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Abbreviated Class Review: First Generation Antipsychotic Drugs (First vs. Second Generation)

Month/Year of Review: November 2013 **End date of literature search:** August 31, 2013

Current Status of Voluntary PDL Class: First Generation Antipsychotics have not previously been reviewed

Research Questions:

- What is the comparative efficacy of first and second generation antipsychotics in the treatment of schizophrenia and schizophrenia-related psychoses?
- What is the comparative efficacy of first and second generation antipsychotics in the treatment of bipolar disorder?
- How do first and second generation antipsychotics differ in type and incidence of adverse events?
- Should first generation antipsychotics be added to the PDL?

Conclusions:

- There is robust evidence to support the use of antipsychotics in the management of schizophrenia. While there is evidence to show that individual second generation antipsychotics are superior to individual first generation antipsychotics, several systematic reviews/meta-analyses demonstrate that second generation antipsychotics, as a class, are not collectively superior to first generation antipsychotics.
- There is evidence to support the use of antipsychotics in the treatment of acute mania, however their role in maintenance treatment is much less clear. Head-to-head studies show that second generation antipsychotics are similar in efficacy to haloperidol, albeit there were large variations in study designs and a lack of large trials. More evidence is needed to evaluate any class effect of first or second generation antipsychotics.
- Assessment of safety in a comprehensive meta-analysis shows that rates and types of adverse effects cannot be generalized across the classes of first and second generation antipsychotics. The favorability of each drug varies depending on the adverse effect in question.
- The decision of what antipsychotic to select should be based on individual patient characteristics and the consideration of the unique side effects of each antipsychotic medication.

Recommendations:

- The selection of the appropriate medication for a patient should be chosen based on the properties of an individual drug, as opposed to a drug group.
- In alignment with the NICE guidelines, patients and providers should work together to determine the best drug therapy for the patient, begin therapy at low doses, frequently assess efficacy and safety, avoid loading doses, and give an adequate trial of 4 to 6 weeks. One particular drug or drug group should not necessarily be used preferentially over all others.
- To reduce the copay burden, first generation antipsychotics should be included on the voluntary PDL list to promote the use of cost-effective and individualized treatment options for schizophrenia and bipolar disorder.
- Further review second generation antipsychotics in upcoming meeting for comparative effectiveness and safety.

Reason for Review:
Recent literature has led health care providers to reevaluate the approach to medication management for schizophrenia and bipolar disorder. As the incidence and overall costs of mental health disorders continues to rise, it is critical to understand how to treat these conditions in the most cost-effective manner. Over $10 billion was spent on second generation antipsychotics in 2008, which accounted for almost 5% of all drug costs.[1] Prescribing patterns indicate that second generation antipsychotics are preferred treatment options, presumably due to a perceived increase in efficacy and/or tolerability, but studies are available that refute the claim of general superiority of second generation antipsychotics over first generation antipsychotics. The purpose of this review is to understand the comparative efficacy of first and second generation antipsychotics and to distinguish any class effects in the treatment of schizophrenia or bipolar disorder.

Currently, all antipsychotics are available without restriction and are not subject to prior authorization. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs, such as prior authorization. Thus, the mental health PDL is strictly voluntary. Second generation antipsychotics have been reviewed for clinical efficacy and safety and specific agents have been chosen as clinically preferred. The advantage to this is the elimination of a copay. Studies in Medicaid patients have shown that copays can be associated with significant reductions in use of clinically important medications. Oregon's Medicaid program currently charges no copayment for preferred PDL generics. Reviewing the first generation agents and adding clinically appropriate agents to the PDL would reduce the copay burden to the client, while improving access to these medications.

Background:
Schizophrenia is a complicated illness that occurs in 0.4% to 1.4% of people in the United States.[2] The incidence is similar between men and women and the causes are not well understood. Schizophrenia, among other psychotic disorders, is managed through the use of antipsychotic medications. First generation antipsychotics (FGAs), otherwise known as 'typical antipsychotics,' have been available since the 1950's. Second generation antipsychotics (SGAs), or 'atypical antipsychotics, have been available since the 1980's.[3]

While antipsychotics revolutionized the treatment of schizophrenia, they are also associated with significant adverse effects. The FGAs are high-affinity antagonists of dopamine D2 receptors, which have been shown to be effective against psychotic symptoms, but are also responsible for many of the FGAs adverse effects, including lethargy, sedation, weight gain, and sexual dysfunction. [4] Extrapyramidal symptoms (EPS) and other movement disorders, such as parkinsonism and dystonia, are known to be some of the most debilitating side effects associated with FGAs. Around 20% of patients taking FGAs develop tardive dyskinesia, which involves abnormal involuntary movements that the user is not aware of.

SGAs were developed to reduce relapse rates and adverse events. Compared to FGAs, SGAs have lower affinity for the D2 receptors and act on other receptors, namely serotonin (5-hydroxytryptamine $_{1A, 2A, 2C, 3, 6, \text{and } 7}$) and norepinephrine ($\alpha_1$ and α_2). The first SGA to be introduced to the market was clozapine in 1971, but was voluntarily withdrawn from the market by the manufacturer due to agranulocytosis. Subsequent SGAs later became first-line treatment for many patients due to a lower potential risk of EPS. However, SGAs are less affordable and are associated with metabolic side effects including weight gain, elevated lipid levels, and the development of type 2 diabetes mellitus.[5]

Almost 6 million people in the United States have bipolar disorder, which counts for 2.6% of the US population over age 18.[67] The role of SGAs in bipolar disorder is much less clear. Maintenance treatment usually consists of a mood stabilizer, such as divalproex or lithium, while SGAs are reserved for the treatment of manic episodes. The first SGA approved for bipolar disorder was olanzapine in 2000. Since then, prescribing SGAs for bipolar disorder has become more widely accepted, with one study showing that the percentage of bipolar disorder treatment visits related to SGAs increased from 18% to 49% between January 1998

and December 2009, despite a lack of strong efficacy or safety evidence for this indication.[8] More recent studies are available that evaluate use of SGAs as an add-on maintenance therapy or single maintenance therapy, but this evidence has yet to be incorporated into treatment guidelines.[9]

Recent literature has led health care providers to reevaluate the approach to medication management for schizophrenia and bipolar disorder. As the incidence and overall costs of mental health disorders continues to rise, it is critical to understand how to treat these conditions in the most cost-effective manner. Over $10 billion was spent on SGAs in 2008, which accounted for almost 5% of all drug costs.[1] Prescribing patterns indicate that SGAs are preferred treatment options, presumably due to a perceived increase in efficacy and/or tolerability, but studies are available that refute the claim of general superiority of SGAs over FGAs. The purpose of this review is to understand the comparative efficacy of FGAs and SGAs and to distinguish any class effects in the treatment of schizophrenia or bipolar disorder.

Methods:
A Medline literature search ending August 2013 for new systematic reviews and randomized controlled trials (RCT's) comparing first generation antipsychotics to second generation antipsychotics. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

1. Systematic Reviews/Meta-analyses:

I. Schizophrenia and schizophrenia-related psychoses

a. Change in Symptoms

Three systematic reviews/meta-analyses assessed the relative impact of FGAs and SGAs on symptom scores in people with schizophrenia or related disorders. Symptoms were typically measured using the change in Positive and Negative Syndrome Scale (PANSS); where PANSS scores were not available, the change in Brief Psychiatric Rating Scale (BPRS) was considered a valid tool.

The largest and most recently completed meta-analysis, published June 2013, was a multiple-treatments meta-analysis which allowed for both direct and indirect comparisons of randomized controlled trials comparing 15 different antipsychotics and placebo in the acute treatment of schizophrenia. Two FGA's were assessed in the review: haloperidol and chlorpromazine. The study included 212 published/unpublished randomized controlled trials with 43,049 participants, and each trial was at least single-blinded. This study created an evidence-based hierarchy of effectiveness, measured by the standardized mean difference in PANSS scores, compared to placebo. In this hierarchy, the FGAs haloperidol and chlorpromazine were the 7th and 12th most effective antipsychotics. Clozapine was more effective than all other studied drugs; amisulpride (not available in the United States), olanzapine, and risperidone were superior to the remaining drugs, aside from paliperidone and zotepine (not available in the United States). There was a wide range of effect sizes, ranging from -0.33 to -0.88. The standardized mean differences in PANSS scores, compared to placebo, with 95% confidence intervals are shown in Table 1.[10]

Table 1. Efficacy of Antipsychotic Drugs Compared to Placebo[8]

Overall change in symptoms, SMD (95% CI)	
Clozapine	-0.88 (-1.03, -0.73)
Amisulpride	-0.66 (-0.78, -0.53)
Olanzapine	-0.59 (-0.65, -0.53)
Risperidone	-0.56 (-0.63, -0.50)
Paliperidone	-0.50 (-0.60, -0.39)
Zotepine	-0.49 (-0.66, -0.31)
Haloperidol	-0.45 (-0.51, -0.39)
Quetiapine	-0.44 (-0.52, -0.35)
Aripiprazole	-0.43 (-0.52, -0.34)
Sertindole	-0.39 (-0.52, -0.26)
Ziprasidone	-0.39 (-0.49, -0.30)
Chlorpromazine	-0.38 (-0.54, -0.23)
Asenapine	-0.38 (-0.51, -0.25)
Lurasidone	-0.33 (-0.45, -0.21)
Iloperidone	-0.33 (-0.43, -0.22)

SMD: standardized mean difference, CI: confidence interval

The results of this review align with a meta-analysis completed several years earlier, which included 150 double-blind studies that compared one of nine different SGAs to haloperidol (n=95), chlorpromazine (n=28), perphenazine (n=5), fluphenazine (n=4), flupenthixol (n=3), perazine (n=3), thioridazine (n=2), levomepromazine (n=2), and clopenthixol, zuclopenthixol, mosapramine, tiothixene, clocapramine, trifluoperazine, periciacine (1 study each). Consistent with the aforementioned meta-analysis, amisulpride [-0.31 (95% CI -0.44, -0.19)], clozapine [-0.52 (95% CI -0.22, -0.05], olanzapine [-0.28 (95% CI -0.38, -0.18)], and risperidone [-0.13 (95% CI -0.22, -0.05)], were more efficacious than the FGAs. The remaining SGAs (aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine) were not significantly different from the FGAs in their effects on overall symptoms, measured by the PANSS or BPRS. The magnitude of effect sizes was considered small to medium by the study authors.[11]

The notion that there is no clear benefit of one class versus the other is supported by a third systematic review and meta-analysis. This analysis included 114 randomized and nonrandomized controlled trials, or cohort studies with a minimum follow-up of up to 2 years, and compared commercially available FGAs and SGAs. This trial evaluated the comparative efficacy on positive and negative symptoms separately, but used the PANSS as the primary scale for outcome measurement. In the assessment of reduction in positive symptoms, there was evidence to show a benefit of risperidone over haloperidol, although the effect size was minimal and not considered clinically significant by study authors. No other differences were observed between haloperidol and the four other SGAs that were studied (clozapine, olanzapine, quetiapine, or aripiprazole). The evidence for negative symptoms was stronger, as there was moderate-strength evidence that showed olanzapine, risperidone, and aripiprazole had statistical benefit compared to haloperidol, however the difference was not considered clinically significant. There was no difference between haloperidol versus clozapine, quetiapine or ziprasidone for the reduction of negative symptoms, presumably due to a lack of precision in effect estimates.[12]

b. Relapse Rates

The National Institute of Health published a systematic review/meta-analysis, which evaluated the comparative efficacy of FGAs and SGAs for relapse prevention in schizophrenia. This analysis included randomized, head-to-head comparisons of oral SGAs and FGAs, with durations of ≥ 6 months. The primary outcome measure was relapse, which was not defined consistently among the 23 studies included in the analysis. Of the 9 studies that did not define relapse rate, hospitalization (n=4) or 'failure to maintain response' (n=5) was used to define relapse. Overall, this study showed that individual SGAs were not consistently superior to FGAs, however when evaluated as a group, treatment with SGAs resulted in superior relapse prevention. Two studies showed that SGAs sertindole and ziprasidone were superior to FGAs, however when requiring ≥ 3 studies per individual antipsychotic, risperidone, clozapine, or olanzapine were not statistically superior to FGAs in preventing relapse. When analyzed as a class, SGAs were significantly superior to FGAs for the prevention of relapse (29% vs 37.5%, p=0.0007). The authors attribute the discrepancy between individual and class effects to the lack of power to detect a difference in individualized studies. A major limitation of this analysis is the inconsistency in the definition of the primary endpoint, in addition to variation in the study methodologies.[13]

c. Quality of Life

Jones et al. investigated whether improvements in health-related quality of life or savings in the use of other health and social care resources would offset the increased acquisition costs of SGAs over FGAs. Study subjects were aged 18-65, had schizophrenia, and a change in drug treatment was being considered for clinical reasons, most commonly suboptimal efficacy or adverse effects. The primary hypothesis was that use of SGAs would be associated with clinically

significant improvement in quality of life across 1 year compared with the use of FGAs. This was measured using the Quality of Life Scale, an interview-based survey with 21 items rated on a 7-point scale from 0 to 6; a higher score reflected normal functioning. Secondary questions concerned wither SGAs (other than clozapine) were associated with fewer adverse effects, improved patient satisfaction, and lower total health care costs. Patients were randomized to either FGAs (n=118) or SGAs (n=109) (other than clozapine). The treating psychiatrists determined individual treatments. The difference in overall quality of life scale estimate at 52 weeks was -1.7 [standard error 1.4 (-4.5 to 1.1); p=0.24], a difference that favored FGAs, but was not statistically significant. No difference was found in side effects using the antipsychotic non-neurological side-effects rating scale (ANNSERS) in the FGAs versus SGAs [10.8 (SD 7.7) versus 12.5 (SD 8.4); p=0.14]. Study participants did not show a preference for either class of drugs, costs were similar, and there was no difference in symptoms. There was a trend for the mean annual cost to be lower for people using FGAs ($34,750) compared to SGAs ($37,185), and the major cost in both groups was psychiatric hospital inpatient admissions (93.2% for FGAs, 81.5% for SGAs).[14]

d. Safety

The multiple-treatments meta-analysis evaluated several safety outcomes as secondary endpoints. The relative effect sizes of antipsychotic drugs compared to placebo are shown in Table 2.

- **All-cause discontinuation** was evaluated as a measure of efficacy and tolerability. All drugs were significantly better than placebo with the exception of zotepine, an SGA that is not currently available in the United States. Additionally, the drugs that were found to be most efficacious had lower rates of discontinuation, with the exception of haloperidol, which was ranked in the middle in terms of efficacy, and lowest for all-cause discontinuation.[10]
- Ziprasidone, lurasidone, and haloperidol were the only drugs that did not produce significantly more **weight gain** compared to placebo. Chlorpromazine had a significant impact on weight gain, in addition to clozapine, iloperidone, sertindole, quetiapine, risperidone, and paliperidone.[10]
- Clozapine, sertindole, olanzapine, quetiapine, aripiprazole, iloperidone, amisulpride, and asenapine did not cause significantly more **extrapyramidal side effects** compared to placebo. Haloperidol caused the most extrapyramidal side effects, in addition to zotepine, with odds ratios ranging from 3.01-4.76. Chlorpromazine did not produce more extrapyramidal side effects than most SGAs.[10]
- Paliperidone, risperidone, and haloperidol had a larger effect on **prolactin increase**, compared to all other drugs, with risperidone and paliperidone having a greater effect than haloperidol.[10]
- Iloperidone, ziprasidone, amisulpride and sertidole were associated with significant **QTc prolongation**. Haloperidol appeared to increase the risk of QTc prolongation compared to placebo, however magnitude of the effect appears to be small (odds ratio: 0.11).[10]
- All but four of the studied drugs increased **sedation** compared to placebo (amisulpride, paliperidone, sertindole, and iloperidone showed no difference compared to placebo. Clozapine appears to be the most sedating (odds ratio: 8.82).[10]

Table 2. Effect Sizes of Antipsychotic Drugs Compared to Placebo for Safety Outcomes[10]

	All-cause discontinuation (OR, 95%CI)		Weight gain (SMD, 95%CI)		Extrapyramidal side effects (OR, 95%CI)	
Better	Amisulpride	0.43 (0.32, 0.57)	Haloperidol*	0.09 (0, 0.17)	Clozapine	0.3 (0.12, 0.62)
	Olanzapine	0.46 (0.41, 0.52)	Ziprasidone*	0.10 (-0.02, 0.22)	Sertindole*	0.81 (0.47, 1.3)
	Clozapine	0.46 (0.32, 0.65)	Lurasidone*	0.10 (-0.02, 0.21)	Olanzapine*	1 (0.73, 1.33)
	Paliperidone	0.48 (0.39, 0.58)	Aripiprazole	0.17 (0.05, 0.28)	Quetiapine*	1.01 (0.68, 1.44)
	Risperidone	0.53 (0.46, 0.60)	Amisulpride	0.20 (0.05, 0.35)	Aripiprazole*	1.2 (0.73, 1.85)
	Aripiprazole	0.61 (0.51, 0.72)	Asenapine	0.23 (0.07, 0.39)	Iloperidone*	1.58 (0.55, 3.65)
	Quetiapine	0.61 (0.52, 0.71)	Paliperidone	0.38 (0.27, 0.48)	Amisulpride*	1.6 (0.88, 2.65)
	Chlorpromazine	0.65 (0.5, 0.84)	Risperidone	0.42 (0.33, 0.50)	Ziprasidone	1.61 (1.05, 2.37)
	Zotepine*	0.69 (0.41, 1.07)	Quetiapine	0.43 (0.34, 0.53)	Asenapine*	1.66 (0.85, 2.93)
	Asenapine	0.69 (0.54, 0.86)	Sertindole	0.53 (0.38, 0.68)	Paliperidone	1.81 (1.17, 2.69)
	Iloperidone	0.69 (0.56, 0.84)	Chlorpromazine	0.55 (0.34, 0.76)	Risperidone	2.09 (1.54, 2.78(
	Ziprasidone	0.72 (0.59, 0.86)	Iloperidone	0.62 (0.49, 0.74)	Lurasidone	2.46 (1.55, 3.72)
	Lurasidone	0.77 (0.61, 0.96)	Clozapine	0.65 (0.31, 0.99)	Chlorpromazine	2.65 (1.33, 4.76)
	Sertindole	0.78 (0.61, 0.98)	Zotepine	0.71 (0.47, 0.96)	Zotepine	3.01 (1.38, 5.77)
Worse	Haloperidol	0.8 (0.71, 0.90)	Olanzapine	0.74 (0.67, 0.81)	Haloperidol	4.76 (3.7, 6.04)
	Prolactin Increase (SMD, 95%CI)		**QTc prolongation (OR, 95%CI)**		**Sedation (OR, 95%CI)**	
Better	Aripiprazole*	-0.22 (-0.46, 0.03)	Lurasidone*	-0.10 (-0.21, 0.01)	Amisulpride*	1.42 (0.72, 2.51)
	Quetiapine*	-0.05 (-0.23, 0.13)	Aripiprazole*	0.01 (-0.13, 0.15)	Paliperidone*	1.40 (0.85, 2.19)
	Asenapine*	0.12 (-0.12, 0.37)	Paliperidone*	0.05 (-0.18, 0.26)	Sertindole*	1.53 (0.82, 2.62)
	Olanzapine	0.14 (0, 0.28)	Haloperidol	0.11 (0.03, 0.19)	Iloperidone*	1.71 (0.63, 3.77)
	Chlorpromazine*	0.16 (-0.48, 0.8)	Quetiapine	0.17 (0.06, 0.29)	Aripiprazole	1.84 (1.05, 3.05)
	Iloperidone*	0.21 (-0.09, 0.51)	Olanzapine	0.22 (0.11, 0.31)	Lurasidone	2.45 (1.31, 4.24)
	Ziprasidone	0.25 (0.01, 0.49)	Risperidone	0.25 (0.15, 0.36)	Risperidone	2.45 (1.76, 3.35)
	Lurasidone	0.34 (0.11, 0.57)	Asenapine*	0.30 (-0.04, 0.65)	Haloperidol	2.76 (2.04, 3.66)
	Sertindole	0.45 (0.16, 0.74)	Iloperidone	0.34 (0.22, 0.46)	Asenapine	3.28 (1.37, 6.69)
	Haloperidol	0.7 (0.56, 0.85)	Ziprasidone	0.41 (0.31, 0.51)	Olanzapine	3.34 (2.46, 4.5)
	Risperidone	1.23 (1.06, 1.40)	Amisulpride	0.66 (0.39, 0.91)	Quetiapine	3.76 (2.68, 5.19)
	Paliperidone	1.3 (1.08, 1.51)	Sertindole	0.9 (0.76, 1.02)	Ziprasidone	3.8 (2.58, 5.42)
	Amisulpride	N/A	Clozapine	N/A	Chlorpromazine	7.56 (4.78, 11.53)
	Clozapine	N/A	Chlorpromazine	N/A	Zotepine	8.15 (3.91, 15.33)
Worse	Zotepine	N/A	Zotepine	N/A	Clozapine	8.82 (4.72, 15.06)

*: no statistically significant difference compared to placebo; Highlighted cells: first generation antipsychotics; OR: odds ratio; SMD: standardized mean difference; CI: confidence interval. *Difference is not statistically significant compared to placebo

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II. Bipolar Disorder

A comparative effectiveness review was published in 2012, which evaluated antipsychotic treatments for bipolar disorder. Overall, 11 trials were included which evaluated 2,217 adult patients and evaluated 4 main outcomes: 1) core illness symptoms; 2) functional outcomes and health care system utilization; 4) other outcomes; 5) subgroup analysis.[3]

Chlorpromazine was compared to clozapine in a 27 patient study. There were no differences found between groups for mood (mania) based on the Young Mania Rating Scale (YMRS). Two trials evaluated haloperidol versus aripiprazole in 679 patients. No differences were found on the improvement of core illness symptoms in any of the various scoring systems. One trial found a increased incidence of relapse rate in the haloperidol group [RR 0.53 (0.4 to 0.71)]. Two trials compared haloperidol with olanzapine in 463 subjects. There was no difference in improvement of core illness symptoms or relapse, response, and remission rates. There was an increase on the number of days worked for pay favoring olanzapine [RR 0.50 (0.32 to 0.70)]. Haloperidol had a favorable outcome on the mental summary score and olanzapine had a favorable physical summary score. One trial evaluated haloperidol versus quetiapine in 201 subjects. Core illness symptoms were not studied. There was no difference in remission rates or response rates. Four trials evaluated haloperidol versus risperidone. Several different evaluation tools were used to evaluate the improvement of core illness symptoms (YMRS being the most common); however none of the trials found a significant difference between the two study groups. One trial compared haloperidol to ziprasidone in 350 subjects. Haloperidol was found to be superior for the improvement of core illness symptoms based on YMRS [RR -5.52 (-7.79 to -3.25)] and response rates [RR 1.09 (1.02 to 1.16)].[3]

The incidence of diabetes mellitus, tardive dyskinesia, and metabolic syndrome were evaluated among the agents included in the above studies. There was no difference in the incidence of diabetes mellitus. Haloperidol showed a statistically significant increase in tardive dyskinesia compared to clozapine [RR 34.5 (95% CI 2.07 to 573.55)]. Haloperidol was also found to have a higher incidence of metabolic syndrome in one trial comparing it to clozapine [RR 0.27 (95% CI 0.10 to 0.75)].[3]

2. New Guidelines:

Schizophrenia:
The 2004 National Institute for Health & Clinical Excellence (NICE) guidelines reviewed 9 randomized controlled trials, which included 1,801 subjects with first-episode or early schizophrenia (including recent onset and treatment-naïve patients).[15] Studies were excluded if subjects had very late onset schizophrenia (onset after age 60), or had other psychotic disorders (bipolar disorder, mania, or depressive psychosis). The trials studied 1 FGA, haloperidol, and three SGAs, olanzapine, quetiapine, and risperidone. The critical outcomes that were included were mortality (suicide), global state [based on the Clinical Global Impression scale (CGI)], mental state (total symptoms, depression), social functioning, study discontinuation rates, and adverse events. The guidelines concluded that there were no differences in clinical efficacy. In terms of safety, the reported rates of metabolic and neurological side effects were consistent with those previously reported for each drug.

For the acute exacerbation or recurrence of schizophrenia, the NICE guidelines evaluated 72 RCTs (n=16,556) with the critical outcomes of mortality (suicide), global state (CGI), mental state (total symptoms, depression), social functioning, study discontinuation rates, and adverse events. They found no differences in efficacy between FGAs (benperidol, chlorpromazine, flupenthixol, fluphenazine, haloperidol, levomepromazine, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, sulpiride, trifluoperazine, zuclopenthixol) and SGAs (amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, sertindole, zotepine). Reported side effects were similar to those described in previous studies.[15]

For relapse prevention, the NICE guidelines evaluated 17 RCTs, which included 3,535 participants and compared FGAs (benperidol, chlorpromazine, flupenthixol, fluphenazine, haloperidol, levomepromazine, pricyazine, perphenazine, pimozide, prochlorperazine, promazine, sulpiride, trifluoperazine, zuclopenthixol) and SGAs (amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, zotepine). The critical outcomes evaluated were global state (relapse), overall treatment failure, and study discontinuation rates. All the antipsychotics reduced the risk of relapse or overall treatment failure. A slight benefit was found for some SGAs over haloperidol, but the evidence was not strong enough to preferentially select an antipsychotic for relapse prevention. The guidelines pooled 138 studies of antipsychotic medications to evaluate metabolic and neurologic side effects. This pooled data did not provide additional insight into long-term adverse effects or clinically significant differences between antipsychotic drugs.[15]

When deciding on a pharmacological intervention for a patient with newly diagnosed schizophrenia, the NICE guidelines recommend providing information and discussing the benefits and side-effect profile of each drug with the service user and to consider:

- The relative potential of individual antipsychotic drugs to cause extrapyramidal symptoms, metabolic side effects and other side effects.
- The views of the caregiver if the patient agrees.

There are no recommendations of specific therapies that should be started. It is recommended that once a medication is selected it should be given for 4-6 weeks at an optimum dosage, and efficacy and side effects should be closely monitored. Loading doses should not be used and as needed medications should have specific dosing instructions and should not go above a maximum dosing.[15]

Bipolar Disorder:

The bipolar disorder guidelines from The American Psychiatric Association (APA) were originally published in 2002 and are somewhat outdated. For the acute treatment of manic or mixed episodes, the APA recommends the initiation of lithium plus an antipsychotic or valproate plus an antipsychotic. The choice of initial treatment should be guided by illness severity and patient preference where possible, keeping in mind the side effect profiles of the individual agents. For less ill patients they state that monotherapy with lithium, valproate, or an antipsychotic may be used, and olanzapine is specifically mentioned as an option. They recommend SGAs over FGAs because of their benign side effect profile [class I recommendation], and they note the benefits of SGAs over haloperidol and chlorpromazine. They also recommend olanzapine or risperidone because of published trials in the use of bipolar disorder [II]. Clozapine is given a class II recommendation for refractory illness. For maintenance treatment of bipolar disorder they recommend that antipsychotics be discontinued unless they are required for control of persistent psychosis [I] or prophylaxis against recurrence [III]. They state that antipsychotics could be considered for maintenance treatment, however there is a lack of evidence to show that they are comparable to lithium or valproate [III].[9]

A guideline watch was developed in 2005 with updates to the 2002 APA guidelines, which incorporated newer studies that evaluated SGAs as monotherapy, and adjunct to mood stabilizers for the acute treatment of mania.[16] Olanzapine was found to be better than placebo for the acute treatment of mania or mixed episodes in two randomized, double-blind, controlled studies. Haloperidol was compared to olanzapine in a randomized, double-blind study and the two groups were found to be equivalent for acute mania, but olanzapine was found to be superior for patients whose index episode did not include psychotic features. When olanzapine monotherapy was compared to divalproex monotherapy in two trials, one found equivalent efficacy and the other found olanzapine to be superior in efficacy, but with a greater incidence of side effects. Olanzapine plus divalproex or lithium was found to be a superior mood stabilizing regimen compared to divalproex or lithium alone. Risperidone monotherapy was evaluated in 3 randomized, double-blind, placebo-controlled trials and was found to be superior to placebo in all three trials for the acute treatment of mania. Risperidone as an adjunctive agent was also found to be beneficial as a mood stabilizer. Aripiprazole and ziprasidone were found to be more effective than placebo for the acute treatment of patients with manic or mixed episodes. Quetiapine was

compared against lithium and haloperidol in patients with manic episodes in two different trials and found to be equivalent. For depressive episodes, olanzapine alone and in combination with fluoxetine were compared to placebo and found to be superior. Quetiapine was also found to be superior to placebo for depression. For maintenance therapy olanzapine was compared to divalproex. The remission rates were not different, however olanzapine had a shorter remission time. Olanzapine was also found to have similar efficacy to lithium in a 52 week study after a manic or mixed episode. The APA has yet to update the guideline recommendations, but information obtained from these studies will be factored into future guidelines and should be considered when treating bipolar disorders.[16]

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

DOSE & AVAILABILITY

MEDICATIONS	INDICATIONS	STRENGTH	ROUTE	DOSAGE and FREQUENCY:
Chlorpromazine[17] (Thorazine)	Schizophrenia	Injection: 25mg/mL (1 mL, 2 mL) Tablet: 10mg, 25mg, 50mg, 100mg, 200mg	PO IV IM	**Oral:** 30-800mg/day in 1-4 divided doses **IM,IV:** Initial 25mg, maximum 400mg/dose every 4-6 hours until patient controlled
Fluphenazine[18] (Prolixin)	Psychotic disorders and schizophrenia	Elixir, oral: 2.5mg/5 mL Injection, oil, as decanoate: 25 mg/mL Injection, solution: 2.5mg/mL Solution, oral [concentrate]: 5mg/mL Tablet: 1mg, 2.5mg, 5mg, 10mg	PO IM	**Oral:** Initial 2.5-10 mg/day in divided doses **IM:** Initial 1.25mg as a single dose, may need 2.5-10 mg/day in divided doses (3-4 times/day) **Long acting IM:** Initial 12.5-25mg every 2-4 weeks
Haloperidol[19] (Haldol)	Management of schizophrenia	Injection, oil, as decanoate: 50mg/mL (1 mL, 5mL),; 100mg/ml (1 mL, 5 mL) Injection, solution: 5mg/mL (1mL, 10mL) Solution, oral: 2 mg/mL (5 mL, 15 mL, 120 ML) Tablet: 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg	PO IM IV	**Oral:** 0.5-5mg 2-3 times/day; usual maximum 30mg/day **IM (as lactate):** 2-5mg every 4-8 hours as needed **IM (as decanoate):** Initial: 10-20 times the daily oral dose administered at 4-week intervals. Maintenance dose: 10-15 times initial oral dose, used to stabilize psychiatric symptoms
Loxapine[20] (Loxitane)	Psychotic disorders	Capsule: 5mg, 10mg, 25mg, 50mg	PO	**Oral:** Initial 10mg twice daily (up to 50 mg/day), increase dose until psychotic symptoms are controlled; usual maintenance: 60-100 mg/day divided doses 2-4 times/day. Maximum 250mg/day.
Perphenazine[21] (Trilafon)	Treatment of schizophrenia	Tablet: 2mg, 4mg, 8mg, 16mg	PO	**Oral:** Non-hospitalized: Initial 4-8mg 3 times/day; reduce dose as soon as possible to minimum effective dosage (maximum 24mg/day) Hospitalized: 8-16mg 2-4 times/day (maximum 64mg/day)
Prochlorperazine[22] (Compro)	Schizophrenia, psychotic disorders	Injection, solution: 5mg/mL (2mL, 10mL) Suppository, rectal: 25mg Tablet: 5mg, 10mg	PO IM IV	**Oral:** 5-10mg 3-4 times/day, titrate slowly every 2-3 days; doses up to 150mg/day may be required. **IM (as edisylate):** Initial 10-20mg, may repeat every 2-4 hours to gain control; convert to oral as soon as possible.

Thioridazine[23] (Mellaril)	Schizophrenia	Oral: 10mg, 25mg, 50mg, 100mg	PO	**Oral:** 150-800mg/day given in 2-4 divided doses.
Thiothixene[24] (Navane)	Schizophrenia	Capsule: 1mg, 2mg, 5mg, 10mg	PO	**Oral:** Mild-moderate psychosis: 6-60mg/day in 2-3 divided doses Rapid tranquilization: 5-30mg
Trifluoperazine[25] (Stelazine)	Schizophrenia	Tablet: 1mg, 2mg, 5mg, 10mg	PO	**Oral:** Outpatients: 1-2mg twice daily Hospitalized or well supervised: 4-40mg/day in 2 divided doses
Aripiprazole[26] (Abilify)	Schizophrenia, Bipolar I	Injection: 9.75mg/1.3mL vial Solution, oral: 1mg/mL Tablets, orally disintegrating: 10mg, 15mg Tablets: 2mg, 5mg, 10mg, 15mg, 20mg, 30mg	PO IM	Schizophrenia: 10-15mg/day, max 30mg/day Bipolar mania, monotherapy: 15mg/day, max 30mg/day Bipolar mania, adjunct to lithium or valproate, 10-15mg/day, max 30mg/day
Asenapine[27] (Saphris)	Schizophrenia, Bipolar I	Tablets, sublingual: 5mg, 10mg Tablets, sublingual, black cherry flavor: 5mg, 10mg	SL	Schizophrenia, acute: 5mg twice daily, max 10mg twice daily Schizophrenia, maintenance: 5-10mg twice daily, max 10mg twice daily Bipolar, monotherapy: 5-10mg twice daily, max 10mg twice daily Bipolar, adjunct to lithium or valproate: 5-10mg twice daily, max 10mg twice daily
Clozapine[28] (Clozaril)	Schizophrenia	Tablets: 25mg, 100mg	PO	Initial: 12.5mg once or twice daily, increase the total daily dosage in increments of 25-50mg per day, if well tolerated. Target dose: 300-450mg per day, in divided doses. Max daily dose: 900mg
Iloperidone[29] (Fanapt)	Schizophrenia	Tablets: 1mg, 2mg, 4mg, 6mg, 8mg, 10mg, 12mg	PO	Initial: 1mg twice daily, then increase by 2mg increments. Target dose: 12-24mg/day.
Lurasidone[30] (Latuda)	Schizophrenia Bipolar I	Tablets: 20mg, 40mg, 60mg, 80mg, 120mg	PO	Schizophrenia: 40-60mg/day Bipolar: 20-120mg/day
Olanzapine[31] (Zyprexa)	Schizophrenia Bipolar I	Zyprexa powder for reconstitution: 10mg Zyprexa Relprevv powder for suspension, extended release: 210mg, 300mg, 405mg Tablet: 2.5mg, 5mg, 7.5mg,	PO IM	Schizophrenia: **Oral:** 5-20mg (doses of 30-50mg/day have been used but not found to improve efficacy) **ER IM injection:** Patient established on oral 10mg/day: initial 210mg every 2 weeks for 4 doses or 405mg every 4 weeks for 2 doses; maintenance 150mg every 2 weeks or 3000mg every 4 weeks. Patients established on oral 15mg/day: initial 300mg every 2 weeks for 4 doses; maintenance 210mg every 2 weeks or 405mg every 4 weeks. Patient

		10mg, 15mg, 20mg Orally disintegrating tablet: 5mg, 10mg, 15mg, 20mg		established on 20mg/day: 300mg every 2 weeks. Bipolar 1: **Oral:** 10-20mg/day. Agitation associated with bipolar disorder or schizophrenia: **Short-acting IM:** 10mg, with maximum total daily dose 30mg
Paliperidone[32] (Invega)	Schizophrenia	Injection, suspension, extended release, as palmitate: 39mg/0.25mL; 78mg/0.5mL; 117mg/0.75mL; 156mg/1mL; 234mg/1.5mL XR tablet: 1.5mg, 3mg, 6mg, 9mg	PO IM	Oral: 3-12mg/day IM: 39-234mg monthly maintenance dose
Quetiapine[33] (Seroquel)	Schizophrenia Bipolar I	Tablet: 25mg, 50mg, 100mg, 200mg, 300mg, 400mg Tablet extended release: 50mg, 150mg, 200mg, 300mg, 400mg	PO	Depression: **Immediate release tablet:** 50-600mg/day **Extended release tablet:** 50-300mg/day Mania: **Immediate release tablet:** 50-800mg/day **Extended release tablet:** 300-800mg/day Schizophrenia: **Immediate release tablet:** 25-800mg/day **Extended release tablet:** 300-800mg/day
Risperidone[34] (Risperdal)	Schizophrenia Biopolar I	Tablet: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg Tablet, orally disintegrating: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg Injection, extended release: 12.5mg, 25mg, 37.5mg, 50mg Solution, oral: 1mg/mL (30 mL)	PO IM	Bipolar mania: **oral:** 1-6mg/day Bipolar I: **IM:** 12.5-50mg every 2 weeks Schizophrenia: **Oral:** 2-16mg/day; IM 12.5-50mg every 2 weeks
Ziprasidone[35] (Geodon)	Schizophrenia Bipolar disorder	Capsule: 20mg, 40mg, 60mg, 80mg Solution reconstituted, IM: 20mg	PO IM	Bipolar: **Oral:** 40-80mg/day Schizophrenia: **Oral:** 20-100mg twice daily Acute agitation (schizophrenia) I**M:** 10mg every 2 hours or 20mg every 4 hours (max 40mg). Switch to

				oral as soon as possible.

DOSE ADJUSTMENTS

MEDICATIONS	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Chlorpromazine[17] (Thorazine)	No adjustments provided	Avoid use in severe hepatic dysfunction	Oral: 0.5-1 mg/kg/dose every 4-6 hours; older children may require 200mg/day or higher IM, IV: 0.5-1 mg/kg/dose every 6-8 hours; maximum dose for <5 years (<22.7 kg); 40mg/day; maximum for 5-12 years (22.7-45.5 kg): 75 mg/day	Initial 10-25mg 1 or 2 times/day, increase at 4-7 day intervals by 10-25mg/day.	Not dialyzable
Fluphenazine[18] (Prolixin)	Use with caution	Use with caution	None	Oral: initial 1-2.5mg daily, titrated gradually	Long acting IM dose effects may last up to 6 weeks ** Not dialyzable
Haloperidol[19] (Haldol)	No adjustments provided	No adjustments provided	Age 3-12 (15-40 kg): Initial: 0.5mg/day given in 2-3 divided doses; increase by 0.5mg every 5-7 days; maximum 0.15 mg/kg/day	No psychiatric dosing adjustments mentioned	No supplemental dose required for hemodialysis or peritoneal dialysis
Loxapine[20] (Loxitane)	No adjustments provided	No adjustments provided	None	Reduced dosing may be indicated due to risks of adverse events associated with high-dose therapy.	IM formulation not available in the United States
Perphenazine[21] (Trilafon)	No adjustments provided	No adjustments provided	None	No dosing adjustments provided, but initiate at lower end of dosing range.	Zero to minimal removal in dialysis
Prochlorperazine[22]	No adjustments	No adjustments provided	Oral, rectal: 2.5mg 2-3	Initiate at low dose.	Hepatic drug metabolism, so

(Compro)	provided		times/day; do not give more than 10mg the first day; increase dosage as needed for maximum daily dose of 20mg for 2-5 years and 25mg for 6-12 years. IM: 0.13 mg/kg/dose; convert to oral as soon as possible		systemic exposure may be increased in hepatic dysfunction.
Thioridazine[23] (Mellaril)	No adjustments provided	No adjustments provided	Schizophrenia: Age 2-12 years: Range 0.5-3 mg/kg/day in 2-3 divided doses Age >12 years: Use adult dosing	Maximum daily dose (800mg), gradual increases recommended	Not dialyzable
Thiothixene[24] (Navane)	No adjustments provided	None adjustments provided	< 12 years: Oral: 0.25mg/kg/day in divided doses >12 years: Adult dosing	1-30mg in divided doses	Not dialyzable
Trifluoperazine[25] (Stelazine)	No adjustments provided	No adjustments provided	6-12 years: Hospitalized or well supervised: 1mg-15mg/day	Use low end of dosing scale	Not dialyzable
Aripiprazole[26] (Abilify)	No adjustments recommended	No adjustment recommended	Schizophrenia, adolescents: 2-10mg/day, max 30mg/day Bipolar mania, pediatrics: 2-10mg/day, max 30mg/day	No adjustment recommended	Oral: administered once daily without regard to meals IM injection: Wait at least 2 hours between doses. Max daily dose=30mg.
Asenapine[27] (Saphris)	No adjustment recommended	Not recommended in severe hepatic impairment	None	None	Tablets should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration.
Clozapine[28] (Clozaril)	May be necessary	May be necessary	None	None	None

Iloperidone[29] (Fanapt)	No adjustment recommended	Not recommended in patients with hepatic impairment	None	None	Administer without regard to meals
Lurasidone[30] (Latuda)	Initial: 20mg/day, max 80mg/day	Initial: 20mg/day Moderate impairment: max 80mg/day Severe impairment: Max 40mg/day	None	None	Take with food (at least 350 calories)
Olanzapine[31] (Zyprexa)	No adjustment required	Dosage adjustment may be necessary; no specific recommendations.	Adolescents ≥ 13 years: oral 2.5-20mg/day.	Consider lower starting doses.	Not removed by dialysis
Paliperidone[32] (Invega)	CrCl 50-70 mL/min: Oral: Initial dose 3mg/day and maximum 6mg/day IM:156 mg day one, followed by 117mg 1 week later, followed by 78mg/month CrCl 10-49 mL/min: initial dose 1.5mg/day and maximum of 3mg daily CrCl <10 mL/min: Use not recommended For IM CrCl<50: use not recommended	No adjustment necessary for mild to moderate (Child Pugh class A or B) impairment. Not studied in severe impairment.	Adolescents 12-17 years: Oral: 3mg/day	No adjustments given, however renal function and orthostatic blood pressure should be monitored	No efficacy benefit of higher doses in children
Quetiapine[33] (Seroquel)	No dosage adjustment required	30% lower clearance in hepatic impairment. Dosage adjustment may be required.	Bipolar disorder of children ≥10 years old 25-600mg/day Schizophrenia adolescents ≥13 ears: 25-800 mg/day	40% lower mean oral clearance in adults >65 years older, therefore dosage adjustment may be needed.	None
Risperidone[34] (Risperdal)	CrCl <30 mL/minute: starting dose of	Child-Pugh class C: Starting dose of 0.5mg	Bipolar mania: Age 10-17; oral: initial 0.5mg	Oral: initial 0.5mg twice daily, titrate slowly	None

	0.5mg twice dail; titration should progress slowly. IM: initiate with oral dosing; if tolerated begin 25mg IM every 2 weeks.	twice daily, titration should progress slowly. IM: initiate with oral dosing of 0.5mg twice daily for 1 week then 2mg daily for 1 week.	daily Schizophrenia: adolescents 13-17 years: oral: initial 0.5mg daily	IM: 25mg every 2 weeks, consider 12.5mg	
Ziprasidone[35] (Geodon)	No dosage adjustment needed	No dosage adjustment recommended; however drug undergoes hepatic metabolism	Not studied	No dosage adjustment recommended	Cyclodextrin, an excipient of the IM formulation is cleared renally; use with caution.

DRUG SAFETY

Safety information, which includes Black Box Warnings, contraindications, and warnings are listed in Table 4. Drugs are categorized in the following manner:

- FGAs: chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, prochlorperazine, thioridazine, thiothixene, trifluoperazine
- SGAs: aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone

Due to the unique safety profile of clozapine, safety information will be reported separately from the other SGAs, in Table 3:

Table 3. Safety Information for Clozapine[28]

Black box warnings ○ Agranulocytosis ○ Orthostatic hypotension ○ Bradycardia and syncope ○ Seizure ○ Myocarditis and cardiomyopathy ○ Increased mortality in elderly patients with dementia-related psychosis Contraindications ○ Hypersensitivity to clozapine or any of its components ○ History of clozapine-induced agranulocytosis or severe granulocytopenia	Warnings ○ Neuroleptic malignant syndrome ○ Metabolic effects – hyperglycemia, dyslipidemia, weight gain ○ QT prolongation ○ Eosinophilia ○ Fever ○ Pulmonary embolism ○ Anticholinergic toxicity REMS programs ○ Registration required

Table 4. Safety Information for FGAs and SGAs[17-35]

All: all drugs listed in the FGA/SGA classification are associated with this safety concern
Most: all but one drug in the FGA/SGA classification are associated with this safety concern
Some: more than one drug in the FGA/SGA classification are associated with this safety concern
One: only drug in the FGA/SGA classification are associated with this safety concern
None: none of the drugs listed in the FGA/SGA classification are associated with this safety concern.

	FGAs	SGAs	Related drug(s)
Black Box Warnings			
↑ QTc interval	One	None	thioridazine
↑ mortality in elderly patients with dementia-related psychoses	All	All	
Suicidal thoughts and behaviors	None	Some	aripiprazole, lurasidone, and quetiapine
Contraindications			
Blood dyscrasias/bone marrow suppression	Some	None	fluphenazine, perphenazine, thiothixene, trifluoperazine
Circulatory Collapse	One	None	thiothixene
Coma/CMS depression	All	None	
Combination with CYP2D6 inhibitors or drugs that prolong the QTc interval	One	None	thioridazine
Hepatic disease	Some	None	fluphenazine, perphenazine, trifluoperazine
Hypersensitivity to ingredient(s)	All	Most	Not included: olanzapine
Hypertensive or hypotensive heart disease	One	None	thioridazine
Parkinson's disease	One	None	haloperidol
Patients on large doses of hypnotics	One	None	fluphenazine
Pediatric surgery/children <2 years or <9kg	One	None	prochlorperazine
Subcortical brain damage	Some	None	fluphenazine, perphenazine
Warnings			
Altered cardiac conduction/QT prolongation	All	Some	asenapine, iloperidone, paliperidone,

			quetiapine, ziprasidone
Anticholinergic effects	Most	None	thioridazine
Antiemetic effects	None	One	risperidone
Cerebrovascular events	None	Most	Not included: ziprasidone
Cognitive impairment	None	Most	Not included: lurasidone
Discontinuation syndrome	None	One	quetiapine
Dysphasia	None	One	quetiapine
Esophageal dysmotility/aspiration	All	One	ziprasidone
Gastrointestinal narrowing	None	One	paliperidone
Hepatic effects	One	None	Fluphenazine
Hyperprolactinemia	All	Some	paliperidone, quetiapine, risperidone, ziprasidone
Hypersensitivity	None	One	asenapine
Hypertension	None	One	quetiapine
Hypotension	Some	Some	chlorpromazine, fluphenazine, prochlorperazine, quetiapine
Hypotension, orthostatic	Most	All	Not included: prochlorperazine
Leukopenia	Most	All	Not included: prochlorperazine
Metabolic effects – hyperglycemia/diabetes mellitus	None	All	
Metabolic effects – weight gain	None	All	
Metabolic effects - dyslipidemia	None	Some	Asenapine, risperidone, ziprasidone (CHECK!!) do not have this warning
Neuroleptic malignant syndrome	All	All	
Ocular effects	Most	Some	Not included: thioridazine Included: quetiapine
Parkinson's disease (increased sensitivity)	None	One	risperidone

Pregnancy, use in	One	None	trifluoperazine
Priapism	None	Some	iloperidone, ziprasidone
Rash	None	One	ziprasidone
Seizures/Convulsions	None	Most	Not included: lurasidone
Suicide	None	Most	Not included: lurasidone
Suicidality and antidepressants	None	One	aripiprazole
Tardive dyskinesia	All	All	
Temperature regulation	Most	Some	Not included: trifluoperazine Included: quetiapine, risperidone