Fine Tuning the Use of Second Generation Antipsychotics

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Abstract

Background: The standard of care for schizophrenia treatment is the class of medications called the second generation antipsychotics (SGA). However, response rates of schizophrenia to SGA are far from ideal, and approximately one third of patients are likely to need high dosing, polypharmacy or switching of antipsychotics. To do this safely, clinicians’ knowledge of SGA pharmacodynamics, pharmacokinetics, therapeutic drug monitoring (TDM) levels, as well as, dose equivalency is imperative.

Aims:
• To review standard dosing, pharmacokinetic, and pharmacodynamic properties of the SGA.
• To further review the use of high, or “super-dosing”, of SGA.
• To investigate the clinical importance of monitoring drug levels for SGA.
• To describe possible SGA dose equivalency.

Materials and Methods: A Medline, PubMed (including observational studies, randomized controlled trials, meta-analyses, and systematic reviews) and textbook review was conducted without any date or language restriction. Each SGA (risperidone, paliperidone, lurasidone, ziprasidone, iloperidone, olanzapine, quetiapine, asenapine, aripiprazole, brexpiprazole and cariprazine) was searched and cross referenced with higher dosing, TDM, pharmacodynamics and pharmacokinetics. All possible studies were included. This paper focused on schizophrenia and use of SGA by oral route. Clozapine was excluded. Although it is an SGA, its properties and efficacy are different enough from other SGA and were felt beyond the scope of this current paper.

Discussion: A discussion of the concepts of pharmacokinetic failure, pharmacodynamic failure, Therapeutic Drug Monitoring, SGA dosing equivalencies and super dosing of SGA monotherapies is presented. SGA have pharmacodynamic and pharmacokinetic profiles which are distinctive and lead to unique side-effect profiles, drug-drug interactions, and clinical effects. For example, a SGA such as olanzapine, quetiapine and ziprasidone have evidence that high dosing is of value. Also, TDM drug monitoring is more clinically relevant in certain SGA like olanzapine, quetiapine, and risperidone. These differences are critically delineated.

Summary: This review article allows for a formal, evidence-based discussion regarding several advanced psychopharmacologic concepts which should allow the individual prescriber to elevate their prescribing practices.

Introduction

Antipsychotics are commonly classified as typical or first-generation antipsychotics, (FGA) and atypical or second-generation antipsychotics (SGA). The SGA antagonize dopamine-2 and serotonin-2A receptors where they classically have less potential to cause extrapyramidal symptoms (EPS). The SGA may be more beneficial for mood improvement and may carry a higher metabolic
side effect risk profile. SGA are now used as first line treatments for psychotic and bipolar disorders per most treatment guidelines. They are secondarily used for other mood and autism spectrum disorders. The Food and the Drug Administration (FDA) has recommendations for SGA dosing including the starting dose, target dose and maximum dose. However about 30 percent of patients will not respond to standard regimens and more heroic dosing strategies or complex polypharmacy approaches may have to be employed. Patients who exhibit hostility or aggression often are prescribed higher than recommended doses especially in inpatient forensic and state hospital settings. When the standard regimented dosing protocols fail, the art of psychopharmacology may need to be applied to achieve symptomatic remission.

The FDA has approved standard dosing for each of the SGA. However, these are based on studies completed with more stable psychiatric populations and are sometimes not adequate for informing clinicians how to treat the outliers: patients who are aggressive, assaultive, disruptive of the milieu, who have high comorbidity, or for patients who seem to clinically not respond to standard protocols. This may lead to unmitigated psychosis for the patient and a sense of helplessness for clinicians. In such situations, clinicians are faced with the dilemma of increasing the dose of SGA (possibly beyond the approved dose), starting antipsychotic polypharmacy (which is frowned upon by current guidelines) or to switch to a different SGA. Therapeutic drug monitoring (TDM) may be used to differentiate pharmacodynamic (the medication does not address the actual biological cause of symptoms) vs pharmacokinetic failure (the SGA is not dosed correctly/therapeutically) to address some of these situations. Clinicians also have to be aware of the side-effects that may increase with higher dosing or with polypharmacy. Side effects that were commonly encountered in FGA due to their property of unmitigated D2 receptors blockade (ex. acute parkinsonism, akathisia, withdrawal dyskinesias [D2 blockade rebound], tardive dyskinesia [D2 receptor super sensitization], hyperprolactinemia, seizures, cognitive impairment) are less commonly seen in SGA. This is due to SGA having 5HT-2A serotonin receptor blockade which increases nigrostriatal dopamine. It is also related to possibly more rapid dissociation of SGA from dopamine receptors where dopamine antagonism is enough for antipsychotic effect but not enough for EPS. Hence SGA with higher affinity, with tighter D2 binding (aripiprazole, cariprazine, lurasidone) have higher chances of motor side effects, while SGA with rapid dissociation and lower potency (quetiapine) have lower risk of motor side effects. Although the risk of motor side-effects is decreased, the risk of metabolic syndrome (weight gain, diabetes mellitus, hypercholesterolemia, and hypertension) increases, especially in SGA with H1 and 5HT-2C serotonin receptor antagonist properties. Cardiovascular events and liver, or pancreatic dysfunction may happen secondary to metabolic syndrome. Some SGA can independently cause liver dysfunction, myocarditis, and neutropenia (direct effects). H1 histamine receptor blockade can lead to sedation as well as binge eating, impulse control disorder and gambling. α1 adrenergic receptor blockade leads to hypotension, fatigue and sexual dysfunction. Anticholinergic blockade can lead to dry mouth, dental caries as well GI side effects and can contribute to cognitive impairment. Hyperprolactinemia can lead to weight gain, sexual dysfunction, as well as osteoporosis and osteopenia leading to fractures. Pneumonia and acute respiratory failure may occur due to central sedation while pulmonary embolism and venous thromboembolism may occur due to hypercoagulability (Table 2).

Besides providing informed consent to patients when using aggressive clinical strategies, it is important for the clinician to have a framework within which they can apply these practices safely. It is also important to remember that most psychosocial interventions (CBT, family intervention, social skills, and cognitive remediation) may help to decrease core symptoms, alleviate residual symptoms, improve social functioning, increase treatment adherence, lower relapse and decrease hospitalization. These when used early in conjunction with antipsychotics may lead to lower dosage possibly of the antipsychotics.

A general treatment algorithm regarding higher dosing of antipsychotics has been recommended by Morrissette and Stahl. This algorithm starts a theoretical clinical discussion which is the basis for this article and serves as a cutting-edge update regarding SGA prescribing. As an example, for a patient who has had a 4 to 6-week trial of a SGA with dose titration per the FDA with an inadequate treatment response, clinicians should obtain a trough plasma level for the SGA. If it is within the therapeutic range, and treatment adherence can be ensured, then consider this now a pharmacodynamic failure. In this case, the drug dosing achieved good plasma levels and then failed to alleviate symptoms. Alternatively, some patients may require extra D2 receptor antagonism, and a slightly higher, off-label dose can be utilized if there are no concomitant excessive side effects. However, sometimes, when drug levels are within therapeutic range (often towards the mid to lower end) without side effects, then pharmacodynamic failure may not have occurred and super dosing to the upper level limits or above may be considered. Of course, if the SGA is within therapeutic range and adverse effects are present then switching to a different SGA may be considered. Finally, if drug levels fall below the proposed therapeutic levels, regardless of approved dosing, a pharmacokinetic failure likely has occurred (rapid metabolizers) and super dosing should be
considered more routinely. Antipsychotic polypharmacy should only be tried after the above approaches have been undertaken.

**Clinical Updates and Discussion**

**Pharmacokinetics**

Pharmacokinetics relates to what the body does to each SGA. How the drug is absorbed, distributed, metabolized and excreted is influenced by many factors including: age, gender, disease, pregnancy, pharmacokinetic genotype, interactions with other drugs, diet and sometimes smoking.

SGA exhibit many similar pharmacokinetic characteristics. Important among these are good absorption from the gastrointestinal tract into the blood stream reaching maximal concentrations within 1–6 hours; variable systemic bioavailability (fraction absorbed) ranging from 5 to essentially 100 %, fast distribution from the blood into the central nervous system, often higher levels in brain CSF than in blood plasma; elimination mainly by hepatic metabolism/excreted renally, elimination half-life mostly between 12–36 hours, use of cytochrome P450 (CYP) and UDP-glucuronosyltransferases (UGT) as major metabolic enzyme systems. Of course, there are exceptions to the rule. For example, with quetiapine or ziprasidone; they display short (about 2–10 hour) elimination half-lives, whereas longer elimination half-lives of 72 hours are noted for aripiprazole, 91 hours for brexpiprazole and 48-96 hours for cariprazine (Table 1).

The main antipsychotic effects of the SGA are derived from their 60-80% antagonism of D2 receptors in the mesolimbic dopamine pathway. Beyond 80 % blockade is the nigrostriatal pathway often leads to EPS. This D2 occupancy can be measured most exactly with PET scanning; but may be more easily measured in clinical practice with plasma antipsychotic levels (TDM).

Pharmacokinetic failure occurs when patients do not reach the estimated 60 percent blockade on standard SGA dose. Some patients may require 61-80 % blockade, again suggesting that high SGA dosing is needed. If plasma levels are within therapeutic level, then the SGA can be dosed higher to maximize the level. Low plasma levels would suggest less than adequate drug concentrations available to bind 60 percent or more of the available D2 receptors.

There are number of factors that lead to this inter and intra-individual pharmacokinetic variability and may cause differences in plasma concentrations. Gender and age may play a role in these variabilities. Female sex hormones may influence the pharmacokinetic process and may lead to differences in efficacies of psychotropics as well. In the elderly, renal excretion and liver function may decrease significantly, glomerular filtration, tubular reabsorption, and secretion, weight and volume of distribution all change with age as well. For example, hepatic clearance can be reduced by up to 30%, which is mainly explained by lessened hepatic blood flow. Clinically, dosing needs to be adjusted up or down in these cases. TDM may guide clinicians in these situations.

Most SGA undergo Phase 1 hepatic metabolism by oxidative, reductive, and hydrolytic enzymes which are predominantly catalyzed by CYP hepatic enzymes (Table 1). Genetic polymorphism influences CYP enzyme activity but may also reduce with age or be affected by renal or hepatic disease. Genetic polymorphisms (especially CYP2D6) are vulnerable to mutation as previously noted. This leads to large inter-individual variability of drug concentrations in the body. Some patients are rapid versus slow metabolizers which can drastically change the halflife and clearance for the drug and change its plasma concentrations. Gender and age may play a role in these variabilities. Female sex hormones may influence the pharmacokinetic process and may lead to differences in efficacies of psychotropics as well. In the elderly, renal excretion and liver function may decrease significantly, glomerular filtration, tubular reabsorption, and secretion, weight and volume of distribution all change with age as well. For example, hepatic clearance can be reduced by up to 30%, which is mainly explained by lessened hepatic blood flow. Clinically, dosing needs to be adjusted up or down in these cases. TDM may guide clinicians in these situations.

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**Table 1. Pharmacokinetics of SGA**

The table lists the pharmacokinetics of all the SGA (except clozapine). It relates to therapeutic doses of the SGA. It includes oral bioavailability with and without food, half life, protein binding and major cytochrome P450 (CYP) isoenzymes responsible for metabolism. – denotes that oral bioavailability is not affected by food. The major source of reference for this data was online packet insert for each individual drug as well as the book “the Second generation Antipsychotics : A review of current treatment indications and dosing strategies”.

<table>
<thead>
<tr>
<th>Oral bioavailability %</th>
<th>Oral bioavailability with food</th>
<th>Half life</th>
<th>Protein binding</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>70</td>
<td>-</td>
<td>3</td>
<td>89</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>28</td>
<td>42</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>~30</td>
<td>60</td>
<td>7</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>96</td>
<td>-</td>
<td>18</td>
<td>93</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>9-19</td>
<td>18-38</td>
<td>18</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>87</td>
<td>-</td>
<td>30</td>
<td>93</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>9</td>
<td>-</td>
<td>7</td>
<td>83</td>
</tr>
<tr>
<td>Asenapine</td>
<td>35</td>
<td>-</td>
<td>24</td>
<td>95</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>87</td>
<td>-</td>
<td>75</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>95</td>
<td>-</td>
<td>91</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>High</td>
<td></td>
<td>48-96</td>
<td>97%</td>
</tr>
</tbody>
</table>
When combining drugs that are inhibitors or inducers of drug metabolizing enzymes, pharmacokinetic drug-drug interactions may occur if the SGA is a substrate of the inhibited or induced hepatic enzyme. These pharmacokinetic interactions occur mostly at the metabolic level and involve changes in activity of CYP Antidepressants (mostly inhibitors of CYP2D6 such as fluoxetine/paroxetine) and antiepileptics (inducers of CYP1A2 and CYP3A4 such as carbamazepine) are a major source of these interactions. For example, these SSRIs increase plasma levels of risperidone/arypirazole/brexpiprazole (substrates for CYP2D6) while, carbamazepine greatly reduces it. Similarly, olanzapine (substrate for CYP1A2) levels are increased with fluvoxamine which is a CYP1A2 inhibitor and decreased with carbamazepine. Quetiapine (substrate for CYP3A4) levels are increased with valproate and decreased with carbamazepine and phenytoin (CYP1A2 and CYP3A4 inducers); aripiprazole (substrate for CYP2D6) is decreased with valproate and ziprasidone (substrate for CYP3A4) is decreased with carbamazepine\textsuperscript{25,24} (Table 1). SGA with high oral bioavailability are less likely to be affected by diet changes or first pass metabolism drug-drug interaction\textsuperscript{25}. Also, SGA are often highly protein bound (Table 1) Co-administration with other drugs which are also highly protein bound (furosemide, spironolactone, ibuprofen, valproic acid etc) may lead to displacement of the antipsychotics and may increase their plasma level.

Finally, smoking is associated with induction of CYP1A2 and may influence elimination of SGA, such as olanzapine, whose metabolism is mainly dependent on CYP1A2\textsuperscript{25}. This is especially important if a patient is smoking more than 10 cigarettes per day. Cessation of heavy smoking (as occurs often while inpatient) under therapy with a CYP1A2 substrate such as olanzapine may require dose reduction\textsuperscript{26}. If smoking escalates later during outpatient treatment, then the dose must be escalated to avoid psychotic breakthrough symptoms. Pharmacokinetics of individual SGA are reviewed in Table 1.

**Pharmacodynamics**

Pharmacodynamics regarding the SGA include their mechanism of action, especially their effects on neurotransmitters and their receptors. (Table 2) This may be additionally influenced by neurogenesis, neurodevelopment/migration and pharmacogenomics\textsuperscript{11,27}. For some patients with psychosis who are taking SGA, there may be no symptom relief with continued psychosis despite even antagonism of 80% of their D2 receptors. This could be attributed to “pharmacodynamic” failure\textsuperscript{4}. Despite achieving adequate plasma drug levels and receptor binding, treatment resistant patients might continue with positive, cognitive and/or aggressive symptoms. The D2 receptor antagonism mechanism of the specific SGA has now failed to provide a therapeutic clinical response regardless of an appropriate pharmacokinetic attempt. In other words, the patient’s psychosis, likely is not caused solely by D2 receptor pathology or an aberrance of the mesolimbic dopamine pathway. The SGA has not addressed the real cause of disease.

Genetic factors can drive pharmacodynamic processes such as interactions of specific SGA with the patient’s genetically determined receptor, enzyme, transporter, carrier protein, or ion channels. Specific sensitivity or protein conformation for all of these are involved in mediating SGA treatment outcome which leads to variability in drug response at the level of the individual patient. Sometimes called “a sample size of one, n=1”. For example, there may be a lack of D2 receptor sensitivity or even hypersensitivity. In psychotic disorders, variation in the dopamine receptor genes (DRD2, DRD3 and DRD4) have extensively been investigated regarding antipsychotic treatment response\textsuperscript{28}. Oftentimes genetic studies, however, do not yield robustly replicable results. Dystonia and TD which may be induced by SGA have been associated with gene variations as well. An example of pharmacogenomics is association of antipsychotic induced development or worsening of Parkinsonism with polymorphisms of RGS2 (regulator of G-protein signaling 2), a gene which plays a role in dopamine receptor signaling\textsuperscript{29}. Pharmacodynamics of individual SGA is reviewed in Table 2.

**Super Monotherapy Dosing of SGA**

The Research on East Asia Psychotropic Prescription (REAP) study reported that the factors associated with higher dosages of antipsychotic use were younger age, multiple previous admissions to hospital, presence of active delusions and antipsychotic polypharmacy\textsuperscript{30}. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study which compared four SGA including (olanzapine, quetiapine, risperidone and ziprasidone) and the FGA perphenazine found that higher dosing may be needed in patients with chronic schizophrenia\textsuperscript{31}. Another study also reported and explained that “heroic measures”, such as high SGA dosing and antipsychotic polypharmacy, are often used in more treatment resistant cases of psychotic disorder when aggression and impulsivity are a key safety concern. This also occurs when pharmacokinetic and pharmacodynamic failures are suspected\textsuperscript{32}. Yet another study noted that elevated dosing occurs more often with forensic patients diagnosed with schizophrenia and most associated with increased SGA dosage were the presence of ongoing delusions and conceptual disorganization\textsuperscript{13,33}. Accordingly, as positive symptoms intensify and/or are refractory to treatment, doses are naturally increased. Overall, studies show that the practice of using high dose antipsychotics is increasing and is often associated with antipsychotic polypharmacy\textsuperscript{34}. 

Table 2. Pharmacodynamic Receptor Actions of SGA

<table>
<thead>
<tr>
<th>Receptor Action</th>
<th>Clinical effects</th>
<th>Clinical application</th>
<th>Example SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2 Antagonism</td>
<td>Sexual dysfunction (Hyperprolactinemia) Akathisia, dystonia, NMS, Parkinsonism, withdrawal dyskinesia, TD Avolition, cognitive impairment, weight gain, seizures</td>
<td>Antipsychotic Antimanic Anti-Aggression</td>
<td>Lurasidone, Asenapine, Paliperidone, Risperidone, Ziprasidone, Iloperidone, Olanzapine, Quetiapine</td>
</tr>
<tr>
<td>D2 partial Agonism</td>
<td>Same as above minus avolition</td>
<td>Same as above plus Antidepressant</td>
<td>Aripiprazole, Brexipiprazole, Cariprazine</td>
</tr>
<tr>
<td>D3 partial Agonism</td>
<td>Less EPS possible, improved cognition, attention, concentration Improved wakefulness</td>
<td>Anti-restless leg syndrome Antidepressant</td>
<td>Aripiprazole, Brexipiprazole, Cariprazine</td>
</tr>
<tr>
<td>SHT1a partial agonism</td>
<td>Reduce negative affect</td>
<td>Anxiolytic Antidepressant</td>
<td>Aripiprazole, Lurasidone, Asenapine, Ziprasidone, Cariprazine, Brexipiprazole</td>
</tr>
<tr>
<td>SHT2a antagonism</td>
<td>Reduce EPS Reduce negative effect Improve sleep efficiency</td>
<td>Antidepressant, hypnotic</td>
<td>Lurasidone, Asenapine, Paliperidone, Risperidone, Ziprasidone, Iloperidone, Olanzapine, Quetiapine, Cariprazine</td>
</tr>
<tr>
<td>SHT2c antagonism</td>
<td>Decrease negative affect Decrease metabolism Improve cognition, weight gain</td>
<td>Antidepressant</td>
<td>Asenapine, Ziprasidone, Olanzapine, Quetiapine, Aripiprazole, Brexipiprazole, Cariprazine</td>
</tr>
<tr>
<td>SHT6 antagonism</td>
<td>Entrain circadian rhythm</td>
<td>-----</td>
<td>Asenapine, Iloperidone</td>
</tr>
<tr>
<td>SHT7 antagonism</td>
<td>Entrain circadian rhythm Improve cognition</td>
<td>Antidepressant, anti-negative symptoms, circadian rhythm, memory, learning and sleep</td>
<td>Lurasidone, Asenapine, Iloperidone, Brexipiprazole, Aripiprazole</td>
</tr>
<tr>
<td>α1 antagonism</td>
<td>Orthostasis, sedation</td>
<td>Antihypertensive Anxiolytic Anti-nightmares</td>
<td>Risperidone, Iloperidone, Asenapine, Olanzapine, Quetiapine, Aripiprazole, Brexipiprazole, Cariprazine</td>
</tr>
<tr>
<td>α2 antagonism</td>
<td>Same as above plus improved cognition</td>
<td>Anti-ADHD Antihypertensive Anxiolytic hypnotic</td>
<td>Risperidone, Paliperidone, Asenapine</td>
</tr>
<tr>
<td>M1 antagonism</td>
<td>Dry mouth, dental caries blurred vision, nausea, vomiting, diarrhea and constipation, worsened cognition, tachycardia, urinary retention</td>
<td>Anti- EPS</td>
<td>Olanzapine, Aripiprazole, Brexipiprazole, Cariprazine</td>
</tr>
<tr>
<td>H1 antagonism</td>
<td>Somnolence, weight gain increased appetite, binge eating, impulse control disorder and gambling,</td>
<td>Anxiolytic, hypnotic</td>
<td>Olanzapine, Quetiapine, Asenapine, Aripiprazole, Brexipiprazole, Cariprazine</td>
</tr>
<tr>
<td>NET inhibition</td>
<td>Increase wakefulness Improved cognition, attention, concentration Reduce negative affect</td>
<td>Anxiolytic, antidepressant, Anti-ADHD</td>
<td>Ziprasidone, Quetiapine</td>
</tr>
<tr>
<td>SERT inhibition</td>
<td>Reduce negative affect</td>
<td>Anxiolytic, antidepressant Ziprasidone</td>
<td></td>
</tr>
</tbody>
</table>

As mentioned previously, definite pharmacokinetic or possible pharmacodynamic failures may make high SGA dosing necessary to obtain possibly greater symptom control. To review, due to patient individual variability, a patient may not achieve a 60% D2 receptor blockade on standard dose, and he/she likely would continue to exhibit psychotic symptoms at which point higher than approved dosing may be beneficial and likely warranted in this specific clinical situation. If plasma levels are low, then super dosing likely should be standard of care. If a patient has achieved greater than 80% blockade or is at maximal approved dosing with maximal plasma levels on standard dose and continues to exhibit positive psychotic symptoms (especially if side-effects are present), then a
pharmacodynamic failure has occurred. For some treatment refractory patients, who have several pharmacokinetic/pharmacodynamic failures well beyond the assumed 80% blockade, then using heroic elevated SGA dosing may be needed for these outlying cases (especially if they do not manifest EPS, QTc prolongation, etc.). In fact, literature seems to suggest that a significant portion of patients could tolerate dosing beyond normal ranges.

New prescribers always must balance the concept that with increased dosage comes the risk of increased side effect burden. For SGA this includes metabolic syndrome (weight gain, diabetes mellitus, hypertension), QTc prolongation, EPS and TD. Therefore, it is always recommended to start low within the FDA approved range to minimize initial side effects, facilitate adherence and then to build rapport along with escalations in dosing. Only about 20 % of patients respond within a few weeks. Earlier monitoring of plasma levels and confirming diagnosis are some steps that may be utilized at this clinical juncture. Next, pharmacokinetic failure should be considered. Only after these have occurred and informed consent given; SGA can be slowly increased outside the dosage recommended by the FDA. The end point would be either clinical effect or unbearable/unsafe side-effects. High dosing is reviewed in Table 3.

**Therapeutic Drug Monitoring (TDM) with SGA**

The therapeutic reference range is defined as the range of drug concentrations in blood that suggests a lower limit below which a drug induced therapeutic response is relatively unlikely to occur and an upper limit above which tolerability decreases or where it is relatively unlikely that therapeutic improvement will occur.

### Table 3. SGA Dosing and TDM Levels

This table includes Food and Drug administration (FDA) approved treatment indications and dosing strategies (initial dose, titration dose, target dose and maximum dos). All except high dosing strategies was garnered from regulatory package inserts. For high dosing multiple sources were used. Key reference was book by O’Dell and Schwartz on second generation antipsychotics. Other key references were from articles by Citrome et al, Morrissette et al, Stahl et al and Moore et al. As it is still debated whether TDM should be routinely used in clinical situations AGNP came up with 4 levels of recommendations based on empirical evidence. Level 1 is strongly recommended; Level 2 is recommended, Level 3 is Useful and Level 4 is Potentially useful. These levels of recommendations are more thoroughly explained in the text related to TDM. Alert levels: are levels of the drug to warn the physician when the drug concentrations are considered to be too high and potentially harmful. As per the article alert levels should lead to dose reduction if patient exhibits adverse reaction. Abbreviations: bid, twice daily.

<table>
<thead>
<tr>
<th></th>
<th>Initial dose</th>
<th>Titration</th>
<th>Target dose</th>
<th>Maximum dose</th>
<th>High dosing</th>
<th>TDM ng/ml</th>
<th>Levels of recommendations as per AGNP</th>
<th>Alert levels ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>1 mg/day</td>
<td>1-2 mg/day</td>
<td>4-6 mg/day</td>
<td>16 mg/day</td>
<td>Higher doses not tolerated</td>
<td>50-200</td>
<td>Level 2</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>6 mg/day</td>
<td>3 mg/5 day</td>
<td>6 mg/day</td>
<td>12 mg/day</td>
<td>Higher doses not tolerated</td>
<td>20-60</td>
<td>Level 2</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20 mg bid</td>
<td>200 mg bid</td>
<td>20-80 mg bid</td>
<td>100 mg bid</td>
<td>Studies show efficacy up to 360 mg/day</td>
<td>20-60</td>
<td>Level 2</td>
<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td>1 mg bid</td>
<td>2,4,6,8,10,12, 6-12 mg bid</td>
<td>12 mg bid</td>
<td>Limited data for high dosing, for safety has been studied up to 32 mg</td>
<td>5-10</td>
<td>Level 3</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>40 mg/day</td>
<td>-</td>
<td>40-160 mg/day</td>
<td>160 mg/day</td>
<td>Limited data for high dosing. Safety has been studied up to 600 mg</td>
<td>Higher than 70</td>
<td>Level 4</td>
<td>120</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5-10 mg/day</td>
<td>5 mg/1 week</td>
<td>10 mg/day</td>
<td>20 mg/day</td>
<td>Forensic settings up to 90 mg/day</td>
<td>20-80</td>
<td>Level 4</td>
<td>150</td>
</tr>
<tr>
<td>Quetiapine IR/XR</td>
<td>25 mg bid</td>
<td>50-300 mg/day</td>
<td>400-800 mg/day</td>
<td>800 mg/day</td>
<td>Forensic settings up to 1800 mg/day</td>
<td>100-500</td>
<td>Level 4</td>
<td>1000</td>
</tr>
<tr>
<td>Asenapine</td>
<td>5 mg bid</td>
<td>5 mg bid/1 week</td>
<td>5 mg bid</td>
<td>10 mg bid</td>
<td>Not well studied</td>
<td>2-5</td>
<td>Level 4</td>
<td>4</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10-15 mg /day</td>
<td>5 mg/2 weeks</td>
<td>10-15 mg /day</td>
<td>30 mg/day</td>
<td>Higher dosing usually not more effective and possibly less effective</td>
<td>150-500</td>
<td>Level 4</td>
<td>1000</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>1 mg/day</td>
<td>2 mg/day on day 5</td>
<td>2.4 mg/day</td>
<td>4 mg/day</td>
<td>No data</td>
<td>40-140</td>
<td>Level 4</td>
<td>3</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>1.5 mg /day</td>
<td>3 mg/day on day 2</td>
<td>1.5-6 mg/day</td>
<td>6 mg/day</td>
<td>No data</td>
<td>10-20</td>
<td>Level 4</td>
<td>3</td>
</tr>
</tbody>
</table>
Unlike the well-studied lithium (Bipolar) and tricyclic antidepressant (Depression) blood levels where this clinical approach is well-defined, the SGA have much smaller trials where levels are correlated to standard trial dosing but not necessarily clinical or safety outcomes. However, these levels do suggest what plasma levels of SGA should be achieved with standard dosing and this can guide treatment to some degree.

TDM is a rough measure of the pharmacodynamic and pharmacokinetic aspect of prescribing and also checks for patient non-adherence. It enables further tailoring of SGA dosage for the individual patient by combining the quantification of drug concentrations in blood, information on drug properties and patient characteristics. It can be used for problem solving. For example, it can help differentiate between pseudo drug resistance (characterized by lower plasma levels due to rapid metabolization or poor adherence (aka pharmacokinetic failure) or true drug resistance (appropriate levels with receptors insensitivity aka pharmacodynamic failure).

The clinical importance of having TDM for antipsychotics is still a matter of debate but it can be useful in case of treatment resistance. The D2 occupancy of SGA is indirectly related to TDM levels (plasma SGA level)\(^1\). SGA Steady-state concentrations in blood tend to correlate with concentrations in brain and ultimately D2 receptor occupancy, much better than they correlate to the prescribed dosages. The TDM task force of the working group on neuropsychopharmacology (Arbeitsgemeinschaft fuer Neuropsychopharmakologie und Pharmakopsychiatrie, AGNP) has divided TDM outcomes into 4 levels: Level 1 (strongly recommended) is for psychotropics like lithium and carbamazepine where TDM is standard of care and highly predictive of outcomes and adverse effects. There is highest possibility of response, when the psychotropic is at high therapeutic concentrations (normal lab value) and, there is risk also of adverse effects and some toxicity. For Level 2 (recommended), ranges were obtained from psychotropics at the therapeutically effective doses and related to ultimate clinical effects. Hence TDM is recommended for dose titration and for special indications or problem solving as mentioned above; TDM will increase the probability of response in non-responders. For SGA at Level 3 (useful) suggests that ranges were computed from drug concentrations at approved doses but not yet linked to clinical outcome. Here, TDM is useful for special indications or problem solving and determining why clinical consequences may have occurred. Clinical improvement may be attained by dose increase in non-responders who display low drug concentrations. For level 4 (potentially useful), drug concentrations in blood do not correlate with clinical effects due to a unique pharmacology of the drug, e. g., irreversible blockade of an enzyme, or dosing can be easily guided by clinical symptoms, e. g., sleep induction by a hypnotic drug. Here, TDM is not recommended for dose titration, but may be potentially useful for special indications or problem solving such as patient adherence\(^11\). (Table 3) Accordingly, the alert levels are significant if patient has adverse effects, but in case these are absent then the drug can be continued if the risk is symptom relapse\(^11\) (Table 3). Finally, AGNP also recommends getting a TDM level when the patient is clinically improved (remitted) so that one can have a baseline for individual patients, which can serve as a guideline to differentiate between future non-adherence or pharmacokinetic alteration in case of relapse or side-effects\(^11\). Later, if needed, the oral or intramuscular dose can be re-titrated to now match the patient’s ideal plasma level.

TDM can be used for special indications. There are also certain populations where getting a TDM level can be more useful than others. Elderly patients are more susceptible to side effects and have less functional metabolic reserve\(^15\). Forensic psychiatric patients with risk of violence and aggressive behavior many times need to be treated with higher doses and a TDM level is highly useful and can be used to delineate their optimal blood levels for symptom control\(^13\). Also, when an SGA changes from the original brand name to a novel generic preparation, or if one generic is changed to another, the actual dose/bioavailability may fluctuate by 15-20%. TDM can be used to make sure that the new preparation oral dose ultimately achieves the absolute plasma level afforded by the original brand name SGA. This should better ensure a sustained clinical response. TDM of SGA is also useful similarly when an oral SGA is converted to the long acting intramuscular depot formulation or vice versa for similar reasons. The goal is to maintain the optimal plasma level regardless of drug preparation chosen. SGA Dosing, as well TDM, are reviewed in Table 3.

SGA Dosing equivalence

When managing schizophrenia treatment resistance, violent aggressivity or remarkable adverse effects, SGA switching or the use of first generation antipsychotics (FGA) is often necessary. To choose an appropriate target dose for the new SGA, two methods can be used; either titrating the dose to the maximum effectiveness and stopping when tolerance/side effects emerge or using dose equivalency data. However, the development of valid and reliable methods of dose comparison is yet to be fully realized as compared to first generation antipsychotics (FGA). Various methods have been used to calculate the dose equivalency and can be broadly divided into calculated methods and consensus methods\(^16\) (Table 4).

Calculated methods can be further divided into; chlorpromazine (FGA) equivalents, the classical mean...
The methods are broadly divided as Consensus method and Calculated method. These methods have been explained in the text related to SGA dose equivalence. The SGA are compared to 1 mg equivalence of olanzapine in all the below mentioned, except for the maximal near effective method. The calculated method has been further divided into the chlorpromazine equivalence (Linear equation) method, the daily defined dose, the minimum effective dose, and the classical mean dose method, and the maximum dose (near effective) method. Although the Linear equation method is a calculated method it was derived from a consensus method. The consensus method by Gardner et al reports clinically equivalent dose when compared to 20 mg of olanzapine. The following table shows the doses of SGA equivalent to 1 mg of olanzapine. Comparison was gathered from articles by Patel et al and Leucht et al. The daily defined dose for iloperidone and brexipiprazole were derived and included in the table. Cariprazine has no data available regarding dose equivalence.

**Table 4. This table includes few of the methods of SGA Dosing Equivalency**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Consensus method</th>
<th>Linear equation</th>
<th>Daily defined dose</th>
<th>Calculated Method</th>
<th>Calculated Method</th>
<th>Maximum Near-effective dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline comparator</td>
<td>Olanzapine 1 mg</td>
<td>Olanzapine 1 mg</td>
<td>Olanzapine 1 mg</td>
<td>Olanzapine 1 mg</td>
<td>Olanzapine 1 mg</td>
<td>N/A</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.30</td>
<td>0.28</td>
<td>0.5</td>
<td>0.27</td>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>0.45</td>
<td>-</td>
<td>0.6</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>8.00</td>
<td>10.48</td>
<td>8.00</td>
<td>5.33</td>
<td>7.9</td>
<td>80-160</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>-</td>
<td>-</td>
<td>1.8</td>
<td>1.07</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>5.33</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>37.04</td>
<td>29.97</td>
<td>40</td>
<td>20</td>
<td>32.3</td>
<td>150-600</td>
</tr>
<tr>
<td>Asenapine</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>1.33</td>
<td>0.9</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1.49</td>
<td>1.34</td>
<td>1.5</td>
<td>1.33</td>
<td>1.4</td>
<td>10</td>
</tr>
<tr>
<td>Brexiprazole</td>
<td>-</td>
<td>-</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>30.30</td>
<td>21.31</td>
<td>30</td>
<td>30</td>
<td>38.9</td>
<td>400-450</td>
</tr>
</tbody>
</table>

Abbreviation - Data not available

The daily defined dose method, the minimum effective dose method, the maximum dose method and the daily defined dose method. Most commonly, chlorpromazine is used as the standard comparative drug.

Chlorpromazine equivalence: Davis in 1974 invented this method for FGA by using chlorpromazine as the standard comparator. Based on randomized, double blind, flexible-dose studies on antipsychotics he identified comparable doses chosen by the clinicians to achieve therapeutic effect. This was then used to calculate dose ratios in relation to 100 mg of chlorpromazine. Leucht et al created the classical mean dose method where he applied Davis classical approach to SGA. They searched randomized double blind flexible-dose trials in acutely ill patients with schizophrenia that examined all available oral SGA, haloperidol and chlorpromazine. They then calculated the mean doses of each drug weighted by sample size and divided them by weighted mean olanzapine dose to obtain “an olanzapine equivalent”. Using chlorpromazine equivalents; Woods developed a novel dose equivalence table for SGA in 2003. He identified the minimum effective doses of the then current five SGA and haloperidol from fixed-dose placebo controlled trials. The minimal effective dose is the lowest fixed dose of each SGA that was consistently more efficacious than placebo in the primary outcome. Chlorpromazine equivalents were then derived from identified doses. In 2013 Leucht, based upon a similar principal of minimal effective dosing, calculated the olanzapine equivalent for eight additional SGA. This is called the minimum effective dose method. As a limitation, the results are not applicable to specific populations such as first-episode psychosis versus refractory patients (Table 4). All the above methods assumed linearity of dose equivalency. These do not account for the fact that a dose response curve is usually sigmoidal in shape. Also, these methods do not take into consideration that SGA can have high degrees of individual patient efficacies as noted earlier.

For the maximum dose method; the near-effective maximum dose which was calculated by Davis & Chen in 2004 is defined as the threshold dose eliciting clinical response with the lowest adverse profile. It can be calculated from dose–response curves which are constructed using data from fixed-dose randomized placebo-controlled studies. Equivalence between antipsychotics is then established by comparing the near-effective doses. Although this approach does use the dose response curve, it is used in preclinical research and there is inadequate data to construct dose response curves for all SGA as such (Table 4). The daily defined dose (DDD) was developed by the World Health Organization (WHO) and uses the average, maintenance dose per day per drug for its main indication for comparison. The primary purpose
of the DDD calculation was essentially to aid comparison of drug utilization, not necessarily to define dose equivalence clinically. A study by Leucht which compared the dose equivalence estimates bases on DDDs with third other methods (minimum effective dose method, classical mean dose method and international expert consensus method) reported that DDDs should only be used for dose equivalence if other more scientific approaches are not available. The article does not mention the DDD for brexpiprazole and iloperidone. However based on their formula to derive doses of each drug that are equivalent to 1 mg of olanzapine (DDD of the drug/10), the DDD of iloperidone and brexpiprazole is derived and included in Table 4. Regarding the Consensus Method, studies have been completed and use the original SGA, risperidone, as the standard comparative. It heavily relies on the knowledge and experience of experts in the field and may vary over time and hence need reassessment. Even in this method, experts assumed linearity of dose and response. In 2003 Kane et al conducted a survey of 49 experts to vary over time and hence need reassessment. Even in this method, experts assumed linearity of dose and response. In 2003 Kane et al conducted a survey of 49 experts to estimate equivalencies for fixed dose of haloperidol and risperidone. The authors found that responses “followed a very linear pattern”. Based on the guidelines established by Kane et al, Andreasen et al in 2010 conducted a linear regression analysis (linear equations) in which dose equivalents of haloperidol (2 mg) and chlorpromazine (100 mg) were used for comparing the SGA. The formulas were solved for chlorpromazine 100 mg and haloperidol 2 mg to derive new chlorpromazine and haloperidol equivalents of the SGA. The resulting equivalents could also be used to calculate the “dose-years” (100 mg/day of chlorpromazine equivalent or 2mg/day of haloperidol dose equivalent taken for 1 year is equal to 1 dose year) (Table 4). The most recent consensus by Gardener et al. in 2010 appears to provide the most complete estimation of equivalencies and specific clinical scenarios. In this method respondents (research and clinical experts) were asked to indicate what dose they consider to be clinically equivalent to 20 mg/day of olanzapine in treatment of reference case, a moderately symptomatic adult man with DSM IV schizophrenia with ≥ 2 years of antipsychotic treatment and not considered treatment refractory. Dosing ratios were than calculated to this dose of olanzapine. The equivalents reported were found to be strongly correlated with the near-effective dose equivalents for ten SGA (Table 4). In spite of the limitation of the dose equivalency methods for SGA, they do provide a rough guideline which would be useful when switching of SGA occurs during routine patient care. SGA equivalence are reviewed in Table 4.

### SGA Profiles

#### Risperidone

**Pharmacodynamics:** Risperidone at lower doses antagonizes 5HT2A serotonin receptors (anti-EPS), while at higher dosage antagonizes dopamine receptors (antipsychotic). This is common amongst the SGA. It also antagonizes alpha-1(α1) norepinephrine receptors leading to possible orthostasis. It has a higher affinity for H1 histamine receptor antagonism and can lead to weight gain and sedation. It is considered most typical of the SGA; possibly due to the poor CNS penetration of risperidone and its active metabolite (paliperidone) it has higher tendency as compared to other SGA to be associated with hyperprolactinemia leading to amenorrhea, galactorrhea, and sexual side-effects. Data indicates that this propensity for prolactin elevation is correlated with the plasma concentrations of the active (9 hydroxy risperidone [paliperidone]) metabolite.

**Pharmacokinetics:** Bioavailability is 70% and protein binding is 89%. Risperidone undergoes 9-hydroxylation in liver which yields the active (9 hydroxy risperidone—paliperidone) metabolite. This metabolite is the active ingredient of the SGA paliperidone. This step is primarily metabolized by CYP2D6 and to a lesser extent CYP3A4. Ultimately the plasma levels are influenced by the genetic variations in the CYP2D6 enzymes (slow/rapid metabolizers). The half-life for the parent compound is 3 hours in rapid metabolizers and 22 hours in slow metabolizers and that for the active metabolite is 22 hours in both. Concomitant use of enzyme inducers should necessitate doubling of the dose and use of enzyme inhibitors should lead to reductions in dose.

**TDM:** The CYP2D6 slow vs rapid metabolizers status affects plasma levels of risperidone vs the 9-OH-RSP metabolite with extensive metabolizers having a higher plasma level of the active metabolite and poor metabolizers having a lower level. Clinical effect is assumed to be due to sum of the parent compound plus its active metabolite. Therefore, monitoring the plasma levels for both the parent risperidone compound and metabolite is recommended. AGNP-TDM guideline reports therapeutic level for risperidone plus 9-OH-RSP is 20 to 60 ng/ml. Parkinsonian side effects are noted at plasma levels of 74 ng/ml or higher. TDM is recommended for identification of non-responders and for determination of “sub-therapeutic” plasma concentrations and for “supra therapeutic” concentrations. TDM can help to determine CYP2D6 inhibition due to either genetically impaired CYP2D6 activity or drug interactions. It is also useful to monitor the TDM while switching from injectable to oral form (or vice versa), so that individual patient’s ideal plasma level is maintained. A study which examined the long-term pharmacokinetics of risperidone found that risperidone plasma concentration/dose ratio (C/D) accumulation peaked 49% at 2 months (from baseline concentration) and 9-hydroxy-RSP and total moiety C/D accumulation peaked 66% at 6 months. This suggests that...
metabolism of the drug may be affected by both CYP2D6 inhibition and DNA regulatory mechanisms. Interestingly, PET study data indicate target concentration of 10-15 ng/ml for optimal results, and concentration above 40 ng/ml may be associated with adverse effects. This recommended level is lower than the AGNP guidelines.

High dosing: Dose titration: With respect to dosing strategies in adults with schizophrenia, a typical initial dose is 1.0-2.0 mg/day, with a target dose of 4.0-6.0 mg/day and a maximum dose of 16.0 mg/day.

The FDA approved maximum dose is 16 mg. Risperidone reaches 70 to 80 percent of D2 occupancy at doses between 2 to 4 mg/day. The risk of EPS increases with dosing and super high dosing has not been recommended. Some studies have reported clinical improvement for some patients for up to 16 mg of risperidone and only 31% of patients for up to 10 mg of risperidone required anti-parkinsonism medications. This again suggests a subgroup which may benefit from higher dosing.

Paliperidone

Pharmacodynamics: It has similar pharmacodynamic profile to parent compound, risperidone, noted just above. Paliperidone antagonizes α1 and H1 receptors, however the affinity for α1 blockade is lower as compared to risperidone so there is less potential for orthostasis. Paliperidone has no affinity for cholinergic muscarinic or β1- and β2-adrenergic receptors. At least one study found that it has lower potential for weight gain when compared to risperidone, quetiapine, aripiprazole and olanzapine. It tends to be less sedative and has less potential for EPS as compared to risperidone. This suggests it could theoretically be better tolerated at higher doses.

Pharmacokinetics: Its bioavailability is 30% and protein binding is 74%. Paliperidone may have a more stable drug concentration due to its OROS (osmotic controlled release oral delivery system) which is a slow release preparation and accounts for less fluctuations in peak to trough plasma levels, leading to lower dose frequency and also improved tolerability. This technology allows the dose to be started at the effective dose and hence initial dose titration is not required. Paliperidone is an extended-release (ER) formulation that is approved for treatment of schizophrenia in adults.

Paliperidone in different than its parent compound, risperidone, pharmacokinetically. Firstly, the half-life of paliperidone is 22 hours both in rapid and slow metabolizers. Secondly, it undergoes mild hepatic metabolism at most, dose adjustment is typically not required in mild to moderate hepatic impairment. Thirdly, it is glucuronidized and easily metabolized without CYP450, so it has less chance of a drug-drug interaction. As it is primarily easily excreted by the kidneys, lowering the dose in case of renal impairment is recommended.

High dosing: Dose titration: Regarding dosing strategies, an average initial dose in adults with schizophrenia or schizoaffective disorder is 6.0 mg/day (no initial dose titration is needed) with a maximum dose of 12.0 mg/day (Table 1). If dose titration is required, an increment of 3.0 mg/day at intervals of greater than 5 days is recommended.

The FDA approved maximum dose is 12 mg. However, 70 to 80 percent D2 occupancy is found at 6 to 9 mg/day and as with risperidone, higher dosing with paliperidone is not often recommended, may not be efficacious and can lead to increased potential for side effects including EPS. However, since it has less possible potential for some side-effects, it can be dosed higher than risperidone.

TDM: AGNP-TDM consensus guidelines range is 20-60 ng/ml and recommendation level is 2 (recommended). A relationship between plasma concentration at therapeutic levels and clinical effects has been demonstrated, making TDM recommended for dose titration and for specific indications or problem solving when there is initial nonresponse. TDM will increase the probability of response in non-responders. At supratherapeutic levels there is increased risk of intolerance. For patients who are non-responders to parent drug risperidone, who are found to be CYP2D6 deficient, or simply cannot mount high enough 9-OH-RSP levels may benefit more from taking this paliperidone product which requires no metabolism.

Ziprasidone

Pharmacodynamics: Just like risperidone, ziprasidone antagonizes 5HT2A serotonin receptors at lower dosages and antagonize D2 dopamine receptors at higher dosage. Ziprasidone may have relatively fewer side-effects and has been shown to have a lower risk of metabolic effects and weight gain. It binds with moderate affinity to H1 and high affinity to α1. It has little or no affinity to M1 and anticholinergic effect is not significant. Therefore sedation, orthostasis and dizziness may be encountered. Interestingly, ziprasidone has some ability to inhibit norepinephrine and serotonin reuptake but has shown limited antidepressant ability. Ziprasidone may lead to increase in QTc by 15.0-20.0 msec. However serial EkG's are not recommended unless there is history of cardiac problems like congenital QTc prolongation, cardiac arrhythmias, recent MI or heart failure. In these cases, careful use, or avoiding it altogether may be necessary. Also, care should be taken when combining with other QTc prolonging drugs (class 1A and class III antiarrhythmics, certain antipsychotics, the fluoroquinolone antibiotics, pentamidine, methadone, and levomethadyl acetate). Monitoring electrolytes would be useful in cases of...
hypokalemia, hypomagnesia, and bradycardia that might prolong the QTc further.

**Pharmacokinetics:** Ziprasidone requires administration with food to maximize absorption and bioavailability (60% with food). It is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2. The dose should be adjusted with the concomitant use of strong inhibitors or inducers of these enzymes. Age and gender do not play a prominent role its pharmacokinetics. Smoking can affect the plasma levels of ziprasidone, as tobacco is a strong inducer of CYP1A2.

**TDM:** Improvement or side effects have not clearly correlated significantly with doses or serum levels globally but TDM can be used for individual dose adjustment. Ziprasidone’s bioavailability and absorption increases while pharmacokinetic variability decreases with the presence of food. Also serum concentrations of ziprasidone are not dose proportional under fasting states but become dose proportional and more linear under fed states. This is important to take into account when measuring the TDM. AGNP TDM guidelines quote a reference range of 50-200 ng/ml and the level of recommendation is 2(recommended) which means it can be used for individual dose adjustment. The probability of EPS may be increased with levels above 200-250 ng/ml.

**High Dosing:** Dose titration: For the treatment of schizophrenia in adults, ziprasidone should be initiated at 20.0 mg twice daily, with subsequent dosage increases up to 80.0 mg twice daily (Table 1). Dosing adjustments should occur in increments of 20.0 mg twice daily at intervals no less than 2 days, with a maximum dose of 80.0 mg twice daily.

FDA approved maximum dose is 160 mg/day. Interestingly, the use of 120 to 160 mg is associated with better adherence than lower dosages. In a study completed at a state hospital, it was noted that 51.6% received a dosage higher than 160 mg/day, and this was associated with improvement in symptoms and did not have significant side-effects. In the same study the average discharge (successful outcome) dose for ziprasidone was 206 mg per day with patients having history of prior admissions and those who carried a diagnosis of schizophrenia getting higher dosages. There have been studies reporting higher doses of ziprasidone up to 360 mg/day in forensic settings and in state hospitals. For titration of ziprasidone to higher doses, daily increases have been tolerated.

**Iloperidone**

**Pharmacodynamics:** This requires a 4-day titration schedule due to its high a1 antagonism and risk for orthostasis. Antihypertensive agents, if combined should be executed with care due to this. Given its weaker affinity for D2 receptors, it appears to have a lower degree of EPS and hyperprolactinemia compared to risperidone and ziprasidone. It is one of the lowest EPS profile SGA available.

Iloperidone is metabolized into two metabolites, P88 and P95, with P88 being similar to iloperidone with its ability to cross blood brain barrier and binding to similar receptors as the parent compound. P95 on the other hand does not cross the blood brain barrier and has a different affinity profile and unlikely to contribute to clinical effects.

Iloperidone has very low antagonistic affinities for the histamine H1 (less sedation and weight gain) and muscarinic M1 (less cognitive and gastrointestinal side-effects). Iloperidone has been shown to prolong the QTc interval by 9ms when it is administered at a maximum dose of 12 mg twice daily and should be discontinued if QTc interval measures > 500 ms. Similar to asenapine, paliperidone, ziprasidone and quetiapine, there is a warning about combining iloperidone with other medications that prolong the QT interval and in those with bradycardia, history of hypokalemia, hypomagnesemia, recent myocardial infarction, uncompensated heart failure or congenital QTc syndrome.

**Pharmacokinetics:** Bioavailability is 100% and protein binding is 95%. Iloperidone is a substrate for CYP2D6 with a half-life of 18 hours for CYP2D6 rapid metabolizers and 33 hours for slow metabolizers. Since it is also a substrate for CYP3A4, dose adjustment is needed when combining with drugs which are either inducers or inhibitors of these enzymes.

**TDM:** AGNP consensus guidelines report a TDM of 5 to 10 ng/ml with possible toxicity when plasma concentrations are above 20 ng/ml. The recommendation level by AGNP is 3 (useful). TDM can be used to control whether plasma concentrations are plausible for a given oral dose. Clinical improvement may be attained by dose incrementation in non-responders who display plasma concentrations that are too low.

**High Dosing:** FDA approved maximum dose is 24 mg. It is a relatively newer and underutilized antipsychotic and has limited data for high dosing. For safety (not for efficacy) it has been tested up to 32 mg.

**Lurasidone**

**Pharmacodynamics:** Lurasidone has a high antagonistic affinity for the 5-HT2A as well as D2 receptor. It has a rather high EPS rate for akathisia reported in 14% of subjects receiving the 80 mg/day dose. Despite the drug’s high affinities for both receptors, the ratio of 5-HT2A blockade/D2 blockade is low which may explain the high akathisia rate. It has the lowest antagonistic affinity in class for the histamine H1 receptor, as well as, low antagonistic...
affinities for acetylcholine muscarinic M1 receptors and α1-adrenoceptors, suggesting low potential for weight gain, sedation, hypotension or cognitive dysfunction.53. Lurasidone, like ziprasidone, has an advantage over other SGA with much less likelihood of metabolic side-effects (weight gain, dyslipidemia and diabetes)61,74.

**Pharmacokinetics:** Lurasidone has a 2-fold increase (18.0-38.0%) in bioavailability when taken with meals and is recommended to be administered with at least 350 kcal of food to ensure maximum absorption. Doubling of the dosage may be required in fasting states.

Lurasidone is a substrate for CYP3A4, and its levels are significantly affected by concomitant administration of CYP3A4 inducers and inhibitors. Its use is contraindicated in presence of strong inhibitors or inducers. When using with moderate inhibitors/inducers dose adjustment by reducing the dose to half when combining with CYP3A4 inhibitors and doubling the dosage in case of inducers may be necessary. Lurasidone is not a substrate for CYP1A2 and hence smoking should not affect dosing. As per one study Lurasidone's dose does not need to be adjusted for age or gender.74.

Lurasidone is highly protein bound which leads to potential drug-drug interactions when combing with other protein bound drugs. Its half-life is affected by both hepatic and renal impairment, using a lower dose of 40 mg/day in such populations is advisable.75.

**TDM:** AGNP TDM consensus guideline for lurasidone is between 15-40 mg/dl and has a level of recommendation of 3 (useful). A relationship between plasma concentration and outcome is not yet demonstrated but aids in clinical problem solving.

**High dosing:** The FDA approved dose for lurasidone is up to 160 mg/day. This is a newer antipsychotic and limited information is available regarding high dosage. Past studies have shown increasing side-effects with higher dosing, however one recent 6 week study found that administering the dose in the evening minimizes the risk of adverse effects.74. Higher dosages have been studied up to 600 mg for safety reasons (QTc prolongation) but not for efficacy.74.

**Quetiapine**

**Pharmacodynamics:** Quetiapine has a very low affinity (lowest among the SGA) for the D2 receptor and a relatively high affinity for the 5-HT2A receptor leading to possibly the lowest EPS rate in class and likelihood of causing hyperprolactinemia of the SGA discussed.76. Quetiapine has two formulations, immediate release (IR) and extended release (XR). Quetiapine's active metabolite is norquetiapine which has a similar binding profile to its parent compound. H1 binding is one of the highest among the SGA leading to its sedative, weight gain propensity, as well as, its antianxiety properties. Quetiapine/norquetiapine more aggressively antagonizes 5HT2C which has antidepressant properties similar to mirtazapine. This property also predisposes to metabolic disorder. Research with quetiapine XR indicated that the risk of metabolic syndrome was equal to placebo at 150 mg/day but doubled with doubling of the dose.77. This SGA also has potent norepinephrine reuptake inhibition (NRI) adding to its antidepressant profile. High antagonism of α1 receptors results in orthostasis, while antagonism of cholinergic receptors could cause constipation, dry mouth, changes in cognition, and vision. Along with asenapine, ziprasidone, paliperidone and iloperidone, quetiapine now carries a warning about QTc interval prolongation.78.

**Pharmacokinetics:** Bioavailability of 9%. It has a higher protein binding of 83% protein.79.

Quetiapine undergoes metabolism in the liver and is a substrate for CYP3A4 enzymes. Use of an inducer requires increasing the dose five times while use of inhibitors requires a decrease of dose to one sixth.80. There is significant reduction in CYP3A4 enzymes after age of 70.81. Also there is some evidence that the elderly have a lesser oral clearance of the drug.82. Thus, dose titration should be slower in elderly and daily total dose needs to be lower.79. There is very little evidence if any that gender affects its metabolism. Elderly patients receiving 300-750 mg/day have a 30-50% lower oral clearance of quetiapine when compared to younger patients on similar dose.83.

**TDM:** The AGNP-TDM consensus guidelines propose a therapeutic range of 100-500 ng/mL and a level of 2 where TDM is recommended for dose titration for clinical problem solving. For all other SGA discussed, clinical effects usually occur at D2 occupancy of 60% and increasing the D2 occupancy above a certain threshold (usually 80%) leads often to increases in EPS. However, for quetiapine, even doses up to 750 mg lead only to 40 to 50% D2 occupancy. Also, plasma concentrations of quetiapine do not correlate with D2 occupancy and plasma concentrations of 800 ng/ml had less than 60% occupancy and had an absence of EPS.54. Finally, clinicians should be aware that if XR formulation was taken in the evening and blood drawn in the morning, expected concentrations are two fold higher than the trough levels.

**High dosing:** FDA approved maximum dose is 800 mg/day. In a naturalistic study completed in state hospital systems, 40 percent of patients with chronic psychosis were on doses above 750 mg/day.82. As noted above striatal D2 occupancy does not correlate with plasma concentration and high dosage are not associated with EPS. Based on the above, it is not surprising that there have been anecdotal reports of dosage use up to 2400 mg when lower doses were felt not to be effective.83. Although there is less likelihood of EPS, use of high dosage is limited by...
side-effects of sedation and other vegetative symptoms. Titration should be at a slower rate for these higher doses.

**Olanzapine**

**Pharmacodynamics:** Olanzapine is most similar in its pharmacodynamic properties to clozapine and has a relatively low affinity for D2 receptors and a stronger binding affinity to 5HT2A receptors. It has moderate affinity to block mscarinic receptors which may lead to dry mouth, constipation, blurred vision, urinary retention, memory problems, and confusion. H1 receptor blockade leads to remarkable sedation and weight gain. \( \alpha \)1 receptor blockade may lead to hypotension and possible orthostasis. Among the discussed SGA, it carries one of the highest risks for metabolic adverse effects and is also implicated in directly causing diabetes mellitus type 273,84.

**Pharmacokinetics:** This drug is extensively eliminated by first pass metabolism with over 40 percent metabolized before reaching systemic circulation. This leads to an oral bioavailability of 80 percent. It has a high protein binding of 93%. It is metabolized hepatically by the UDP glucuronosyltransferase family, while metabolism through CYP2D6/CYP1A2 are minor pathways. Genetic variations in UDP glucuronosyltransferase lead to interindividual variability in clinical effects. Concomitant use of inducers (smoking) or inhibitors (fluvoxamine) of CYP1A2 may influence plasma concentrations. Smokers and men show a greater clearance and thus a lower plasma concentration than nonsmokers and women85. Smoking cessation may be associated within a few days of an increase in side effects from olanzapine as its plasma levels have likely increased.

**TDM:** AGNP TDM consensus guidelines recommends plasma concentrations of 20-50 ng/ml and the level of recommendation is 1 (strongly recommended) as there is significant evidence that plasma concentrations are related to receptor occupancy and clinical outcomes86,87. Lab alert levels are above 150 ng/ml and are associated with higher rates of EPS11,54. There is large intra and interpatient variability with plasma olanzapine concentrations. The intra-patient differences are accounted by difference in daily dose, duration of treatment, smoking status etc. The plasma concentration/dose ratio accumulation peak after 4 months is 31% above baseline and 47% after 18 months with no clear plateau. It appears that both CYP inhibition and DNA regulatory mechanisms are involved in metabolism. The interpatient factors are genetic variations in enzymes, gender etc. Long term TDM can thus optimize treatment. TDM of 15-20 should be targeted for patients with schizophrenia19.

**High dosing:** The FDA recommended dose is 10-20 mg/day. Up to this dose, the D2 receptor occupancy varies from 71 to 80%84. A study in patients receiving olanzapine up to 45 mg found a dose dependent increase in D2 occupancy and patients tended not to exhibit any EPS88. A state hospital study found that doses often exceeding 20 mg were used in more than 50 percent of patients. Higher doses of 40-60 mg appear to be more useful with more aggressive patients, who have higher levels of psychopathology and who are generally treatment resistant89. Interestingly, a follow up prospective study with a small sample size and no placebo group demonstrated no improved efficacy and higher risk of weight gain and hyperprolactinemia associated with the use of higher doses90. Yet another study found no statistically significant difference between 20 and 40 mg, but did find that severely ill patients had better responses while on higher doses91. Some forensic settings have reported dosage as high as 90 mg/day in treatment resistant patients1.

**Asenapine**

**Pharmacodynamics:** Asenapine antagonizes 5-HT2A with a 20 times higher affinity (one of the highest among SGA) as compared to D2 receptor antagonism with low potential for EPS. Its remarkably high affinity for the H1 receptor may lead to sedation and/or some weight gain. It has low affinity for cholinergic receptors. It may also prolong the QTc interval and hence caution is needed in patients with past history of cardiac disease or current use of QTc prolonging medications.

**Pharmacokinetics:** Asenapine is the only SGA administered sublingually and it dissolves in seconds. Bioavailability increases from 5% to 35% when the drug is taken sublingually and falls significantly if patient swallows it whole or rinses his/her mouth out too quickly after taking it sublingually. Nothing else should be taken orally for 10 minutes following dosing to allow for maximum mucosal absorption. Asenapine is metabolized by glucuronidation by UGT1A4, and oxidation by CYP1A2, CYP3A4 and CYP2D6. Hence care needs to be taken while combining this drug with inducers or inhibitors of these enzymes.

**TDM:** The AGNP-TDM consensus guidelines suggest a therapeutic range of 2–5 ng/ml. TDM is potentially useful but should be restricted to special populations as plasma concentration has not correlated with clinical response as of yet11,24.

**High Dosing:** High dosing has not been well studied, nor reported in the literature.

**Aripiprazole**

**Pharmacodynamics:** Aripiprazole is a partial D2 and D3 agonist and a 5HT2A antagonist. This D2, D3 partial agonism is shared by two other newer drugs, cariprazine and brexipiprazole. As psychosis is felt to occur as a result of excessive dopaminergic neuronal firing, a partial agonist
will still afford a net diminishing of neuronal firing as it acts less than a full agonist (endogenous dopamine). Antipsychotic effects occur at 60-80 percent D2 occupancy. Due to this unique binding profile clinicians have to balance its dosage. On one hand, higher doses are needed to overcome the partial D2 agonism for antipsychotic effects to occur, while on the other hand, very high doses could theoretically make it less effective. Also, in the presence of another D2 antagonist (antipsychotic) aripiprazole and similar drugs would act as a partial D2 agonist. With a very high D2 affinity, this drug could easily displace other antipsychotics so that antipsychotic polypharmacy may actually worsen psychosis. D3 partial agonism does not add to the antipsychotic effects but may be helpful in improving cognition and as an antidepressant theoretically.

The two notable side-effects with aripiprazole are moderate akathisia [23 % of patients] and some weight gain. The high potential for akathisia may be due to high D2 affinity as well as enhanced monoaminergic activity. Weight gain and consequent cardiometabolic sequelae may be due to moderate affinity to antagonize H1 receptors. Weight gain potential is highest for brexpiprazole, followed by aripiprazole, and then cariprazine. Moderate antagonism of α1 receptors would account for its hypotension side-effects. The M1 antagonism is very weak leading to minimal anticholinergic side-effects. As compared to other D2 partial agonists, it has lower potential for EPS and dystonia but has a higher potential for akathisia.

**Pharmacokinetics:** Bioavailability is 90% and protein binding is 99%. It is metabolized in the liver via CYP3A4 and CYP2D6 enzymes and its major active metabolite dehydro-aripiprazole represents 45% of resultant plasma aripiprazole concentrations. Clinicians have to be mindful about the CYP2D6 genetic variations leading to interpatient variability in metabolism and must be careful during concomitant use of inducers or inhibitors of either enzymes and dosing needs to be halved when used concomitantly with a CYP2D6 inhibitors. Akathisia can occur with concomitant use of SSRI and SNRI due to cumulative monoaminergic effects.

Age gender, hepatic, renal impairment, and smoking do not significantly affect metabolism.

**TDM:** AGNP TDM consensus guideline for TDM is 150-500 ng/ml, and it calculates the concentration of aripiprazole as well as its active metabolite dehydroaripiprazole. The recommendation level is 2 (recommended). Interestingly, the CYP2D6 genotypes significantly affected the plasma concentration of aripiprazole (but not of dehydroaripiprazole) in Asian patients.

**High dosing:** The FDA approved highest dose is 30 mg/day and there is not much data supporting dosing above this. Some data has suggested a state dependent dosing for aripiprazole with augmentation for treatment resistant depression benefitting from a lower dose of 2 mg, psychosis or schizophrenia being treated between the dose of 15 to 30 mg, and a starting loading dose of 30 mg for patients with acute mania. Some studies also suggest that treatment of psychosis or schizophrenia requires nearly complete saturation of D2 receptors, with doses of 15 mg leading to at least therapeutic D2 occupancy correlating with plasma concentration of 100 ng/ml or higher. Doses of 30 mg/day will lead to this level in nearly every patient.

Another review reported a 10% above label dosing in NY State hospitals. These higher doses are usually used in acute mania or treatment resistant schizophrenia. Doses of 40 mg have 96.8% D2 occupancy so further increase may not lead to clinical improvement. Dosing may follow a U shaped curve and sometimes super dosing might actually be less effective with higher adverse effect profile.

**Brexpiprazole**

**Pharmacodynamics:** As noted above, brexpiprazole also is a partial D2 and D3 agonist. Comparatively, it has the highest antagonism for 5HT2a which lowers the potential for EPS, and in fact, akathisia is known to be 50 percent less as compared to aripiprazole and cariprazine. It has the strongest binding to H1 receptors and is most likely to cause increased appetite among the three partial agonist drugs, and so has the greatest potential for metabolic adverse-effects. It also has the strongest α1 antagonism and consequent risk of elevated hypotension. Like the other two drugs it has very weak M1 binding.

**Pharmacokinetics:** Bioavailability is 95% and the protein binding is 99%. It has a long half-life of 91 hours and is primarily metabolized by the liver. It is substrate for CYP3A4 and CYP2D6. As for aripiprazole, doses need to be adjusted for poor/rapid metabolizers of CYP2D6 or if given with strong inducers or inhibitors of either of this enzyme. If given with a strong CYP2D6 or CYP3A4 inhibitor halving the dose, while in presence of a strong CYP3A4 inducers doubling the dose of the drug is recommended.

Brexpiprazole’s protein binding is not affected by warfarin, diazepam, or digoxin dosing. Metabolism is mediated primarily by the CYP3A4 and CYP2D6 enzymes and its major metabolite is DM-3411. This metabolite does not seem to play a role in clinical improvement.

**TDM:** The AGNP-consensus guideline TDM are 40-140 ng/ml. The level of recommendation is 3 (useful). Plasma concentration are not affected by its major metabolite DM-3411.

**High dosing:** This newer SGA has little data in this area.

**Cariprazine**

**Pharmacodynamics:** This is the newest antipsychotic
to receive FDA approval and also is a partial D2 and D3 agonist. It binds to 5HT2A but the affinity to this receptor is lower, leading to increased vulnerability for EPS which has been the most common side-effects associated with high dosing. In fact, amongst the three partial agonists, cariprazine has the highest potential for EPS (except akathisia) and somnolence. It does antagonize the H1 receptor leading to more sedation and weight gain. As mentioned above, the antagonism of M1 receptors is extremely weak. The possibility of orthostasis is low due to weak α1-adrenergic receptor binding.

**Pharmacokinetics:** Cariprazine has 100% bioavailability and high protein binding. It is metabolized in the liver by CYP3A4 enzymes to two active metabolites, didesmethyl cariprazine (DDCAR) and desmethyl cariprazine (DCAR). It has the longest half-life among the three partial agonists of 3 weeks. The active metabolites are similar to the parent compound in that they have similar binding profiles and longer half-lives. Care should be taken when combing with CYP3A4 inhibitors or inducers, with recommendations of halving the dose of cariprazine when taken along with a strong CYP3A4 inhibitor.

This has longest SGA half-life (if its active metabolite is included, equaling as long as 3 weeks); aripiprazole and brexpiprazole follow with 94 and 91 h, respectively.

**TDM:** The AGNP TDM consensus guideline is 10-20 ng/ml and the level of recommendation is 3 (useful). TDM can be used for special indications or problem solving. Interestingly, one of the two major active metabolites of cariprazine, (DDCAR) approaches steady state concentrations around 4-8 weeks, with a half-life between 1-3 weeks, so that any dose change would not reflect in the plasma concentrations immediately and may take weeks to establish. Thus, it would be advisable to monitor for acute side-effects for a prolonged clinical period.

**High dosing:** This has not been well studied for this newest SGA.

**Conclusions**

This paper attempts to update the reader regarding clinically relevant concepts of SGA pharmacokinetics, pharmacodynamics, therapeutic drug monitoring, and dosing equivalencies as advanced practice ideas whereby a clinician may better monitor SGA use and make improved clinical decisions on a per patient basis. In addition, there is a micro-review of each SGA which suggests that they are simply not "me-too drugs" but each may have a unique clinical identity that may better serve patients at the level of the individual patient being seen. These concepts may help clinicians decide amongst a variety of SGA, but more importantly teach the clinician how to dose and utilize each agent to its fullest extent.

**Conflict of interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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