Update on Typical and Atypical Antipsychotic Drugs

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Abstract

Antipsychotic drugs (APDs) are best classified as typical or atypical. The distinction is based solely on their ability to cause extrapyramidal side effects (EPS), including tardive dyskinesia (TD). The two classes differ in mechanism of action, with atypical APDs providing important modulation of serotonergic neurotransmission. TD increases the death rate and can be minimized by limiting use of typical APDs. Clozapine is unique among the atypical APDs in its efficacy for ameliorating psychosis in patients with treatment-resistant schizophrenia (TRS), for reduction of suicide, and for improving longevity. The typical and atypical APDs do not differ in improving psychopathology in non-TRS. The atypicals vary in metabolic side effects: some have little burden. Cognitive benefits of the atypical APDs may be superior for some domains of cognition and require less use of anticholinergic drugs, which impair memory, for treatment of EPS. Overall, choosing among the atypical APDs as first-line treatment represents the best course for schizophrenia and most likely other disorders for which APDs are used.

EPS: extrapyramidal side effects

DA: dopamine

CIS: cognitive impairment in schizophrenia

TD: tardive dyskinesia

INTRODUCTION

Antipsychotic drugs (APDs) ameliorate hallucinations and delusions in patients with neuropsychiatric disorders, particularly schizophrenia and bipolar disorder, but they vary in efficacy and side effects, as well as mechanism of action (1, 2). APDs are used off-label in the treatment of many other disorders, most commonly treatment-resistant depression, dementia, obsessive-compulsive disorder, aggression, autism spectrum disorders, pervasive developmental disorder, and sleep disorders, but psychotic disorders are their main indication. The two main classes of APDs are known as typical and atypical. Because of significant disagreement about their differences and their relative merits, a review is timely.

Discussions of APDs are sometimes framed as a "before and after" contrast in which the fulcrum is the discovery of phenothiazines. Some observers believe there have been no advances in the treatment of schizophrenia—save for clozapine, the prototypical atypical APD—since the serendipitous discovery, in 1952, of the phenothiazine chlorpromazine, the first robustly effective APD (3). A second way to sort the APDs is to distinguish two generations; the 1955 discovery of clozapine, a dibenzodiazepine, marked the beginning (and, some would argue, the apogee) of the second-generation APDs (4). A third classification is pharmacologic, based on ascribing exclusive importance to dopamine (DA) D_2 receptor blockade for the mechanism of action of chlorpromazine-like drugs to distinguish them from clozapine and related drugs. Clozapine's mechanism of action is believed to include more potent blockade of 5-HT_{2A} than of DA D_2 receptors (5, 6) as well as other non–D_2 DA receptor–mediated actions (7). A fourth possibility is a functional classification based on liability to cause extrapyramidal side effects (EPS). At clinically effective doses, the side-effect profile of the "typical" APD, exemplified by chlorpromazine, differs from that of the "atypical" APD, of which clozapine is the prototype (8). Atypical APDs produce a markedly lower incidence of EPS at usual clinical dosages of both. A search on PubMed shows a four-to-one preference in publications of human and nonhuman studies to characterize the APDs as typical or atypical, rather than as first or second generation. Thus, this review utilizes the typical/atypical APD nomenclature for discussing APDs in current use and development.

Comparison of typical and atypical APDs is of considerable importance because some have disputed the value of this distinction. Criticism is based mainly on the results of the US Clinical Antipsychotic Trials in Interventions Effectiveness (CATIE) (9) and the Cost Utility of the Latest APDs in Schizophrenia Study (CUtLASS) (10), which suggested no differences in either overall efficacy or tolerability between typical and atypical APDs, with the exception of clozapine. The CATIE study also compared the effects of typical and atypical APDs on cognition. This is a critical issue because of the importance of cognitive impairment in schizophrenia (CIS) for functional outcome in schizophrenia (11). Two major goals of current drug discovery are the development of novel APDs that not only produce minimal EPS but improve CIS as well—e.g., selective muscarinic, 5-HT_{2C}, or metabotropic glutamate receptor agonists—and drugs that only improve cognition, e.g., alpha 7 nicotinic receptor agonists (12).

ATYPICAL ANTIPSYCHOTIC DRUGS: DEFINITION

An atypical APD is most accurately and simply described as one that produces minimal EPS at clinically effective doses (8). The origin of this definition was the observation that chlorpromazine, and other relatively selective D_2 receptor antagonist–based APDs, produced a variety of EPS, including the sometimes fatal tardive dyskinesia (TD) and neuroleptic malignant syndrome, due mainly to blockade of DA D_2 receptors in the dorsal striatum (13). These side effects of chlorpromazine and its relatives are linked to their antipsychotic mechanism of

action, namely blockade of DA D_2 receptors in the limbic region of the brain, but occur at higher D_2 receptor occupancy rates (13, 14). Also related to D_2 receptor blockade is elevated plasma prolactin, which is under tonic inhibition by D_2 receptors in the anterior pituitary gland (15). Hyperprolactinemia has been implicated in causing galactorrhea and gynecomastia, dysphoria, osteoporosis, and breast cancer (16). However, the relationship between hyperprolactinemia and these conditions when found in APD-treated psychiatric patients is not robust (17). Most atypical APDs produce little or no effect on plasma prolactin levels in humans, but risperidone and its active metabolite, paliperidone, are exceptions; these two drugs produce significantly higher plasma prolactin levels than any typical APD (18). In summary, the distinction between typical and atypical APDs was based on their differences in EPS, not their relative efficacy for psychopathology, cognition, or effects on prolactin secretion.

PHARMACOLOGY AND MECHANISM OF ACTION OF ATYPICAL ANTIPSYCHOTIC DRUGS

Two classes of atypical APDs are in current use, and several more are in development. The largest group of atypical APDs, of which clozapine is the prototype, consists of those that are more potent antagonists of 5-HT_{2A} than of D_2 receptors (6, 19). These will be referred to as 5-HT_{2A}/D_2 antagonists. Others in clinical use include asenapine, blonanserine, iloperidone, lurasidone, melperone, paliperidone, quetiapine, risperidone, ziprasidone, and zotepine (20, 21). Aripiprazole, an atypical APD, differs in that it achieves diminished D_2 receptor stimulation via partial DA D_2 agonism, thus reducing presynaptic DA release, and diminished activation of postsynaptic D_2 receptors because of its weak intrinsic agonist activity (22). The mechanism by which 5-HT_{2A} antagonism contributes to the antipsychotic actions and low EPS potential of these drugs has been discussed elsewhere (19, 23).

The mechanism of action of the second group of atypical APDs has been postulated to be D_2/D_3 receptor antagonism, but most of these drugs also have serotonergic effects that may contribute to their atypical profiles (23). These include amisulpride, a potent 5-HT_7 antagonist (24), and cariprazine, which is also a potent 5-HT_{2B} antagonist and 5-HT_{1A} partial agonist (25). A number of typical APDs, including chlorpromazine and haloperidol, are also potent D_3 antagonists. Other D_2/D_3 antagonists with preclinical profiles consistent with atypicality, tellingly, have a variety of serotonergic actions, including 5-HT_{2A} antagonism and 5-HT_{1A} partial agonism (26). Thus, the distinction between these two classes of atypical APDs is not absolute.

PRECLINICAL STUDIES COMPARING ATYPICAL AND TYPICAL ANTIPSYCHOTIC DRUGS

All APDs are effective in various rodent models that predict antipsychotic activity. These include (*a*) blockade of conditioned avoidance responding; (*b*) inhibition of the locomotor activity produced by the indirect DA agonist amphetamine, or by the N-methyl-D-aspartate (NMDA) receptor antagonists phencyclidine (PCP), ketamine, or dizocilpine (MK-801); and (*c*) inhibition of the DA agonist apomorphine- or PCP- induced impairment in prepulse inhibition. The atypical APDs are far more potent antagonists of NMDA receptor–mediated locomotor activity than are the typical APDs. Both classes of atypical APDs previously mentioned have also been shown to be effective in widely utilized but more controversial models of CIS, e.g., reversal of acute or subchronic PCP- or MK-801-induced impairment in novel object recognition, reversal learning, attentional set shifting, and social interaction (23, 27). The typical APDs are generally inactive or much weaker in the CIS models, whereas the atypical APDs are generally effective in both acute and subchronic models and at comparable doses (27, 28). Associated pharmacologic

TRS: treatment-resistant schizophrenia

studies suggest that their efficacy in these models cannot be attributed solely to D_2 receptor antagonism (23, 27). Rapid dissociation from the D_2 receptor has been suggested to be the basis for the atypical properties of not only clozapine and quetiapine, two drugs with low affinity for the D_2 receptor, but also other atypical APDs such as olanzapine and risperidone (5, 29). The latter proposal is unlikely because both compounds have a high affinity for the D_2 receptor and, thus, dissociate as slowly from the D_2 receptor as haloperidol (19).

5-HT_{1A} partial agonism, direct or indirect, is characteristic of almost all atypical APDs of the 5-HT_{2A}/D_2 antagonist type; it is an important complement to 5-HT_{2A} antagonism and is absent from typical APDs (30). Both serotonergic actions hyperpolarize pyramidal glutamatergic neurons in cerebral cortex and hippocampus, as well as many, but not all, GABAergic interneurons, ventral tegmental DA neurons, and the serotonergic neurons in the dorsal and median raphe that project throughout the brain and to the spinal cord (31). Clozapine, aripiprazole, lurasidone, quetiapine, and ziprasidone are direct-acting 5-HT_{1A} agonists (23, 30). Other atypical APDs are indirect 5-HT_{1A} agonists, as various of the actions relevant to antipsychotic activity or efficacy in models of CIS can be blocked by 5-HT_{1A} antagonists (4, 30), including enhancement of cortical and hippocampal DA (32) and acetylcholine efflux (33, 34). Several novel APDs in development have relatively potent 5-HT_{1A} partial agonist and weak 5-HT_{2A} antagonist properties, e.g., PF-217830, adoprazine, SSR181507, and F15063 (30).

Multiple types of evidence from animal models relevant to CIS (e.g., acute and subchronic NMDA receptor antagonism, neurodevelopmental and transgenic mouse models) support the conclusion that the atypical APDs, because of their serotonergic actions, are superior to typical APDs with regard to prevention or amelioration of cognitive impairments (27, 35). Results in animal models indicate that 5-HT_{1A} partial agonism and 5-HT_6 and 5-HT_7 receptor antagonism have procognitive effects (35); some atypical APDs are potent antagonists of 5-HT_6 or 5-HT_7 or both (e.g., clozapine and lurasidone). The differences among the atypical APDs with regard to action at these receptors may account for individual differences in patient response to specific atypical APDs. This is especially plausible because mutations in the 5-HT receptors and their signaling systems have been found in patients with schizophrenia (36). Alpha$_2$ adrenergic blockade of some APDs may also contribute to their atypical properties (7).

In summary, there is extensive evidence for major differences in the pharmacology of atypical versus typical APDs. The atypical APDs related to clozapine share 5-HT_{2A} receptor blockade and 5-HT_{1A} partial agonism, two effects that profoundly affect brain function, as well as additional actions on other 5-HT and other relevant receptors, which would be expected to expand their potential to achieve clinical benefits exceeding those due to D_2 receptor blockade, in at least some patients. However, some of the pharmacologic differences may also lead to adverse consequences of some atypical APDs, e.g., weight gain that is due, in part, to histamine H_1 and 5-HT_{2C} antagonist properties, but these features are lacking in many atypical APDs (37).

CLINICAL EFFECTS OF CLOZAPINE AND OTHER ATYPICAL ANTIPSYCHOTIC DRUGS

Clozapine: The "Gold Standard"

An evaluation of the role of the atypical APDs in current use must recognize the special case of clozapine, whose efficacy and side-effect burden are sufficiently distinctive that it cannot be readily included in a general presentation of even the atypical APDs that share its 5-HT_{2A} receptor preferences. Clozapine is often referred to as the gold standard among the atypical APDs (38, 39) because of its exceptional efficacy in treating positive symptoms in treatment-resistant schizophrenia (TRS) patients (40). The success of clozapine created the expectation, ultimately

disproven, that all atypical APDs would have similar benefits (4). Thus, clozapine is discussed separately to clarify what it shares with other APDs and what is unique. The reader is referred to a recent review of clozapine for more detailed consideration of its history and utilization (4).

Efficacy for Positive Symptoms in Treatment-Resistant Schizophrenia

Clozapine was the first APD shown to be effective to treat psychotic symptoms in the majority of the ~30% of patients with schizophrenia who remain psychotic despite two or more adequate trials with other APDs, typical or atypical (40, 41). At six weeks, the response rate (improvement ≥20% in overall psychopathology) to clozapine in TRS patients is ~30%. Another 30%–40% of patients have been reported to respond when treatment is extended to six months, so it is important that trials of clozapine last six months when possible (4, 41). The advantages of clozapine in TRS have been confirmed in almost all clinical trials (9, 42). Trials with short duration (<6 months), underdosage of clozapine, inadequate power, or diffuse requirements for entry sometimes fail to show differences between clozapine and typical or other atypical APDs. Clozapine also has advantages over other APDs in decreasing aggressiveness or violence in psychiatric patients, controlling psychosis in Parkinson's disease, and reducing the risk of developing TD, while also treating established TD (4).

Although clozapine is the only drug approved for TRS, there is some evidence that high doses of olanzapine, the atypical APD pharmacologically closest to clozapine, may be as effective as clozapine in TRS. In a randomized double-blind trial with 20 TRS patients per group, olanzapine 25–45 mg/day was as effective as clozapine 300–900 mg/day (43). A six-month trial was required to achieve improvement in >50% of the patients with either treatment. Some TRS patients were reported to respond to standard doses of aripiprazole 15–30 mg/day or perphenazine 8-64 mg/day (44). There is no evidence that doses of typical APDs higher than those optimal for non-TRS patients will lead to improvement in psychosis in TRS (1). Efforts to improve response to clozapine when it is less than satisfactory (by adding other APDs or a mood stabilizer, such as lamotrigene or valproic acid), have not reliably demonstrated efficacy (4). Addition of electroconvulsive therapy has been effective in many such patients (45).

Clozapine Reduces Suicide Risk

Clozapine is also indicated for reducing the risk for suicide in patients with schizophrenia or schizoaffective disorder. Robust evidence from clinical trials and epidemiology shows that clozapine is effective to prevent recurrent suicide attempts (46, 47). It is the only drug approved for use to prevent suicide. However, it is rarely used for this purpose (4).

Other Uses

Clozapine is also useful for patients with schizophrenia who cannot tolerate other APDs because of EPS sensitivity (1, 4). It is used to decrease aggression and has been reported to reduce substance abuse (4, 48). The ability of clozapine to improve cognition is discussed subsequently because it shares this important effect with other atypical APDs.

Clozapine-Induced Agranulocytosis and Other Side Effects

Unfortunately, clozapine has numerous side effects, including agranulocytosis; eosinophilia and fever at treatment onset; sedation; metabolic side effects, including hyperlipidosis, type II diabetes, and weight gain; major motor and myoclonic seizures; myocarditis; hypersalivation; urinary incontinence; sweating; constipation; and ileus (49). These have contributed to gross underutilization in the United States compared to other advanced countries (50).

With the exception of agranulocytosis and myocarditis, these side effects rarely require discontinuation of clozapine when properly

managed. Preparing patients for the occurrence of these side effects and vigorous management to minimize their severity can minimize discontinuations. Clozapine has been found to rarely cause dystonic reactions, neuroleptic malignant syndrome, or TD (4, 49). In a pharmacoepidemiologic study of >66,000 patients with schizophrenia treated with APDs in Finland, comparing the effects of all APDs on all-cause mortality, cardiovascular disease, and suicide, only clozapine was reported to be associated with decreased mortality, in large part because of its ability to prevent suicide (51). This led to the recommendation that clozapine be used as a first-line treatment because of the worldwide 15–20-year decrease in longevity in patients with schizophrenia (52) despite the fact that agranulocytosis affects 0.8% of patients, almost always within 1–12 months of initiating treatment (4, 49). With mandatory weekly monitoring of the white blood cell and absolute neutrophil counts for 6 months, then biweekly for 6 months, and monthly thereafter, leukopenia or agranulocytosis is promptly detected. Following withdrawal of clozapine, prompt treatment, and prevention of infection, mortality is 1 per 10,000 (4). Several reports have indicated that the risk for agranulocytosis may be predicted by specific single nucleotide polymorphisms in the human leukocyte antigen region, consistent with an autoimmune mechanism for its etiology (53). Rapid relapse may occur when clozapine is stopped abruptly for any reason (4).

Clozapine is effective to treat psychosis of Parkinson's disease without causing significant worsening of motor symptoms (54), mostly likely via blockade of 5-HT_{2A} receptors (55). A selective 5-HT_{2A} receptor blocker, pimavanserin, is also effective in L-DOPA psychosis (56).

Use of Atypical Antipsychotic Drugs in Non-Treatment-Resistant Schizophrenia

As mentioned above, there is considerable controversy over whether atypical APDs are superior to typical APDs for non-TRS with regard to efficacy to treat psychosis (57, 58). A randomized blinded trial comparing clozapine to low-dose typical APDs in non-TRS found that clozapine was not superior with regard to psychopathology, quality of life, and global function and EPS. However, significantly more relapse/rehospitalization and dropouts occurred with typical APD treatment and, most importantly, clozapine was more effective to treat CIS (59, 60).

After the introduction of risperidone, olanzapine, quetiapine, and other 5-HT_{2A} receptor–targeting atypical APDs, these drugs became the most widely prescribed and studied treatments for schizophrenia and other indications for APDs. As we write this, PubMed lists 2,510 publications of randomized controlled trials reporting data on all clinical uses of atypical APDs and another 2,176 peer-reviewed reports based on nonrandomized clinical trials. Although one meta-analysis of randomized blinded clinical trials comparing typical and atypical APDs found that the first approved group of atypical APDs was superior to haloperidol, regardless of dose of haloperidol (61), other meta-analyses found no differences between atypical and typical APDs with regard to improvement in psychopathology (62, 63). These and other meta-analyses reported clozapine to be superior to the other atypical APDs, often combining the results for TRS and non-TRS with the other atypical APDs. An advantage of the atypical APDs with regard to frequency and severity of EPS, which contributes to lower rates of discontinuation, was evident in studies in which the doses of drugs were flexible, as they are in clinical practice (62). Fixed-dose comparative studies that limit the typical APDs to doses sufficient for efficacy show a smaller difference in risk for EPS compared to atypical APDs. However, in clinical practice, higher dosages of typical APDs, together with polypharmacy, lead to added EPS burden and higher dropout rates (64, 65).

These meta-analyses were based mainly on short-term "efficacy" trials, usually industry-funded randomized controlled trials. "Effectiveness" trials, not supported by industry, are

proposed as better reflecting the results to be expected in clinical practice (66). Drug company sponsorhip has now been shown not to lead to bias in randomized controlled trials of APDs (67). The CATIE trial, sponsored by the National Institute of Mental Health, enrolled 1,493 patients and was to be the largest and longest (up to 18 months) double-blind randomized effectiveness trial comparing a typical APD (perphenazine) and four atypical APDs (olanzapine, quetiapine, risperidone, and ziprasidone). Perphenazine was selected over haloperidol, the most widely used typical APD. The highly publicized primary endpoint finding was difference in time to discontinuation, which favored olanzapine, with improvement in psychopathology a secondary endpoint, which also slightly favored olanzapine (9). However, subsequent independent scrutiny of the design and data analysis of this study revealed serious flaws, leading to the conclusion that it was impossible to draw conclusions about the relative merits of the drugs from CATIE's findings (1, 68–71). These flaws included allowing patients to remain on the same drug they had been receiving prior to randomization, which affected many of those randomized to risperidone or olanzapine (9), and olanzapine dosage up to 30 mg/day (9), three times the dose found to be effective for non-TRS (72). None of the other atypical APDs were permitted to exceed the upper limit of the dosages recommended for non-TRS patients. As mentioned above, at 30 mg per day, in a trial of at least six months duration, olanzapine would be expected to be effective in up to 60% of TRS patients, of which there were a substantial number in the trial (43, 71).

A much smaller (277 patients total) and shorter (one year) effectiveness-type study in Great Britain, the Cost Utility of the Latest APDs in Schizophrenia Study (CUtLASS), included only patients who had an inadequate response or suffered adverse effects to prior treatment and so were unrepresentative of schizophrenia patients as a whole (10). CUtLASS considered amisulpride an atypical APD, which is correct, and sulpiride a typical APD, which it is not, because of its low EPS profile and extensive preclinical literature demonstrating its atypical profile (73, 74). There is no reason to classify sulpiride as a typical APD simply because it lacks 5-HT_{2A} receptor antagonism (57). Of the patients in the so-called typical APD group, 49.1% received sulpiride, an atypical APD! Other issues include the self-selection of drug treatment by clinicians (who avoided prescribing actual typical APDs for most patients by assigning them to sulpiride), permitting patients to switch from one class of drugs to another, and using initial assignment to treatment for data analysis. These methodological problems render the data from CUtLASS of no use for evaluating the differences between typical and atypical APDs.

A third nonindustry effectiveness study, the European First Episode Study (EUFEST), was a one-year, 500-patient, randomized open comparison of amisulpride, haloperidol, olanzapine, quetiapine, and ziprasidone (75). The primary outcome measure was again time to discontinuation, and olanzapine was found to be superior to the typical APD, haloperidol, which may be more representative of D_2 antagonists than perphenazine. Of the patients treated with haloperidol, 72% discontinued within 12 months, compared to 40% for amisulpride, 33% for olanzapine, 53% for quetiapine, and 45% for ziprasidone, all significantly lower than haloperidol. In accord with efficacy studies, symptom reduction was nearly identical in all treatment groups (75). Olanzapine was also found to lead to longer time to discontinuation than other APDs, with the exception of clozapine, in a national epidemiologic study of first hospitalization for schizophrenia (76). That study also provided additional evidence for the benefits of long-acting injectable APDs for patients with schizophrenia.

Taken together, the symptom-reduction results of CATIE and EUFEST were clearly in accord with the majority of the meta-analyses of the efficacy studies, with the exception of one (61) that favored the atypical APDs. Nevertheless, the principal investigators of the CATIE and CUtLASS studies, news media, and editorials in leading medical journals, e.g., *Lancet*

and *American Journal of Psychiatry*, interpreted the combined results of the two studies as an unexpected and devastating rebuke of the value of the atypical APDs. They concluded that the atypical APDs provided nothing that would justify their incremental cost (57, 58, 77), while acknowledging that there were some patients for whom they might provide benefit. Their de facto conclusion was that the atypical APDs should be a second-line treatment. This was supported by a formal cost-effectiveness analysis (CEA) (78) and was the basis for a lament that it was not possible to put restrictions on access to the atypical medications, which would mean prolongation of expenditures that would provide "no benefit for public health" (79). This conclusion has been challenged, not only because of the myriad serious shortcomings of the clinical components of the study but also because the CATIE study was not designed to draw conclusions on cost effectiveness, was grossly underpowered for this purpose, and employed analytically unsound CEA methodology (80). Based on prescription data, the recommendation from CATIE and CUtLASS to reconsider typical APDs as first-line treatments has been largely ignored by clinicians when they are given the opportunity to make a choice. However, some pharmacy management bodies in the United States and United Kingdom require failure on a typical APD before permitting the use of an atypical APD in the treatment of psychosis. In conclusion, the effectiveness studies intended to clarify the "real-world" differences with regard to clinical benefits between typical and atypical APDs did not answer this question. They did, at least, spark discussions about methodology and provide the basis for power calculations that would enable future studies of this kind to be more informative.

CHOOSING AN ATYPICAL OVER A TYPICAL ANTIPSYCHOTIC DRUG

Why then prefer atypical APDs, which usually do cost more than typical APDs, and what is the basis for choosing among the atypical APDs? Few reliable data suggest any overall differences between the typical and atypical APDs or among the atypical APDs in regard to improvement in psychopathology in non-TRS patients when the drugs are used in equivalent dosages in randomized controlled trials. But that is not the only basis for choosing an APD. The key issues driving such decisions are EPS, metabolic side effects, potential to improve cognition and depression, and relapse prevention.

Extrapyramidal Side Effects

Both CATIE and CUtLASS questioned the conclusion that the atypical APDs were superior on the basis of fewer EPS (9, 10, 81). However, EUFEST clearly demonstrated increased parkinsonism and akathisia with haloperidol, despite low doses (75). As discussed above, doses of typical APDs in clinical practice are often much higher than that used in CATIE and increase with chronicity (64, 65). Anticholinergic drugs are often started with typical APDs and worsen cognition (82). Acute and subacute EPS predict the development of TD. TD risk is lower with atypical APDs, which thus minimize the mortality due to TD (83–85). The cumulative incidence of TD is ~5% per year, beginning in the first year of use, even with low dosages. The mean cross-sectional prevalence of TD with typical APDs is 24%. As patients age, the annual incidence of TD after the age of 45 years is 25%–30% after one year of treatment. The mortality rates in patients with TD are significantly higher (hazard ratio, 2.62; 95% confidence interval, 1.58–4.33; $p = 0.0006$) (86). Thus, it is highly questionable to discount the risk for TD when choosing an APD, as advocated by Rosenheck et al. (79), who based their recommendations on a two-year study that did not permit patients with TD to receive perphenazine. The evidence is clear: typical APDs are more likely to cause TD, and with it, increased mortality. Consistent with this conclusion, there is extensive evidence for increased mortality with haloperidol compared to atypical APDs in patients with dementia and older patients with schizophrenia (87).

Cognitive Effects of Atypical Antipsychotic Drugs

Virtually all patients with schizophrenia suffer from cognitive impairment (87). CIS is a key factor in poor functional outcome in schizophrenia (11). It is present at first diagnosis but tends to worsen over time. As reviewed elsewhere, typical APDs have generally been found to be ineffective against CIS and to be associated with worsening when anticholinergic drugs are required to control EPS (87). Clozapine was the first atypical APD reported to improve some domains of cognition: semantic memory, declarative memory, and processing speed (88). Subsequent meta-analyses of >40 studies concluded that these improvements also occurred with risperidone and olanzapine (89, 90). The CATIE study failed to find a meaningful difference between typical and atypical APDs with regard to improvement in cognition (91). As discussed, there is abundant evidence from rodent and primate studies based on animal models of CIS that the atypical APDs are far more effective to reverse and even prevent cognitive impairment (24, 29, 36). An examination of the clinical studies of the effects of atypical APDs on CIS indicates 30%–50% of patients have large improvements (≥0.5 standard deviations) in specific cognitive domains or composite scores (92, 93). This is more useful than examination of group data because some individuals will become more impaired after treatment with specific drugs (89, 94). Development of biomarkers based on genetic variation is needed to provide targeted therapy for CIS.

Metabolic Side Effects of Antipsychotic Drugs

There is a marked variation in the ability of different typical and atypical APDs to cause insulin resistance and its consequences: weight gain, glucose dysregulation, type 2 diabetes mellitus, and lipid increases (95). Ziprasidone, aripiprazole, asenapine, iloperidone, and lurasidone produce the lowest overall increases in these measures and olanzapine and clozapine the greatest, with quetiapine, risperidone, and low-potency typical APDs intermediate (95). However, any APD, typical or atypical, may be associated with considerable weight gain in individual patients. The weight gain of atypical APDs may be mainly related to H_1 receptor blockade (37) and individual variations in the associated receptors and signaling systems for these and other receptors involved in energy metabolism. Monitoring of weight and lipids and encouragement of exercise and low-calorie, low-fat diets are needed to minimize the potential health hazards of APD treatment (95). A recent study found less weight gain with risperidone 2 mg/day supplemented by pimavanserin, a selective 5-HT_{2A} antagonist, compared to risperidone 6 mg/day. It is possible that the results of this study will generalize to other atypical APDs, thereby permitting a reduction in the doses and a corresponding decrease in metabolic side effects (96). Metformin has been helpful to reverse weight gain in some recent studies (97).

A recent meta-analysis of 23 studies, mean duration 62 weeks, found that atypical APDs as a group prevented relapse (29.0 versus 37%; $p = 0.001$), treatment failure ($p = 0.003$), and hospitalization ($p = 0.004$) (98). The number needed to treat, 17, was the same as that in the EUFEST trial (75). A recent pragmatic study of the antidepressant properties of olanzapine, quetiapine, risperidone, and ziprasidone in hospitalized, acutely psychotic patients reported a steady decline in depression ratings, equivalent for all drugs (99).

CONCLUSIONS

Atypical APDs are a diverse group of compounds, which cause fewer EPS at clinically effective doses than typical APDs. Clozapine and quetiapine produce the fewest EPS within the class and risperidone the most. Less risk for causing TD, which increases mortality, is a prime reason for preferring these agents, especially one of those that cause the fewest metabolic side effects, e.g., aripiprazole, lurasidone, or ziprasidone. The atypical APDs all have potent effects on one or more 5-HT

receptors. It is likely that the 5-HT_{2A}, 5-HT_{1A}, and 5-HT_{2C} receptor effects are the most important for their low EPS profile. Combined 5-HT_{2A} antagonism and 5-HT_{1A} partial agonism in vivo, relative to diminished D_2 receptor stimulation, may be the main cause of their differences from typical APDs. Because of the increased mortality and morbidity associated with EPS, the atypical APDs are recommended even though they do not surpass typical APDs in the ability to ameliorate psychosis. Clozapine has been shown to ameliorate positive symptoms in a large proportion of TRS patients, reduce the risk for suicide, and decrease overall mortality, but its side effects have led to underutilization. Olanzapine, at high doses, and aripiprazole may also be useful for TRS. In preclinical models of CIS, atypical APDs far surpass typical APDs for preservation or restoration of cognitive function. Complementary clinical evidence supports greater efficacy of some atypical APDs to improve some domains of cognition in some patients with schizophrenia. Numerous novel atypical APDs are in various stages of development, with one nearing the end of a phase III pivotal trial.

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