Chapter 5
Should High Dose or Very Long-Term Antipsychotic Monotherapy Be Considered Before Antipsychotic Polypharmacy?

Stephen M. Stahl and Debbi A. Morrissette

Abstract Standard doses of all antipsychotics target 60–80% occupancy of dopamine D2 receptors. However, many patients do not respond adequately in 2–6 weeks to standard doses of one or more antipsychotics given as sequential monotherapies, as suggested by contemporary treatment guidelines for schizophrenia. The reasons for such inadequate treatment responses are several, and include both pharmacokinetic and pharmacodynamic failures. That is, some patients at standard doses do not attain 60–80% D2 occupancy. Factors accounting for this include not only noncompliance, but also failure to absorb, rapid metabolism, CYP450 2D6 polymorphisms, and others. In addition, some patients at standard doses attain 60–80% D2 occupancy but do not respond adequately to this. Common problems among such patients are hostility, aggression, assaultiveness and violence as well as continued positive symptoms of psychosis. At least two approaches may be considered for such pharmacokinetic and pharmacodynamic failures: namely, high dose monotherapy, and very long treatment times when feasible. High doses of a single agent are actually better studied than antipsychotic polypharmacy with two or more antipsychotics, especially for certain agents, and provides an approach that is potentially simpler, safer and more effective for overcoming both pharmacokinetic and pharmacodynamic treatment failures, and allows a strategy to optimize antipsychotic

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treatment without polypharmacy. In addition, certain patients have very late onset improvements, measured in months or years, and very long term treatment data for antipsychotics in schizophrenia are beginning to emerge for patients who are not in urgent management situations as an alternative to antipsychotic polypharmacy.

Keywords Monotherapy • High-dose • Pharmacodynamic • Pharmacokinetic • Treatment resistance • Violence

Abbreviations

5HT	Serotonin
D	Dopamine
EPS	Extrapyramidal side effects
H	Histamine
M	Muscarininc
NET	Norepinephrine transporter
SERT	Serotonin transporter

5.1 Introduction

Schizophrenia is the most common form of psychosis, affecting approximately 1% of the population [1]. Based on the dopamine hypothesis of schizophrenia, standard treatment involves the use of antipsychotics to block dopamine D2 receptors. However, a portion of patients with schizophrenia are "treatment-resistant", failing to respond to multiple monotherapy trials of antipsychotics at standard doses. Unfortunately, insufficient treatment of psychosis often manifests as violent and aggressive behaviors that are dangerous to the patient and others and warrant treatment strategies that are not considered first-line, evidence-based practices. Such treatment strategies include both polypharmacy (simultaneous use of two antipsychotics) and high-dose antipsychotic monotherapy. In this chapter, we present an argument for why high-dose monotherapy should be considered for treatment-resistant patients prior to resorting to polypharmacy. Additionally, we discuss how "time" may be a necessary component of the treatment regimen for many patients with schizophrenia.

5.2 Symptoms and Circuits of Schizophrenia

Psychosis can be considered a set of symptoms in which a person's mental capacity, affective response and capacity to recognize reality, communicate, and relate to others is impaired [2]. The domains of schizophrenia include positive symptoms such as

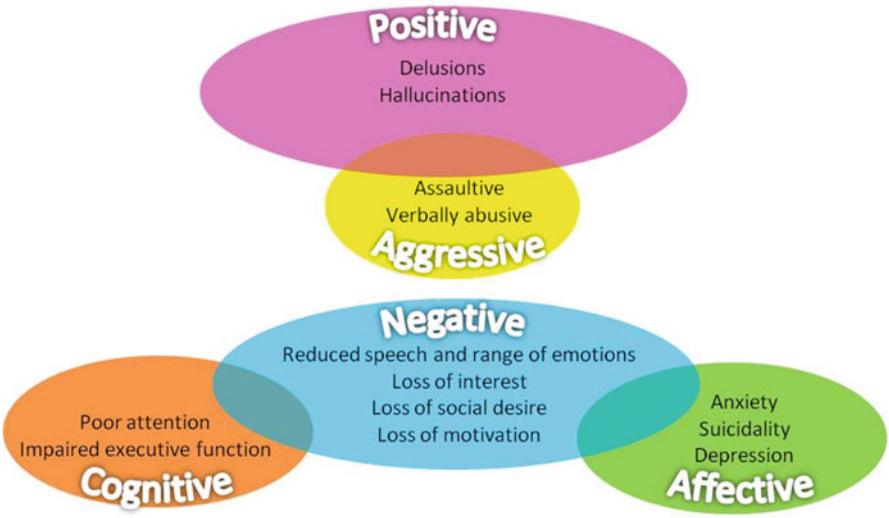

Fig. 5.1 Overlapping symptoms of schizophrenia. The symptom domains of schizophrenia (positive, negative, aggressive, cognitive, and affective) often have overlapping clinical features. It is not surprising that treatments that are effective for one symptom domain (e.g. positive symptoms) may alleviate symptoms from overlapping domains (e.g. aggressive symptoms) (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

hallucinations and delusions, negative symptoms including anhedonia, affective symptoms, cognitive symptoms, and aggressive symptoms (Fig. 5.1). In some instances, such as with positive and aggressive symptoms, the domains overlap; thus effective treatments may alleviate symptoms in more than one domain. Each of the symptom domains of schizophrenia is hypothesized to be due to dysfunction in specific neural circuitry (Fig. 5.2). Positive symptoms are thought to be caused by excessive dopamine in mesolimbic pathways; negative symptoms arise with low levels of dopamine in prefrontal cortex, mesocortical circuits, and reward areas, including the nucleus accumbens; cognitive symptoms are associated with hypoactivation of dopamine pathways in the dorsolateral prefrontal cortex; affective symptoms are due to underactivity in ventromedial and prefrontal cortices; and aggressive symptoms stem from excessive reactivity in the amygdala coupled with inadequate prefrontal regulation [2, 3].

5.3 Treating Schizophrenia

Treatment of schizophrenia with antipsychotics is focused on their ability to antagonize dopamine D2 receptors in the mesolimbic pathway. The first-generation antipsychotics were designed to tightly bind D2 receptors (Fig. 5.3). These conventional

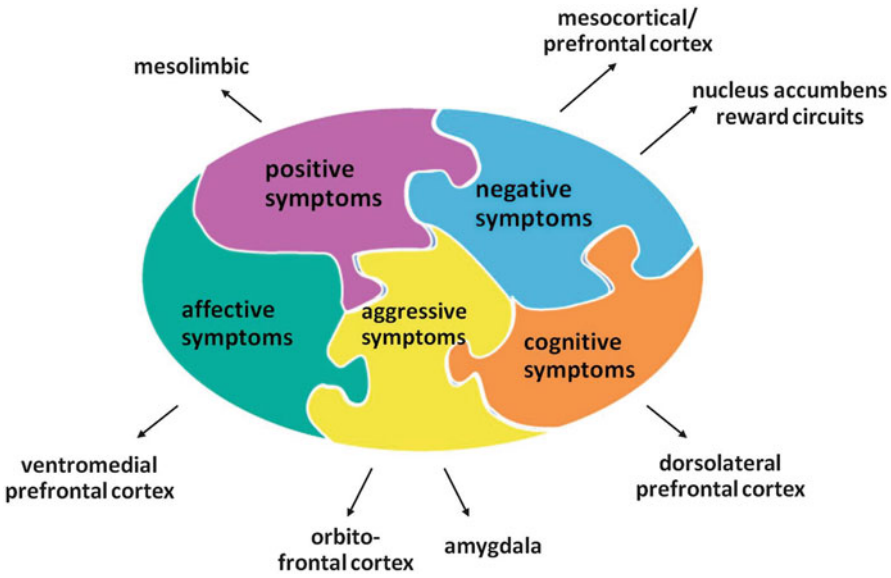

Fig. 5.2 The symptom domains and brain circuits of schizophrenia. Schizophrenia encompasses many different and sometimes overlapping symptom domains including positive, negative, affective, cognitive, and aggressive. Each of these symptom domains is thought to be related to dysfunction in discrete brain circuits. For example, hyperdopaminergia in the mesolimbic system is hypothesized to underlie positive symptoms of schizophrenia (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

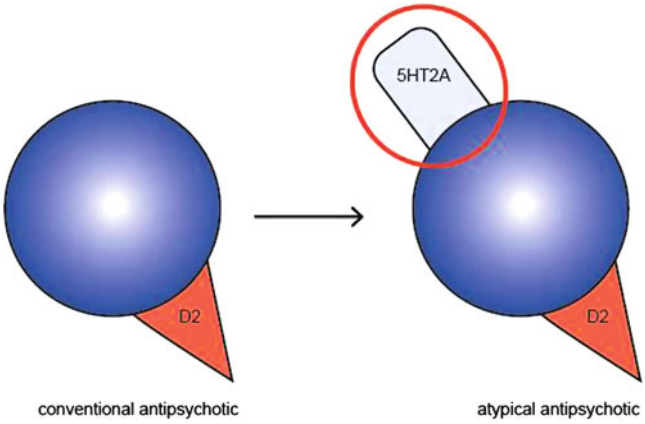

Fig. 5.3 Conventional vs. atypical antipsychotics. Conventional antipsychotics are defined by their antagonism of dopamine D2 receptors. What makes an antipsychotic atypical is the additional property of serotonin 5HT2A antagonism. In addition to D2 and 5HT2A receptor antagonism, individual atypical antipsychotics have a variety of binding affinities for additional receptors that gives each atypical agent a unique binding profile (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

antipsychotics are effective at ameliorating positive symptoms for many patients; however, the indiscriminate antagonism of D2 receptors in nigrostriatal as well as mesolimbic pathways often has disturbing motor effects including extrapyramidal symptoms (EPS) and akathisia. Additionally, antagonism of D2 receptors throughout the brain is hypothesized to actually worsen existing cognitive and affective symptoms by further impairing dopamine activity in already hypoactive brain areas (Fig. 5.4).

The second-generation antipsychotics were developed as a means to block D2 receptors while avoiding some of the negative consequences of excessive and indiscriminate D2 receptor antagonism. All atypical antipsychotics bind serotonin 5HT2A as well as D2 receptors. The antagonism of 5HT2A receptors tempers some of the effects of D2 receptor antagonism, potentially preventing the development of EPS (Fig. 5.5). Atypical antipsychotics also binds to other receptors in addition to D2 and 5HT2A; each individual agent has a unique binding profile that lends it additional therapeutic and adverse effects (Table 5.1). Most notably, although the atypical antipsychotics (as a class) have less propensity to cause EPS compared to the conventional antipsychotics, there is increased risk for cardiometabolic issues with the atypical antipsychotics [2].

As aforementioned, the primary focus of schizophrenia treatment is on the amelioration of positive symptoms. Biochemical and imaging studies have shown that blockade of at least 60% of D2 receptors by antipsychotic treatment is necessary in order to reduce psychosis [4]. At greater than 80% occupancy of D2 receptors, the threshold for EPS is reached in many patients. Thus, antipsychotics at standard doses aim to achieve between 60 and 80% D2 receptor occupancy (Fig. 5.6) [4–7].

5.4 When Standard Treatment Fails

Treatment guidelines advocate sequential trials of antipsychotic monotherapies at standard doses (Fig. 5.7) [8]. It is important that each monotherapy trial is continued for an adequate length of time; data indicate that the downstream effects of D2 receptor blockade by an antipsychotic often take more than 6 weeks to manifest [9, 10]. In fact, it may be necessary to treat schizophrenia with an antipsychotic for as long as 1–2 years before a significant improvement in psychotic symptoms is evident [2].

The failure of a patient to respond to standard dose antipsychotic monotherapy of adequate duration may be due to medication nonadherence or to either pharmacokinetic or pharmacodynamic failures [5]. Pharmacokinetic interactions describe the effects of a biological system on a medication and include rapid metabolization, cytochrome P450 polymorphisms, poor absorption (e.g. due to gastric bypass), and interactions with other medications/substances. In the case of pharmacokinetic failure, plasma drug levels do not reach adequate levels (and therefore D2 receptor occupancy is less than 60%) despite standard antipsychotic doses (Fig. 5.8a). Oftentimes, pharmacokinetic failure presents as a lack of both therapeutic and

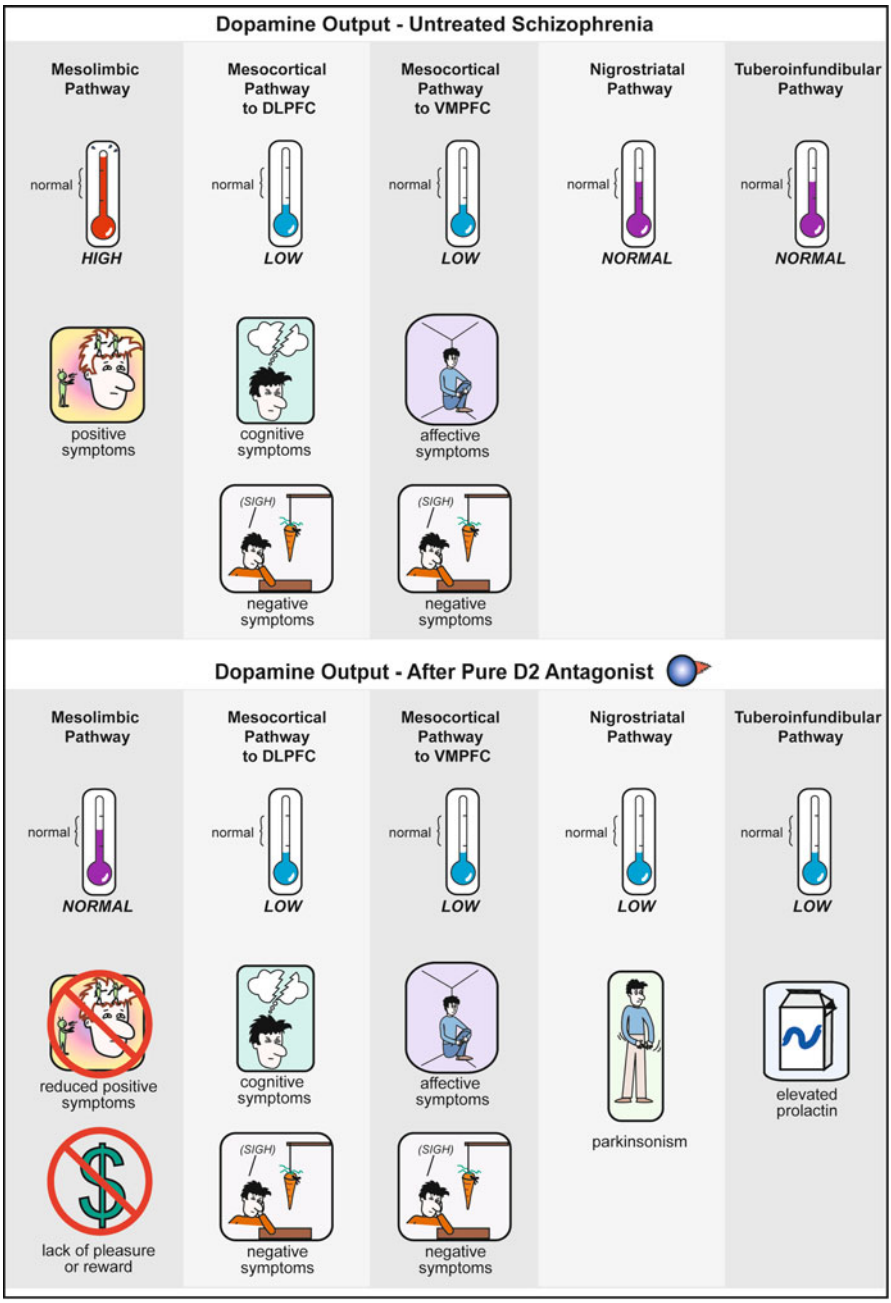

Fig. 5.4 Effect of D2 antagonism on various circuits. Although D2 antagonism in mesolimbic pathways can be an effective treatment for positive and aggressive symptoms of schizophrenia, it may actually exacerbate the cognitive and negative symptoms of schizophrenia. Additionally, blockade of D2 receptors in nigrostriatal and tuberoinfundibular pathways can lead to the development of troubling side effects such as movement disorders and hyperprolactinemia, respectfully (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

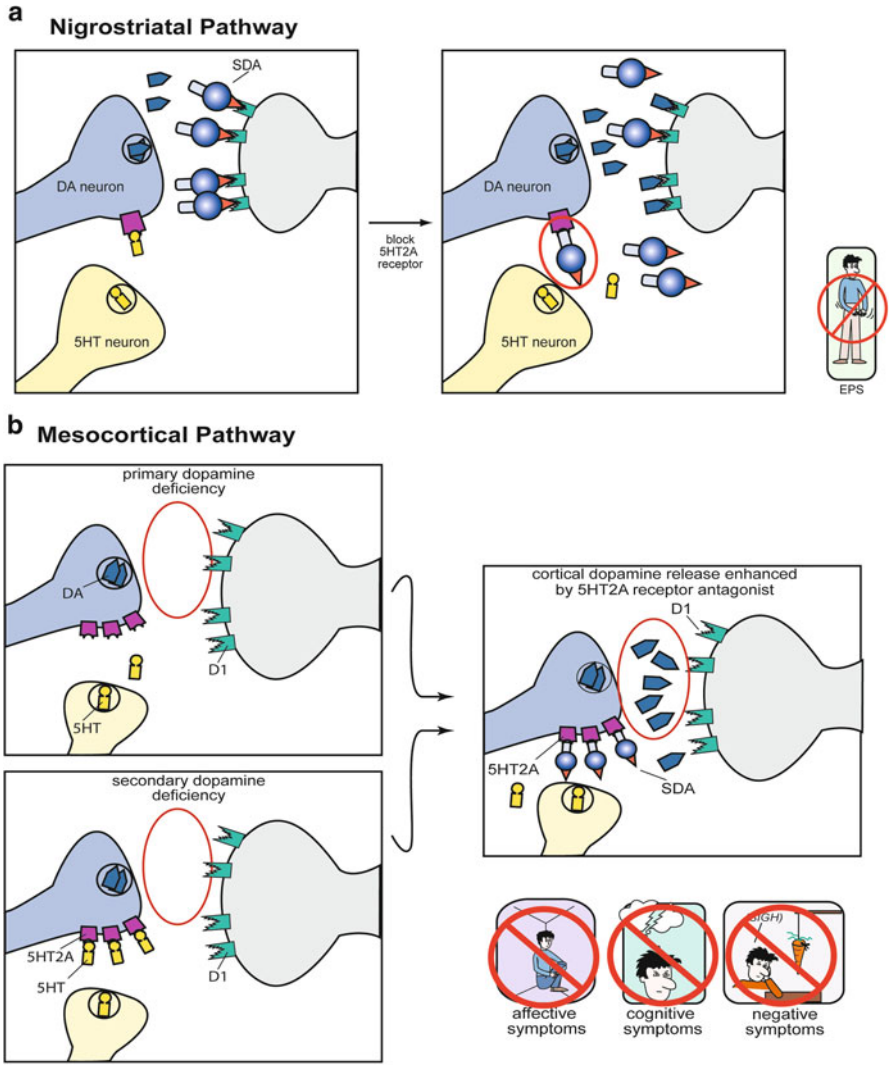

Fig. 5.5 Antagonism at serotonin 5HT2A receptors. **a** Dopamine D2 antagonism in the nigrostriatal pathway can lead to the development of extrapyramidal symptoms (EPS). The additional binding of atypical antipsychotics (i.e. serotonin dopamine antagonists or SDAs) to serotonin 5HT2A receptors found on dopaminergic neurons increases the release of dopamine in the striatum, preventing the development of EPS. **b** In the mesocortical pathway, binding of a SDA to 5HT2A receptors disinhibits cortical release of dopamine preventing further exacerbation of the hyperdopaminergic condition thought to underlie affective, cognitive, and negative symptoms of schizophrenia (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

Table 5.1 Vast molecular polypharmacy of atypical antipsychotics

Drug	D2 Antag	D2 PA	D3	5HT1A	5HT2A	5HT2C	5HT7	α1	M1	M3	H1
Aripiprazole		+++	+++	+++	++	++	+++	++			++
Asenapine	+++		+++	++	++++	++++	++++	+++	++	++	+++
Clozapine	+		+	+	++	++	++	+++	+++	++	+++
Iloperidone	+++		++	++	+++	+	++	+++			++
Lurasidone	+++		?	+++	++	+	++++	++			
Olanzapine	++		++		+++	++	+	++	++	++	+++
Paliperidone	+++		+++	+	++++	++	+++	+++			++
Quetiapine	+		+	+*	++*	+*	++*	+++	++*	++*	+++*
Risperidone	+++		+++	+	++++	++	+++	+++			++
Ziprasidone	+++		+++	++	++++	++	+++	++			++
Therapeutic Effects	Reduced positive symptoms	Reduced positive symptoms	Reduced positive symptoms; Reduced negative symptoms; Procognitive; Antidepressant	Reduced EPS; Reduced hyperprolactinemia; Antidepressant; Anxiolytic	Reduced EPS; Reduced hyperprolactinemia	Antidepressant	Reduced circadian rhythm dysfunction; Reduced negative symptoms; Procognitive	Reduced nightmares	Reduced EPS	Reduced EPS	Hypnotic
Side Effects	EPS; Hyperprolactinemia; Increased negative symptoms; Increased cognitive deficits; Sedation	Relatively lower risk of EPS	Unknown	Unknown	Cardiometabolic	Cardiometabolic	Unknown	Dizziness; Sedation; Hypotension	Constipation; Sedation; Dry mouth; Blurred vision	Cardiometabolic; Constipation; Sedation; Dry mouth; Blurred vision	Cardiometabolic; Sedation

+ weak binding affinity (100>Ki<1000)
++ moderate binding affinity (10>Ki<100)
+++ strong binding affinity (1>Ki<10)
++++ very strong binding affinity (Ki<1)
? No data yet available
*Binding property due primarily to the metabolite norquetiapine

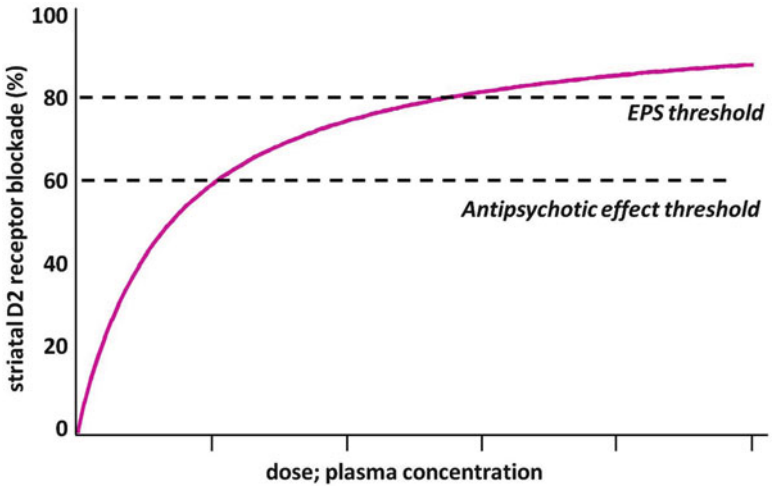

Fig. 5.6 Hypothetical thresholds for antipsychotic drug effects. Blockade of at least 60% of dopamine D2 receptors in the striatum is necessary to ameliorate positive symptoms of schizophrenia. However, when 80% or more of D2 receptors are blocked, extrapyramidal side effects (EPS) are likely to occur. Standard doses of antipsychotics are based on achieving the 60% D2 receptor occupancy without exceeding the 80% EPS threshold. Note that the slope of the curve flattens out with increasing dose; i.e. at higher doses, large increases in dose are needed in order to obtain substantial increases in D2 receptor occupancy (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

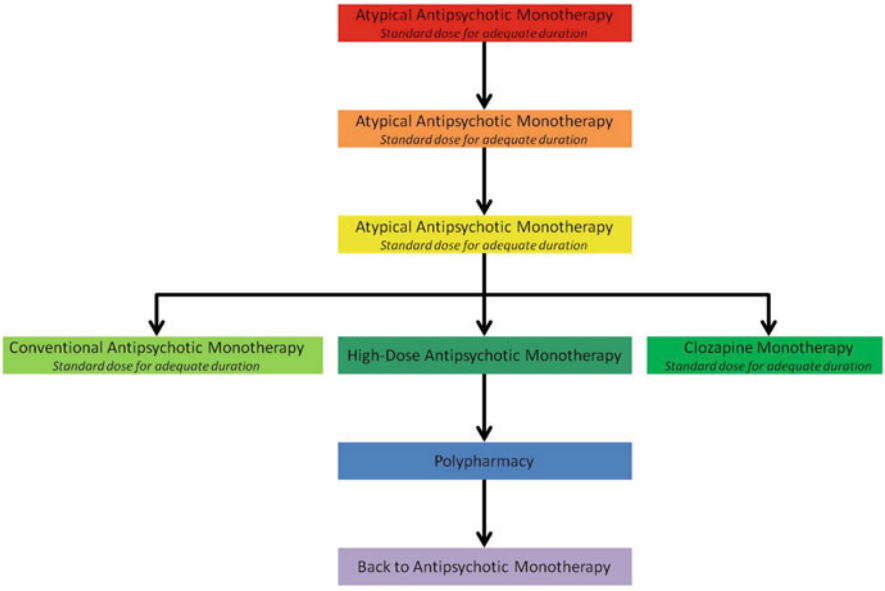

Fig. 5.7 Proposed treatment algorithm for treatment-resistant schizophrenia. Following inadequate response to several different atypical antipsychotic monotherapies, each at standard doses for an adequate length of time, there are several strategies that can be employed. Conventional antipsychotic monotherapy is not a first-line treatment due to the risk for adverse events including movement disorders; however, some patients may respond better to a conventional antipsychotic rather than an atypical one. Clozapine monotherapy is also reserved for treatment-resistant or violent patients due to increased risk for dangerous side effects (e.g. agranulocytosis). High-dose antipsychotic monotherapy also increases the risk for adverse effects but may be necessary in order to overcome pharmacokinetic or pharmacodynamic failures. Antipsychotic polypharmacy (the simultaneous use of two antipsychotics) should be reserved for cases when all other strategies fail. If polypharmacy proves unsuccessful, the patient should be returned to antipsychotic monotherapy (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

adverse effects at standard antipsychotic doses. Therapeutic drug monitoring can also sometimes be used to determine if a pharmacokinetic issue underlies treatment nonresponse (as long as nonadherence can be ruled out) [11, 12]. Solutions to pharmacokinetic failure include increasing the antipsychotic dose to achieve sufficient plasma levels (Fig. 5.8a), switching to a different antipsychotic monotherapy (such as one with a sublingual or intramuscular formulation), or simply taking the antipsychotic with food. Pharmacodynamic interactions describe how the medication affects the biological system [5]. With pharmacodynamic failure, there is a lack of therapeutic response despite attaining adequate plasma drug levels (Fig. 5.8b) [5]. This lack of response can be due to inherent issues in D2 receptor density or sensitivity. Data are accumulating to suggest that some patients develop a form of "dopamine supersensitivity" whereby increasing doses of antipsychotics may be necessary in order to reduce psychotic symptoms [13–15]. Interestingly,

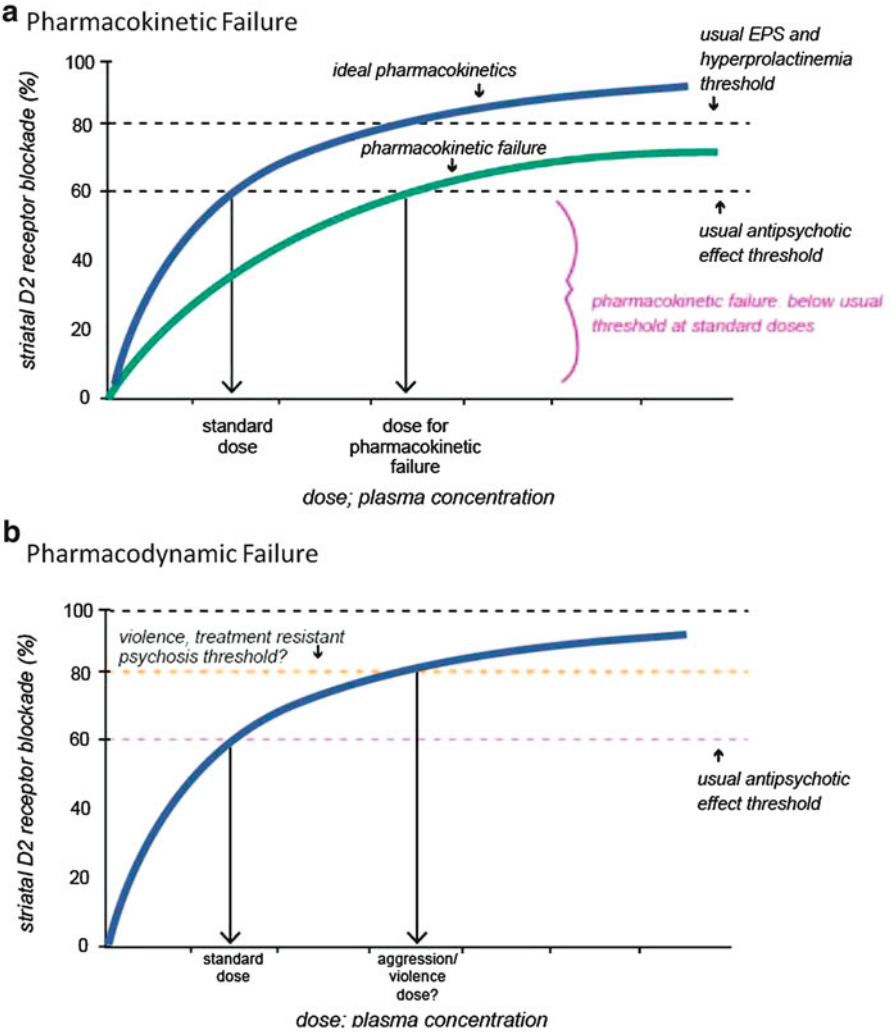

Fig. 5.8 Pharmacodynamic and pharmacokinetic failures. The failure of a patient to respond to antipsychotic treatment may be due to either pharmacokinetic or pharmacodynamic failures. **a** Pharmacokinetic failures describe cases where the therapeutic threshold (~60% D2 receptor occupancy) is not achieved despite dosing at standard therapeutic levels. **b** Pharmacodynamic failures describe cases where occupancy of greater than 80% of D2 receptors by a D2 antagonist maybe required before therapeutic effects are achieved; in other words, pharmacodynamic failures may alter the threshold for therapeutic effects from antipsychotic drugs (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

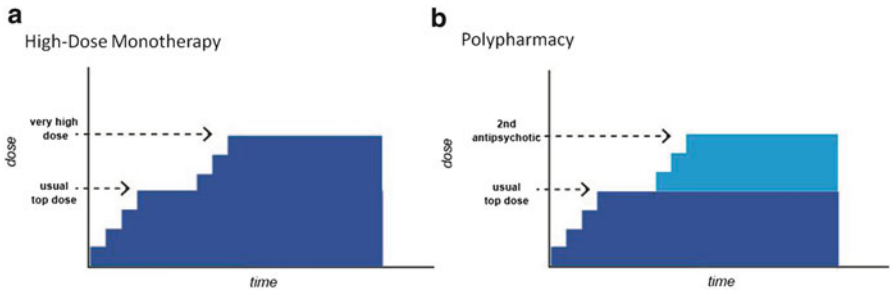

Fig. 5.9 Strategies to increase dopamine D2 receptor occupancy. For patients who are nonresponsive (and possibly violent) despite adequate trials of antipsychotic monotherapies, it may be necessary to employ strategies aimed at overcoming pharmacokinetic or pharmacodynamic failures. **a** High-dose therapy involves increasing an antipsychotic monotherapy beyond standard therapeutic doses using a slow uptitration. **b** For polypharmacy, a second antipsychotic is added to antipsychotic monotherapy, both at standard therapeutic doses (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

several factors can increase dopamine supersensitivity, including illicit drug use, social isolation, birth injuries, and genetic polymorphisms [15]. These treatment-resistant patients may present with excessively psychotic symptoms and aggression leading to institutionalization in forensic settings. For these individuals, it may be necessary to use treatment strategies aimed at greater than 80% occupancy in order to relieve psychotic symptoms (Fig. 5.8b).

Unfortunately, the most likely candidates for high-dose or otherwise heroic treatment measures are most often excluded from clinical trials because they are too psychotic, too substance-abusing, too aggressive, or too treatment-resistant to meet inclusion criteria or give informed consent [5, 16, 17]. Likely, these are the patients with pharmacodynamic or pharmacokinetic issues that require dosing to exceed the 80% receptor occupancy threshold (Fig. 5.8a and b). Unfortunately, it may be difficult for the prescribing clinician to know the best strategy for obtaining this high D2 receptor occupancy given the paucity of studies that include the patients who require it.

Essentially, there are two treatment strategies that can increase D2 receptor occupancy beyond the 80% threshold: polypharmacy (the simultaneous use of two antipsychotics) and high-dose antipsychotic monotherapy (Fig. 5.9). Although data supporting the use of antipsychotic polypharmacy are quite limited, this practice is very common in psychiatry; as many as 30% of patients receive antipsychotic polypharmacy [18, 19]. In fact, despite several guidelines recommending that polypharmacy should only be used as a last resort (following failure of several monotherapies and a trial of clozapine), many clinicians attempt polypharmacy as the rule, rather than the exception [12, 20]. Polypharmacy is often employed as a method for increasing dopamine D2 receptor occupancy, but also may be used to recruit additional properties of antipsychotics in order to treat non-positive symptoms such as depression and anxiety [20]. As mentioned previously, atypical antipsychotics

bind to a variety of receptors, some of which are hypothesized to have therapeutic benefit (Table 5.1). Unfortunately, each atypical antipsychotic also binds to receptors associated with increased risk of intolerable effects (e.g. sedation) so using two antipsychotics simultaneously can increase the side effect burden. There is also a risk of drug-drug interactions with antipsychotic polypharmacy that may exacerbate intolerable effects [21]. Simultaneous use of two antipsychotics also further complicates the treatment regimen; both intolerability and complicated treatment regimens are known to negatively impact treatment adherence [22]. On top of antipsychotic polypharmacy, additional drugs (such as anticholinergics) may be required in order to treat the intolerable side effects caused by polypharmacy, thus further increasing the cost and complication of the treatment regimen [8]. There are even some data to suggest that polypharmacy may increase the risk of serious consequences, including diabetes and cardiovascular mortality [23]. A recent study by Langle et al. [18]. also suggested that patients with schizophrenia on antipsychotic polypharmacy have a worse clinical course compare to those on monotherapy.

5.5 Time as a Drug

The downstream effects of D2 receptor blockade may take more than 2–6 weeks to manifest. In such cases, it may be that time itself is a "drug". In a study of 118 patients with first-episode schizophrenia or schizoaffective disorder, it was shown that only approximately 20% of patients had responded to antipsychotic treatment at 4 weeks; however, by week 52, 87% of patients had responded to treatment [10]. Individually, antipsychotic treatments including risperidone, olanzapine, and ziprasidone have shown that continued treatment over the long-term may be needed for some patients. A 12-month study of risperidone showed that the percentage of patients with schizophrenia showing 30% and 60% improvement increased significantly over the duration of the study (Janssen, data on file). Similar data were found in a 7 month study of olanzapine treatment for schizophrenia (Eli Lilly, data on file). Ziprasidone treatment of schizophrenia over 196 weeks also supported continued increases in remission rates and improvement in negative symptoms with time [24, 25].

Oftentimes a second antipsychotic is added to the first when there is inadequate response following only a few weeks of monotherapy; however, response to antipsychotic monotherapy may take as long as 16-weeks to manifest. Adding a second antipsychotic may therefore be superfluous and add only to the monetary and physical cost of treatment without adding any therapeutic benefit [8]. In support of this idea, recent studies have shown that as many as two-thirds of patients treated with antipsychotic polypharmacy can be successfully switched to monotherapy [19, 26]. The Essock et al. [19]. study in particular showed that not only did patients who were switched from polypharmacy to monotherapy have no worsening of symptoms or increased hospitalization, but many had reversal of the metabolic effects that were presumably due to antipsychotic polypharmacy.

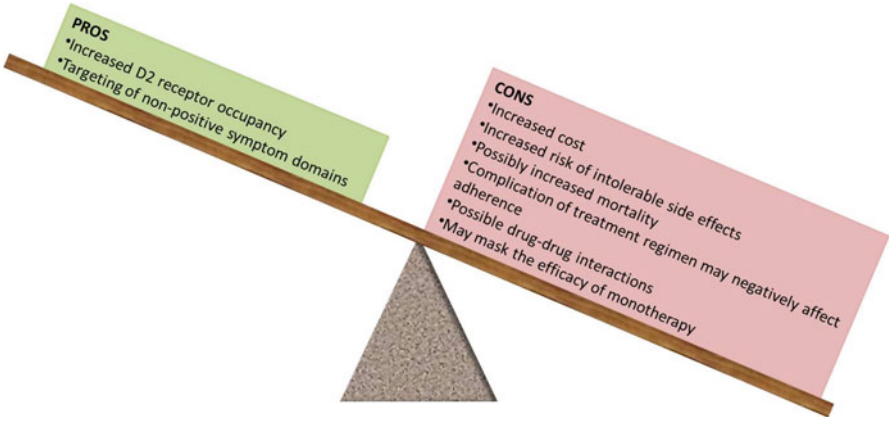

Fig. 5.10 Pros and cons of antipsychotic polypharmacy. The risks inherent with the simultaneous administration of two different antipsychotics far outweigh the possible benefits

5.6 High-Dosing of Atypical Antipsychotics

High-dose monotherapy is another strategy for increasing D2 receptor occupancy. Although this strategy may also increase the risk of intolerable side effects (notably EPS and akathisia) and is also associated with higher costs than standard dose monotherapy, there are significantly fewer disadvantages when compared with antipsychotic polypharmacy (Fig. 5.10). If it is necessary to increase D2 receptor occupancy in order to ameliorate positive symptoms in a particular subset of treatment-resistant, highly psychotic, and/or violent patients, logic would favor the simpler strategy that is associated with fewer adverse consequences.

As with all off-label practices, dosing of antipsychotics above standard therapeutic levels warrants informed consent and increased monitoring of the patient. As the pharmacodynamic and pharmacokinetic characteristics vary from patient to patient, it is virtually impossible to predict what daily dose will be needed in order to achieve an antipsychotic effect [27]. Antipsychotic dosing should be started at the low FDA-approved dose and then titrated upward accordingly until therapeutic efficacy or intolerable side effects occur [28]. The standard dose ranges for atypical antipsychotics and special considerations for high dosing are summarized in Table 5.2. In the following sections, we review the art and science of prescribing each of the FDA-approved atypical antipsychotics at high-doses. As antipsychotics are dosed at a level that blocks 60–80% of D2 receptors (with the exception of clozapine), it is important to note that any receptor binding that is stronger than that of D2 receptors will also be occupied at levels greater than 60% and will likely cause additional therapeutic and adverse effects. It is essential to keep the relative receptor binding affinities in mind when dosing an atypical antipsychotic at higher-than-usual levels to attain >80% occupancy of D2 receptors so that potential effects of binding to receptors other than D2 can be anticipated and monitored.

Table 5.2 Dosing atypical antipsychotics

Medication	Usual dose range (mg/day)[a]	Considerations for high dosing
Clozapine	300–450	Maximum dose is 900 mg/day. Doses above 550 mg/day may require concomitant anticonvulsant administration to reduce the chances of seizure
Risperidone	2–8	FDA-approved up to 16 mg/day. Very high doses usually not tolerated
Paliperidone	3–6	Maximum dose is generally 12 mg/day
Olanzapine	10–20	Some forensic settings up to 90 mg/day
Quetiapine	400–800	Some forensic settings up to 1,800 mg/day
Ziprasidone	40–200	Must be taken with food. PET data support >120 mg/day. Some forensic settings up to 360 mg/day may be appropriate
Aripiprazole	15–30	Higher doses usually not more effective and possibly less effective
Iloperidone	12–24	High dosing not well-studied and may be limited due to risk of orthostatic hypotension
Asenapine	10–20	High dosing not well-studied
Lurasidone	40–160	Must be taken with food. Nightly administration may improve tolerability. High dosing not well-studied but some patients may benefit from doses up to 160 mg/day

[a]Based on oral formulation in adults

5.6.1 Clozapine

Although clozapine is not recommended as a first-line treatment strategy due to the risk for serious adverse effects, most notably agranulocytosis, in patients who have failed several first-line atypical antipsychotic monotherapies a trial of clozapine is recommended. Clozapine has been well-documented for treatment-resistant patients and those who are violent or aggressive and is therefore recommended for such patients [29, 30]. Interestingly, the antiaggressive effects of clozapine are somewhat independent of its ability to improve positive symptoms [31]. Usual doses of clozapine (plasma levels of 400–600 ng/mL) actually bind less than 60–80% of dopamine D2 receptors but clozapine often has antipsychotic effects at 20–67% D2 occupancy suggesting that the antipsychotic effects of clozapine go beyond its ability to block D2 receptors [7]. This is not surprising given the vast binding profile of clozapine. Clozapine has relatively weak affinity for dopamine D2 receptors compared to its affinity for many other receptors including histaminic H1, adrenergic alpha-1, serotonin 5HT2B, and muscrinic M1 receptors, as well as a host of other receptors. Due to these high binding affinities for receptors other than D2, high-dosing of clozapine may cause sedation (due to antagonism of M1, H1, and alpha-1 receptors), hypersalivation and constipation (due to antagonism of M1), cardiometabolic issues (antagonism of H1 and 5HT2C receptors as well as the hypothesized

receptor "X"), and seizures (mechanism unknown) [2]. A meta-analysis by Davis and Chen [16] showed that patients with high plasma levels of clozapine responded more frequently than those with low plasma levels, indicating that doses above 400 mg/day may be required by many patients. Titration of clozapine to high doses should be done by increasing the dose every 5–7 days [5].

5.6.2 Risperidone/Paliperidone

Risperidone and its active metabolite paliperidone have similar receptor binding profiles with relatively strong affinity for dopamine D2 receptors. In the "average" patient, dosing of risperidone at 2–4 mg/day is associated with 70–80% D2 receptor occupancy and is rarely useful at doses above 8 mg/day [2, 6] Both risperidone and paliperidone are associated with increased risk of EPS in a dose-dependent manner, so care must be exercised when increasing the dose of these agents [16]. Titration of risperidone or paliperidone to high doses should be executed by increasing the dose every 5–7 days [5]. One pharmacokinetic difference between paliperidone and risperidone is that paliperidone is not metabolized in the liver so has less chance of drug-drug interactions or effects from cytochrome P450 polymorphisms [2]. Paliperidone may also be more tolerable, with less sedation and fewer EPS and should be dosed higher than risperidone [2]. Both of these agents are also available as long-acting depot formulations so an alternative strategy for achieving high D2 receptor occupancy would be the simultaneously use the depot formulation along with its oral counterpart.

5.6.3 Olanzapine

Olanzapine is perhaps the most well-studied atypical antipsychotic in terms of its use at high doses [8]. The risk of EPS is minimal, even at high doses of olanzapine; however, among the atypical antipsychotics olanzapine carries one of the greatest risk for cardiometabolic effects due to its strong binding affinity for histaminic H1 and serotonin 5HT2C receptors [2]. Doses of olanzapine between 10 and 20 mg/day often correspond to 60–80% D2 receptor occupancy but at plasma levels above 700–800 ng/mL olanzapine is associated with QTc prolongation [2, 7, 11]. Olanzapine has also been shown to improve both cognitive and aggressive behavior in patients with schizophrenia [31]. Several studies have indicated that olanzapine may be most effective at higher doses (40–60 mg/day) and may be useful in treatment-resistant violent patients in forensic settings at doses as high as 90 mg/day [8, 11, 20, 28]. Olanzapine titration to higher doses should take place with dose escalation every 5–7 days [5]. Olanzapine is also available in a long-acting depot formulation that can be supplemented with oral olanzapine to achieve high D2 receptor occupancy.

5.6.4 Quetiapine

Quetiapine is available as both immediate release (IR) and extended release (XR) formulations. Quetiapine binds dopamine D2 receptors with relatively weak affinity; it has far greater affinity for many other receptors including histaminic H1, adrenergic alpha-1, and serotonin 5HT2C receptors, as well as the norepinephrine transporter (NET). Because of this binding profile, high "Papa Bear" doses of at least 800 mg/day are usually required for quetiapine to have antipsychotic effects. Quetiapine has a very low risk of EPS associated with it, even at high doses, but is associated with a moderate risk for sedation and metabolic syndrome due to its high binding affinity for H1 and 5HT2C receptors. Most literature suggests that 1,200 mg/day is no more effective than 600 mg/day but anecdotal use in forensic settings of doses up to 1,800 may be effective in violent patients who tolerate but do not respond to lower doses [2, 16, 28]. Titration of quetiapine usually involves daily dose increases but the dose should be increased at a slower rate when exceeding 800 mg/day [2, 23].

5.6.5 Ziprasidone

Ziprasidone has a fairly high binding affinity for dopamine D2 receptors, surpassed only by its affinity for serotonin 5HT2A and 5HT1B receptors. Ziprasidone is associated with virtually no risk of metabolic effects and earlier concerns about QTc prolongation have not been supported [2]. Importantly, ziprasidone must be taken with food in order to optimize its absorption. There are data to suggest that higher doses of ziprasidone may be most effective and doses as high as 360 mg/day have been reported [2, 11, 20, 28]. For titration of ziprasidone to high doses, daily increases in dose can be done [5].

5.6.6 Aripiprazole

Aripiprazole is a unique member of the approved atypical antipsychotics. Rather than dopamine D2 receptor antagonism, it acts as a partial agonist at D2 receptors. What this partial agonism means is that in the presence of a full D2 receptor agonist (e.g. dopamine), aripiprazole will act as an antagonist at D2 receptors; however, in the presence of a D2 receptor antagonist (e.g. another antipsychotic), aripiprazole will act more as a D2 receptor agonist [2]. Due to this partial agonism and its very high binding affinity for D2 receptors, aripiprazole may actually be less effective for psychosis at higher doses and may reduce the effectiveness of another antipsychotic if an attempt polypharmacy is made [2]. Aripiprazole is not associated with significant risks for sedation, EPS, or metabolic syndrome but may cause akathisia in some

patients. Although the initial titration of aripiprazole can be rapid, dose increases after a steady state has been reached should be done every 10–14 days [5].

5.6.7 Asenapine, Iloperidone, and Lurasidone

Asenapine, iloperidone, and lurasidone are the newest atypical antipsychotics on the market so less is known regarding their use at high doses. When looking to use a high-dose strategy, it would be prudent to first try a high-dose trial of one of the older atypical antipsychotics that have more clinical experience.

Asenapine has moderate binding affinity for dopamine D2 receptors and is usually not associated with increased risk for EPS or metabolic syndrome. Asenapine is available only as a sublingual formulation and therefore may be a good option for patients who have pharmacokinetic failures in response to other antipsychotics due to hepatic metabolism or poor absorption [2]. Doses as high as 30–40 mg/day can be used but must be administered 10 mg at a time given at least 1-h apart. The titration of asenapine should be done by increasing the dose every 5–7 days [5].

Iloperidone is most distinguished by its high binding affinity for adrenergic alpha-1 receptors. Due to this binding property, iloperidone has a high risk of orthostatic hypotension and sedation associated with it, so must be titrated slowly and is not recommended for use at high doses [2].

Lurasidone is the newest antipsychotic approved for use in the United States. It has moderately high binding affinity for dopamine D2 receptors but is most notable for its antagonism of serotonin 5HT7 receptors. Lurasidone is approved up to 80 mg/day but may be more effective in some patients at doses as high as 160 mg/day [2]. Importantly, lurasidone should be taken with food to optimize absorption. Although the original trials on lurasidone suggested that side effect risk increased with higher dosing, recent data indicate that administration of lurasidone in the evening may minimize the risk of adverse side effects [32].

5.7 Conclusions and Future Directions

For many patients with schizophrenia, standard dose antipsychotic monotherapy is ineffective due to pharmacokinetic or pharmacodynamic failures. Often these patients are extremely psychotic and may be excessively violent and aggressive. It is imperative for the safety of both the patient and those with whom the patient interacts that effective treatment strategies are found and utilized. Unfortunately, these difficult-to-treat patients are most often excluded from clinical drug trials leaving a tremendous gap in our understanding of what treatment strategies to employ. Future research that includes treatment-resistant, violent, aggressive patients is needed in order to fill this gap. In the meantime, high-dose antipsychotic monotherapy is supported by both research and a wealth of clinical experience

with treatment-resistant and violent patients, particularly in forensic settings. It is also important that treatment with an antipsychotic monotherapy be given ample time to work as data are accumulating to suggest that many patients require long-term antipsychotic treatment before optimal therapeutic benefits are observed. Another strategy that is commonly employed for the treatment of these resistant patients is the use of antipsychotic polypharmacy. Although the practice of polypharmacy is common (even in not-so-difficult-to-treat patients), there is very little evidence to support its efficacy and many health, monetary, and practical issues should warrant using polypharmacy only as a last resort.

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