Antipsychotic Drugs: A Concise Review of History, Classification, Indications, Mechanism, Efficacy, Side Effects, Dosing, and Clinical Application

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The introduction of the first antipsychotic drug, chlorpromazine, was a milestone for psychiatry. The authors review the history, classification, indications, mechanism, efficacy, side effects, dosing, drug initiation, switching, and other practical issues and questions related to antipsychotics. Classifications such as first-generation/typical versus second-generation/atypical antipsychotics are neither valid nor useful; these agents should be described according to the Neuroscience-based Nomenclature (NbN). Antipsychotic drugs are not specific for treating schizophrenia. They reduce psychosis regardless of the underlying diagnosis, and they go beyond nonspecific sedation. All currently available antipsychotic drugs are dopamine blockers or dopamine partial agonists. In schizophrenia, effect sizes for relapse prevention are larger than for acute treatment. A major unresolved problem is the implausible increase in placebo response in antipsychotic drug trials over the decades. Differences in side effects, which can be objectively measured, such as weight gain, are less equivocal than differences in rating-scale-measured (subjective) efficacy. The criteria for choosing among antipsychotics are mainly pragmatic and include factors such as available formulations, metabolism, half-life, efficacy, and side effects in previous illness episodes. Plasma levels help to detect nonadherence, and once-daily dosing at night (which is possible with many antipsychotics) and long-acting injectable formulations are useful when adherence is a problem. Dose-response curves for both acute treatment and relapse prevention follow a hyperbolic pattern, with maximally efficacious average dosages for schizophrenia of around 5 mg/day risperidone equivalents. Computer apps facilitating the choice between drugs are available. Future drug development should include pharmacogenetics and focus on drugs for specific aspects of psychosis.

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The introduction of the first antipsychotic drug, chlorpromazine, was a game changer for psychiatry. Nevertheless, this drug class is controversial due to side effects and a general negative attitude toward pharmacological treatment of mental disorders among many lay people who favor psychotherapy even for schizophrenia (1), although as monotherapy it is not effective. This article summarizes essential facts about antipsychotics. Most statements are based on findings in schizophrenia, where most studies have been conducted. Antipsychotics are not exclusively used for the treatment of schizophrenia, however; they work against psychotic symptoms regardless of their origin.

HISTORY

In the early 1950s, the French navy doctor Henri Laborit, a man of many talents who was later suggested for the Nobel prize (2), tested chlorpromazine (synthesized by Paul Charpentier, at the chemical and pharmaceutical company Rhône-Poulenc) to explore whether it could improve anesthesia in soldiers. By chance, he discovered that patients exhibited a state of indifference after receiving it, which might also be beneficial for psychiatric patients (3). Jean Delay and Pierre Deniker, in Paris, picked up on his observation and found chlorpromazine to indeed be effective. They called it a "neuroleptic," a vague term intended to signify a "taking hold" of the nervous system (ancient Greek *lepsis*=seizure, capture, grasp). Another term for chlorpromazine and subsequent antipsychotics was "major tranquilizers," indicating their use for severe disorders, in contrast to "minor tranquilizers" like meprobamate, which were used primarily for milder conditions, such as anxiety. As neither term was entirely fitting, the terms neuroleptic and major tranquilizer were later abandoned in favor of the term "antipsychotic," which describes their main effect.

The discovery was revolutionary because until then, aside from insulin coma with limited efficacy in some patients and malaria therapies for neurosyphilis, there was no effective pharmacological treatment of psychosis. Chlorpromazine and subsequent antipsychotics helped to empty out inpatient

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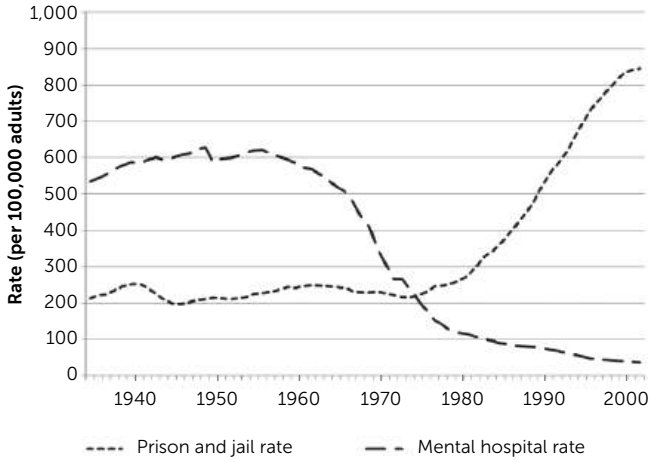
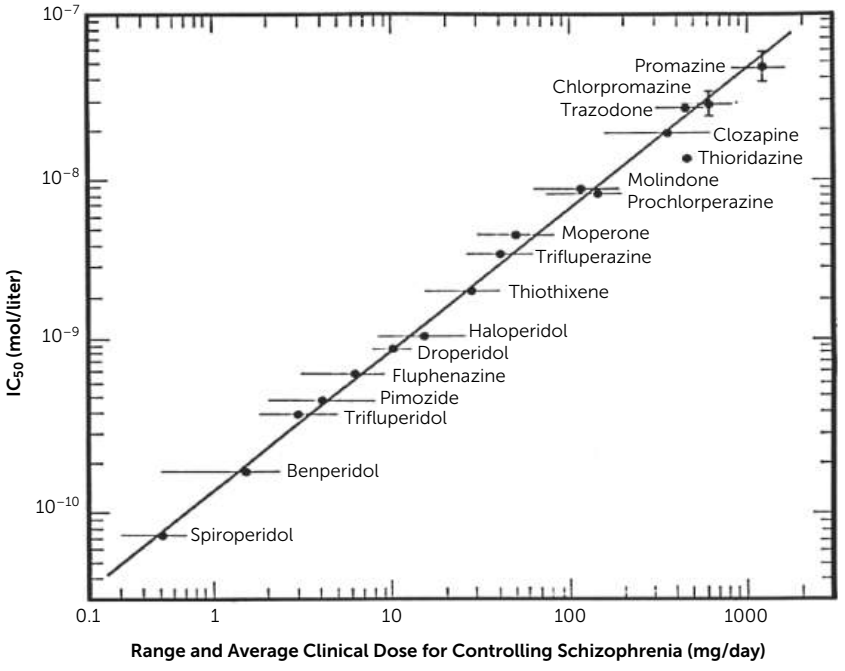
FIGURE 1. Reduction in mental hospitalization rates and increase in incarceration rates in the United States[a]



[a] Modified and reproduced with permission from reference 5 (B.E. Harcourt, An institutionalization effect: the impact of mental hospitalization and imprisonment on homicide in the United States, 1934–2001, Journal of Legal Studies 2011, vol. 39, pp. 39–83).

FIGURE 2. Clinically used antipsychotic doses and dopamine binding[a]



[a] Reproduced with permission from reference 12 (P. Seeman, Dopamine receptors and the dopamine hypothesis of schizophrenia, Synapse, 1987, vol. 1, pp 133–152).

wards in psychiatric hospitals. In the United States, hospital beds were drastically reduced from the 1950s to the 1980s (4). Most people with schizophrenia are now treated as outpatients, with occasional short hospitalizations, in contrast to lifetime hospitalization. However, this deinstitutionalization is not without criticism, as many patients became homeless or incarcerated in the absence of sufficient ambulatory care (Figure 1).

Arvid Carlsson (together with Paul Greengard and Eric Kandel) received the Nobel Prize in Medicine in 2000 for the insights he gained into the dopamine system in the 1960s. In 1968, Philip May and colleagues showed that antipsychotic drugs and ECT were superior to psychodynamic therapy (6, 7). Phil Seeman and colleagues (8) found that clinical efficacy depended on the affinity of a given antipsychotic to dopamine receptors, underlining that dopamine binding is the core target of antipsychotics. In 1958, Belgian pharmacologist Paul Janssen developed haloperidol, which produced many extrapyramidal side effects but few autonomic side effects (e.g., tachycardia, hypotension) and little sedation. Therefore, in contrast to thioridazine, also licensed in 1958, which was virtually free of extrapyramidal side effects and thus clearly an "atypical" antipsychotic, it could be given in very high doses. Indeed, in the 1970s, high haloperidol dosages of up to 100 mg/day were given under the incorrect assumption that "more helps more" (9, 10). Today, it is known that the maximum effective dosage of haloperidol, on average, is approximately 6.3 mg/day (11) (Figure 2).

Clozapine sparked a scientific debate between the German psychiatrists Hanns Hippius, who was involved in its development in the 1960s (13, 14), and Hans-Joachim Haase. The latter had posited in the 1950s that there could be no antipsychotic effect without extrapyramidal motor side effects (15). As clozapine contradicted this point of view, ironically clozapine's trade name in Germany became "Leponex." It was a play on words: The Latin word "lepus" means "Hase" (rabbit) in German. Thus, Lepon(-)ex means "(Hans-Joachim) Haase out." However, Haase deserves credit for his "neuroleptic threshold" method, which posits that optimal efficacy of antipsychotics is achieved once patients experience minimal extrapyramidal side effects (16, 17). This theory was substantiated by multiple medical theses (17) and in a landmark study by McEvoy et al. (18), who found that 3.4 mg/day of haloperidol was as effective as dosages up to 10 times higher.

Clozapine was taken off the market in the early 1970s due to deaths from agranulocytosis. In a few countries, including Germany, it was quickly reintroduced after protests (13). When John Kane, Herbert Meltzer, and others observed that switching their patients to other medications was often not possible because they relapsed and failed to respond to alternative medications (19), they conducted a randomized controlled trial, which demonstrated clozapine's superior efficacy in patients with highly treatment-resistant illness (20). This led to the reintroduction of clozapine in the United States and the development of numerous new antipsychotics, although none achieved the efficacy of clozapine, and not all of them improved negative symptoms more than did haloperidol or

TABLE 1. Neuroscience-based Nomenclature (NbN): drugs for psychosis[a]

Former Terminology	NbN—Pharmacology Based Nomenclature		Drugs
	Pharmacological Domain	Mode of Action	
First-generation antipsychotic	Dopamine	Antagonist (D_2)	Fluphenazine, haloperidol, perphenazine, pimozide, sulpiride, zuclopenthixol, loxapine
	Dopamine, serotonin	Antagonist (D_2, 5-HT_2)	Chlorpromazine, flupentixol, pipotiazine, thioridazine, trifluoperazine
Second-generation antipsychotic	Dopamine	Antagonist (D_2)	Amisulpride (at low dose presynaptic dopamine antagonist)
	Serotonin, dopamine	Antagonist (5-HT_2, D_2)	Asenapine, blonanserin, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, perospirone, risperidone, sertindole, ziprasidone, zotepine
	Dopamine, norepinephrine, serotonin	Antagonist (5-HT_2, alpha-1, alpha-2, D_2)	Clozapine, quetiapine
	Dopamine, serotonin	Partial agonist (D_2, 5-HT_{1A}) and antagonist (5-HT_{2A})	Aripiprazole, brexpiprazole, cariprazine
	Serotonin	Antagonist	Pimavanserin[b]

[a] Modified and reproduced with permission from https://nbn2r.com/.
[b] Approved only for hallucinations and delusions associated with Parkinson's disease psychosis.

were free of extrapyramidal motor side effects (21–30). Meta-analyses had shown by the end of the 1990s that not all new drugs are better than old ones (21–23), and the large, industry-independent Clinical Antipsychotic Trials of Intervention Effectiveness study confirmed this notion (31). Originally called "atypical" antipsychotics, a partly marketing-driven term, these newer antipsychotics were later referred to as second-generation antipsychotics. As a group, they significantly improved the risk of extrapyramidal motor side effects and tardive dyskinesia (32), but they brought new issues, such as weight gain and associated metabolic changes (33, 34).

After the development of the first partial dopamine agonist, aripiprazole, numerous other mechanisms of action were tested. In particular, substances acting on the glutamate system were considered a promising target, but large development programs on bitopertin (35, 36) and LY2140023 (37, 38) failed. Thus, all currently licensed antipsychotics primarily act through the dopaminergic system, which significantly limits treatment options. However, with the discovery of xanomeline, the first antipsychotic that does not primarily act through the dopaminergic system, a drug with a new mechanism is within reach (see below).

CLASSIFICATION

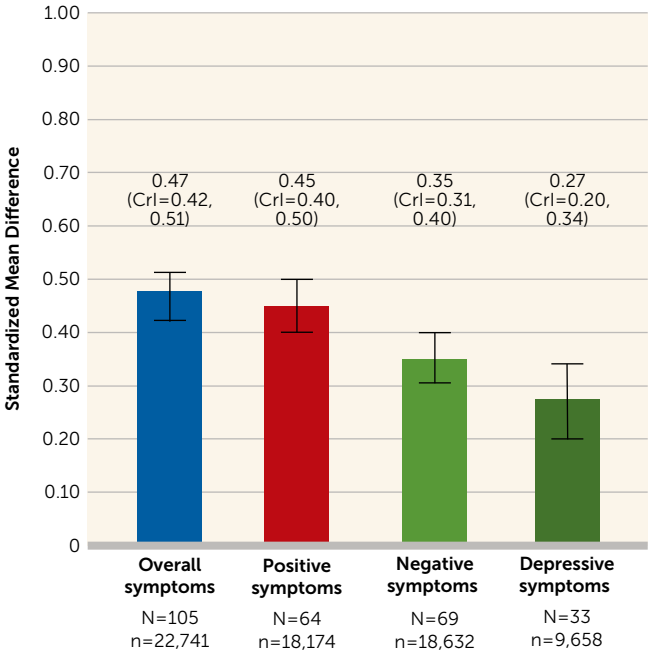
Previous classifications of antipsychotics by chemical structure or into high-potency/low-potency antipsychotics or "typical/first-generation" versus "atypical/second-generation" are not valid (39). Notably, low-potency antipsychotics are not less efficacious than high-potency ones (40), only higher dosages are needed. Not all second-generation antipsychotics are free of extrapyramidal side effects (e.g., risperidone), while some first-generation antipsychotics virtually are (e.g., thioridazine) (26). The current classification is the Neuroscience-based Nomenclature (NbN), which categorizes psychotropic drugs by their main assumed mechanism of action (Table 1). It has been accepted by major organizations, including the American College of Neuropsychopharmacology, the European College of Neuropsychopharmacology, and the International College of Neuropsychopharmacology, and many psychiatric journals (39). A more refined approach based on in vitro binding profiles has also recently been proposed (41). NbN is better than the previous classifications, but the problem is that we still do not know the *exact* mechanisms of action of these drugs and to what extent their effects on various receptors contribute to the antipsychotic effects. More systematic reviews of the preclinical literature (42) are needed to help to better understand drug mechanisms and evaluate the evidence for any given mechanism, thereby facilitating drug development, and ultimately helping to bridge the still wide gap between preclinical and clinical research.

INDICATIONS

The main indication for the use of antipsychotics is schizophrenia. However, these medications also work in mania, and some have an indication for bipolar or psychotic depression (43, 44), agitation, psychosis in dementia (brexpiprazole) (45), and irritability in autism (aripiprazole, risperidone) (46). There is also considerable off-label use, with varying evidence to support their use for generalized anxiety disorder (quetiapine) (47), insomnia (sedating antipsychotics), and Tourette's syndrome (48) and as add-ons to serotonergic antidepressants for obsessive-compulsive disorder (49). The official indications differ between countries so that the respective regulations must be followed. Three issues are worthwhile mentioning:

1. Antipsychotics are not "anti-schizophrenia" drugs; they work for psychosis irrespective of the cause (50).
2. The names of the drug classes do not necessarily describe what they are effective for. For example, in a historically

FIGURE 3. Efficacy of antipsychotic drugs versus placebo in different domains of schizophrenia[a]



[a] Data are from reference 57. CrI=credible interval; N=number of studies; n=number of participants.

pivotal study (51), chlorpromazine was effective not only for schizophrenia but also for depression. Similarly, antidepressants are not only efficacious for depression but are at least as efficacious, if not more efficacious, for anxiety disorders. Quetiapine is efficacious in major depressive disorder (44) and bipolar depression (43), and it ranks relatively low in efficacy for schizophrenia (26).

3. Antipsychotics are not simply sedatives because the efficacy effect size of antipsychotic over barbiturates is about the same as over placebo (52).

MECHANISM OF ACTION

For all currently available antipsychotics, a blockade of postsynaptic dopamine receptors or partial dopamine agonism is assumed to be the primary mechanism of action. The question of how an overall lower occurrence of extrapyramidal motor side effects with second-generation antipsychotics can be explained has not been conclusively clarified. Important theories include stronger binding to serotonin receptors than to dopamine receptors (53), partial agonism (e.g., aripiprazole), mesolimbic selectivity (e.g., amisulpride) (54), loose binding (55), and simultaneous anticholinergic effects (e.g., clozapine). Effects on receptors other than dopamine or serotonin are responsible for many side effects of antipsychotic drugs, such as sedation and weight gain (blockade of histamine receptors) as well as postural hypotension (alpha receptor blockade). Another crucial question remains as to how exactly antipsychotic drugs exercise their effects on symptoms. They are generally thought to mainly alleviate positive symptoms. However, in early trials (56) and meta-analyses of trials in acutely ill patients, improvements in positive symptoms were paralleled by improvements in negative symptoms and depression, even with the dopamine blocker haloperidol (24, 57) (Figure 3). One explanation is that reductions of negative symptoms in acutely ill patients are secondary to improvements in positive symptoms. Thus, patients who are preoccupied by their hallucinations and delusions may withdraw socially, and social withdrawal is part of negative symptoms. If the positive symptoms are successfully treated, such negative symptoms may improve in parallel. However, one study using data from 4,397 patients compared several theoretical models as to how antipsychotics may work with general equation modeling. It rather suggested that one central mechanism mediates the improvement not only of positive symptoms but also of negative symptoms and affective symptoms (58).

Finally, antipsychotic drugs with a primarily cholinergic rather than dopaminergic mechanism of action are in sight. Xanomeline-trospium could be the first one available, as there have now been three positive phase 3 trials with solid effect sizes compared with placebo (59). However, ultimately the cholinergic effects are thought to link back into dopamine (detailed reviews are provided by Paul et al. [60] and McCutcheon et al. [61]). Nevertheless, the new primary mechanism may open new avenues for subgroups of patients and for combining antipsychotics, for which there was previously no good rationale since the primary mechanism of all available drugs was dopaminergic (62).

DRUG EFFICACY IN THE ACUTE PHASE

It is undisputed that antipsychotic drugs are efficacious for the acute treatment of schizophrenia (26, 63) and bipolar mania (64). Nevertheless, the size of the effect in the acute phase is debated.

A pivotal early study funded by the National Institute of Mental Health (NIMH) found a large standardized mean difference of approximately 0.8 for five phenothiazines compared with placebo, with 61% of the drug-treated and 22% of the placebo-treated patients at least much improved (65). In contrast, the average effect size of all studies is 0.47, and only 23% of drug-treated versus 14% of placebo-treated patients are much improved (57). Chronicity of illness, which is a known effect moderator (66), plays a role in the difference because approximately 50% of the participants in the NIMH study were in their first episode and/or were antipsychotic naive, while participants in modern studies usually have chronic illness with an exacerbation of their positive symptoms. Indeed, a single-arm meta-analysis of studies in first-episode patients found higher drug response (50% were at least much improved and 80% were at least minimally improved [67]) than in chronic patients (23% much improved and 51% at least minimally improved). However, none of the first-episode studies were placebo controlled

(the NIMH study was not included because only 50% of patients were in their first episode) (65). We recently found that drug effects are smaller in placebo-controlled trials than in head-to-head trials, which was eventually mediated by higher dropout rates in the former (68). Currently, there is not a single antipsychotic drug trial in treatment-naive first-episode patients (57, 69), except a post hoc analysis of a lurasidone trial in adolescents, which found a higher effect size in treatment-naive patients than in patients who had received treatment (70). We did not find the same effect in all other subsamples of antipsychotic-naive patients in adolescent studies (71). We found also no difference in an individual-patient-data meta-analysis in effect sizes between patients who entered the trials untreated compared with those who had received treatment (L. Brandt et al., unpublished 2024 data). A trial in antipsychotic-naive patients could show that the effect size compared with placebo is higher than that in chronic patients, but a higher placebo effect due to spontaneous remissions could also (in part) work against a larger effect size.

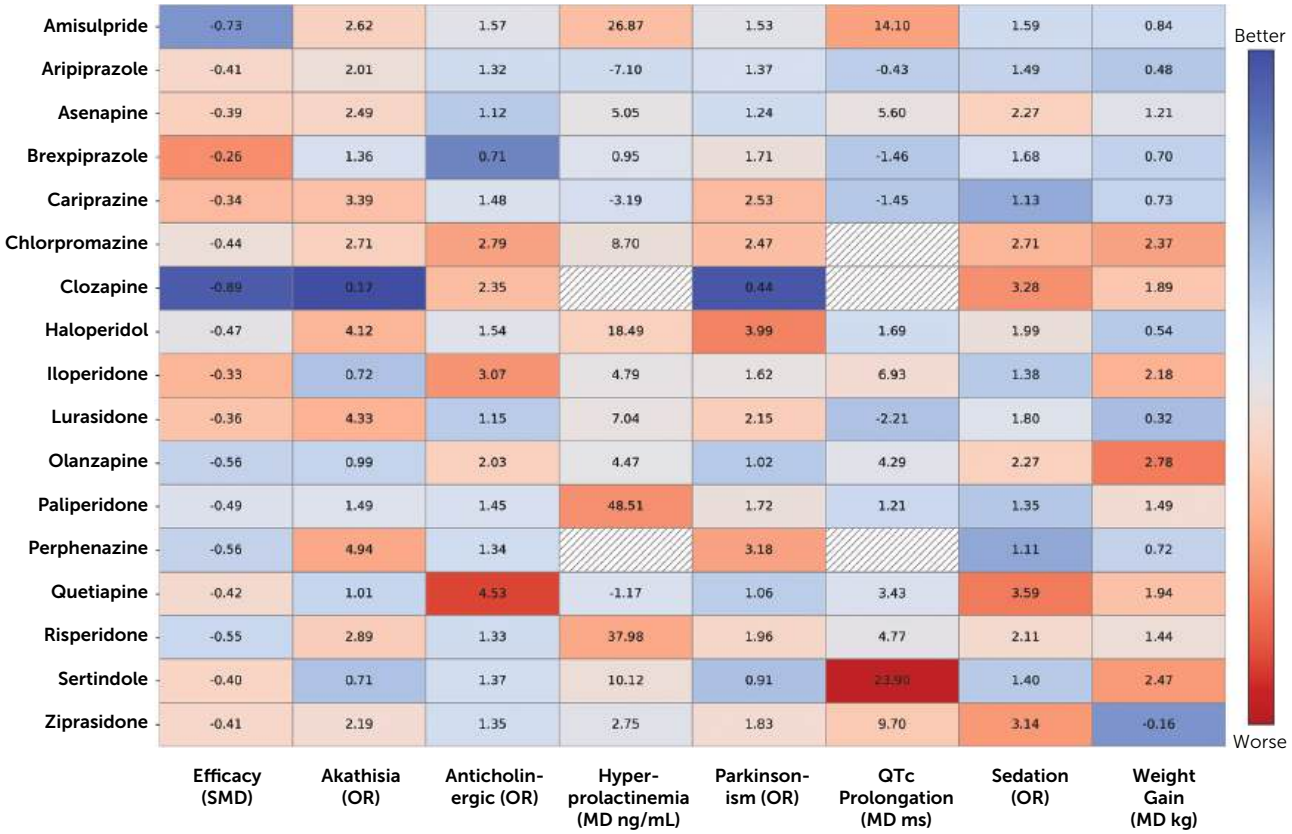
Blinding, high dropout rates, and increase in placebo response are among the most important methodological concerns for antipsychotic drug trials. With regard to the first, lack of integrity of the blind due to correctly guessing, from side effects, which drug one is receiving does not explain the superiority of antipsychotics, because in studies using active placebo—that is, comparator substances that mimic side effects but are not efficacious, such as barbiturates or promazine—the effect size was approximately the same (0.56) (52) as in the bulk of studies using inactive placebo (0.47) (57). Nevertheless, whether blinding worked or whether group assignment could be guessed from side effects is rarely tested. In an analysis of all placebo-controlled antipsychotic drug trials in schizophrenia since the introduction of chlorpromazine, only four studies, all on first-generation antipsychotics, tested blinding, and in all four, group assignment could be guessed (72). The success of blinding should always be tested. However, we found no evidence for unblinding exaggerating effect sizes in randomized controlled trials comparing antipsychotics with one another (73). Moreover, large-scale meta-epidemiological analyses in other areas found no major effects of blinding (74). As for the second methodological concern, even in short-term trials, dropout rates often exceed 50% (the average is 37% [57]). Even the best statistical imputation method may not appropriately account for such high attrition. The third concern in this area is the unresolved problem of the increasing response to placebo in such trials (27, 57, 75, 76). While in studies in the late 1960s and early 1970s there was on average no placebo response, in recent studies patients in the placebo group improved on average by 10 points on the Positive and Negative Syndrome Scale (PANSS) (27, 76). The reasons are not clear; meta-regression analyses identified factors such as large sample size and industry sponsorship being associated with higher placebo response and the resulting lower effect sizes (27, 76). What is behind these effects is unclear, but extreme cases—for example, up to 15 PANSS points in recent studies on TAAR agonists (77)—can in our opinion only be explained either by patients not having acute schizophrenia at the start of the study or by co-treatment with antipsychotics in the placebo groups. Pharmaceutical companies should take plasma levels to check whether co-treatment in part explains placebo effects.

DRUG EFFICACY FOR RELAPSE PREVENTION IN THE MAINTENANCE PHASE

The efficacy of antipsychotics for relapse prevention in schizophrenia is even clearer than for the acute phase, and the effect sizes are larger. An obvious reason for the higher effect size compared with acute treatment is that in studies on relapse prevention, only patients who benefited from antipsychotics are included, whereas in the acute studies, there is a mix of drug responders, placebo responders, and nonresponders. In the most up-to-date meta-analysis of the effects of antipsychotics for relapse prevention (78), 61% relapsed on placebo, compared with 24% on antipsychotics, and rehospitalization rates were 18% and 7%, respectively, within 9–12 months. This effect size is one of the largest among medical drugs (79, 80). Antipsychotics were effective for first-episode and multiple-episode patients, patients in remission, and patients who were only stable at baseline. Similarly, several antipsychotics have been shown to prevent the occurrence of new episodes of bipolar disorder and are thus mood stabilizers (81). In observational studies, the rehospitalization risk remained higher when stopping antipsychotics compared with continuing them even when patients had used them for an average of 7 years (82).

The question is less whether relapse prevention is indicated but more for whom, for how long, with which drug, and on what dosage. Several factors fuel the debate. First, relapse of schizophrenia can be described as an intermediate outcome in terms of severity. To make an extreme comparison, it is less severe than death, but more severe than a minor headache. For some patients, relapse results in long hospitalizations and/or losing a job or a relationship. But there are certainly also milder relapses that can be stopped by restarting antipsychotics. Second, the course of schizophrenia is highly variable; approximately 15% of patients fail to respond from the start (83), 20% only have one episode within 5 years (84, 85), and in between there are multiple individual courses. There is a debate as to whether antipsychotics lead to some loss in brain volume (86–88). "Receptor supersensitivity" means that the brain reacts to continuous dopamine blockade by making dopamine receptors more sensitive and/or by expressing more dopamine receptors, which can be shown in animals (89, 90). Supersensitivity is an explanation for tardive dyskinesia and exacerbations of illness despite adherent use of an antipsychotic

FIGURE 4. Efficacy and safety of various second-generation antipsychotics in schizophrenia[a]



[a] The data, listed here in alphabetical order by antipsychotic, are derived from reference 26. Color mapping was obtained by standardizing all variables to a common metric and calculating the z scores using the same assumptions as in the supplementary material from reference 122. Values for dichotomous events are reported as odds ratios, and continuous variables are reported as mean differences. Anticholinergic side effects include constipation, sedation, blurred vision, and urinary retention. The effect of clozapine on prolactin levels has been excluded from the heatmap due to a clear artifact in the source data (26), which were derived from small outlier studies. OR=odds ratio; MD=mean difference; SMD=standardized mean difference.

("breakthrough psychosis") (91). Furthermore, abrupt withdrawal can lead to rebound side effects and "rebound psychosis" (92). Withdrawal side effects have been shown to occur in approximately 10% of patients (93). Rebound psychosis is difficult to prove, because it is reasonable that symptoms were suppressed by antipsychotics and reemerge when medication is stopped. Various analyses of speed of withdrawal (78), a recent trial (94), and subgroup analyses have not provided evidence for rebound psychoses (78, 95). Antipsychotics should always be reduced very slowly, however, to allow the brain to readapt (ideally by tapering down over months rather than weeks). However, an important consideration, which has been shown repeatedly, is that if patients in remission stop treatment and relapse, only approximately half of them will go into remission again (96–99). Thus, it might be important to avoid relapses in order to prevent the development of treatment resistance. In schizophrenia, it is more efficacious to give antipsychotics continuously rather than intermittently (100, 101), but if patients do not accept continuous treatment, intermittent treatment and monitoring of early warning signs is better than no treatment (101).

DIFFERENCES IN EFFICACY IN RELATION TO SIDE EFFECTS BETWEEN ANTIPSYCHOTIC DRUGS

Network meta-analyses in acutely ill patients in short-term randomized controlled trials (26), acutely ill patients in long-term randomized controlled trials (63), and randomized relapse prevention studies (102, 103) have provided certain efficacy patterns (see Figure 4). These patterns are not unlike those in nationwide registry studies from Finland and Sweden (104–107). However, efficacy differences are not unequivocal. One reason is the above-described variability in placebo response, although these problems have to some degree been ruled out by sensitivity analyses excluding placebo-controlled trials (26). Moreover, because efficacy is evaluated by rating scales, there is subjectivity. The evidence on objective outcomes such as weight gain, metabolic disturbances (33, 34), prolactin levels, QTc prolongation, and use of antiparkinsonian medication as a proxy for extrapyramidal side effects is less equivocal, and the differences between the most extreme drugs are more pronounced. Nevertheless, even small differences in efficacy can sometimes decide whether someone can continue employment or

avoid hospital admission. Observational studies have complemented the picture for rare side effects such as neuroleptic malignant syndrome (108), for which randomized controlled trials are too small. Sedation is an important and common side effect of antipsychotic drugs and may lead to nonadherence, but it is poorly measured by open interviews. This side effect clearly needs to be better understood.

CHOOSING AMONG THE ANTIPSYCHOTICS

The World Health Organization (WHO) Collaborating Center for Drug Statistics Methodology lists 68 drugs in the category of antipsychotics (http://www.whocc.no/). The WHO List of Essential Medicines—drugs that should be available everywhere—includes only the following antipsychotics: aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, haloperidol decanoate, olanzapine, paliperidone, quetiapine, risperidone, and zuclopenthixol decanoate (109).

There are no (biological) markers to provide guidance on which antipsychotic is best for which patient. Selection criteria are therefore mainly pragmatic, based on whether a drug is licensed in a country, whether it is available in the needed formulation (e.g., as rapid-dissolving tablets or as long-acting injectable if use of the latter is planned for relapse prevention), differences in side effects and efficacy, previous efficacy and avoiding side effects experienced by a patient with a drug, patient preference (shared decision making), drug-drug interactions, and comorbidities (e.g., avoiding olanzapine in patients with diabetes) (110).

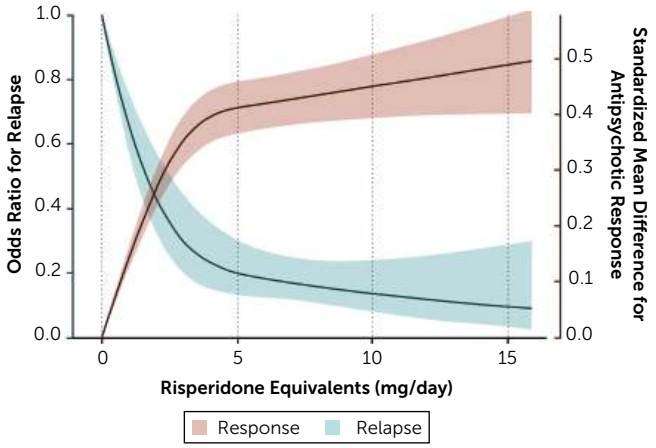
The debate on whether second-generation ("atypical") antipsychotics should be preferred to first-generation ("typical") antipsychotics was mainly driven by the much higher acquisition costs of the former. It could be said that the problem of extrapyramidal side effects of most old antipsychotics was replaced by weight gain, although not all new drugs cause weight gain (and not all old antipsychotics cause extrapyramidal side effects). Nevertheless, due to stricter regulations, new drugs have been much more thoroughly examined before they are licensed. Thus, their efficacy and side effects are well characterized. In contrast, the evidence for old drugs, other than haloperidol and chlorpromazine, is scarce and uncertain, and often not compatible with modern standards (26, 111, 112). Because many second-generation antipsychotics are now available as relatively cheap generics, we recommend their use (26, 111, 112). Moreover, given the uncertainties around differences in drug efficacy, initial drug choice should be mainly guided by side effects.

A meta-analysis (113) did not find clear differences in the effects of antipsychotics between chronic patients with acute exacerbations of schizophrenia (the "general subgroup"), first-episode patients, adolescents, elderly patients, patients with treatment-resistant illness, patients with predominant negative symptoms, and patients with concomitant substance use. Women respond better than men (66, 114), but the impact on treatment choice is not clear. Thus, evidence derived from the general subgroup for which most data are available can be used for guidance (26, 63). The choices for these subgroups are again mainly "pragmatic"—for example, prioritizing side effects even more in first-episode patients (because they respond better than do chronic patients) (66, 115) and in children/adolescents and the elderly (because they are more sensitive to side effects). Similarly pragmatically, high-potency dopamine blockers such as haloperidol may be avoided in patients with concomitant substance abuse because the effects of many illicit drugs are related to a dopamine reward that patients seek. Substance abusers may either increase their use to override the dopamine blockade, or they may stop taking such an antipsychotic. Long-acting injectable formulations may also be useful in patients with concomitant substance abuse, because nonadherence is frequent (116). There are two situations where drug choice is data driven rather than based on merely pragmatic criteria. In treatment-resistant illness, clozapine is the drug of choice (eventually, after a trial with olanzapine) (117). In patients suffering mainly from negative symptoms, low-dose amisulpride (which has a dose-dependent mechanism of action) and cariprazine (mainly a D_3 partial agonist) are the only drugs with enough evidence to recommend them (118). If cognitive deficits are the focus, strong D_2 blockers, such as haloperidol or fluphenazine, and anticholinergic and sedating drugs, such as clozapine, should be avoided (119, 120). The risk of birth complications seems to be relatively low with antipsychotics, especially after the first trimester, and it should be weighed, in individualized shared decision making, with risks for the mother and unborn child related to exacerbations of psychosis. Nevertheless, recommendations change, and thus expert advice should be sought. Similarly, small amounts of antipsychotics can pass into breast milk, so breastfeeding should be avoided when possible.

A free online tool to choose among the antipsychotics, the "Shared Decision-Making Assistant" app (121; https://ebmpp.org/de/tools/sdma-app), psymatik.com, and our Illuminatum.de website, will help patients make informed choices (122). Shared decision making is important because different patients will value different aspects differently. For example, for some patients, avoiding weight gain will be a priority, while for others, sexual side effects are more disturbing, and there are also patients who will want the most efficacious drug irrespective of side effects. Moreover, not every patient will experience every side effect. Among the first-generation antipsychotics, only haloperidol and perphenazine are presented in the app, because information on others is scarce (26, 111, 112).

Pharmacogenetics could be a tool to move forward with the individualization of treatment. It is well established that genetic polymorphisms of cytochrome enzymes have an impact on the pharmacokinetics and metabolism of antipsychotics (see below). In contrast, there are very few data on the effects of genetic polymorphisms on pharmacodynamics. Evidence that patients with certain single-nucleotide

FIGURE 5. Antipsychotic dose response in acute treatment and in relapse prevention of schizophrenia[a]



[a] Data are from Figure 3 of reference 11 and Figure 1 of reference 124; here, the two figures are merged.

polymorphisms of genes related to neuroreceptors respond better to iloperidone (123) is one of few examples. One reason why such approaches are not pursued vigorously may be that the pharmaceutical industry would prefer to develop drugs for all patients rather than only for subgroups.

ANTIPSYCHOTIC DOSAGES FOR ACUTE TREATMENT, DOSAGE INCREASE, FREQUENCY OF DOSING, AND SWITCHING

As for many medications, the dose-response curves of antipsychotics have a hyperbolic shape—that is, from a certain dosage onward, the efficacy approaches a plateau, so that higher dosages do not lead to more efficacy but more side effects (11, 124, 125). This is probably due to the fact that dopamine receptors are sufficiently bound so that higher dosages may mainly have effects on other receptors, and thus side effects, relative to efficacy, are promoted. The therapeutic window for antipsychotics has been shown to be approximately 65%–80% dopamine receptor occupancy (126–128). The plateau dosage is, on average, reached at approximately 5 mg/day of risperidone equivalent (11, 124). The dose-response curves for side effects vary between antipsychotics, but it is clear that several increase beyond dosages of 5 mg/day risperidone equivalent (129–131). A similar plateau dose-response relationship is seen with antidepressants, where the plateau dosage is approximately 30–40 mg/day fluoxetine equivalent (132). The International Consensus Study of Antipsychotic Dosing provides valuable information, including for patient subgroups (133, 134). We have produced an Excel sheet to convert dosages based on various methods ("international consensus," "maximum effective dose method," "minimum effective dose method," "classical mean dose method") (https://ebmpp.org/de/tools/dose-calculator).

If possible, antipsychotics should be carefully titrated ("start low, go slow, but go") in order to avoid untoward side effects and "overshooting." Some antipsychotics always need to be titrated—for example, quetiapine, to avoid postural hypotension due to alpha receptor blockade—while for others the full dose can be administered on the first day, which can be useful in the case of emergencies (see the medication's summary of product characteristics [SPC]). Moreover, a very small and thus inconclusive meta-analysis suggested that fast titration is more efficacious than slow titration (135).

The half-life determines how often an antipsychotic drug must be given; if the half-life is short, the drug must be given more frequently. The half-life of many antipsychotics is between 12 and 36 hours. Thus, many antipsychotics can be given once daily at night, which makes adherence easier and may help reduce the experience of side effects, because plasma level peaks are reached during sleep. As a rule of thumb, it takes five half-lives of drug administration until steady state is reached. Drugs with a long half-life, such as aripiprazole (~60–80 hours) and cariprazine (~48–96 hours for parent drug, 1–3 weeks for active metabolites), have the advantage that patients are still covered if a dose is missed. On the other hand, switching to them from another antipsychotic takes more time. All these remarks are crude rules of thumb; the SPCs of individual drugs should be consulted. The APA schizophrenia guideline provides useful tables as well (110).

If switching is necessary, antipsychotics are usually cross-tapered—that is, the first drug is gradually tapered down and the next one is simultaneously increased. The speed of this process depends on the drug; for example, clozapine needs very slow up-titration. If a sedating drug is switched to a less sedating one, especially if the second one has a long half-life (for example, if switching from olanzapine to aripiprazole), more time is needed. Moreover, studies have not found major differences between "cross-tapering," "overlap and taper" (the full dosage of the first drug is maintained until the full dosage of the second drug has been reached), and fast changing in emergency situations (e.g., occurrence of a severe side effect). Detailed information is provided on the website SwitchRx (https://www.switchrx.com/).

ANTIPSYCHOTIC DOSING IN RELAPSE PREVENTION

Interestingly, the average maximum effective dosage for relapse prevention in stable chronic patients with schizophrenia was 5 mg/day risperidone equivalent, as well (124) (Figure 5). This finding could be described as "what made you well keeps you well." It is important because previous studies had tried to find "minimum effective doses" that sufficiently prevent relapses but are associated with a minimum of side effects. They failed in the sense that the lower dosages were always associated with more relapses (e.g., 136, 137). The methodological problem was that they examined fixed dosages assuming a linear pattern. But the

dose-response relationship is hyperbolic (see above) and highly individual. Some patients will need dosages higher than 5 mg/day risperidone equivalent, and others will need lower dosages. For example, 2.5 mg/day risperidone equivalent was associated with clearly higher relapse rates than 5 mg/day, but was still much more effective than placebo (124). In conclusion, patients are safest if they stay on a standard dosage. However, if side effects are intolerable, the only way to find out whether lower dosages are sufficient is by careful, very slow down-titration. This will allow the brain to readapt to lower dosages over months rather than weeks. A dedicated strategy based on the relationship between antipsychotic dosage and dopamine binding has been suggested (138).

FORMULATIONS

Depending on the country and the drug in question, antipsychotics are available as tablets, extended-release tablets, rapidly dissolving tablets, liquids, dermal patches, intravenous solutions, and short-acting and long-acting intramuscular or subcutaneous formulations with injection intervals ranging between 1 week and 6 months. The APA schizophrenia guideline provides relevant information in tables (110). Short-acting intramuscular antipsychotics should be used only in emergency situations when the patient cannot consent. The most important debate is around long-acting injectable antipsychotics for relapse prevention. Given the high frequency of nonadherence in schizophrenia (up to 50% in the long term) (116), long-acting injectables have obvious advantages for long-term treatment, as evidence suggests reduced relapse and rehospitalization rates compared with oral formulations (139). Concerns remain with regard to uncontrollable side effects, especially malignant neuroleptic syndrome, although recent analyses suggest no difference in frequency and mortality compared with oral antipsychotics (108).

DRUG METABOLISM AND PLASMA LEVELS

Most antipsychotic drugs are metabolized in the liver via various cytochrome enzymes, and only a few (in particular amisulpride and paliperidone) are mainly excreted via the kidneys, which has implications for drug choice and dosing in patients with liver or kidney disease. When drugs competing for a cytochrome enzyme are combined or patients are slow metabolizers (approximately 6% for CP2D6 in the European population) (140, 141), plasma levels increase. In contrast, some drugs induce cytochrome enzymes, and some people are ultrarapid metabolizers (approximately 3% for CP2D6 in the European population) (140, 141), leading to lower plasma levels of antipsychotics (the APA schizophrenia guideline provides useful tables [110]). Dosage titration is usually based on efficacy and side effects. But plasma level measurement is useful in many situations, such as poor adherence, nonresponse despite a sufficient dosage (especially clozapine), or pronounced side effects despite a low dosage. The American Society of Clinical Psychopharmacology and the Arbeitsgemeinschaft für Neuropsychopharmakologie provide detailed information (142, 143).

OUTLOOK

The fundamental challenge in psychiatry is the lack of biomarkers. Psychiatry was set on the wrong track early on. Anecdotally, Alois Alzheimer and Franz Nissl, leading neurobiologists at the time and in Emil Kraepelin's team, assigned a disease to neurology when they found a biological correlate under their microscopes, and to psychiatry when they found nothing (4). Therefore, psychiatry comprises, by definition, mainly those diseases of the brain without visible or circumscribed pathology. The lack of biological markers renders our discipline vulnerable to criticism, up to some stating that psychiatric disorders do not exist (144). It also makes the understanding of their pathophysiology and drug development difficult. These are easier when there are biomarkers, such as in multiple sclerosis, for example. In addition, there are no ideal animal models, because, to put it boldly, we do not know whether mice hear voices. Therefore, it is not surprising that most drug discoveries were made by serendipity, including the new drug xanomeline-trospium. Xanomeline was originally tested to combat the cholinergic deficit in Alzheimer's disease. Whereas it was not well tolerated by patients with Alzheimer's disease, an improvement in psychotic symptoms was observed (60). The antipsychotic effect was subsequently confirmed in schizophrenia (145), and the drug was combined with trospium, a peripheral anticholinergic, to reduce peripheral side effects. Various molecules with related mechanisms are now being tested. We hope that the Research Domain Criteria approach, which moves away from psychopathological signs alone to cross-diagnostic functions, will help drug development (146). Moreover, the identification of pharmacogenetic predictors would enhance personalized pharmacotherapy. Finally, there should be more emphasis on the development of drugs that target specific symptoms of schizophrenia, such as negative symptoms or cognitive deficits, rather than trying to find the "magic bullet" that improves them all.

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Examination Questions for "Antipsychotic Drugs: A Concise Review of History, Classification, Indications, Mechanism, Efficacy, Side Effects, Dosing, and Clinical Application"

1. **Which of the following is suggested as a potential mechanism for the reduction of extrapyramidal motor side effects in second-generation antipsychotics?**
   A. Stronger binding to serotonin receptors than dopamine receptors
   B. Blockade of histamine receptors
   C. Cholinergic rather than dopaminergic mechanism
   D. Improvement in negative symptoms secondary to positive symptom improvement
2. **Which factor is identified as a significant contributor to the smaller drug effects observed in placebo-controlled antipsychotic trials compared to head-to-head trials?**
   A. Higher dropout rates in placebo-controlled trials
   B. The use of first-generation antipsychotics in head-to-head trials
   C. Failure of blinding due to side effects
   D. Larger sample sizes in placebo-controlled trials
3. **What is the suggested dopamine receptor occupancy range associated with the therapeutic window for antipsychotics?**
   A. 50%–65%
   B. 65%–80%
   C. 80%–95%
   D. 40%–60%