) and the smallest proportion discontinuing in treatment failure (64%). The numerically worst result was quetiapine, with a median time to discontinuation of just 4.6 months, with 82% of patients discontinuing. CATIE also measured the duration of successful treatment, an endpoint that required that the patient be only mildly or moderately ill, and improved two points from baseline on the 7-point Clinical Global Impression scale. The median duration of successful treatment was 1 month for four of the five drugs, and 3 months for olanzapine.

Because of the systematic use of measurement scales and detailed disclosure of results [35, 37], the CATIE trial also provided insights into the extent of adverse effects on the extrapyramidal motor system, both from prior exposure to antipsychotic drugs, and from the study drugs. At baseline, 35% of the enrolled patients had parkinsonism measured using the Simson–Angus Scale. In addition, 31% showed evidence of either borderline or full tardive

dyskinesia using the AIMS. For this trial, akathisia was measured separately from other EPS, with 23% meeting the criteria using the Barnes Akathisia Rating Scale [37]. At the trial conclusion, the investigators calculated the 12-month event rates only among those patients free of the specific EPS adverse effects at baseline. They reported finding no statistically significant differences between the four second-generation agents. The covariate-adjusted, 12-month event rate for parkinsonism was 37–44%; for akathisia, 35%; and for tardive dyskinesia, 8.3–11.8%. CATIE not only provided evidence that the enrolled patients had substantial impairment of the extrapyramidal motor system at baseline, but also demonstrated that these adverse effects continued to occur in the subset of patients not already showing previous injury, a result similar to what had been observed for first-generation antipsychotic drugs many years earlier [3].

6.1 Other Harms Assessed

CATIE also systematically surveyed other possible harms using a questionnaire rather than relying on information spontaneously volunteered by participating patients, finding 66.7% of patients experienced moderate or severe harms [36]. Sexual impairment was reported by 19–27% of patients on treatment. Another 24–30% of patients reported hypersomnia and other sedating effects. In addition, 20–24% of patients reported anticholinergic effects such as urinary hesitancy, constipation, and dry mouth. Smaller percentages reported incontinence and nocturia, menstrual irregularities, insomnia, and orthostatic hypotension. This trial also provides insight into the extent to which adverse effects of drugs are understated by the standard practice of relying on spontaneously volunteered adverse effects rather than using a questionnaire or checklist. In CATIE, spontaneously volunteered events captured only 51% of those ascertained by questionnaire.

Substantial differences between the study drugs as well as variations in results on the same drug emerged from the assessment of weight gain, an adverse effect shared by both first- and second-generation antipsychotic drugs. The largest effects on weight were reported for olanzapine: 30% of patients reported clinically significant weight gain, with patients gaining a mean of 2 lb a month. Ziprasidone showed the smallest, with 7% of patients reporting clinically significant weight gain. Among patients taking quetiapine, risperidone, and perphenazine, 12–14% had clinically significant weight gain.

The unexpected but convincing finding when CATIE was reported in 2005 was that the study did not detect any advantage for second-generation agents measured as either benefit or harms. These findings were confirmed in two other comparative trials, a US Veterans Administration Cooperative Study comparing olanzapine and haloperidol, completed in 2003 [38], and the British National Health Service study, CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study), reported in 2006, comparing 13 first-generation with four second-generation antipsychotic drugs [39]. The extent of movement disorders with long-term treatment was measured in a systematic assessment of 209 Danish institutionalized patients, finding 68% were impaired [40]. It reported that 28.4% had tardive dyskinesia, 56.2% had parkinsonism, 4.6% had akathisia, and 5.7% had tardive dystonia. The Danish study also detected no difference in impairment between those with a medication history of first-generation antipsychotic drugs, second-generation antipsychotic drugs, or both.

7 Pragmatic Treatment Comparisons

An additional question is whether an experienced practitioner can achieve substantially better results than seen in the clinical trials reported in this review. A physician initiating treatment can adjust doses, switch medications, and freely use concomitant medications to manage side effects. Furthermore, the trials in this review were conducted in a narrowly defined population with chronic schizophrenia or early psychosis, with most patients in their late 20s or 30s. Antipsychotic drugs are also used in elderly patients with dementia, patients with bipolar disorder, post-traumatic stress disorder, and treatment-resistant depression, and in children with autism or conduct disorders.

Many of these issues were addressed in a large pragmatic trial of atypical antipsychotic drugs in older patients that was funded by the US National Institutes of Health [41]. It compared the four most widely used antipsychotic drugs, quetiapine, risperidone, aripiprazole, and olanzapine. The patient population also differed from the major trials in that participants had to be over 40 years of age; the mean age enrolled was 67 years. The patients had to have some form of psychosis, but widely varied underlying illnesses were allowed. In the trial, 61% of the patients were being treated for indications such as dementia, depression, and post-traumatic stress disorder. While the underlying diagnoses were diverse, the population had substantial psychosis at baseline, with a mean BPRS score of 40.1. The novel feature, however, was that the patients and physicians were allowed substantial choice among the agents. Each participant could accept randomization to one of all four drugs, or veto one or two of them. Only 16.6% of patients agreed to randomization including four drugs. In addition, each physician had complete flexibility in

adjusting the dose for each patient and was allowed to change it at any time. The trial enrolled 332 patients, and was intended to provide 2 years of follow-up.

The older patients' trial detected no measurable effects of treatment on the underlying psychopathology measured by the BPRS, whether comparing drugs, changes over time, or BPRS subscales. Treatment failure in these older adults was more frequent than in the CATIE patient population, ranging from 78.6% for quetiapine to 81.5% on aripiprazole. The median time to treatment failure was 26 weeks, but 25% discontinued in 6 weeks or less. While quetiapine appeared to have the lowest rate of treatment failure, it was discontinued early by the data safety and monitoring board for an unexpectedly high incidence of serious adverse events.

While some argue that the rigid clinical trial designs for marketing approval underestimate true treatment benefits in clinical practice, an alternative theory is that they may overstate benefits. Marketing approval trials are designed and conducted by manufacturers with a major financial interest in the outcome. Patients most likely to benefit can be selected through use of inclusion and exclusion criteria. Comparator drugs may be administered sub-optimally with doses that are too high or insufficient. None of the trials in this review had a truly untreated group of patients free of abrupt discontinuation effects and with psychosocial interventions to manage their disorder without antipsychotic drugs. Two investigators in this flexible pragmatic trial discussed the failure to equal or exceed the expected benefits from published studies in an accompanying editorial, "Atypical Antipsychotics for Older Adults: Are They Safe and Effective as We Once Thought?" [42]. The answer to the title question was negative. They wrote, "Thus, the overall results of our study suggested that the commonly used atypical antipsychotic drugs were neither safe nor effective in the treatment of psychotic disorders in middle-aged and older adults."

8 Conclusions and Comments

This reappraisal of key studies illustrates the numerous drawbacks of antipsychotic drugs. Treatment failure occurs in a substantial majority of patients and failure rates increase with duration of therapy. Antipsychotic drugs impair multiple body systems, including the extrapyramidal motor system, glycemic metabolism, vascular control, and sexual function. When beneficial effects on psychosis are measured, the mean improvements in psychosis are minimal, on the order of 20%, accomplished only with co-administration of other psychotropic medications, and rarely sustained over time. The findings of substantial harms are robust, and seen in studies of short and long duration, with first- and second-generation agents, and with rigid protocols, and those providing treatment flexibility.

However, this review has limitations to consider. From a vast literature assembled over 60 years, we focus on 10 studies of mechanism of action, 5 clinical trials reviewed in depth, and a further 16 clinical trials examined more briefly. This review does not systematically analyze differences between antipsychotic drugs, which vary despite all depending on high levels of D_2 receptor occupancy. Antipsychotic drugs vary in chemical structure, in duration of occupancy and affinity for D_2 receptors, and bind various other neuroreceptors; they cause different degrees of sedation. We excluded clozapine, with a different benefit-and-risk profile, and lithium, which is classified as an antipsychotic drug but has a different mechanism of action and indications. The harms evaluated are limited to only those reported in reasonable detail in the key studies in this review. However, other types of studies associate antipsychotic treatment with cognitive impairment and decline, cardiovascular adverse effects, and increased mortality. The review also focused primarily on the core patient population with schizophrenia or psychosis and did not examine its use to control behavior in children, elderly individuals with dementia, and in patients with treatment-resistant depression.

Most documented harms from antipsychotic drugs appear to result from their primary mechanism of action, blocking normal signaling through D_2 receptors. These receptors are so widely distributed throughout the brain and central and peripheral nervous systems, mediate so many types of basic functions, and interact with so many other neurotransmitters that therapeutic drugs that obstruct their normal function place patients at high risk of harms, a risk that increases with continued exposure. It is time for regulators and the medical community to conduct an independent scientific and clinical reassessment of the appropriate use of antipsychotic drugs given the now thoroughly documented capacity to harm. Research is also needed into alternative approaches to treating psychosis that do not depend on extensive occupancy of D_2 receptors.

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Compliance with Ethical Standards

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Conflict of interest Thomas J. Moore and Curt D. Furberg declare that they have no conflicts of interest relevant to this study.

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