Treatment Strategies for Dosing the Second Generation Antipsychotics

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SUMMARY

Background: The second generation antipsychotics now have clinical approvals for the treatment of schizophrenia, bipolar depression, bipolar mania, autism, major depressive disorder and are used furthermore off-label to treat other mental disorders. Each agent is unique in its pharmacodynamic profile and allows for unique dosing strategies to be employed when treating these different disorders. **Aims:** To review relevant data regarding the second generation antipsychotics and their empirical dosing strategies. To further review and comment theoretically in these areas where substantial, definitive data are lacking. **Materials and Methods:** A MEDLINE and recent textbook review was conducted regarding each second generation antipsychotic and cross-referenced with searches for major mental disorders. The findings are compiled in the review below. **Discussion:** The second generation antipsychotics are clearly delineated in the treatment of psychosis and mania and share similar mechanisms of action to achieve these results: dopamine-2 receptor antagonism for efficacy and serotonin-2a receptor antagonism for EPS tolerability. From here, each agent has a unique pharmacodynamic and pharmacokinetic profile where some agents carry more, or less antidepressant, anxiolytic, or hypnotic profiles. Choosing an agent, and dosing it in low, middle, or high ranges may result in differential effectiveness and tolerability. **Conclusion:** The second generation antipsychotics have many clinical applications in psychiatric practice. This article serves to review this and also suggests ways clinicians may optimize treatment based upon patient diagnosis and utilizing appropriate dosing of each individual second generation antipsychotic.

Introduction

Clinicians have been using and dosing the antipsychotics since the 1950s. These initial, first generation antipsychotics (FGA) were uni-dimensional in certain ways. First of all, these drugs were approved to treat one major illness, schizophrenia. Second, clinicians and researchers were aware that they were dopamine-2 (D2) receptor antagonists in regards to pharmacological actions. The high potency FGA agents were very clean drugs in regard to promoting antipsychotic effects and the low potency FGA added additional pharmacodynamic components that essentially dictated side effects, especially sedation and orthostasis, more so than effectiveness in reducing psychosis associated with schizophrenia. Finally, clinical management dealt solely with increasing the FGA dose, to increase D2 blockade, to dampen dopaminergic hyperactivity in limbic neurocircuits in hopes of alleviating psychosis. In other words, clinicians increased the dose unilaterally until symptoms of psychosis abated. The goal was to

reach a high dose, often as quickly as possible to help ameliorate the patient's symptoms. This simplistic, unidirectional dosing strategy has become more complicated as newer, second generation antipsychotic agents (SGA) became available. This article seeks to review and discuss clinical dosing strategies and patient care issues in regard to the eight currently available SGA.

Clinical Dosing of Second Generation Antipsychotics

With the advent of the second generation, or atypical, antipsychotics in the mid-1990's clinicians noticed that these agents were certainly safer in regard to inducing less extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), but also more challenging in regard to dosing. For example, the first modern atypical antipsychotic, risperidone, was studied and approved at a dosing strategy of rapid escalation within 3 days to a 6 mg divided

dose. Despite package insert data regarding low EPS rates, clinicians quickly learned that EPS were very frequent with this dosing strategy and in many cases hurt patient compliance and thus overall effectiveness. Good clinical sense dictated a slower titration rate to spare side effect burden. Olanzapine was approved next, and it was suggested to dose this drug at 10 mg per day initially. Timid from risperidone experiences, clinicians often dosed olanzapine more slowly and at lower ineffective doses initially. As a result, this agent had less EPS issues, but did not have initial and readily apparent efficacy compared to the package insert information. Consequently, the dose of olanzapine was raised to over 10 mg as clinical experience showed that this created more antipsychotic efficacy.

The next three approved SGAs, quetiapine, ziprasidone, and aripiprazole, had equal fates and were ideally to be dosed in practice to 600 mg, 160 mg, and 30 mg, respectively. Again, clinicians often under dosed these in fear of adverse effects but likely at the expense of solid efficacy in some patients [1]. Finally, there are very few data or clinical experiences at the date of this writing regarding the ideal clinical doses for newest agents, paliperidone, asenapine, and iloperidone. It does seem apparent that clinicians have become more comfortable with the aforementioned agents' full dosing range over the years in regard to treating schizophrenia and perhaps the full dosing range of the newest SGAs will follow suit [2].

Dosing the SGAs became more difficult as pharmaceutical companies began to investigate treating other psychiatric disorders such as bipolar mania, bipolar depression, and unipolar major depressive disorder. The FDA package insert and suggested dosing strategies appear to be 'loading' strategies in regards to treating acute mania. Clinicians were asked to dose the agents very high and very quickly to achieve antimanic efficacy within a few hospital days. Risperidone again was dosed from 4 to 6 mg, but olanzapine was initiated at 15 mg, quetiapine at 600 mg, ziprasidone at 120 mg, and aripiprazole at 30 mg, which were considered aggressive initial doses compared to initial doses of these same agents when used to treat schizophrenia [3–5]. Clinicians now have to make an accurate diagnosis, and per the FDA, dose agents more or less aggressively. The final and most recent complication in regard to clinical dose is the approval and use of aripiprazole and quetiapine XR for the adjunctive treatment of major depressive disorder [6,7]. The former agent is initially dosed at 2–5 mg instead of the usual 10–30 mg noted previously for schizophrenia and mania. The latter agent is dosed from 50 mg initially to either 150 mg or 300 mg in depression. These two dosing strategies bring clinicians back to low and slow dosing in this new patient population.

In order to bring this back to the schizophrenia population, the dosing strategy for efficacy is still similar to the FGA. Clinicians should start at the low FDA recommended dose but titrate upwards accordingly until efficacy or intolerable side effects occur. The problem is that patients tend to have comorbid illnesses. What if a patient has schizoaffective disorder or major depression following the resolution of a psychotic break? What dosing strategy should then be used? Patients also can become resistant clinically to the drug that they are on, or develop side effects that require a change of antipsychotics. Switching among the original first generation agents was relatively easy as clinicians could use a table

of potency values [8] and switch drugs almost over night in many cases. The newer antipsychotics really do not have a potency chart to guide instant cross-titrations and often require a more gradual cross titration approach. Dosing again has become more complicated and there are often conflicts between the evidence base for dosing in these situations versus dosing in clinical practice [9].

The next part of this manuscript will deal with specific dosing issues and strategies regarding each individual SGA and will discuss in a bit more detail the pharmacodynamic and pharmacokinetic principles behind the clinical use of each SGA in day to day clinical practice. The authors will begin discussion about SGAs with more simple pharmacological properties and move towards those with more complexity.

Specific Dosing Strategies and Issues Amongst the SGAs

Common Features

All second-generation agents act as D2 receptor antagonists [10]. This is similar to first generation drugs. This ultimate dampening of presumed limbic dopaminergic hyperactivity in schizophrenia or mania leads to clinical effectiveness and reduction of psychosis or mania. This is not a new mechanism of action but a tried and true tool in psychopharmacologic practice. Some agents have higher affinity for this action and can loosely be assigned a potency (affinity) level in rank order (high to low D2 affinity) as follows: aripiprazole, risperidone, paliperidone, ziprasidone, olanzapine, iloperidone, asenapine, and quetiapine [11–13]. The exact positioning on this pathway is difficult to assess as some studies are *in vitro*, some *in vivo*, and oftentimes different laboratories will use differing assessment protocols.

Overall SGA potency values are difficult to truly assess as all SGAs antagonize serotonin-2a (5HT-2a) receptors as well as D2 receptors [10]. This common pharmacodynamic property serves a few important functions. First, this antagonism makes these agents fairly selective for antagonizing the limbic dopamine system while sparing other dopamine pathways. 5HT-2a receptor antagonism tends to allow more dopamine activity and neurotransmission to occur in the nigrostriatal system to avoid EPS, in the mesocortical system to avoid iatrogenically induced negative symptoms, may allow subtle improvement in negative symptoms [14,15], and finally in the tuberoinfundibular pathway to help avoid prolactinemia and its sequelae. Ultimately, 5HT-2a receptor antagonism allows the SGA to be named "atypical" in that they have a much lower rate of TD and EPS. This common, dual receptor antagonism pharmacodynamic profile amongst the second generation drugs actually makes them selective agents in that they dampen dopaminergic activity where it is critical for the treatment of positive schizophrenia symptoms while remarkably lowering potential EPS.

As noted above, FDA regulatory trials suggest a clear dosing and titration schedule, which in theory gives clinicians reproducible results in their patients. Each SGA has a very unique pharmacokinetic and pharmacodynamic profile which lends each SGA to a set of unique dosing strategies that may not be found in each drug's official FDA package insert. The following section will take the

reader through the similarities and discrepancies between clinical trial results and those sometimes used in clinical practice for each SGA.

Risperidone

This drug appears to be absorbed consistently after ingestion and has a high affinity for D2 receptor antagonism. An average dose in schizophrenia or bipolar mania might be 3–4 mg/d [16,17]. Dosing in autism in children to adolescents is 1–3 mg/d [18]. There appears to be state dependent dosing in that lower doses may better treat younger patients with autism and agitation where slightly higher doses are needed to stop bipolar mania in adults. This makes dynamic sense as higher doses will allow for better D2 receptor occupancy. Once this antagonism reaches 60% or more, antipsychotic effects likely occur. At lower doses, this drug likely has little antipsychotic effect.

Risperidone is not indicated for depression or anxiety, but some evidence exists for its efficacy in these areas nonetheless. In resistant depression, lower than 'antipsychotic' doses (0.5–3 mg/d) were found to be effective in a 4 week study by Keitner et al. allowing for faster response, remission and improved quality of life when used as an augmentation strategy [19]. A smaller, open-label study suggested that low dose risperidone also helped Selective Serotonin Reuptake Inhibitor (SSRI) non-responsive depressed patients to improve and promoted elevated brain derived neurotrophic levels (BDNF) [20]. A small, randomized, cross-over study suggested that even lower dosed (0.5–2 mg/d) risperidone was effective in treating depression and suicidality symptoms in particular [21]. This series of risperidone for depression findings brings the authors to a very important point and likely a commentary that will run throughout this article. The SGA are drugs that can function on multiple levels to treat different symptoms and syndromes. Risperidone here makes the case that moderate to high doses, 3 mg/d and above, are needed for antipsychotic and antimanic potential. Three milligrams per day and less seem to help depressive symptoms. It follows that there is a relative lack of D2 receptor blockade at these low doses, so where does the antidepressant effect come from? One study suggests that BDNF increases at low risperidone doses. Perhaps consistent with other literature, this neurotrophic factor allows for healthier neuronal connectivity and neurotransmission to alleviate depression [22]. Outside of the BDNF hypothesis, what does risperidone's pharmacodynamic profile suggest to clinicians? Risperidone has affinity, even at low doses, to antagonize 5-HT_{2a} receptors. This effect tends to maintain or even increase dopaminergic activity in select dopamine pathways [10]. When this occurs in the nigrostriatal system, there is less risk for EPS. If this occurs in cortical pathways, more DA activates the frontal lobe, which may allow for better attention, concentration, and executive functioning. These cognitive symptoms are often noted and are diagnostic for depression and certain anxiety disorders. All SGAs possess this property to some degree. If they can promote selective dopaminergic activity in certain brain areas at these low doses, antidepressant effects may be seen in the absence of antipsychotic effects. Risperidone is a fairly Spartan drug in terms of additional pharmacologic binding properties. It possesses 5HT-2a receptor blockade and may promote

BDNF at low doses affording treatment of depressive symptoms. At higher doses, the D2 receptor antagonism becomes stronger and allows, likely for a dose–response curve where antipsychotic and antimanic effects occur.

Paliperidone

This drug is the active metabolite of risperidone noted above. It is approved for treating psychosis from schizophrenia at doses of 6–12 mg/d [23,24]. A MEDLINE search suggests no findings for its use in the treatment of depression. As the active metabolite of risperidone it offers a very similar DA-2/5HT-2a receptor antagonism to the risperidone parent product. Without an evidence base, it could be suggested that paliperidone might have the same ability as risperidone to treat depression symptoms but this is unfounded as yet. Similarly, lower doses of paliperidone would be more effective in depression than in schizophrenia. This metabolite seems to have less orthostasis and metabolic risks than the parent drug according to its receptor pharmacology and available data [24,25].

Olanzapine

Olanzapine is the SGA with the molecular structure most similar to that of clozapine which is sometimes noted to be the most efficacious antipsychotic [3,26]. Olanzapine appears to be absorbed consistently after ingestion and has a relatively high affinity (though less than risperidone and paliperidone) for D2 receptor antagonism. An average dose in schizophrenia or bipolar mania might be 10–15 mg/d [27,28]. In regard to ultimate dosing strategies in the persistently mentally ill, Citrome and Kantrowitz (2009) suggest an average dose of 22.5 mg/d with greater than 50% receiving above FDA regulatory dose limits. The authors also comment on anecdotal case reports of patients taking 60 mg/d with good effect [29]. A follow-up prospective study regarding 10, 20, 40 mg/d doses did not reveal statistical improvement at the higher dose, but did reveal a clear side effect, dose–response curve for weight gain and prolactinemia. This study was limited by small sample size and lack of a placebo group however [30]. A larger, 20 versus 40 mg/d study suggested no difference in doses except patients with more significant baseline symptoms responded preferentially to the higher, 40 mg/d dose [31]. These data reinforce clinical intuition. The more severely ill, or psychotic, a patient is, the higher the dose of antipsychotic needed. This makes theoretical sense in that as a clinician increases an SGA's dose, there is an increase D2 receptor occupancy and antagonism. Increasing dopamine blockade at greater doses lowers psychotic symptoms. Sometimes, off-label dosing above regulatory guidelines is needed for ultimate symptom reduction. Similar to other off-label practices, full informed consent and increased drug monitoring should proceed and follow super dosing practices. This dosing makes dynamic sense as higher doses will allow for better DA-2 receptor occupancy. Once this antagonism reaches 60% or more, antipsychotic and antimanic effects likely occur. Olanzapine is not approved for dosing in autism. Olanzapine monotherapy is not indicated for depression or anxiety, but some evidence exists for its efficacy in these areas nonetheless [32,33]. Olanzapine, however,

when combined with the unipolar antidepressant, fluoxetine, is FDA approved as a combined therapy for either bipolar depression or treatment resistant unipolar depression. Dosing in these two types of depression is as follows in regard to olanzapine to fluoxetine ratios: 3–18 mg/d plus 25–75 mg/d [34,35].

Olanzapine itself, has a slightly more complicated pharmacodynamic profile when compared to risperidone and paliperidone. Olanzapine certainly binds to D2 receptors to dampen dopaminergic activity. It also has the ability to antagonize 5-HT_{2a} receptors thus keeping EPS rates low when compared to FGAs. Olanzapine blocks 5-HT_{2c} receptors as well. This action at 5HT_{2C} receptors is more potent than for the previous two SGAs (risperidone and paliperidone) and could contribute to the clinical effectiveness of olanzapine as 5HT_{2C} blockade may allow better norepinephrine and dopamine cortical activity through enhancing mesocortical pathways [10]. Enhancing dorsolateral prefrontal cortex DA activity through this 5-HT_{2c} receptor antagonism, in theory, might enhance cognition, attention, concentration, and executive functioning. Olanzapine also has higher affinities to antagonize cholinergic muscarinic receptors and histamine-1 (H-1) receptors. Anticholinergic dry mouth, constipation, blurred vision, and memory problems, sedation, weight gain, and metabolic disorder side effects are likely to occur, respectively [36].

The SGA class carries FDA warnings now about increasing the risk of metabolic disorders. Olanzapine, carries one of the highest risks based upon the full evidence base available regarding the SGAs. Patients with a strong family or personal history of diabetes, hypertension, hypercholesterolemia should be screened prior to use of olanzapine and throughout its longitudinal use. In fact, this practice should likely be implemented for all SGA use and possibly with other psychotropics known to promote weight gain and metabolic clinical syndromes [37–43].

Quetiapine

This drug similarly started out indicated for schizophrenia and bipolar mania comparable to risperidone and olanzapine. Similarly, higher doses (400–800 mg/d) are required to control the symptoms associated with these disorders [44,45]. Its D2 receptor antagonism is quite weak compared to all other SGA and may be considered as a low potency or low affinity drug. This does not suggest it has low effectiveness, but rather requires more dosing milligrams to maintain at least 60% receptor occupancy to stop psychosis or mania. For example, 4 mg of risperidone or 15 mg of olanzapine may prove effective where 400–800 mg of quetiapine is needed. This low affinity may allow for quetiapine to maintain a lower EPS side effect profile as a benefit [46].

A slow release, once daily version of quetiapine has been approved which may improve compliance. Absorption of the immediate and slow release products is predictable, though the slow release product achieves peak plasma levels, and likely sedating side effects, 3–4 h post dose. In regards to dosing quetiapine higher than the FDA norm, Citrome et al. (2007) reported that in a New York State hospital system 40% or more of persistently ill patients were receiving greater than 750 mg/d [47]. A review paper comments that the use of quetiapine at doses greater than 800 mg/d up to 2400 mg/d has been noted in anecdotal reports [48].

This drug also is now approved as a monotherapy for bipolar depression and also as an augmentation strategy that is, added to SSRI or SNRI antidepressants, in unipolar major depressive disorder. Similar to the lower dose effectiveness potential in the off-label use of risperidone in depression, multiple, confirmative, regulatory studies have consistently shown that lower doses of quetiapine are quite effective in treating depressive states. For example, 300 mg will treat bipolar depression as a monotherapy and 150–300 mg will treat unipolar depression as an augmentation approach [49,50]. Quetiapine also has some limited data in the treatment of anxiety at doses of 50–300 mg/d [51–53]. Treating depression or anxiety at these lower doses likely does not inhibit dopamine transmission compared to higher doses.

Quetiapine is the only SGA approved as a monotherapy for bipolar depression. In theory it has very good antidepressant potential as such and observing its unique pharmacodynamic profile is worthy of discussion. To complicate matters, this drug has an active metabolite, norquetiapine, and between the parent drug and its metabolite many antidepressant and anxiolytic properties emerge [54]. This drug has remarkable H-1 receptor antagonism and similar to olanzapine may promote sedation and metabolic disorder onset. H-1 receptor antagonism is the theoretical mechanism of anxiolysis utilized by the FDA approved agent, hydroxyzine [46]. H-1 receptor blockade can produce fatigue as a side effect but also somnolence as a bona fide clinical hypnotic effect. Over the counter diphenhydramine products are approved for treating insomnia as is the recently FDA approved low dose doxepin hypnotic agent [55]. Sometimes these side effects cause patients to stop taking this medication and sometimes these clinical effects improve sleep or agitation similar to other antihistamine products. Quetiapine is quite low in anticholinergic activity so these side effects are largely avoided. Quetiapine has 5HT-2a and 2c antagonism, which lowers EPS rates and improves cognition likely as discussed for other SGAs. The norquetiapine metabolite has two interesting features. First, it allows for 5HT-1a receptor agonism. The serotonergic, FDA approved anxiolytic buspirone works through this purported mechanism in the treatment of generalized anxiety disorder [46,56]. Second, this metabolite has a very potent norepinephrine reuptake inhibitor (NRI) property which is similar to NRI properties possessed by FDA approved unipolar antidepressants such as venlafaxine, duloxetine, bupropion, nortriptyline, and desipramine [46]. Similar to these FDA approved agents in clinical application, one might expect improvements in cognition, energy, concentration, depression, and anxiety as a result. Again, it is likely that at lower doses of quetiapine, the drug is less effective at antagonizing and lowering dopamine activity resulting in an inability to treat psychosis and mania at low doses, but clinically has the potential to treat depression at low doses based on the serotonergic and noradrenergic pharmacodynamic properties noted above and per confirmatory regulatory trials showing clinical efficacy [57,58].

Quetiapine's adverse effect profile shows remarkable sedation, favorable EPS rates, and a fair risk for metabolic disorders. Until recently, it was unclear if metabolic symptoms emerged in a dose-dependent fashion or if any exposure to quetiapine created risk for weight gain, hyperlipidemia, or hyperglucosemia. Quetiapine XR has now been studied from 50 to 600 mg/d in a myriad of psychiatric disorders and regulatory data would suggest that

doses around 150 mg/d may be safer than those at 300 mg/d. For example, weight gain and hyperglycemia nearly comparable to placebo rates, whereas 300 mg nearly doubled these two side effects' prevalence in acute studies. This data was obtained when quetiapineXR was being studied for antidepressant augmentation in unipolar depression [4].

Ziprasidone

This drug, similar to many other SGAs, is indicated for schizophrenia and bipolar mania treatment [59–61]. This drug has a relatively high affinity for D2 receptor antagonism and treats psychosis and mania with average doses of 120–180 mg/d. Interestingly, using the maximal FDA dose in the schizophrenia and bipolar populations has been found to promote longer, sustained ziprasidone use amongst patients. In theory this is due to clear dose–response effects at the higher doses where symptoms are controlled better due to D2 receptor blockade. Patients remain on their ziprasidone longer due to improved clinical effectiveness [62]. The same author observed that dosing typically rose above 180 mg/d to an average of 206 mg/d in theory for the treatment of more refractory, state-hospitalized patients [63]. In fact, almost 50% of patients were treated at doses greater than the approved maximum of 160 mg/d [47]. Ziprasidone appears to have the greatest anecdotal evidence for dosing above the usual FDA approved limits.

Ziprasidone possesses the common D2 and 5-HT_{2a} receptor dual antagonism properties well documented for other SGA. It also antagonizes 5-HT_{1a} receptors and inhibits NRI similar to norquetiapine above. This drug, however, may be unique in its ability to also act as an SSRI and inhibit the serotonin transporter system [64,65]. This SSRI mechanism is commonly used to treat unipolar depression and many anxiety disorders. Currently, unlike quetiapine and the olanzapine–fluoxetine combination, ziprasidone is not approved for the treatment of depression or anxiety, but has fewer published data showing some potential antidepressant effects compared to the limited data of risperidone in depression or anxiety [66].

Stahl and Cutler et al. [67] suggest that in clinical practice, similar to quetiapine, Ziprasidone may be effective in treating anxiety and depression at low doses where DA-2 antagonism is not needed. Large-scale studies in bipolar depression have failed to show consistent results, but smaller studies and those that focus on dysphoric symptoms of mania have concluded with positive results [66,68,69]. One open-label study for a unipolar depression augmentation approach and another for treatment resistant generalized anxiety, both at a low 80 mg/d dose, were effective in reducing symptoms [70,71], but a follow-up study in depression was less conclusive, especially at higher doses [72]. Similar to lower dosed risperidone and quetiapine, lower doses of ziprasidone may be effective in the treatment of anxiety or depression, where higher doses are needed for mania or psychosis.

Pharmacokinetically, ziprasidone is unique in that it clearly requires it to be taken with food to allow for adequate absorption and bioavailability [61] and is clearly a drug that should be taken twice a day per regulatory agencies and studies. In regards to adverse effects, this agent is clinically known to avoid remarkable weight gain and metabolic disorders when compared to other

SGAs and was the first SGA noted to prolong QTc cardiac intervals [73].

Aripiprazole

Aripiprazole might be considered an *atypical* atypical. It stands alone with a unique SGA mechanism for dampening dopamine transmission. It is actually a partial D2 receptor agonist, which is a unique pharmacodynamic property amongst the SGAs [10]. This suggests a dopamine balancing property where aripiprazole can partially stimulate dopamine in areas of low dopamine concentration, and given its partial agonist properties, actually blocks the full agonist dopamine in areas of high dopamine concentration. This may occur in the dopamine mesolimbic system where dopamine hyperactivity is felt to cause psychosis and mania.

Aripiprazole is fairly unique in another property where it is also a dopamine-3 (DA-3) receptor partial agonist. This property likely does not add to antipsychotic or antimanic activity but might, in fact, lend to promoting dopamine transmission in cortical areas. This may have pro-cognitive and antidepressant effects in clinical practice [10]. Aripiprazole carries previously mentioned 5HT-2a receptor antagonism and 5HT-1a receptor agonism properties, which again diminishes EPS, promotes cognition, and antidepressant potential.

In regard to dosing, aripiprazole shows a difference depending upon which illness is being treated similar to other SGAs. Originally approved for treating psychosis from schizophrenia at doses starting from 15 mg up to 30 mg/d, this drug was secondarily approved to treat mania starting at 30 mg/d [5,74,75]. This higher dosing strategy uses aripiprazole's high D2 receptor affinity, despite partial D2 receptor agonism to lower dopamine neurotransmission. There is very little literature evidence showing super dosing above the approved limit of 30 mg/d. Citrome et al.'s (2007) review again would offer about a 10% above label dosing in a New York State hospital system [47].

More recently, this agent was also approved for treating unipolar depression in those patients who failed to respond to initial antidepressant dosing. Aripiprazole was the first FDA approved drug for use as an augmentation strategy in major depressive disorder, where quetiapineXR was approved later [5,76]. Dosing in major depressive disorder is again low and ranges from 2 to 15 mg/d with the average dose being approximately 10 mg/d, which is much lower than doses used in schizophrenia or mania [77]. At these doses, a reduction in dopamine transmission is not required. Instead, promoting dopamine, norepinephrine and serotonin likely occurs as the principal mechanism of action. More recently, this drug was approved for treating irritability due to autism in children in low doses of 2–15 mg/d [78].

In regard to treating anxiety disorders, this drug contains robust activity partially agonizing 5HT-1a receptors similar to the mechanism of action for the FDA approved anxiolytic buspirone (mentioned in regards to norquetiapine and ziprasidone). Small open-label studies exist for generalized anxiety disorder (GAD) or panic disorder (PD) with suggested effectiveness in these patients at doses on average of 13.9 mg/d [79,80]. Again, similar to previously noted SGAs, lower doses of aripiprazole seem to be effective in treating depression and anxiety where higher doses are required for mania and schizophrenia.

From an adverse effect point of view, aripiprazole is known for its higher probability of inducing akathisia (sometimes greater than 20%) [5] compared to other SGAs. This may be due to its high D2 receptor affinity, but also may be due to its overall monoaminergic activity where restlessness and agitation may be confused with more traditional akathisia. This agent, similar to ziprasidone, is felt to be more metabolically friendly in regards to minimizing weight gain. Finally, this drug is known to be a p450 2D6 liver enzyme substrate. Its daily dosing should be halved with a maximum daily dose of only 15 mg/d in patients who are simultaneously taking a strong 2D6 inhibitor such as fluoxetine or paroxetine [5].

Asenapine

Asenapine was simultaneously approved for treating schizophrenia or bipolar mania very recently [81–84]. Similar to other SGAs, asenapine may treat these symptoms with a lower risk of EPS due to its D2/5HT-2a receptor blockade. This drug's molecular structure is similar to the antidepressant mirtazapine [81] and may promote cortical serotonin and norepinephrine activity [85]. This drug is new and a MEDLINE search suggests no evidence for using it in the treatment of depression or anxiety. Its pharmacodynamic profile suggests some treatment possibilities in these clinical areas however. Its 5HT-1a, 5HT-2a, and 5HT-2c receptor pro-cognitive and antidepressant potentials are similar to SGAs mentioned earlier and as noted above, it has a structure similar to mirtazapine with documented serotonin and norepinephrine activation in the cortex.

Dosing typically is 5 mg twice daily with a maximum daily dose allowed up to 20 mg [81]. Unique to this SGA is that it must be taken sublingually and without food or drink 15 min thereafter to ensure absorption [81]. This is the exact opposite of ziprasidone oral tablets which require food to be absorbed. This drug is a known substrate for the p450 1A2 liver enzyme system and asenapine blood levels may increase when administered with 1A2 inhibitors such as fluvoxamine. Very little experience and no literature exist for use of this agent outside the dose range of 10–20 mg/day.

Iloperidone

Iloperidone is the most recently approved SGA for the treatment of schizophrenia [86,87]. Similar to other SGAs, iloperidone may treat these symptoms with a lower risk of EPS due to its D2/5HT-2a receptor blockade. This drug is new so there is also no evidence yet for using it in the treatment of depression or anxiety. Its pharmacodynamic profile [88] suggests some treatment possibilities in these clinical areas however. Its relative lack of 5HT-1a receptor agonism, 5HT-2c receptor antagonism, and Selective Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) potential allows for a pharmacodynamic profile more similar to that of risperidone, iloperidone, and olanzapine than that of quetiapine, ziprasidone, or asenapine [10,86]. A MEDLINE search reveals no papers study-

ing iloperidone in regard to treating depression, anxiety, or bipolar disorder.

The recommended starting dose for iloperidone is 1 mg twice daily. It has a complicated titration schedule and requires increases to reach the target dose range of 6–12 mg twice daily. These daily dosage adjustments proceed from 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, 10 mg twice daily, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively. Efficacy was demonstrated at a dose range of 6 to 12 mg twice daily for schizophrenia [89,90].

This drug is a known substrate for the p450 2D6 liver enzyme system and iloperidone blood levels may increase when administered with 2D6 inhibitors such as paroxetine or fluoxetine similar to precautions with aripiprazole. Iloperidone also has been noted to increase cardiac QTc intervals by 9 msec and carries precautions similar to that of ziprasidone [86].

Summary

In this article, the SGAs are discussed, from the most simplistic SGA, pharmacodynamically speaking, to the most complicated, and the authors conclude briefly with the two most recently approved SGAs. In general, all of the SGAs possess the pharmacologic actions needed to ameliorate psychosis, some if not all of the SGAs have properties to ameliorate mania, and more recently some SGAs have shown ability to treat depression and autism. The authors have attempted to describe how these properties lend themselves to treating psychosis, mania, depression, and sometimes anxiety in clinical practice as well. In order to stop mania or psychosis, it is a clear principle that each SGA must be used near the peak of its daily dose range. This optimizes D2 receptor blockade. This is also where EPS will most likely occur. The second principle suggests that some of the SGA are now well-defined multifunctional drugs [91]. They have FDA approvals in areas of adult or child schizophrenia and bipolar disorder, autism, and depressive disorders. Many of the non-dopaminergic properties of these drugs occur at lower doses and lend themselves to treat depressive disorders in particular. Side effects are likely less at lower doses, which is common amongst most classes of medications. With the advent of studying depressive disorders at lower doses, regulatory data are starting to reveal this fact in a more stringent manner. These agents may be flexibly used as monotherapies and appear to be antidepressant/anxiolytic at one dose and anti-manic/antipsychotic at the next higher dose. As add-on or augmentation therapies, the dose range is also varied depending upon which symptoms the clinician aims to treat. These drugs certainly carry side effects, which vary to some degree but all patients on SGAs should be routinely monitored for TD, EPS, and metabolic disorders.

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Conflict of Interest

Thomas L. Schwartz, MD, is an associate professor of psychiatry at Upstate Medical University and has served as a Consultant to PamLab. He has served on speakers bureaus for Pfizer Inc; Wyeth Pharmaceuticals, AstraZeneca, and Merck pharmaceuticals and received research and/or grant support from Cephalon, Forest, Cyberonics.

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