Review

Practical guidelines for the use of new generation antipsychotic drugs (except clozapine) in adult individuals with intellectual disabilities

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ARTICLE INFO

Article history:
Received 15 September 2008
Accepted 16 October 2008

Keywords:
Antipsychotic medication
Aripiprazole
Olanzapine
Paliperidone
Quetiapine
Risperidone
Ziprasidone
Individuals with intellectual disabilities

ABSTRACT

New generation antipsychotic (NGA) drugs introduced to the US market after clozapine (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) are frequently used in individuals with intellectual disabilities (ID). However, there is very limited research to fully establish evidence-based or personalized medicine approaches for their use in this population. These guidelines take a pragmatic approach to establishing frameworks for their use by utilizing the prescribing information and reviewing the available literature on other relevant neuropsychiatric disorders. In the absence of expert consensus guidance and well-controlled comparison trials, we present a set of guidelines to inform initiation, dosing and monitoring of use in adults. Further, in these guidelines we provide practical information on drug–drug interactions and adverse drug reactions, and a brief review of discontinuation syndromes, potential for abuse, use during pregnancy and cost considerations. We also provide drug utilization review forms for each NGA to facilitate implementation of these guidelines, these guidelines provide a practical and necessary resource for practitioners treating psychiatric disorders and challenging behaviors in adult individuals with ID.

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Contents

1. Introduction ................................................................. 615
   1.1. Evidence-based medicine ........................................ 615
   1.2. Personalized prescription ....................................... 616
   1.3. Development of these guidelines .............................. 616
   1.4. Comparison with clozapine .................................... 618
   1.5. Comparison with older generation (conventional) antipsychotics .... 618
2. Indications and contraindications .................................... 619
   2.1. Indications are present ......................................... 619
      2.1.1. Indications for long-term treatment ..................... 619
      2.1.2. Indications for short-term injections ................... 620
   2.2. Absolute contraindications are absent ....................... 620
      2.3. Relative contraindications .................................. 621
3. Documentation and assessments before and during antipsychotic treatment .......... 622
   3.1. Documentation before starting ................................ 622
      3.2. Initial workup ................................................ 622
      3.3. Monthly monitoring .......................................... 622
      3.4. Semiannual monitoring ..................................... 622
      3.5. Annual monitoring ......................................... 622
4. Dosage in adults ....................................................... 622
   4.1. Aripiprazole ..................................................... 623
      4.1.1. Administration pattern .................................. 623
      4.1.2. Initial dosing, titration and maximum dosing .......... 623
      4.1.3. Dosing modification associated with drug–drug interactions (DDIs) .... 623
   4.2. Olanzapine ....................................................... 623
      4.2.1. Administration pattern .................................. 623
      4.2.2. Initial dosing, titration and maximum dosing .......... 625
      4.2.3. Dosing modification associated with DDIs ............. 625
   4.3. Paliperidone ..................................................... 625
      4.3.1. Administration pattern .................................. 625
      4.3.2. Initial dosing, titration and maximum dosing .......... 625
      4.3.3. Dosing modification associated with DDIs ............. 625
   4.4. Quetiapine ....................................................... 626
      4.4.1. Administration pattern .................................. 626
      4.4.2. Initial dosing, titration and maximum dosing .......... 626
      4.4.3. Dosing modification associated with DDIs ............. 626
   4.5. Risperidone ...................................................... 626
      4.5.1. Administration pattern .................................. 626
      4.5.2. Initial dosing, titration and maximum dosing .......... 626
      4.5.3. Dosing modification associated with DDIs ............. 627
      4.5.4. Special considerations for long-acting risperidone injections .......... 627
   4.6. Ziprasidone ...................................................... 628
      4.6.1. Administration pattern .................................. 628
      4.6.2. Initial dosing, titration and maximum dosing .......... 628
      4.6.3. Dosing modification associated with DDIs ............. 628
   4.7. New generation antipsychotic (NGA) intramuscular (IM) dosing ............... 628
5. Comparison of drug–drug interactions (DDIs) and drug metabolism ................. 629
   5.1. NGA metabolism ................................................ 629
   5.2. Effects of other drugs on NGAs ............................... 629
   5.3. Effects of NGAs on other drugs ................................ 631
6. Adverse drug reactions .................................................. 631
   6.1. Lethality ........................................................... 631
      6.1.1. Lethality during overdosing ................................ 631
      6.1.2. Adverse drug reactions (ADRs) and lethality ........... 631
   6.2. Most frequent ADRs .............................................. 632
      6.2.1. Extrapyramidal symptoms (EPS) .......................... 633
      6.2.2. Metabolic syndrome ....................................... 634
1. Introduction

The decision to prescribe a new generation antipsychotic (NGA) drug for an individual with intellectual disabilities (ID) is complex. As with all drugs, the prescribing decision demands consideration of both risks and benefits. However, the dearth of available literature on NGA use in the ID population leaves the prescriber with little guidance as to specific risks and benefits and requires extrapolation from available studies covering different populations. These guidelines provide a summary of relevant information from the prescribing information as well as from review of the available literature on relevant neuropsychiatric disorders in populations without IDs.

The limitations of such an approach and the cautious skepticism one must maintain when leaving the terra firma of evidence-based medicine is not lost on the authors and is encouraged in the clinician.

1.1. Evidence-based medicine

In the last 15 years a quiet revolution has occurred in medicine. We now operate under the principles of evidence-based medicine. Few would deny that high levels of evidence, such as double-blind and randomized clinical trials, are ideal in helping physicians select treatment for their patients. However, there are limitations to evidence-based medicine, which are relevant for the treatment of individuals with ID in general and for the use of NGA drugs in particular.

First, treatment information provided by evidence-based medicine is systematically biased. The quality of evidence is heavily influenced by the amount of research required and the ease with which desired outcomes can be quantified. Therefore, it is more likely that there will be outcome evidence for the treatment of acute conditions in otherwise relatively healthy people than for the management of chronic conditions in those with multiple health care needs (Hope, 1995; Lowey, 2007). Moreover, the pharmaceutical companies fund the majority of the clinical trials, and it is evident that, despite the implied integrity of the scientific methodologies, pharmaceutical company funding can introduce bias into the results (Lowey, 2007). Feinstein and Horwitz (1997) emphasized that randomized trial information is seldom available for issues in etiology, diagnosis, and prognosis; furthermore, clinical decisions that depend on pathophysiologic changes, psychosocial factors, and patients’ preferences that incorporate strategies offering comfort and reassurance are underrepresented in these studies.

Second, there is limited systematic information on the use of NGAs in adult individuals with IDs; therefore, most of the information currently available was obtained from other populations, particularly those with schizophrenia. Some data are beginning to emerge. For example, risperidone has been evaluated in an 8-week double-blind randomized study in individuals with autistic disorder.
(McCracken, McGough, & Shah, 2002), but the study was limited to children, thereby reducing its direct application to the growing population of adults with ID.

1.2. Personalized prescription

In the last 10 years, another paradigm has been evident in medicine. Advances in genetic testing and the completion of the Human Genome Project in 2000 have raised the hope of establishing personalized prescription (de Leon, Susce, & Murray-Carmichael, 2006). Unfortunately, it is not frequently recognized that the personalized medicine approach may directly collide with the evidence-based medicine approach. While the evidence-based medicine approach focuses on the best evidence for the average patient and ignores the outliers, personalized medicine focuses on the outliers. The sad truth is that randomized trials in outlier subgroups are not likely to be conducted due to lack of funding (de Leon, 2006). Moreover, we have not developed the methodological and statistical tools needed for focusing on the unusual individuals instead of the statistically defined average patient. Nor have we delineated the clinical implications of the differential risk of using these drugs in the general population vs. in a subgroup that is at increased risk for adverse drug reactions (ADRs; de Leon, Armstrong, & Cozza, 2005; de Leon, Susce, et al., 2005). An example of the latter group is individuals who, due to a genetic defect, are missing one of the major enzymes metabolizing risperidone (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005).

The tensions between evidence-based medicine and personalized medicine, and between group treatment and individual treatment, reflect the misguided tensions between the camps of those proclaiming medicine as science versus medicine as art (Jenicek & Hitchcock, 2005). These guidelines reflect such unresolved tensions in medicine and reveal the limited scientific evidence supporting the use of NGA drugs in individuals with ID. Despite such limitations, providing the best available scientific information obtained from related studies will allow physicians to offer informed decisions in providing personalized prescriptions for individuals with ID by taking into account unique characteristics of the individual. Contraindications, drug–drug interactions (DDIs), and ADRs can be used to select the best NGA drug for a specific individual. Recommendations for personalizing the dosing of NGA drugs by considering co-medications and other factors are discussed in the section on dosing.

Scientific developments are providing us with the first hints of how pharmacogenetics may be used to personalize antipsychotic treatment (Arranz & de Leon, 2007; de Leon & Diaz, 2007; de Leon et al., 2006), but personalizing medication will probably always be a complex process combining genetics, environmental information (such as co-medications), and personal characteristics including gender, age, and comorbid conditions (de Leon et al., 2007).

1.3. Development of these guidelines

Due to insufficient evidence one could wait until additional studies with high quality evidence are published. Unfortunately, these studies may never get published; meanwhile, thousands of individuals with ID are treated with NGA drugs in the US. The dangers of an excessive focus on the scientific approach for clinical practice have been stressed by Knotterus and Dinant (1997), who described medicine-based evidence as a prerequisite for evidence-based medicine, proposing that research should accommodate clinical reality, not ignore it.

The practitioner needs to be aware that these guidelines have been developed using package inserts (Astra Zeneca, 2007a, 2007b; Eli Lilly and Company, 2007; Janssen, 2007a, 2007b, 2007c; Otsuka, 2007; Pfizer, 2007) and by reviewing the available literature on related neuropsychiatric disorders in individuals with and without ID. Any attempts to systematically review the limited information on individuals with ID will benefit older drugs and penalize newer ones. Among the previously published literature up to December 2007, the recommended readings include a limited review of the literature pertaining to the use of NGA drugs in individuals with IDs (Ananth, Parameswaran, Gunatilake, Burgoune, & Sidhom, 2004). The review primarily focuses on risperidone and it provides specific risperidone dosing guidelines that are incorporated into this practical guideline. Table 1 describes selections from the limited available bibliography on the use of NGA drugs in individuals with ID.
Thus, these guidelines provide recommendations based upon incomplete data and represent an evolving dialogue between available data for each NGA drug and clinical experience gained by treating individuals with ID. The available data provide at best an approximation that may indirectly inform guidelines for the use of NGA drugs in the ID population. Relying exclusively on available studies renders one vulnerable to the limitations of evidence-based medicine, which is founded upon aggregate data that may not be representative of the individual patient at hand; however, reliance upon the accumulated clinical experience of treating individuals renders one vulnerable to erratic changes in one's heuristic as unwarranted generalizations are made from the individual to the general population. One's judgment is influenced by recent or memorable cases (often composed of outliers or deviations from the norm), recall bias, and idiosyncratic cognitive style.

Further complicating the present task is the comparison between individual NGA drugs; such information would prove useful in generating guidelines but again the effort is hindered by insufficient comparison data. Only one large trial comparing them has been conducted, but it was conducted in individuals diagnosed with schizophrenia (Lieberman et al., 2005) and did not include all currently available NGA drugs. In any event, these guidelines provide specific information in three areas: indications and contraindications, assessments before and during antipsychotic treatment, and dosing. To simplify, the indications and assessment are unified for all drugs. These guidelines compare the information available on other illnesses to facilitate clinical decisions by comparing the risks associated with individual agents regarding DDIs, ADRs, and other issues.

Some of the statements comparing different compounds are admittedly arbitrary, but are intended to establish a framework for clinicians. This framework is not intended to replace, but to augment...
individual judgment and clinical expertise. Moreover, the field continues to evolve and emerging literature may become available following the development of these guidelines in December 2007.

1.4. Comparison with clozapine

Clozapine, another NGA drug, is probably the most effective in treatment-refractory psychosis and has particularly good anti-aggressive and anti-suicidal properties. Unfortunately, it has greater toxicity and is not used as frequently as it should be in the US. The lack of inclusion in this review is due to the publication of a prior guideline focused only on clozapine (Sabaawi, Singh, & de Leon, 2006).

1.5. Comparison with older generation (conventional) antipsychotics

The focus on NGA drugs should not be interpreted as an endorsement of these drugs over the conventional drugs, but rather an acknowledgment that conventional drugs have largely been superseded by NGA drugs in the US market. The pharmaceutical companies have enthusiastically advocated NGA drugs as a revolutionary advance over the conventional drugs. There is no doubt that widespread use of NGA drugs has proved advantageous for pharmaceutical companies because the more expensive NGA drugs have become a major revenue stream for the pharmaceutical industry and a burden for the health care system (Duggan, 2005). For example, a recent cost-effectiveness analysis of a large pragmatic trial in schizophrenia suggests that perphenazine may be more cost-effective than the NGA drugs for the average individual with chronic schizophrenia (Rosenheck et al., 2006).

After discussing the differences in cost between the two generations of drugs, it is fair to acknowledge that there may be differences in their ADRs. These differences defy marketing simplification suggesting, for example, that NGA drugs do not cause extrapyramidal symptoms (EPS), but cause more metabolic ADRs. EPS are a major problem for the conventional drugs, at least in the dosages used in the past. A review of the NGA drug trials which have used conventional drugs as a comparison suggests that the former group tends to be associated with more reversible EPS (Leucht, Pitschel-Walz, Abraham, & Kissling, 1999) and with reduced propensity to cause tardive dyskinesia (TD) (Correll, Leucht, & Kane, 2004). However, these trials were conducted on carefully selected samples (i.e., excluding individuals with co-morbidities) and were funded by pharmaceutical companies. The post-marketing naturalistic studies suggest that NGA drugs may not be as remarkably different from the conventional drugs when used in actual practice and that they are also associated with EPS. For example, a large geriatric study could not find remarkable differences between NGA and conventional drugs regarding the occurrence of TD (Lee et al., 2005) or parkinsonism when high doses of NGA drugs were used (Rochon et al., 2005). Similarly, in a sample of individuals with severe mental illness, taking conventional drugs was associated with an increased risk for TD, particularly with use extending beyond 5 years, but a significant number of the individuals exposed only to NGA drugs developed TD (de Leon, 2007).

The other side of the coin is that conventional antipsychotics are not free of metabolic ADRs. Metabolic complications were frequently described in individuals taking conventional antipsychotics but this finding was largely overlooked (de Leon, 2008). As a matter of fact, low potency conventional antipsychotics, such as the phenothiazines, may cause rates of weight gain between those of risperidone and olanzapine (Allison et al., 1999). Phenothiazines may also cause direct increases in lipid levels as olanzapine, quetiapine, and clozapine do (de Leon & Diaz, 2007; Meyer & Koro, 2004). The possibility that phenothiazines may have direct effects on glucose, similar to those of clozapine and olanzapine, has not been well studied.

The prolongation of QTc is an ADR of conventional drugs that has clearly been neglected by psychiatrists for many years. The large health databases in the 1990s definitively established that conventional antipsychotics, particularly phenothiazines, are unequivocally associated with increases in sudden deaths, probably mediated by prolongation of QTc (Harrison & Krishnan, 2002). Hopefully, no similar data will emerge after NGA drugs have been used for many years.
2. Indications and contraindications

2.1. Indications are present

There are indications for long-term treatment (oral and long-acting injections) and short-term intramuscular injections. The drugs specifically approved by the Food and Drug Administration (FDA) as of December 2007 are described in Table 2.

2.1.1. Indications for long-term treatment

At least one of the following clinical indications is present and documented in the chart prior to treatment:

(a) DSM-IV-TR diagnosis of schizophrenia. Although FDA approval was limited to schizophrenia (see Table 2), we think that most physicians would consider it standard clinical practice to prescribe NGAs for the other psychoses included under the DSM-IV-TR category “Schizophrenia and Other Psychotic Disorders”. Examples of other psychotic disorders included in this category are schizoaffective disorder and psychotic disorders due to general medical condition.

(b) DSM-IV-TR diagnosis of bipolar disorder, including (1) acute treatment during a current manic or mixed episode, (2) acute bipolar depression, and (3) maintenance of bipolar I disorder.

(c) Adjunct treatment for DSM-IV-TR diagnosis of major depressive disorder. Until the recent approval of aripiprazole for this indication, we would have included this category in off-label use (see [e] below), but since its approval we think that most physicians would consider it standard clinical practice to prescribe any NGA for this indication.

Table 2

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<td>Mania</td>
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A: adults; adol: adolescents; c: children.

a The FDA has approved for manic and mixed episodes.
b Carbamazepine is an inducer. The olanzapine and quetiapine studies did not include patients taking carbamazepine. The risperidone adjunct study failed for carbamazepine while it was successful for lithium and divalproex sodium.
c The FDA has approved the combination of olanzapine and fluoxetine for acute bipolar depression.
d The FDA approved aripiprazole for the adjunctive treatment of major depressive disorder in patients who cannot find sufficient relief for their symptoms with antidepressants alone.
(d) Severe persistent aggression or self-injurious behavior with evidence that a behavioral treatment, as part of a formal training program, was adequately implemented and found to be ineffective. FDA approval is limited to one NGA, risperidone, for irritability in children with autistic disorder (see Table 2). We think that most physicians would consider it standard clinical practice to prescribe any NGA for this indication. A careful consideration of the risk and benefits of each case and the treatment setting is needed (Matson & Wilkins, 2008) because in a recent study of outpatients with ID, 4 weeks of treatment with placebo was associated with a decrease in aggressive behaviors, even larger than with risperidone and haloperidol treatments (Tyrer et al., 2008). Thus, once the aggressive behavior is stabilized on an antipsychotic, it appears reasonable to decrease the antipsychotic to the optimally effective dose to treat aggression (Janowsky, Barnhill, Shetty, & Davis, 2005; Janowsky, Barnhill, Khalid, & Davis, 2006). Moreover, it may be possible to discontinue the antipsychotic completely.

(e) Frequent off-label uses of NGAs include dementia-related psychosis and aggression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders and Tourette's syndrome (Shekelle et al., 2007). Such off-label uses require additional documentation justifying the off-label use. Specific risks associated with special populations need to be documented as should the particular aspect of the informed consent process pertaining to the off-label use and the specific risk. For example, there is an increased risk of mortality associated with the use of antipsychotics in individuals with dementia (reviewed in Section 6.1.2.).

2.1.2. Indications for short-term injections

At least one of the following clinical indications is present and documented in the chart prior to treatment with an intramuscular (IM) NGA:

(a) The main indication for short-term intramuscular injections (aripiprazole, olanzapine and ziprasidone) is for acute agitation in individuals with DSM-IV-TR diagnosis of bipolar mania, schizophrenia, schizoaffective disorder or another psychotic disorder.

(b) A second indication that will require additional documentation sufficiently justifying the off-label use is special circumstances (e.g., inability to use oral route, uncooperativeness, etc.), with the goal of switching as soon as possible to oral preparations.

2.2. Absolute contraindications are absent

(a) Hypersensitivity to the specific NGA.

(b) Only for ziprasidone: preexisting prolonged QT syndrome (with persistent findings of QTc interval >500 ms), history of arrhythmia; recent myocardial infarction, or uncompensated heart failure. Similarly, absolute contraindications are the concomitant use of drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have shown this effect (e.g., dofetilide, sotalol, quinidine, other Classes Ia and III anti-arrhythmics, mesoridazine, chloroquine, chlorpromazine, droperidol, pimozide, sparflaxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus). It appears reasonable to include haloperidol in this list of drugs to avoid when prescribing ziprasidone. If these drugs can be discontinued and are then eliminated from the body, ziprasidone treatment can be considered. To avoid neglecting any of these contraindications in an emergency situation, and as there are other IM compounds, IM ziprasidone should only be administered in individuals with IDs who are taking oral ziprasidone. The presence of certain sensory or physical abnormalities may indicate an underlying syndrome associated with prolonged QTc such as congenital deafness and Jervell and Lange–Nielsen syndrome (Tuncer et al., 2000) or clinodactyly, low-set ears and micrognathia and Andersen–Tawil syndrome (Yoon et al., 2006). These examples highlight the potential vulnerabilities shared by embryologic development of organ systems that may be manifested by easily discernable physical and sensory abnormalities and potentially unappreciated cardiac anomalies. Congenital deafness and physical abnormalities suggestive of an underlying congenital syndrome should increase the suspicion of underlying cardiac abnormalities, including prolonged QTc syndrome.
(c) Phenylketonuria for orally disintegrating tablets of olanzapine or aripiprazole. These tablets contain phenylalanine.

2.3. Relative contraindications

Relative contraindications are considered and there is a discussion in the chart indicating that the benefit outweighs the risk, with documentation:

(a) Metabolic syndrome or its components are present, or there is high risk for them; the list includes (1) obesity, abdominal obesity, or personal history of high body mass index [BMI]; (2) diabetes mellitus, glucose intolerance, hyperglycemia, family history of diabetes; (3) hypertriglyceridemia or hypercholesterolemia (currently or historically). If any of these are present, clinicians should consider ziprasidone and aripiprazole as better options. These NGAs, excluding clozapine, do not appear to worsen hypertension directly in the average patient (de Leon & Diaz, 2007), but it is always possible that if they cause obesity they may secondarily contribute to hypertension and, in rare individuals, directly increase blood pressure (Markham-Abedi, McNeely, & de Leon, 2007). Two additional issues, co-medication and baseline BMI, should be considered when deciding on the NGAs. First, other medications may also influence weight gain (e.g., lithium, valproic acid, mirtazapine or paroxetine may be associated with weight gain), while bupropion and topiramate may be associated with weight loss (Fava, 2000; Laimer et al., 2006; Rosenstock et al., 2007; Zimmermann, Kraus, Himmerich, Schuld, & Pollmächer, 2003). Second, for individuals with low BMI, clinicians should be aware that paradoxically these individuals may be at greater risk for very high weight gain. For example, in a long-term olanzapine study, the median increase after 39 weeks or more was 5.9 kg, but it was 8.1 kg for individuals with lower BMI (<23.6), 6.9 kg for individuals with an intermediate BMI (23.6–27.6) and 3.8 kg for individuals with a higher BMI (>27.6) (Kinon, Basson, Gilmore, & Tollefson, 2001). Thus, it may be safer to start the worst offender NGAs for weight gain in individuals with low BMI, but these individuals may be at greater risk of developing very significant weight gain.

(b) Concomitant use of medications known to cause elevated blood glucose (e.g., steroids, niacin, thiazide diuretics).

(c) Dementia (the data of increased risk of mortality is in the elderly, whereas the antipsychotic risks associated in younger populations such as dementia associated with Down’s Syndrome which can develop as early as the late 30s or early 40s is unknown), cerebrovascular disease and conditions that would predispose individuals to hypotension (e.g., dehydration, hypovolemia and treatment of antihypertensive medications).

(d) Severe cardiovascular disease, history of myocardial infarction or ischemia, or heart failure.

(e) History of prolactin-sensitive breast cancer. Prolactin may increase the risk for some breast cancers and also stimulate their growth (Clevenger, Furth, Hankinson, & Schuler, 2003).

(f) Liver disease, history of hepatitis or treatment with potentially hepatotoxic drugs.

(g) Ziprasidone: history of sudden death in the family, personal history of syncope, cardiovascular disease or electrolyte abnormalities that may contribute to QTc prolongation. Serum electrolyte abnormalities (e.g., low potassium) should be corrected before starting ziprasidone.

(h) Olanzapine, due to its potential antimuscarinic activity, should be used with caution in individuals with decreased gastrointestinal motility, urinary retention, benign prostate hyperplasia, xerostomia, narrow-angle glaucoma and myasthenia gravis. A recent study suggested that quetiapine may have clinically relevant antimuscarinic activity (Chew et al., 2006). Combined use of medications with antimuscarinic activity may significantly impact cognition in individuals with limited cognitive reserve or brain pathology decreasing baseline cognitive functioning.

(i) From these NGAs, those with major risk of causing hypotension are quetiapine, olanzapine IM, risperidone, and ziprasidone. Clinicians should use these drugs cautiously in individuals predisposed to hypotension, taking medication with potential to induce hypotension, including some antihypertensives, or in individuals with underlying heart disease. Individuals with ID may have more difficulty expressing symptoms related to hypotension such as presyncope or
lightheadedness so additional effort is required to monitor these complications more directly, such as obtaining orthostatic blood pressure changes.

3. Documentation and assessments before and during antipsychotic treatment

We developed these recommendations after reviewing multiple guidelines in this area (American Diabetes Association [ADA], American Association of Clinical Endocrinologists [AACE], American Psychiatric Association [APA], & North American Association for the Study of Obesity [NAASO], 2004; Cohn & Sernyak, 2006; Faulkner & Cohn, 2006; Marder et al., 2004; Melkersson, Dahl, & Hulting, 2004) and we may have erred on the side of safety while being practical. For example, recommending baseline and annual EKGs for all NGAs appears reasonable, due to the associated risk of metabolic syndrome; the emphasis on cardiovascular protection during an epidemic of obesity does not exclude individuals with ID (Kwok & Cheung, 2007; Wilkinson, Culpepper, & Cerreto, 2007).

3.1. Documentation before starting

There is chart documentation (prior to treatment) including: (1) informed consent; (2) weight and height (with ideal body weight noted); (3) waist circumference; (4) personal history of high BMI, diabetes mellitus and hyperlipidemia; (5) family history of diabetes mellitus.

3.2. Initial workup

The recommended work up includes (1) glycosylated hemoglobin level (Hgb A1C), (2) fasting serum glucose, (3) lipid panel, (4) electrolytes, (5) liver function tests, (6) serum prolactin, (7) TD rating (e.g., Dyskinesia Identification System: Condensed User Scale, DISCUS, Sprague et al., 1984), (8) EKG, and (9) vital signs. If an individual has low renal function, creatinine clearance should be measured before starting paliperidone or risperidone.

3.3. Monthly monitoring

Recommended monitoring includes weight. If it is not done at the health facility, it should at least be done at the living setting with attention to the differences between scales.

3.4. Semiannual monitoring

The recommended monitoring includes (1) fasting blood glucose, (2) lipid panel, and (3) TD rating (e.g., DISCUS). For ziprasidone, the first semiannual monitoring should include an EKG, unless an EKG was completed after reaching the maximum ziprasidone dose. In later semiannual monitoring, an EKG should be done when the ziprasidone dose is increased to a maximum and no EKG at that maximum dose was completed in the past.

3.5. Annual monitoring

The recommended monitoring includes (1) serum prolactin level, (2) breast examination (including a note regarding presence or absence of galactorrhea in women and gynecomastia in men), (3) when it is appropriate, assess in males changes in libido and erectile and ejaculatory function, and in females changes in menstruation or libido, (4) waist circumference, (5) annual routine eye examination for individuals taking quetiapine (current thought is that carcinogenesis secondary to quetiapine is unlikely) (Fraunfelder, 2004), and (6) EKG.

4. Dosage in adults

Each compound is reviewed separately for (1) administration pattern, (2) initial dosing, titration and maximum dosing; (3) dosing modification associated with DDI. The initial dosing, titration and
maximum dosing recommended by the package insert is provided in Table 3 for comparative purposes. Due to the lack of information on individuals with ID, their reduced cognitive functioning, and the potential for simultaneous use of two antipsychotics during cross-titration, the lowest possible initial doses are recommended and documentation of the justification for higher dosages is required. Appendix 1 includes instructions to monitor orthostatic changes in blood pressure and pulse that should be used in individuals taking oral quetiapine, IM olanzapine, oral risperidone and oral/IM ziprasidone unless the individual cannot stand (wheelchair or bedridden). Dosages may need to be modified if the NGA drug is co-prescribed with inducers or inhibitors (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; Spina & de Leon, 2007). The principles of the effects of inducers and inhibitors have been reviewed elsewhere (Armstrong, Cozza, & Sandson, 2003).

4.1. Aripiprazole

4.1.1. Administration pattern

Oral morning doses are recommended to avoid insomnia (Sullivan et al., 2007; Travis et al., 2005). Clinicians should be aware that steady state aripiprazole concentrations may require up to 2 weeks from the last increase (Harrison & Perry, 2004).

4.1.2. Initial dosing, titration and maximum dosing

Initial oral doses >5 mg/day require justification. If treatment is well-tolerated and symptoms persist, the dosage can be increased every 2 weeks. The maximum recommended dose in the absence of DDIs is 30 mg/day (see Table 2). In geriatric subjects (>65 years) aripiprazole clearance is 20% lower. The package insert recommends no dose modification (McGavin & Goa, 2002; Otsuka, 2007), but lower doses may be considered.

4.1.3. Dosing modification associated with drug–drug interactions (DDIs)

Initial and maintenance dosages account for DDIs (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; Otsuka, 2007) and careful attention should be paid after discontinuation of inducers or inhibitors:

(a) The dose should be doubled if used with carbamazepine, a cytochrome P450 3A (CYP3A) inducer. The dose should be increased if used with other CYP3A inducers (e.g., phenytoin, phenobarbital, primidone, some glucocorticoids or rifampin).

(b) The dose should be halved if used with ketoconazole, a CYP3A inhibitor. The dose should be decreased if used with other cytochrome P450 2D6 (CYP2D6) inhibitors (e.g., paroxetine or bupropion) or with CYP3A inhibitors (e.g., itraconazole, fluconazole, erythromycin, fluoxetine, fluvoxamine, clarithromycin, or diltiazem). The lowest possible dose should be prescribed if used with fluoxetine, a CYP2D6 and CYP3A inhibitor.

4.2. Olanzapine

4.2.1. Administration pattern

Oral olanzapine is usually administered once a day. Clinicians should be aware that it takes 1 week to see the whole effect of a dose increase.

Table 3
Oral and long-acting injections: Initial dosing, titration and maintenance dosages in mg/day described in the package insert as of December 2007.

<table>
<thead>
<tr>
<th></th>
<th>Aripiprazole</th>
<th>Olanzapine</th>
<th>Paliperidone</th>
<th>Quetiapine</th>
<th>Quetiapine ER</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial dose</td>
<td>10–15</td>
<td>5–10</td>
<td>6</td>
<td>25 bid</td>
<td>300</td>
<td>2</td>
<td>20 bid</td>
</tr>
<tr>
<td>2 adol</td>
<td>5&lt;sup&gt;a&lt;/sup&gt; deb</td>
<td>0.5 bid deb&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Table 3 (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Aripiprazole</th>
<th>Olanzapine</th>
<th>Paliperidone</th>
<th>Quetiapine</th>
<th>Quetiapine ER</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Titration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25–50 bid/tid</td>
<td>300–400</td>
<td>300–400</td>
<td>300–800</td>
<td>0.5 adol 1–2 D</td>
<td>0.5–1 adol</td>
<td>4–16c</td>
</tr>
<tr>
<td></td>
<td>by day 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1–6 adol</td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>10–30</td>
<td>St. up 20</td>
<td>St. up 12</td>
<td>150–750</td>
<td>300–800</td>
<td>Up to 160</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 adol</td>
<td>30 no better</td>
<td>St. up 800</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Mania</strong></td>
<td>Initial dose</td>
<td>30</td>
<td>10–15</td>
<td>50 bidd</td>
<td>2–3</td>
<td>40 bid</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5 c</td>
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<tr>
<td><strong>Depression</strong></td>
<td>Initial dose</td>
<td>50 at night</td>
<td></td>
<td>400–800</td>
<td>1–6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>300–600</td>
<td></td>
<td>St. up 800</td>
<td>0.5–6 c</td>
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<tr>
<td><strong>Autistic disorder</strong></td>
<td>Initiation</td>
<td>Children &lt;20 kg</td>
<td></td>
<td>0.25</td>
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<td></td>
<td></td>
<td>Children ≥20 kg</td>
<td></td>
<td>0.5</td>
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<tr>
<td></td>
<td></td>
<td>Titrationsfd</td>
<td></td>
<td>0.25–0.50 at</td>
<td>≥2 weeks</td>
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<tr>
<td><strong>LONG-ACTING</strong></td>
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<tr>
<td><strong>Schizophrenia</strong></td>
<td>Initial dose</td>
<td></td>
<td></td>
<td>25 mg every 2 weeksf</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.5 mg every 2 weeks impaired</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Titration</td>
<td></td>
<td></td>
<td>↑ of 12.5 (≥2 weeks)f</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td></td>
<td></td>
<td>Up to 50 mg every 2 weeksf</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

bid: twice a day; tid: three times a day; deb: debilitated; adol: adolescents; imp: impaired; c: children; St. up: studied up to this dose; D: daily.

- **a**: An initial oral dose of 5 mg/day for debilitated patients, those who have a predisposition to orthostatic hypotension or are expected to metabolize olanzapine slowly (e.g., geriatric non-smoking females).
- **b**: The package insert recommends initial doses of 0.5 mg bid in elderly or debilitated patients, patients with severe renal or hepatic impairment, and in patients predisposed to hypotension or for whom hypotension would pose a risk. Doses in these patients should not be more than 0.5 bid. Increases in doses above 1.5 bid should occur at intervals of at least 1 week. In some patients lower titration may be indicated.
- **c**: The package insert describes the effective dose range 4–16 mg/day while the target dose is 4–8 mg/daily.
- **d**: Monotherapy or added to lithium or valproic acid.
- **e**: The package insert recommends dosages for patients <20 kg of 0.25 mg/day at initiation, increasing to a recommended dosage of 0.5 mg/day after 4 days, and if there is not enough response after 2 weeks, increasing in increments of 0.25 mg/day at ≥2 week intervals.
- **f**: The package insert recommends dosages for patients ≥20 kg of 0.5 mg/day at initiation, increasing to a recommended dosage of 1 mg/day after 4 days, and if there is not enough response after 2 weeks, increasing in increments of 0.5 mg/day at ≥2 week intervals.
- **g**: The package insert recommends an initial dose of 25 mg every 2 weeks, and increasing the dose in 12.5 mg increments up to 50 mg maximum; the upward dose adjustment should not occur more frequently than every 4 weeks. Doses higher than 50 mg every 2 weeks will need justification as they did not provide additional benefits in the clinical trials.
- **h**: The lowest dose possible is used for the elderly, those with renal or hepatic impairment and those taking CYP2D6 and/or CYP3A inhibitors. The package insert recommends 12.5 mg every 2 weeks for patients with renal or hepatic impairment or those taking drugs that inhibit risperidone metabolism, but if they can tolerate 2 mg/day of oral risperidone, the package insert recommends 25 mg every 2 weeks. The package insert recommends a starting dose of 12.5 mg every 2 weeks for patients taking CYP inhibitors such as paroxetine and fluoxetine.
4.2.2. Initial dosing, titration and maximum dosing

Due to the lack of data, particularly in the context of reduced cognitive functioning, it may be reasonable to consider conservative dosing (see Table 3), such as using initial doses of 2.5 mg once daily and increases of 2.5 mg. Higher dosages may need justification. Slow titration should be considered when hypotension or sedation or other transient symptoms occur. Females tend to metabolize olanzapine more slowly than males. Non-smokers metabolize olanzapine more slowly than smokers (smoking induces olanzapine metabolism) (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; Spina & de Leon, 2007). There is one circumstance in which the effect of smoking may have clinical relevance, i.e., olanzapine doses should be decreased in smokers who stop smoking (de Leon, 2004a). Lower doses may be used in geriatric individuals (olanzapine yields a half life 1.5 times higher in geriatric individuals).

4.2.3. Dosing modification associated with DDIs

Initial and maintenance dosages account for DDIs (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; Spina & de Leon, 2007) and careful attention should be paid after discontinuation of inducers or inhibitors:

(a) Approximately twofold increase in dose if used with carbamazepine, a metabolic inducer. Similar changes may be needed for other metabolic inducers (e.g., phenytoin, omeprazole, phenobarbital, or rifampin).

(b) Lower dose if used with CYP1A2 inhibitors (e.g., fluvoxamine, high dose caffeine, ciprofloxacin, or cimetidine).

(c) Consider temporarily lowering olanzapine dose during infectious process including pneumonias, other respiratory infections with fever, and other possibly serious infections or appendicitis (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005).

4.3. Paliperidone

4.3.1. Administration pattern

Paliperidone is the active metabolite from risperidone, 9-hydroxyrisperidone. The tablets should not be chewed, divided or crushed. The company recommends once daily administration in the morning and reports that up to 5 days may be required to see the effects of a dose increase (Janssen, 2007a).

4.3.2. Initial dosing, titration and maximum dosing

Although the pharmaceutical company recommends initial doses of 6 mg (Janssen, 2007a), it appears safer to recommend an even lower dosage of 3 mg/day. Initial doses >6 mg will definitely need justification. No titration is recommended. The company recommends that, if needed, dose increments should be 3 mg/day up to a maximum recommended dose of 12 mg/day (Janssen, 2007a).

Hepatic impairment may not require dose adjustments. Lower doses are needed for renal impairment. For mild impairment (>50 ml/min to 80 ml/min) recommended doses are 6 mg/day. For moderate to severe impairment (>10 ml/min to <50 ml/min) recommended doses are 3 mg/day. The company recommends no dose modifications for the elderly as long as their renal function is normal (Janssen, 2007a).

4.3.3. Dosing modification associated with DDIs

There are almost no data on drug–drug interactions. In vitro studies from the company suggest some influence of CYP2D6 and CYP3A metabolism. More than half of the drug appears to be eliminated as an active compound in the urine. Due to the lack of independent data, practitioners should cautiously interpret statements from the company about the lack of paliperidone risk for DDIs. It is likely that CYP3A inducers may increase paliperidone metabolism. Anticonvulsant inducers appear to increase 9-hydroxyrisperidone metabolism twofold in individuals taking risperidone (de Leon et al., 2007). Thus, a watchful attitude toward DDIs is recommended until more data are available. Topiromate is an example illustrating the impact of CYP3A inducers in drugs with limited metabolism.
under normal conditions. Under normal conditions only 20% of topiromate is metabolized in monotherapy, but topiromate clearance increases twofold when taking carbamazepine or phenytoin because they increase the activity of CYP3A and the percentage of topiromate metabolized (Bialer et al., 2004). It is possible that paliperidone may behave as topiromate when CYP3A inducers are added.

4.4. Quetiapine

4.4.1. Administration pattern

For schizophrenia and mania the package insert recommends twice a day dosing, but for bipolar depression once a day dosing at bedtime is recommended (Astra Zeneca, 2007a; Gunasekara & Spencer, 1998). According to the Seroquel XR package insert (Astra Zeneca, 2007b), it should be administered once daily in the evening without food or with a light meal. The XR tablets should be swallowed whole and not split, chewed and crushed.

4.4.2. Initial dosing, titration and maximum dosing

There are no published dosing data on the use of quetiapine in adult individuals with ID. Initial quetiapine doses such as those recommended in schizophrenia (≤25 mg bid) appear reasonable. In our experience, monitoring the orthostatic changes is the key element in titration speed (see Appendix 1). Maximum recommended dosage, in the absence of DDI, is 800 mg/day. The package insert recommends a slower rate of dose titration for those who have a predisposition to hypotensive reactions, the elderly and those with hepatic impairment. In the elderly, it recommends a lower target dose, and for those with hepatic impairment it recommends a starting dose of 25 mg/day and lower daily increments (25–50 mg/day) up to an effective dose.

According to the package insert, individuals on standard quetiapine can be switched to the equivalent total daily dosage of Seroquel XR, taken once daily (Astra Zeneca, 2007b). The recommended initial XR dose is 300 mg. Dose increases can be made at intervals of 1 per day and in increments of up to 300 mg. A 200 mg dose of Seroquel XR is available when lower initial doses are desired. For those with hepatic impairment or the elderly, the recommendation is to initiate treatment with 25 mg daily with the immediate release form and titrate slowly. Once a total daily dose of 200 mg or greater has been achieved, one can switch to Seroquel XR at the dose equivalent of the immediate release. A similar strategy is recommended in the ID population, allowing for lower initial doses and slower titration than can be achieved with the extended release formulation.

4.4.3. Dosing modification associated with DDIs

Initial and maintenance dosages account for DDIs (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; Spina & de Leon, 2007) and careful attention should be paid after discontinuation of inducers or inhibitors:

(a) Higher doses (up to a fivefold increase) if used with CYP3A, inducers (e.g., carbamazepine, phenytoin, barbiturates, some glucocorticoids, or rifampin).

(b) Lower doses if used with CYP3A inhibitors (e.g., ketoconazole, itraconazole, fluconazole, erythromycin, fluoxetine, fluvoxamine, clarithromycin or diltiazem). As quetiapine is definitively a wide therapeutic window drug, the increase of blood levels associated with co-administration of inhibitors may have relatively little clinical relevance.

4.5. Risperidone

4.5.1. Administration pattern

Risperidone can be administered twice a day or once a day.

4.5.2. Initial dosing, titration and maximum dosing

The package insert describes the dose recommendation from the schizophrenia trials, completed when NGAs were used and individuals and physicians were more tolerant of ADRs (Janssen, 2007b).
These trials demonstrated efficacy from 4 to 16 mg/day. Soon after the widespread use of risperidone, it became obvious that doses of 16 mg/day were too high. Lemmens, Brecher, and Van Baelen (1999), after combining 27 double-blind and open studies, suggested that 4 mg/day is the optimal dosage and that risperidone was associated with a dose-dependent increase of EPS across a range of 8–16 mg/day. In reviewing these controlled and naturalistic studies, Williams (2001) suggested that 4–8 mg/day was the optimal range for the average individual for maximal efficacy and minimal ADRs. Therefore, the recommendation was a target dosage of 6 mg/day, titrated in 2-mg increments over 3 days with subsequent adjustment of the dose to 4 or 8 mg/day depending on effectiveness and ADRs. The subjects in early trials were generally individuals with chronic schizophrenia who had experienced many years of medication and high doses of medication. Thus, Williams (2001) recommended lower doses for those with lack of exposure to antipsychotics, and for geriatrics and individuals with dementia. The package insert recommended much lower doses for the treatment of bipolar mania than for schizophrenia and suggests much slower titration schedules for elderly or debilitated individuals, individuals with severe renal or hepatic impairment, and individuals predisposed to hypotension or for whom hypotension would pose a risk.

The brain abnormalities associated with ID probably involve pharmacodynamic changes that will require dosing adjustments when prescribing risperidone more so than other NGAs. Although there is no complete agreement on how to define atypicality among the antipsychotics and what the pharmacokinetic mechanisms are behind atypicality, we believe most clinicians agree that risperidone in high doses has a profile similar to some typical antipsychotics (e.g., haloperidol) and can easily produce EPS. A panel chosen by risperidone’s marketer (Aman & Gharabawi, 2004) reviewed initiation and target doses for the use of risperidone for adults with ID. The panel considered four major indications for risperidone treatment: psychosis, aggression, irritability and impulse control disturbances. The doses varied for some of these indications, depending on the severity of the symptoms. A simplified version of their recommendation can be summarized by separating psychosis from the other three target symptoms: aggression, irritability and impulse control disturbances. For psychosis in individuals with ID, the panel recommended initial doses of 1–2 mg/day and target doses of 4–6 mg/day. For very severe cases of the other target symptoms, initial doses of 1–2 mg/day and target doses of 2–4 mg/day were recommended, while lower doses were recommended for less severe cases.

Lower initial and target doses than those recommended by Aman and Gharabawi (2004) may be needed for elderly or debilitated individuals, and individuals with severe renal or hepatic impairment. Regarding titration, monitoring the orthostatic changes is the key element in titration speed (see Appendix 1). Thus, the approved maximum recommended dose in schizophrenia was 16 mg/day. Due to the progressively lower doses used in more recent studies it appears that, in the absence of DDIs, doses higher than 8 mg/day are high and may need justification in individuals with ID.

4.5.3. Dosing modification associated with DDIs

Initial and maintenance dosages account for DDIs (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; de Leon et al., 2007; Spina & de Leon, 2007) and careful attention should be paid after discontinuation of inducers or inhibitors:

(a) Approximately twofold increase in dose if used with carbamazepine, a metabolic inducer. Similar changes may be needed for other metabolic inducers (e.g., phenytoin, phenobarbital, rifampin, and possibly oxcarbazepine).

(b) Lower doses if used with CYP2D6 (e.g., paroxetine, or bupropion) and/or CYP3A inhibitors (e.g., ketoconazole, itraconazole, fluconazole, erythromycin, fluvoxamine, clarithromycin or diltiazem). The lowest possible dose should be prescribed if used with fluoxetine, a CYP2D6 and CYP3A inhibitor. Avoid combining risperidone with cimetidine, grapefruit juice or protease inhibitors.

4.5.4. Special considerations for long-acting risperidone injections

Long-acting risperidone should be injected into the gluteal muscle and care must be taken to avoid inadvertent injection into a blood vessel. Tolerability should be established with an oral dose prior to
initiating treatment with intramuscular injections. Moreover, oral risperidone should be continued for 3 weeks after the first injection (Janssen, 2007c).

There are no published data on the use of long-acting risperidone injections on individuals with IDs and no published recommendations on dosing for these individuals. Currently it seems reasonable to use oral doses to orient initial doses of long-acting risperidone injections. If the individual can tolerate 2 mg/day of oral risperidone, the package insert recommends 25 mg every 2 weeks. If the individual is taking <2 mg/day of oral risperidone, the recommended dose would be 12.5 mg every 2 weeks. The lowest dose possible is used for the elderly, especially those with renal or hepatic impairment, as well as those taking CYP2D6 and/or CYP3A inhibitors.

There are no data on how to appropriately monitor orthostatic hypotension on long-acting risperidone injections. It may be safer to monitor for the first 3 weeks after adding the first injection and, if there are signs of hypotension, consider decreasing oral doses to compensate for the progressive increase of blood levels released from long-acting injections.

Doses higher than 50 mg every 2 weeks will need justification in individuals with IDs as they did not provide additional benefits in the published schizophrenia clinical trials. Clinicians should review the prior section on DDIs, because inducers of risperidone metabolism may require higher doses, ≥50 mg every 2 weeks. Further, they should be aware that some preliminary information suggests that occasionally some individuals have detectable levels with oral risperidone and undetectable concentrations with long-acting injections, suggesting that long-acting formulations in those individuals may not be effective.

4.6. Ziprasidone

4.6.1. Administration pattern

Oral ziprasidone needs to be administered with food and typically is done on a twice a day schedule (Pfizer, 2007).

4.6.2. Initial dosing, titration and maximum dosing

The package insert recommends different initial oral doses for schizophrenia and bipolar mania (twice that of schizophrenia) (Gunasekara, Spencer, & Keating, 2002; Pfizer, 2007). If the treatment is well tolerated and symptoms persist, the dose is increased at intervals of no less than two days. The dose is titrated more slowly in older individuals or if sedation or orthostatic changes develop. As there are little data on dosing for individuals with ID, slow titrations are recommended. Initial oral doses >20 mg bid need justification and careful attention should be paid to orthostatic changes (see Appendix 1). Doses above 200 mg/day (100 mg twice a day) have not been systematically evaluated. Thus, the maximum recommended dose in the absence of DDIs is 200 mg/day.

4.6.3. Dosing modification associated with DDIs

DDIs are probably less relevant for ziprasidone than for other NGAs (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005) and can probably be ignored. If DDI interactions are being considered, initial and maintenance doses can be:

(a) Approximately 1/3 higher if used with carbamazepine, phenytoin, phenobarbital, or other CYP3A inducers.
(b) Approximately 1/3 lower if used with strong CYP3A inhibitors, including ketoconazole or erythromycin. Similarly, a lower dose is recommended if used in combination with other CYP3A inhibitors such as fluvoxamine or fluoxetine, itraconazole, fluconazole, erythromycin, clarithromycin or diltiazem.

4.7. New generation antipsychotic (NGA) intramuscular (IM) dosing

There are no data on the use of NGA IM dosing for those with IDs. Thus, practitioners should try to avoid it as much as possible. Not describing its potential use may be interpreted as an endorsement for
typical IM (e.g., haloperidol and chlorpromazine IM) use in individuals with ID. Although physicians may have more experience with typical IMs, and atypical IMs may be much less expensive, one needs to acknowledge that, similarly, there are no well-conducted studies on the use of typical IMs to control agitation in individuals with IDs. Using the practical approach defended by these guidelines, we provide information given in the package inserts and it will be up to each physician to use it wisely.

The company recommends aripiprazole IM doses of 9.75 mg for agitation (9.75 mg is 1.3 ml of a solution that has a total of 2 ml with 7.75 mg/ml) (Otsuka, 2007), but it may be safer to use 7.75 mg (1 ml) or less in individuals with IDs. The safety of daily doses totaling more than 30 mg or injections given more frequently than every 2 h has not been adequately evaluated in clinical trials. Thus, the maximum recommended total daily IM dose in the absence of DDIs is 30 mg/day. Likewise, the minimum recommended interval for IM injections is 2 h.

IM olanzapine initial doses of 2.5 mg appear to be reasonable in this population. If necessary, 10 mg injections may be repeated no more frequently than 2 h after the initial dose and 4 h after the second dose for a maximum of 30 mg total dose per day. Monitor pulse and blood pressure before giving olanzapine IM doses and after 30 min. It appears reasonable to pay close attention to orthostatic changes (see Appendix 1) for olanzapine IM dosing because studies suggest that orthostatic changes are possible.

Use intramuscular ziprasidone only in individuals who have taken oral ziprasidone before to avoid the potential for QTc prolongation. If intramuscular use is necessary, the dose is initiated at 10 mg, as required, up to a maximum daily dose of 40 mg. If needed, doses of 10 mg are administered no more frequently than every 2 h or doses of 20 mg are administered no more frequently than every 4 h up to a maximum daily dose of 40 mg. Monitor pulse and blood pressure before giving olanzapine IM doses and after 30 min. According to the drug company, IM injections of ziprasidone should not be given more than three consecutive days (Pfizer, 2007).

5. Comparison of drug-drug interactions (DDIs) and drug metabolism

5.1. NGA metabolism

The best way to predict DDIs is to know the main metabolic pathway of the pertinent drugs. Table 4 provides a summary of the main metabolic pathways (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; Sandson, Armstrong, & Cozza, 2005; Spina & de Leon, 2007). The published information on paliperidone is very limited (Vermier, Boom, Naessens, Talluri, & Eerdekens, 2005). The p-glycoprotein is a transporter that may have important influence on antipsychotic response but is not well understood (Arranz & de Leon, 2007; de Leon et al., 2007).

5.2. Effects of other drugs on NGAs

Table 5 summarizes our current knowledge of the most important DDIs with psychotropic drugs by comparing these NGAs (de Leon, 2004a, 2004b; de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005).

Table 4

<table>
<thead>
<tr>
<th>Intramuscular injections: initial dosing, titration and maintenance dosages in mg/day described in the package insert as of December 2007.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aripiprazole</strong></td>
</tr>
<tr>
<td><strong>Initial dose</strong></td>
</tr>
<tr>
<td><strong>Maximum daily dose studied</strong></td>
</tr>
<tr>
<td><strong>Minimum dosage interval (h)</strong></td>
</tr>
<tr>
<td><strong>Minimum dosage interval (h)</strong></td>
</tr>
</tbody>
</table>

* An initial dose of 2.5 mg IM are recommended for debilitated patients, those who have a predisposition to orthostatic hypotension or are expected to metabolize olanzapine slowly (e.g., geriatric non-smoking females).
Table 5
Metabolic pathways for atypical antipsychotics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main elimination pathway</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>CYP2D6 and CYP3A</td>
<td>CYP2D6 and FMO</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>CYP1A2 and UGT1A4</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Renal excretion</td>
<td>Possibly CYP3A, CYP2D6 and glucuronidation</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>CYP3A</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6 and CYP3A</td>
<td>Renal excretion</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Aldehyde oxidase</td>
<td>CYP3A</td>
</tr>
</tbody>
</table>

CYP1A2: cytochrome P450 1A2; CYP2D6: cytochrome P450 2D6; CYP3A: cytochrome P450 3A; FMO: flavin-containing monooxygenase system; UGT1A4: Uridine 5′-diphosphate glucuronosyltransferase 1A4.

2005; Sandson et al., 2005; Spina & de Leon, 2007). This information aids in rational decision making and selection of an NGA drug in individuals with ID; it also clarifies dosing needed to compensate for potential DDIs, including the effects of inducers and inhibitors. The DDIs associated with co-prescription of most relevant medical medications has been described in the dosing section for each drug in this guideline and in prior review articles (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; Sandson et al., 2005; Spina & de Leon, 2007). It is also important to remember that for olanzapine metabolism, caffeine is an inhibitor and smoking is an inducer (de Leon, 2004a).

Carbamazepine, phenytoin, phenobarbital and primidone are the anticonvulsants that are powerful inducers (see Table 6). Practitioners should be aware that the current information on oxcarbazepine is rather limited, but suggests fewer risks of DDIs than carbamazepine. Prior review articles provide more details on all anticonvulsants (de Leon, 2004b; de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; Sandson et al., 2005; Spina & de Leon, 2007). The table includes antidepressants that may require decreased dosing of the NGAs when they are co-administered. Table 6 does not specify that if sertraline is used in high doses, there may also be a need to lower NGA doses. Co-administration of citalopram or escitalopram probably does not require lowering NGA doses (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005; Spina & de Leon, 2007).

Understanding the therapeutic window concept is important in determining the clinical relevance of DDIs (de Leon, 2007). Co-prescription of inhibitors may not be very clinically relevant for quetiapine ADRs, because quetiapine is probably a drug with a very wide therapeutic window. Good tolerance of high doses twice as high as recommended (1600 mg/day) has been described (Bobes et al., 2002), and in a study in state hospitals in New York (Citrome, Jaffe, Levine, & Lindenmayer, 2005), the proportion of individuals receiving dosages >750 mg/day was 34% (and >1200 mg/day was 3%). As risperidone has a relatively narrow window, adding an inhibitor may have much more clinical relevance relative to causing ADRs.

Table 6
Most important DDIs with psychotropic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Olanzapine</th>
<th>Paliperidone</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++</td>
<td>Unknown but likely</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>++</td>
<td>Unknown but likely</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++</td>
<td>Unknown</td>
<td>Possibly ++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>Unknown</td>
<td>Possibly ++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>0</td>
<td>Unknown</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

The risk for DDIs is described using 0 = absent, + = mild, ++ = moderate and +++ = severe and refers to the effects on the drug levels. Clinical relevance is also influenced by the width of the therapeutic window.
Adding an inducer to an NGA can be associated with loss of efficacy. Besides the therapeutic window, the effect size of the decrease in antipsychotic levels caused by the inducer is probably very relevant. The effects are very important (a decrease by a factor of five times the plasma level) for quetiapine; intermediate (a decrease by a factor of two to three times the plasma level) for aripiprazole, risperidone and olanzapine; and small for ziprasidone (a decrease by a factor of 1.5 times the plasma level) (de Leon, Armstrong, et al., 2005; de Leon, Susce, et al., 2005). Limited experience with combinations of both inhibitors and inducers suggests that the effects of inducers are more important and tend to overcome those of the inhibitors (de Leon et al., 2007).

5.3. Effects of NGAs on other drugs

NGA drugs appear to be neither significant inhibitors nor inducers of metabolic enzymes. Their package inserts describe them as unlikely to cause DDIs. However, in unusual polypharmacy situations where individuals take drugs with a narrow therapeutic window, adding a NGA may be the straw that breaks the proverbial camel’s back through competitive inhibition of multiple drugs vying for particular metabolic enzymes. In fact, some case reports suggest that atypical antipsychotics may potentially behave as competitive inhibitors in rare instances of polypharmacy (Fitzgerald & Okos, 2002; Rogers, de Leon, & Atcher, 1999).

6. Adverse drug reactions

ADR is the term most frequently used today for describing what psychiatry textbooks used to call side effects. This section focuses first on the lethality associated with ADRs, and then the most frequent ADRs are described.

6.1. Lethality

The lethality of the NGAs can be established in two ways: by studying lethality in intentional overdoses and by studying lethality associated with ADRs.

6.1.1. Lethality during overdosing

NGA drugs appear to be less toxic than conventional antipsychotics and clozapine. Available studies suggest that they are very rarely lethal after intentional overdosing; fatalities are usually associated with taking several medications, making it difficult to pinpoint the NGA as responsible for the death (Burns, 2001; Capel, Colbridge, & Henry, 2000; Trenton, Currier, & Zwemer, 2003). Future studies of lethality during intentional overdosing are important for clinicians seeking to understand the toxicity risks of high doses of NGAs and their relative safety levels, as opposed to them simply being “newer”, with less available data (Dubois, 2005).

6.1.2. Adverse drug reactions (ADRs) and lethality

Before the mortality data are reviewed, one has to remember that Feinstein (1996) strongly criticized the limited validity of using information from vital statistics (e.g., “cause of death” coming from death certificates) because it may simply note only one from among multiple causes and ignore pathophysiological processes. Thus, an epidemiological association between death and taking an antipsychotic does not establish a causal relationship between the antipsychotic and the patient’s death. Similarly, if an individual patient is taking an antipsychotic when he/she dies, that fact does not establish a causal relationship between the antipsychotic and the patient’s death. Death from other disease processes while on an NGA is more likely than death caused by an NGA. Therefore, it is important to have a reasonable pathophysiological mechanism explaining a death caused by an antipsychotic. This is particularly important since schizophrenia has been definitively associated with increased mortality (Auquier, Lancon, Rouillon, & Lader, 2007; Saha, Chant, & McGrath, 2007) and many individuals with schizophrenia take antipsychotics; therefore antipsychotics may be blamed for deaths associated with schizophrenia or its associated factors.
A recent article reviewed the serious ADRs, including deaths, reported to the FDA from 1998 to 2006; it described olanzapine as associated with 1005 serious ADRs and 9 deaths, and risperidone as associated with 1093 serious ADRs and 9 deaths (Moore, Cohen, & Furberg, 2007). As noted by Moore et al., the report of a serious ADR to the FDA does not guarantee a causal association between the drug and the ADR.

Deaths on therapeutic doses that can be directly attributed to an NGA with an established pathophysiological mechanism are probably rare. It appears that three possible serious ADRs (neuroleptic malignant syndrome, diabetic coma, and pancreatitis) are potentially lethal and have been associated with the use of NGAs. Two other related issues for which it is even harder to establish causal connections are the increased mortality rate in individuals with dementia and the potential of prolonging QTc.

The risk of neuroleptic malignant syndrome is substantially lower with NGAs than with conventional antipsychotics, but has been documented on all NGAs. A review identifying 68 published cases described three deaths, or 4%, associated with NMS (Ananth et al., 2004). Undiagnosed diabetes mellitus can progress to ketoacidotic or hyperosmolar coma, both of which are associated with substantial mortality rates. Olanzapine has rarely but clearly been associated with diabetic coma (Henderson, 2002); furthermore, it is possible that risperidone (Koller, Cross, Doraiswamy, & Schneider, 2003) and quetiapine (Koller, Weber, Doraiswamy, & Schneider, 2004) may also be associated with diabetic comas. Pancreatitis is a potentially lethal illness rarely associated with NGAs; however, it is difficult to establish a causal connection with the antipsychotic treatment. Olanzapine has rarely but clearly been associated with diabetic coma (Henderson, 2002); furthermore, it is possible that risperidone (Koller, Cross, Doraiswamy, & Schneider, 2003) and quetiapine (Koller, Weber, Doraiswamy, & Schneider, 2004) may also be associated with diabetic comas. Pancreatitis is a potentially lethal illness rarely associated with NGAs; however, it is difficult to establish a causal connection with the antipsychotic treatment. Koller, Cross, Doraiswamy, and Malozowski (2003) identified 192 cases of pancreatitis during antipsychotic treatment with any antipsychotic (including haloperidol and clozapine) and found a mortality rate of 11%. These 192 cases included many with other possible causes of pancreatitis, particularly valproic acid.

When compared to placebo, there is an increased death rate in elderly individuals with dementia on several NGA drugs. This increase in mortality may be partially explained by an increase in stroke (Sink, Holden, & Yaffe, 2005). The stroke risk may not be higher than in individuals with dementia taking conventional antipsychotics (Herrmann & Lanctôt, 2006). Venous thromboembolism may also be slightly increased in elderly individuals taking NGA or conventional antipsychotics (Liperoti et al., 2005). A recent article reported that the increased mortality of individuals with dementia taking antipsychotic treatment is probably multifactorial and not well understood (Kales et al., 2007). A recent cohort study suggested greater mortality in the elderly taking conventional antipsychotic drugs than in those taking NGA drugs (Schneeweiss et al., 2007).

Prolongation to QTc has been definitively associated with increased sudden deaths in individuals taking conventional antipsychotics; however, there are no clear data that NGAs can lead to torsades de pointes (Titier et al., 2005). As a matter of fact, there are no definitive cases of deaths associated with arrhythmias in individuals taking ziprasidone (Simpson & Albanese, 2005; Trenton et al., 2003). Moreover, ziprasidone overdoses may be associated with QTc values in the normal range (Gómez-Criado et al., 2005). In a prospective randomized study, the increases in QTc were low on olanzapine (1.7 ms), risperidone (3.9 ms), and quetiapine (5.7 ms); were only modest on ziprasidone (15.9 ms); were clearly lower than on thoridazine (30.1 ms) (Harrigan et al., 2004).

In summary, physicians should be particularly vigilant to the development of potentially lethal complications such as neuroleptic malignant syndrome, diabetic coma, pancreatitis, stroke in elderly individuals and risk of arrhythmias in individuals taking NGAs, independently of whether the NGAs have a causal relationship, reveal a shared underlying factor, or contribute to a multifaceted pathophysiological process.

6.2. Most frequent ADRs

Table 7 summarizes our current knowledge of more frequent ADRs by comparing these NGA drugs (Cutler, 2003; Haro & Salvador-Carulla, 2006; Katz, 2004; Newcomer, 2007; Rosenbaum, Arana, Hyman, Llabate, & Fava, 2005; Tandon, Targum, Nasrallah, & Ross, 2006; Weiden et al., 2007). The table tends to be conservative, meaning that if there is doubt or a discrepancy in the literature, the highest score was selected.

Therapeutic interventions to use after ADRs develop must address the nature of the ADR and the context within which it occurred. Broad ranging strategies include changing the NGA treatment
These therapeutic interventions that apply to all ADRs are only briefly examined for the most important ADRs: EPS, metabolic syndrome, and hyperprolactinemia. If other ADRs require treatment, changing the NGA treatment (decreasing dosage, stopping or switching to another) appears to be the most reasonable choice.

6.2.1. Extrapyramidal symptoms (EPS)

EPS were usually considered the most important ADRs for conventional antipsychotics. The review of the NGA trials, which used conventional antipsychotics as a comparison, suggests that NGAs tend to be associated with less reversible EPS symptoms (Leucht et al., 1999), and with less propensity to cause TD (Correll et al., 2004; Nasrallah, 2006). Systematic review of TD in adults, the elderly or children are limited by the relatively short duration of the studies (Correll & Kane, 2007; Correll et al., 2004; Dolder & Jeste, 2003; Nasrallah, 2006). Naturalistic studies suggest that NGAs may not be remarkably different from conventional antipsychotics when used in real world settings and are associated with an increased risk of EPS (de Leon, 2007; Lee et al., 2005).

Parkinson's disease is an ideal model for testing the potential for EPS. Experience with using NGAs in individuals with Parkinson's disease suggests that quetiapine (with clozapine) is the NGA with the best EPS profile (Fernandez, Trieschmann, & Friedman, 2003; Katz, 2004). There is limited experience with aripiprazole in individuals with Parkinson's disease. The main EPS in individuals with schizophrenia and mania who are taking aripiprazole appears to be akathisia. Olanzapine and ziprasidone probably have an intermediate EPS profile (Fernandez et al., 2003; Katz, 2004), while risperidone is the worst of these NGAs for EPS, and clearly has a dose-related profile, with increasing EPS from 8 to 16 mg/day (Lemmens et al., 1999).

Studies of EPS typically describe the response of the average individual to the use of NGA drugs. However, there are individuals that for unknown reasons, possibly genetic, may be particularly prone to EPS with some NGA drugs than with others. An example of this would be an individual who develops a catatonic episode only on ziprasidone and has no such reaction on all other NGA drugs (Markham-Abedi et al., 2007).

There are three main reversible EPS: acute dystonic reactions, parkinsonism and akathisia. The acute dystonic reactions are relatively rare on NGA drugs (Raja & Azzoni, 2001). There are no systematic treatment studies of acute dystonic reactions on NGA drugs, but they are short-lived and it is assumed that they should respond to anticholinergic medications in parenteral and oral forms (to avoid relapse), as do the acute dystonic reactions seen on conventional antipsychotics (Raja, 1998). Parkinsonism on conventional antipsychotic drugs was frequently managed by adding anticholinergics (antiparkinsonians with antimuscarinic activity) or a dopaminergic agonist, amantadine. Anticholinergics can cause their own ADRs and amantadine may lose its efficacy due to tolerance. Parkinsonism should be treated first by decreasing doses or switching to an NGA with a more favorable profile.
EPS risk profile; adding anticholinergics should be considered a secondary action because the antimuscarinic activity of anticholinergic medication may interfere with cognition, a worrisome prospect in individuals with ID.

Akathisia may respond to dose reduction or switching to another NGA drug. Adding other medications to treat akathisia has its own set of problems. The most frequently used are beta-blockers and benzodiazepines and, if the individual has parkinsonian symptoms, anticholinergic medications (Iqbal, Lambert, & Masand, 2007; Rosenbaum et al., 2005).

There are no reliable, effective treatments for TD, so when there are early signs, practitioners should try lowering the dose, discontinuing or switching the NGA drugs (Kane, 2006; Sachdev, 2000). Once TD is clearly developed the ideal option is to slowly taper and use antipsychotic doses as low as possible. Tardive dystonia is a more disabling form of TD that may require more aggressive pharmacological treatments (Raja, 1998).

Close monitoring of the early signs of TD in individuals with ID is needed (Bodfish, Newell, Sprague, Harper, & Lewis, 1996; Sachdev, 1992). It not clear whether or not brain damage in general, or IDs in particular, increase the TD risk (Sachdev, 2000). In a recent large TD survey in youth and adults with ID, profound mental retardation was a newly described specific TD risk factor (Wszola, Newell, & Sprague, 2001). Increasing age, anticholinergic use, and longer duration of antipsychotic treatment, particularly of conventional antipsychotics (Wszola et al., 2001), were also TD risk factors in a large clinical study of US adults with severe mental illness (de Leon, 2007), as well as in many prior studies (Sachdev, 2000).

6.2.2. Metabolic syndrome

The effects of NGA drugs on weight ranges from a maximum on olanzapine to a minimum on ziprasidone and aripiprazole (Allison et al., 1999; Newcomer, 2007; Newcomer & Haupt, 2006). Olanzapine may also have a direct effect on glucose metabolism (Newcomer, 2007; Newcomer & Haupt, 2006), and olanzapine and quetiapine probably interfere directly in lipid metabolism (de Leon & Diaz, 2007; Meyer & Koro, 2004).

Nutritional consultation and appropriate dietary and exercise interventions should be implemented if any of the following weight gain indicators occur: (1) weight increase of 5% in 1 month, 7.5% in 3 months or 10% in 6 months; (2) waist circumference increases to more than 35 inches in females and more than 40 inches in males; (3) BMI increases from normal to overweight (less than 25 to 25 or higher) or from overweight to obese (25–29.9 to 30 or higher). Regarding secondary complications, (1) a fasting blood glucose level of 100 mg/dl or higher should prompt appropriate medical interventions that may include a glucose tolerance test and discontinuation of the NGA drug or switching to another, particularly aripiprazole or ziprasidone, and (2) an abnormal lipid (triglyceride or cholesterol level) result should prompt an appropriate medical intervention that may include adding lipid lowering agents, discontinuation of the NGA drug, or switching to another NGA, particularly aripiprazole or ziprasidone.

6.2.3. Prolactin and sexual side effects

Some of the antipsychotic sexual ADRs may be associated with hyperprolactinemia (Cutler, 2003), whereas others may not. Priapism is probably not explained by hyperprolactinemia. Priapism has even been associated with aripiprazole (Mago, Anolik, Johnson, & Kunkel, 2006), which should not cause hyperprolactinemia. It is believed that priapism may be associated with α receptor blockade.

Prolactin elevations are probably higher with risperidone, while aripiprazole may decrease prolactin (Haddad & Wieck, 2004). If prolactin-related symptoms such as menstrual cycle changes, galactorrhea, gynecomastia or sexual dysfunction occur, consider risk/benefits and the possibility of stopping the antipsychotic or switching to an antipsychotic with less risk of hyperprolactinemia, such as ziprasidone or quetiapine, or to aripiprazole, which may decrease prolactin levels. A prolactin level above 200 ng/ml may be a sign of pituitary adenoma, and should prompt an evaluation including a magnetic resonance imaging (MRI) of the head with a pituitary protocol, and, if needed, consultation with a neurosurgeon (Verhelst & Abs, 2003). Practitioners should be aware that the onset of new headaches or impaired vision, classically bitemporal hemianopsia, may be a sign of pituitary adenoma (Melkerson & Hulting, 2000).

In individuals treated with oral NGA drugs, a 72-h cessation of the antipsychotic should be accompanied by a fall in the prolactin level to a near normal level if the antipsychotic is the cause of the
hyperprolactinemia (Haddad & Wieck, 2004). Practitioners should remember that other causes of hyperprolactinemia are pregnancy and hypothyroidism (Miller, 2004).

6.2.4. Sedation and activation
Sedation is more prevalent with olanzapine and quetiapine than with the other NGA drugs. Individuals frequently develop tolerance early in treatment. Early activation, including insomnia, may occur with aripiprazole and ziprasidone. In aripiprazole, activation may be a sign of akathisia. Ziprasidone may be activating at low doses (Weiden et al., 2007).

6.2.5. Orthostatic changes
Three oral NGA drugs, quetiapine, risperidone and ziprasidone, can cause orthostatic changes; therefore, the manufacturers recommend titrating initial doses (Astra Zeneca, 2007a, 2007b; Janssen, 2007b; Pfizer, 2007). Olanzapine IM appears to have more risk of orthostatic hypotension than the oral form (see Appendix 1 for monitoring to prevent orthostatic changes).

6.2.6. Gastrointestinal symptoms
Gastrointestinal (GI) symptoms/nausea may occur more frequently with aripiprazole and ziprasidone (Weiden et al., 2007). Individuals usually develop tolerance to them. All antipsychotics may interfere with swallowing, cause esophageal dysmotility and contribute to aspiration. Practitioners should be careful using any antipsychotic in patients with dysphagia.

6.2.7. Seizures
All of these NGA drugs (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone) probably have potential for decreasing the seizure threshold. A recent review suggested that it is possible that olanzapine and quetiapine may be the worst among them (Alper, Schwartz, Kolts, & Khan, 2007).

6.2.8. Antimuscarinic symptoms
Dry mouth, constipation and urinary retention were associated with the use of low-potency conventional antipsychotics. NGA drugs (besides clozapine) clearly have less potential to cause them. Olanzapine and perhaps quetiapine may have clinically relevant antimuscarinic activity (Chew et al., 2006).

6.2.9. Transaminase elevations and other laboratory abnormalities
The risk of transaminase elevations may be higher with olanzapine than with the other NGA drugs described in this guideline. The olanzapine package insert describes a 1% discontinuation on oral trials due to transaminase elevations. Quetiapine has rarely been associated with TSH elevations (Dobbs, Brahm, Fast, & Brown, 2004; Nasrallah & Tandon, 2002).

6.2.10. Paliperidone
There is limited information available on paliperidone, but it is expected to have a profile similar to that of risperidone. One difference may be that the company does not recommend the need for titration, suggesting that paliperidone should not cause orthostatic hypotension, as risperidone initial doses may cause it. It is peculiar that in spite of paliperidone’s status as supposedly not causing orthostatic changes (or having antimuscarinic activity), tachycardia was higher with paliperidone than in placebo in a 6-week double-blind placebo-controlled study (frequency of tachycardia was 10% in placebo, 18% in paliperidone 6 mg/day, 14% in paliperidone 9 mg/day, 22% in paliperidone 12 mg/day, and 14% in 10 mg/day of olanzapine) (Kane et al., 2007). Similarly, postural hypotension appears higher than in placebo (1% in placebo, 3% in paliperidone 6 mg/day, 2% in paliperidone 9 mg/day, 5% in paliperidone 12 mg/day, and 5% in 10 mg/day of olanzapine) (Kane et al., 2007). The package insert notes that individuals should be warned about the possibility of orthostatic hypotension (Janssen, 2007a). As we lack experience, this guideline does not recommend monitoring orthostatic changes. It cannot be ruled out that this recommendation may be changed in the future.
7. Guidelines and drug utilization reviews for each NGA

These guidelines are organized to avoid repeating the information for each NGA compound. It may be difficult to conceptualize how they will apply to specific oral and IM compounds. Thus, we have included 11 drug utilization reviews (DURs) as a part of these guidelines. The three DURs for IM compounds present the indication, dose and ADRs for IM aripiprazole, IM olanzapine and IM ziprasidone (see Appendices 2–4). The seven DURs for oral compounds present the indication, dose, relative contraindications, baseline information, baseline monitoring studies, monthly monitoring, semiannual monitoring, annual monitoring, actions to take after metabolic abnormalities develop, actions to take after high prolactin levels and/or related symptoms develop, and ADRs for aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone (see Appendices 5–9 and 11). The DUR for long-acting risperidone injections (Appendix 10) follows the same format as oral compounds.

DURs were developed in the 1980s and implemented in the 1990s for ambulatory Medicaid patients to improve the quality of drug therapy (The US Pharmacopeia Drug Utilization Review Advisory Panel, 2000). More recent literature suggests that traditional retrospective DURs are not good at preventing DDIs (Peng et al., 2003); they can only document them after the fact. Prospective DURs involve reviewing each prescription for an individual patient before it is dispensed to identify DDIs, contraindications, therapeutic duplication, or potential ADRs (Fulda, Lyles, Pugh, & Christensen, 2004).

Therefore, these 11 DURs, or variations based on them, can be used in a retrospective way to verify the quality of NGA drug therapy at any health facility. These 11 DURs can also be used in a prospective way by incorporating them in a computerized prescription or medical record to establish that the NGAs are prescribed properly and train/remind the prescribing clinicians of the need to prescribe them carefully for individuals with ID.

8. Other issues

Some of the seven NGA drugs described in these guidelines have been on the market for several years (oral risperidone since 1993; Seroquel XR less than 1 year). Unfortunately, these time frames are not long enough to understand all of the implications of their use. The first conventional antipsychotics were developed in the 1950s, but some crucial issues such as the mortality associated with long QTc were not understood until the 1990s. There are several clinical issues that physicians may face when prescribing NGA drugs that are not well understood even in individuals with schizophrenia; thus, they may not have enough information to incorporate them into a guideline for individuals with schizophrenia. Consequently, information regarding these issues in individuals with ID is almost non-existent. Instead of ignoring these issues, we have briefly described some of them in this section and provided some references for further reading for those interested prescribing clinicians who may be facing these issues in the treatment of individuals with IDs. We think that some limited knowledge of these practical issues is better than complete ignorance or lack of acknowledgment of their existence. The selected issues are (1) discontinuation syndromes, (2) the potential for abuse, (3) pregnancy, (4) cost, and (5) therapeutic drug monitoring (TDM), which is usually called blood levels in psychiatric journals.

8.1. Discontinuation syndromes

NGA drugs should be discontinued slowly by tapering doses in all individuals, but particularly in those with ID in whom symptoms and signs are much more difficult to interpret. Unfortunately, abrupt discontinuations occur in the real world due to serious ADRs or the individual’s non-adherence to treatment. There are a series of syndromes associated with the abrupt discontinuation of conventional antipsychotics that may occur also in individuals taking NGAs, but information about them is very limited. There are four major syndromes described in individuals taking conventional antipsychotic drugs or clozapine: (1) cholinergic rebound; (2) withdrawal dyskinesia; (3) withdrawal psychosis, and (4) activation syndrome (Lambert, 2007; Stanilla, de Leon, & Simpson, 1997).

Cholinergic rebound manifested by nausea/vomiting, diarrhea, diaphoresis, restlessness and insomnia has been described with abrupt discontinuation in individuals taking phenothiazines and anticholinergics (Simpson, Amin, & Kunz, 1994) and clozapine (de Leon, Stanilla, White, & Simpson,
1994), and appears to respond to anticholinergic medications (de Leon et al., 1994). Olanzapine probably has much less antimuscarinic binding than phenothiazines and clozapine. There are no published cases of olanzapine being associated with cholinergic rebound but it cannot be ruled out that if used in high doses and abruptly stopped it may be associated with cholinergic rebound. Two cases of cholinergic rebound when switching from clozapine to olanzapine suggest that olanzapine’s antimuscarinic properties may be limited (Delassus-Guenault et al., 1999). Quetiapine has some antimuscarinic properties, but it should be even less likely than olanzapine to cause cholinergic rebound. There are two published cases of quetiapine withdrawal with nausea, dizziness and anxiety after discontinuation (Kim & Staab, 2005; Thurstone & Alahi, 2000). It is not clear that these two cases were explained by cholinergic rebound; another mechanism, perhaps serotonergic, may be involved. Neither of these cases was treated with anticholinergics; successful treatment with anticholinergics would support the diagnosis of cholinergic rebound. It is relatively safe to assume that aripiprazole, paliperidone, risperidone and ziprasidone should not cause cholinergic rebound.

Withdrawal dyskinesias have been described in individuals abruptly discontinued from conventional antipsychotics and from clozapine (Lambert, 2007; Stanilla et al., 1997). Withdrawal dyskinesias probably can occur in individuals who are discontinued abruptly from NGA drugs and are not started on another antipsychotic (Michaelides, Thakore-James, & Durso, 2005).

Withdrawal psychosis with the appearance of new psychotic symptoms and/or delirium has been described in individuals who have been discontinued abruptly from clozapine (Stanilla et al., 1997). Nayudu and Scheftner (2000) described an individual who appeared to have a presentation compatible with delirium and myclonic jerking after abrupt olanzapine discontinuation.

Lambert (2007) described an activation syndrome manifested by insomnia, restlessness, irritability and anxiety after stopping a sedating antipsychotic; the brain would have become used to the sedating effects. If this syndrome exists, it may happen to individuals who have been abruptly withdrawn from olanzapine or quetiapine. We have some experience with a similar syndrome in a few individuals with ID that were stabilized for many years on conventional antipsychotic drugs, particularly thioridazine, and deteriorated (particularly presenting anxiety symptoms) when switched to NGAs, but never reaching prior functioning levels. Some other clinicians have described what appeared to be long-term thioridazine withdrawal behavioral deterioration (May et al., 1995; Sovner, 1995). This phenomenon has not been well characterized in the literature. It cannot be completely ruled out that these cases of long-term worsening after thioridazine withdrawal were not directly explained by the withdrawal, but were the relapse of persisting anxiety syndromes that were masked by thioridazine.

8.2. Potential for being abused

The traditional wisdom is that conventional antipsychotics have no potential for being abused. Moreover, sometimes they cause dysphoria (Van Putten & Marder, 1987). A recent brain imaging study on risperidone and olanzapine described how higher dopamine blockade may be associated with more negative subjective experience, suggesting that NGAs also are not likely to be abused (Mizrahi et al., 2007). However, there are several case reports suggesting that quetiapine may be different from other antipsychotics and it is possible that olanzapine can be abused as well.

Although quetiapine may have potential for abuse, its mechanism is not well understood. The case reports include intra-nasal (Pierre, Shnayder, Wirshing, & Wirshing, 2004), IV (Hussain, Waheed, & Hussain, 2005; Waters & Joshi, 2007), and oral abuse (Pinta & Taylor, 2007; Reeves & Brister, 2007). Moreover, Tarasoff and Osti (2007) reported that in Las Vegas a single pill of quetiapine is sold for $3–8 on the black market (versus $5–7 for diazepam). Thus, clinicians prescribing quetiapine to individuals with ID may need to be aware that diversion to the black market is possible, particularly in correctional or forensic facilities.

8.3. Pregnancy

As NGA drugs, except for risperidone, have much lower effects on prolactin than conventional antipsychotics, women taking other NGA drugs besides risperidone may have more risk of unplanned pregnancies than women taking conventional antipsychotics. There is very limited information on the
safety of taking NGA drugs during pregnancy (Cohen, 2007; McKenna et al., 2005; Yaeger, Smith, & Altshuler, 2006), but as NGA drugs are more and more frequently used in children and adolescents for long-term treatment, it is likely that in the future more pregnancies will occur in women taking these drugs. The NGA drugs appear to pass through the placenta but the passage may vary with each compound (Newport et al., 2007).

The package inserts are not helpful because they place NGA drugs in the FDA’s Category C (risk cannot be ruled out). If psychotropics are used during pregnancy, Gold (2000) recommends the need for careful documentation, including (1) consent form, (2) note describing the process used to obtain consent, (3) rationale for using the medication, (4) indication that the patient was advised that use is not approved by the FDA, (5) risk/benefits, (6) alternative treatments with risk/benefits, and (7) indication about how the indication was understood.

An area mentioned by pharmacological journals and not receiving attention in psychiatric journals is that pregnancy may change the ability to metabolize NGA drugs. There is a decrease of CYP1A2 activity during pregnancy (Anderson, 2005; Hodge & Tracy, 2007). It has been suggested that early in pregnancy the dosage of CYP1A2 substrates should be cut by one-third and that in the second and third trimesters, the dosage should be cut by one-half to two-thirds (Anderson, 2005). This recommendation may apply to olanzapine, a CYP1A2 substrate. It is possible that CYP3A activity may be increased in pregnancy but it has not been well-studied (Anderson, 2005; Hodge & Tracy, 2007). Quetiapine is dependent on CYP3A for its metabolism; therefore, it is possible that pregnancy may be associated with a decrease in quetiapine levels. In summary, clinicians need to be aware that, at least with olanzapine, the pre-pregnancy dosage may become more “toxic” as the pregnancy progresses. With quetiapine, the pre-pregnancy dosage may become less effective.

8.4. Cost

The switch from conventional to NGA drugs has been associated with a remarkable increase in drug costs. As a matter of fact, antipsychotics are the fourth largest group of medications with annual costs in excess of $10 billion, with NGAs accounting for 90% of the US antipsychotic market (Kim, Levy, & Pikalov, 2007). It has been estimated that 23% of the more medically vulnerable population – people eligible for both Medicare and Medicaid – take antipsychotics. In fact, it is estimated that 80% of US antipsychotic prescription costs are paid by the public sector (Kim et al., 2007).

A California study estimated that the cost for antipsychotic drugs multiplied by a factor of 6.1 (610%) from 1993 to 2001, without reduced expenses in other types of medical care (Duggan, 2005). Currently, it is estimated that nearly one-third of the direct cost of treatment for schizophrenia is due to the cost of NGAs (Freedman et al., 2006). It is not clear that NGA drugs are more cost-effective than conventional drugs, because the studies evaluating the cost-effectiveness of various NGA drugs have too many limitations to reach clear conclusions (Barbui, Lintas, & Percudan, 2005).

In the US, the cost of NGA drugs varies in different institutions; therefore, US clinicians prescribing these drugs to individuals with ID may need to get information about costs from their administration and collaborating pharmacies at their specific site of practice. For example, Basil, Mathews, Adetunji, and Budur (2006) described the cost for a 30-day supply from a chain pharmacy in Ohio in September 2005. From the lowest to the highest, the costs were: $178 for quetiapine 100 mg twice a day, $251 for risperidone 4 mg once a day, $299 for ziprasidone 80 mg twice a day, $303 for aripiprazole 15 mg once a day, $330 for risperidone 2 mg twice a day, $389 for olanzapine 15 mg once a day, $460 for quetiapine 300 mg twice a day, $520 for olanzapine 20 mg once a day, $520 for aripiprazole 20 mg once a day, and $637 for quetiapine 400 mg twice a day.

Thus, it appears that cost may be an important consideration when deciding which antipsychotic to prescribe. Generic risperidone has been available in several European countries for more than 2 years and has become available in the US in 2008. Recent information suggests that due to a lawsuit, olanzapine will not become generic in the US until 2011, although it is already generic in Canada (Editor, 2008).
8.5. Therapeutic drug monitoring (TDM)

No good published information addresses the meaning of TDM in individuals with ID who are taking NGA drugs. Moreover, the TDM information in schizophrenia is rather limited. The pharmaceutical companies have extensive information from their clinical trials but very limited information has been published.

If a clinician wants to use TDM to help make decisions for individuals with ID taking NGA drugs, he/she needs to be aware that this is uncharted territory. It is important to consider some practical issues regarding the collection and interpretation of the results (summarized in Table 8). Only risperidone and olanzapine TDM may have enough information to make consideration worthwhile.

There are two major indications for TDM: attempting to establish the therapeutic window and attempting to establish unusual patterns in the relationship between concentration and dose (C/D ratio) in steady state conditions (Baumann et al., 2004; Hiemke et al., 2004; Mauri et al., 2007). Information on the therapeutic window is seriously limited by the lack of publication of the prospective randomized trials from pharmaceutical companies. Table 9 provides a summary of two recent TDM reviews and their recommendations for risperidone and olanzapine (Hiemke et al., 2004; Mauri et al., 2007).

The NGA drugs follow linear kinetics. This means that the concentration increases linearly with the dose. Therefore, the relationship between them, called the C/D ratio, is relatively constant and an average C/D represents all average patients well. An individual with a very low C/D ratio is not taking the medication or, because of genetic and/or environmental reasons, is a rapid metabolizer. An individual who has a very high C/D ratio because of genetic and/or environmental reasons is a poor metabolizer. Thus, TDM can be used to determine treatment adherence and to understand how much DDIs are contributing to dosing confusion and how to correct for it. Table 10 provides some simple guidelines on how to interpret C/D ratios for risperidone and olanzapine.

Table 8
Practical issues regarding the collection and interpretation of TDM.

1. Blood collection is usually done in the early AM before the patient has taken the morning medication, when blood levels are the lowest (trough levels). Levels at other times cannot be interpreted easily.
2. The NGA treatment should be in steady state. Using the 5-half-lives rule, clinicians need to wait at least five days after the NGA dose changes to draw a level in steady state. A period of 7-half-lives may be safer to be sure that the patient is in steady state. In summary, in patients taking only an NGA or with co-medication with no important DDIs, clinicians need to worry only about the NGA’s half-life.
3. Unfortunately, if there are important co-medications (e.g., inducers or inhibitors) there is reason for concern. Ideally, the clinician needs to wait until the effects of the inducer and inhibitor on the NGA reach steady state. If the patient is taking an NGA and inducers, the clinician ideally should wait up to 6 weeks after any changes in inducer dosing. Any level drawn earlier than 6 weeks is likely to underestimate the effects of the inducer. Similarly, one should wait at least 2–3 weeks after inducer discontinuation to see its effects. Most inhibitors of NGA metabolism will be in steady state after 1 week on stable inhibitor doses. Fluoxetine is an exception. Its metabolite, norfluoxetine, has such a long half life that it may take up to 2–3 months for an average subject to reach steady state. Any level drawn earlier than 2–3 months after adding fluoxetine is likely to underestimate the inhibitor effects of fluoxetine.
4. Other antipsychotics (and some antidepressants) can interfere with the determination of an NGA (e.g., clozapine and quetiapine can interfere with risperidone determination).
5. There is some information on risperidone and olanzapine TDM. The information on aripiprazole, quetiapine, and ziprasidone is considered so preliminary that it is not reviewed here. Due to the short half-life of quetiapine and ziprasidone, their levels fluctuate greatly during the day, making them unlikely to be good candidates for TDM. There is no information on quetiapine levels in patients taking Seroquel XL. Interpreting paliperidone TDM is challenging because there is no information on 9-OH-risperidone on patients taking paliperidone, but there is information on 9-OH-risperidone in patients taking risperidone (de Leon, Sandson, & Cozza, 2008). TDM on long-acting risperidone cannot be interpreted using TDM information on oral risperidone (de Leon et al., 2008).
6. For some antipsychotics, it is important to determine the active metabolite (Hendset, Haslemoe, Rudberg, Refsum, & Molden, 2006). For risperidone TDM, it is necessary to determine the main metabolite that is active, 9-OH-risperidone. It is possible that it may be necessary to determine some of the olanzapine metabolites but commercial laboratories do not do it.
7. Most commercial laboratories report their levels in ng/ml. If they are reported nMol/l they need to be converted (see table in Baumann et al., 2004).

Note: ng/ml = nanograms/milliliter; nMol/l = nanomoles/liter.
These guidelines take the pragmatic approach of reviewing the NGA drugs available in the US market after clozapine: aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. There is very limited scientific information following evidence-based medicine or personalized medicine approaches providing recommendations on their use in individuals with ID. These guidelines are also pragmatic in that they were developed using package inserts and a review of the available literature on other disorders.

These NGA drugs are less toxic than clozapine, which may have a role in more difficult cases and may have some advantages over conventional antipsychotics. They produce less EPS, but they are not completely free of them. Metabolic syndrome complications may be worse with some of these NGAs.
than with high-potency conventional antipsychotics. The NGA drugs are definitely more expensive than the conventional antipsychotics.

In the absence of consensus guidelines and well-controlled comparison trials, we presented a set of guidelines to ensure proper utilization of aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone in individuals with ID. These guidelines provide practical information on dosing, DDIs and ADRs. DURs are provided to facilitate their implementation and to monitor their use. In addition, these guidelines briefly considered some other issues: discontinuation syndromes, the potential for abuse, pregnancy, cost, and TDM.

The procedures contained in these guidelines may not fully account for all of the possible risks of treatment in this population because of the limited studies available; thus, there will be a need to periodically update this guide as new knowledge becomes available. Nevertheless, we believe that these guidelines will provide a useful resource for psychiatrists who treat challenging behaviors in individuals with ID.

Acknowledgments

Conflict of interest statement: In 2007, Dr. de Leon received researcher-initiated grants from Roche Molecular Systems, Inc., and from Eli Lilly (the latter as co-investigator). Before 2007, Dr. de Leon received one researcher-initiated grant from Eli Lilly (2000) and was on the advisory boards of Bristol-Myers Squibb (2003/04) and AstraZeneca (2003). He personally develops his presentations for lecturing and has never lectured using any pharmaceutical company presentations. His lectures have been supported once by Bristol-Myers Squibb (2006), three times by Eli Lilly (2003, 2006, and 2006), twice by Janssen (2000 and 2003), twice by Lundbeck (both in 1999), twice by Pfizer (2001 and 2001) and, one time by Sandoz (1997). He has never been a consultant nor had any other financial arrangements with these companies nor owns any of their stocks. Drs. Greenlee, Barber, Sabaawi and Singh do not have any conflict of interest with pharmaceutical drug companies.

The authors have exerted every effort to ensure that drug selection and dosage set forth in this paper are in accordance with current recommendations and practice at the time of writing (December 2007). However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the practitioner is urged to review the research literature and check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. Care has been taken to confirm the accuracy of the information presented and to describe generally accepted practices. However, application of this information in a particular situation remains the professional responsibility of the practitioner, and the authors are not responsible for errors or omissions or for any consequences from application of the information presented.

Appendix 1. Consideration of orthostatic changes for dose titration

Instructions

1. Use these instructions for oral quetiapine, IM olanzapine, oral risperidone and oral/IM ziprasidone unless the individual cannot stand (wheelchair or bedridden). In that situation in which orthostatic changes cannot occur, if he/she is known to try to get up and not follow recommendations, he/she should be monitored closely until the dose is stable.
2. If the individual refuses checks for vital signs due to agitation, and the decision is made to give the medication to calm the agitation, the patient should be observed closely and orthostatic changes measured when calmer.
3. Symptoms of orthostatic hypotension are documented if the individual can verbalize.
4. Ideally one should start to monitor orthostatic changes 1 week before starting oral quetiapine, risperidone or ziprasidone. This will provide a baseline to better interpret changes after drug onset.
5. Pulse and blood pressure are monitored prior to dose administration: (a) for oral medication, monitor for 1 week after starting or increasing the dose and until the psychiatrist decides that the dose is stable; (b) for IM dosing, monitor before each dosing and 30 min after administration.
6. Pulse and blood pressure are recorded first in the seated position after 3 min and then in the standing position after 2 min. If any recorded item lies outside the parameters listed below, the measure is repeated after 15 min. If the item is then within the parameter, the atypical may be given. If it is still outside the parameter, the physician is called to assess the individual before dose administration.
A modification of the scale originally developed for the study by Simpson et al. (1994).

Appendix 2. Drug utilization review: IM aripiprazole

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM ARIPIPRAZOLE</td>
<td>YES NO NA</td>
</tr>
</tbody>
</table>

1. **Indication**: Check one of the following indications for use

- Acute agitation in patients with DSM-IV-TR diagnosis of schizophrenia, bipolar mania or other psychotic disorder.
- In special circumstances (e.g., inability to use oral route, uncooperativeness, etc.) with the idea of switching as soon as possible to oral preparations. An explanatory note in the chart is needed.

To meet indication criteria, at least one indication is present

2. **Dose**:

- The initial dose was not higher than 9.75 mg (or justification was provided).
- The maximum total daily IM dose in the absence of drug-drug interactions was ≤ 30 mg/day. If the highest dosage is > 30 mg/day, to meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.
- The interval between IM injections was ≥ 2 hours.
- Doses account for the need for decreased doses when co-administered with other drugs that inhibit CYP2D6 (paroxetine, bupropion or fluoxetine) or CYP3A (erythromycin, cimetidine or fluvoxamine).
- Doses account for the need for increased doses when co-administered with other drugs that induce CYP3A (carbamazepine, phenytoin, phenobarbital, primidone, some glucocorticoids or rifampin).

To meet dose criteria all are Yes or NA

3. **Adverse drug reactions (ADR) due to IM aripiprazole**: Check left boxes to indicate which ADRs are present

- Long QTc
- Extrapyramidal symptoms
- Sedation
- Activation
- Orthostatism
- Sexourinary
- GI/Nausea or worsening dysphagia
- Seizure
- ↑ AST/ALT
- Other ______________

If any ADR is present check Yes (this prompted some intervention and consideration of risk/benefit for future injections) or No. If no ADRs are present check NA.
Appendix 3. Drug utilization review: IM olanzapine

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IM OLANZAPINE</strong></td>
<td>YES NO NA</td>
</tr>
</tbody>
</table>

1. **Indication**: Check one of the following indications for use
   - Acute agitation in patients with DSM-IV-TR diagnosis of schizophrenia, bipolar mania or other psychotic disorder.
   - In special circumstances (e.g., inability to use oral route, uncooperativeness, etc.) with the idea of switching as soon as possible to oral preparations. An explanatory note in the chart is needed.

   *To meet indication criteria at least one indication is present.*

2. **Dose**:
   - The initial dose was ≤ 2.5 mg or justification was provided.
   - The maximum total daily IM dose in the absence of drug-drug interactions was ≤ 30 mg/day. If the highest dosage is >30 mg/day, to meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.
   - The interval between 10 mg IM injections was repeated no more frequently than two hours after the initial dose and four hours after the second dose.
   - Dose titration took into account orthostatic changes. Orthostatic pulse and blood pressure was monitored prior to all IM doses.

   *To meet dose criteria all are Yes.*

3. **Adverse drug reactions (ADR) due to IM olanzapine**: Check left boxes to indicate which ADRs are present
   - Long QTc
   - Extrapyramidal symptoms
   - Sedation
   - Activation
   - Orthostatism
   - Sexual
   - GI/Nausea or worsening dysphagia
   - Seizure
   - ↑ AST/ALT
   - Other

   *If any ADR is present check Yes (this prompted some intervention and consideration of risk/benefit for future injections) or No. If no ADRs are present check NA.*
Appendix 4. Drug utilization review: IM ziprasidone

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IM ZIPRASIDONE</td>
<td>YES NO NA</td>
<td></td>
</tr>
</tbody>
</table>

1. **Indication**: Check one of the following indications for use
   - [ ] Acute agitation in patients with DSM-IV-TR diagnosis of schizophrenia, bipolar mania or other psychotic disorder.
   - [ ] In special circumstances (e.g., inability to use oral route, uncooperativeness, etc.) with the idea of switching as soon as possible to oral preparations. An explanatory note in the chart is needed.
   
   To meet indication criteria at least one indication is present and oral ziprasidone has been previously used.

2. **Dose**:
   - [ ] The initial dose was not higher than 10 or 20 mg.
   - [ ] The maximum total daily IM dose in the absence of drug-drug interactions was ≤ 40 mg/day. If the highest dosage is > 40 mg/day, to meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.
   - [ ] The interval between IM injections was ≥ 2 hours for 10 mg doses or ≥ 4 hours for 20 mg doses.
   - [ ] Dose titration took into account orthostatic changes. Orthostatic pulse and blood pressure was monitored prior to all IM doses.

   To meet dose criteria all are Yes.

3. **Adverse drug reactions (ADR) due to IM ziprasidone**: Check left boxes to indicate which ADRs are present
   - [ ] Long QTc
   - [ ] Extrapyramidal symptoms
   - [ ] Sedation
   - [ ] Activation
   - [ ] Orthostatism
   - [ ] Sexurinary
   - [ ] GI/Nausea or worsening dysphagia
   - [ ] Seizure
   - [ ] ↑ AST/ALT
   - [ ] Other

   If any ADR is present check Yes (this prompted some intervention and consideration of risk/benefit for future injections) or No. If no ADRs are present check NA.
### Appendix 5. Drug utilization review: oral aripiprazole

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL ARIPIRAZOLE</strong></td>
<td>YES NO NA</td>
</tr>
<tr>
<td><strong>1. Indications:</strong> Check one of the following indications for use</td>
<td></td>
</tr>
<tr>
<td>□ DSM-IV-TR diagnosis of schizophrenia</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ DSM-IV-TR diagnosis of bipolar disorder</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ Severe persistent aggressive or self-injurious behaviors with evidence that behavioral treatment was ineffective</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ An explanatory note in the chart justifying the off-label use for another psychosis including schizoaffective disorder, dementia, depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders or Tourette’s syndrome</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td><strong>To meet indication criteria at least one indication is present</strong></td>
<td>☐ ☐</td>
</tr>
<tr>
<td><strong>2. Dose:</strong></td>
<td></td>
</tr>
<tr>
<td>Oral morning doses (or justification was provided)</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>The initial dose were ≤ 5 mg or justification was provided.</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>The highest dosage was ≤ 30 mg/day. This is the highest recommended dosage in the absence of drug-drug interactions. If the highest dosage is &gt;30 mg/day, to meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>Doses account for the need for decreased doses when co-administered with other drugs that inhibit CYP2D6 (paroxetine, bupropion or fluoxetine) or CYP3A (ketocnazole, erythromycin, or fluvoxamine)</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>Doses account for the need for increased doses when co-administered with other drugs that induce CYP3A (carbamazepine, phenytoin, phenobarbital, primidone, some glucocorticoids or rifampin)</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td><strong>To meet dose criteria all are Yes or NA</strong></td>
<td>☐ ☐</td>
</tr>
<tr>
<td><strong>3. Relative contraindications:</strong> Check any present</td>
<td></td>
</tr>
<tr>
<td>□ Metabolic syndrome or its components are present or there is a high risk for them</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ Concomitant use of medications known to cause elevated blood glucose (e.g., steroids, niacin, thiazide diuretics)</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ Dementia, cerebrovascular disease and conditions that would predispose individuals to hypotension</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ Severe cardiovascular disease, history of myocardial infarction or ischemia, or heart failure</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ History of prolactin-sensitive breast cancer</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ Liver disease, history of hepatitis or treatment with potentially hepatotoxic drugs</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td><strong>If any of the above are checked, rationale is documented in chart to meet relative contraindication criteria. If none are present check NA.</strong></td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td><strong>4. Baseline information:</strong> Check all documented baseline information</td>
<td></td>
</tr>
<tr>
<td>□ Weight and height (with ideal body weight noted)</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ Waist circumference</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ Personal history of high BMI, diabetes mellitus and hyperlipidemia</td>
<td>☐ ☐ ☐</td>
</tr>
<tr>
<td>□ Family history of diabetes mellitus</td>
<td>☐ ☐ ☐</td>
</tr>
</tbody>
</table>
Appendix 5. (Continued)

<table>
<thead>
<tr>
<th>Target Drug Review Criteria</th>
<th>Criteria Met</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Aripiprazole</strong></td>
<td></td>
</tr>
<tr>
<td><em>Answer Yes (all documented) or No.</em></td>
<td></td>
</tr>
</tbody>
</table>

5. Baseline monitoring studies:
- Glycosylated hemoglobin level (Hgb A1C)
- Fasting serum glucose
- Lipid panel
- Electrolytes
- Liver function tests
- Serum prolactin
- DISCUS rating
- EKG
- Vital signs

*Answer Yes (all completed) or No.*

6. Monthly monitoring:
- Monthly weights

*Answer Yes (all monthly weights completed) or No.*

7. Semiannual monitoring:
- Fasting blood glucose
- Lipid panel
- DISCUS rating

*Answer Yes (all completed semiannually) or No.*

8. Annual monitoring:
- Serum prolactin level
- Breast examination
- Sexual/menstrual changes were assessed or was not appropriate to do it
- Waist circumference
- EKG

*Answer Yes (all completed annually) or No.*

9. Actions after metabolic abnormalities develop due to aripiprazole:
- Check left box when weight increases > 5% in 1m, 7.5% in 3 m or 10% in 6 m, or waist circumference increases to > 35 (females) / 40 inches (males) or BMI increases from < 25 to ≥ 25 or from 25-29.9 to ≥ 30. Check Yes/No to indicate that this prompted nutritional consultation.
- Check left box when fasting glucose ≥ 100 mg/dl. Check Yes/No to indicate that this prompted nutritional consultation.
- Check left box when lipid levels become abnormal. Check Yes/No to indicate that this prompted nutritional consultation.
Appendix 5. (Continued)

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL ARIPIPRAZOLE</td>
<td></td>
</tr>
<tr>
<td>Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.</td>
<td></td>
</tr>
<tr>
<td>10. Actions in relation to the development of high prolactin levels and/or related symptoms due to aripiprazole:</td>
<td></td>
</tr>
<tr>
<td>□ Check left box when menstrual cycle changes, or when galactorrhea, gynecomastia or sexual dysfunction occur. Check Yes/No to indicate that this prompted appropriate consideration of risk/benefits.</td>
<td></td>
</tr>
<tr>
<td>□ Check left box when prolactin &gt; 200 ng/ml. Check Yes/No to indicate that this prompted brain MRI and consultation with expert, if needed.</td>
<td></td>
</tr>
<tr>
<td>Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.</td>
<td></td>
</tr>
<tr>
<td>11. Other adverse drug reactions (ADRs) due to aripiprazole: Check left boxes to indicate which ADRs are present</td>
<td></td>
</tr>
<tr>
<td>□ Long QTc</td>
<td>□ Extrapyramidal symptoms</td>
</tr>
<tr>
<td>□ Sedation</td>
<td>□ Activation</td>
</tr>
<tr>
<td>□ Orthostatism</td>
<td>□ Sexuinary</td>
</tr>
<tr>
<td>□ GI/Nausea or worsening dysphagia</td>
<td>□ Seizure</td>
</tr>
<tr>
<td>□ ↑ AST/ALT</td>
<td>□ Other</td>
</tr>
<tr>
<td>Answer Yes (intervention or benefit/risk discussion after ADRs developed) or No (neither intervention nor benefit/risk discussion after ADRs developed). If no ADRs are present check NA.</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 6. Drug utilization review: oral olanzapine

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL OLANZAPINE</strong></td>
<td>YES NO NA</td>
</tr>
</tbody>
</table>

#### 1. Indications: Check one of the following indications for use
- [ ] DSM-IV-TR diagnosis of schizophrenia
- [ ] DSM-IV-TR diagnosis of bipolar disorder
- [ ] Severe persistent aggressive or self-injurious behavior with evidence that behavioral treatment was ineffective
- [ ] An explanatory note in the chart justifying the off-label use for another psychosis including schizoaffective disorder, dementia, depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders or Tourette’s syndrome

*To meet indication criteria at least one indication is present*

#### 2. Dose:
- [ ] Once a day administration
- [ ] The initial doses were ≤ 2.5 mg or justification was provided
- [ ] The highest dosage was ≤ 20 mg/day. This is the highest recommended dosage in the absence of drug-drug interactions. If the highest dosage is >20 mg/day, to meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.
- [ ] Doses account for the need for decreased doses when co-administered with other drugs that inhibit CYP1A2 inhibitors (e.g., fluvoxamine, high dose caffeine, ciprofloxacin, or cimetidine).
- [ ] Doses account for the need for increased doses when co-administered with drug inducers (carbamazepine, phenytoin, omeprazole, Phenobarbital, or rifampin).

*To meet dose criteria all are Yes or NA*

#### 3. Relative contraindications: Check any present
- [ ] Metabolic syndrome or its components are present or there is a high risk for them
- [ ] Concomitant use of medications known to cause elevated blood glucose (e.g., steroids, niacin, thiazide diuretics)
- [ ] Dementia, cerebrovascular disease and conditions that would predispose individuals to hypotension
- [ ] Severe cardiovascular disease, history of myocardial infarction or ischemia, or heart failure
- [ ] History of prolactin-sensitive breast cancer
- [ ] Liver disease, history of hepatitis or treatment with potentially hepatotoxic drugs
- [ ] Olanzapine, due to its potential antimuscarinic activity, should be used with caution in patients with decreased gastrointestinal motility, urinary retention, benign prostate hyperplasia, xerostomia, narrow-angle glaucoma and myasthenia gravis
- [ ] Patients predisposed to hypotension, taking medication with potential to induce hypotension, including some antihypertensives or those with underlying heart disease

*If any of the above are checked, rationale is documented in chart to meet relative contraindication criteria. If none are present check NA.*
### TARGET DRUG REVIEW CRITERIA

<table>
<thead>
<tr>
<th>ORAL OLANZAPINE</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
</tr>
</tbody>
</table>

### 4. Baseline information: Check all documented baseline information

- ☐ Weight and height (with ideal body weight noted)
- ☐ Waist circumference
- ☐ Personal history of high BMI, diabetes mellitus and hyperlipidemia
- ☐ Family history of diabetes mellitus

*Answer Yes (all documented) or No.*

### 5. Baseline monitoring studies:

- ☐ Glycosylated hemoglobin level (Hgb A1C)
- ☐ Fasting serum glucose
- ☐ Lipid panel
- ☐ Electrolytes
- ☐ Liver function tests
- ☐ Serum prolactin
- ☐ DISCUS rating
- ☐ EKG
- ☐ Vital signs

*Answer Yes (all completed) or No.*

### 6. Monthly monitoring:

- ☐ Monthly weights

*Answer Yes (all monthly weights completed) or No.*

### 7. Semiannual monitoring:

- ☐ Fasting blood glucose
- ☐ Lipid panel
- ☐ DISCUS rating

*Answer Yes (all completed semiannually) or No.*

### 8. Annual monitoring:

- ☐ Serum prolactin level
- ☐ Breast examination
- ☐ Sexual/menstrual changes were assessed or was not appropriate to do it
- ☐ Waist circumference
- ☐ EKG

*Answer Yes (all completed annually) or No.*

### 9. Actions after metabolic abnormalities develop due to olanzapine:
### Appendix 6. (Continued)

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL OLanzAPINE</strong></td>
<td>YES NO NA</td>
</tr>
</tbody>
</table>

- Check left box when weight increases > 5% in 1m, 7.5% in 3 m or 10% in 6 m, or waist circumference increases to > 35 (females) / 40 inches (males) or BMI increases from < 25 to ≥ 25 or from 25-29.9 to ≥ 30. Check Yes/No to indicate that this prompted nutritional consultation.

- Check left box when fasting glucose ≥ 100 mg/dl. Check Yes/No to indicate that this prompted nutritional consultation.

- Check left box when lipid levels become abnormal. Check Yes/No to indicate that this prompted nutritional consultation.

Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.

### 10. Actions in relation to the development of high prolactin levels and/or related symptoms due to olanzapine:

- Check left box when menstrual cycle changes, or when galactorrhea, gynecomastia or sexual dysfunction occur. Check Yes/No to indicate that this prompted appropriate consideration of risk/benefits.

- Check left box when prolactin > 200 ng/ml. Check Yes/No to indicate that this prompted brain MRI and consultation with expert, if needed.

Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.

### 11. Other adverse drug reactions (ADRs) due to olanzapine:

Check left boxes to indicate which ADRs are present

- Long QTc
- Sedation
- Orthostatism
- GI/Nausea or worsening dysphagia
- ↑ AST/ALT

Extrapyramidal symptoms
Activation
Secourinary
Seizure
Other__________

Answer Yes (intervention or benefit/risk discussion after ADRs developed) or No (neither intervention nor benefit/risk discussion after ADRs developed) or NA (because no ADR developed).
Appendix 7. Drug utilization review: oral paliperidone

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL PALIPERIDONE</td>
<td>YES NO NA</td>
</tr>
</tbody>
</table>

1. **Indications**: Check one of the following indications for use

- [ ] DSM-IV-TR diagnosis of schizophrenia
- [ ] DSM-IV-TR diagnosis of bipolar disorder
- [ ] Severe persistent aggressive or self-injurious behaviors with evidence that behavioral treatment was ineffective
- [ ] A thoughtful note in the chart justifying the off-label use for another psychosis including schizoaffective disorder, dementia, depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders or Tourette’s syndrome

To meet indication criteria at least one indication is present

2. **Dose**:

- The tablets were not divided or crushed.
- The initial dose was ≤ 6 mg administered in the morning. Other initial doses were justified.
- The highest dosage was ≤ 12 mg/day. If the highest dosage is >12 mg/day, to meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.
- Lower doses were used for renal impairment. For mild impairment (≥ 50 ml/min to 80 ml/min) recommended doses are 6 mg/day. For moderate to severe impairment (≥ 10 ml/min to < 50 ml/min) recommended doses are 3 mg/day.

To meet dose criteria all are Yes or NA.

3. **Relative contraindications**: Check any present

- [ ] Metabolic syndrome or its components are present or there is a high risk for them
- [ ] Concomitant use of medications known to cause elevated blood glucose (e.g., steroids, niacin, thiazide diuretics)
- [ ] Dementia, cerebrovascular disease and conditions that would predispose individuals to hypotension
- [ ] Severe cardiovascular disease, history of myocardial infarction or ischemia, or heart failure
- [ ] History of prolactin-sensitive breast cancer
- [ ] Liver disease, history of hepatitis or treatment with potentially hepatotoxic drugs

If any of the above are checked, rationale is documented in chart to meet relative contraindication criteria. If none are present check NA.

4. **Baseline information**: Check all documented baseline information

- [ ] Weight and height (with ideal body weight noted)
- [ ] Waist circumference
- [ ] Personal history of high BMI, diabetes mellitus and hyperlipidemia
- [ ] Family history of diabetes mellitus

Answer Yes (all documented) or No.
<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL PALIPERIDONE</td>
<td>YES NO NA</td>
</tr>
</tbody>
</table>

5. Baseline monitoring studies:
- Glycosylated hemoglobin level (Hgb A1C)
- Fasting serum glucose
- Lipid panel
- Electrolytes
- Liver function tests
- Serum prolactin
- DISCUS rating
- EKG
- Vital signs
- When patient has low renal function: creatinine clearance

*Answer Yes (all completed) or No.*

6. Monthly monitoring:
- Monthly weights

*Answer Yes (all monthly weights completed) or No.*

7. Semiannual monitoring:
- Fasting serum glucose
- Lipid panel
- DISCUS rating

*Answer Yes (all completed semiannually) or No.*

8. Annual monitoring:
- Serum prolactin level
- Breast examination
- Sexual/menstrual changes were assessed or was not appropriate to do it
- Waist circumference
- EKG

*Answer Yes (all completed annually) or No.*

9. Actions after metabolic abnormalities develop due to paliperidone:
- Check left box when weight increases > 5% in 1m, 7.5% in 3 m or 10% in 6 m, or waist circumference increases to > 35 (females) / 40 inches (males) or BMI increases from < 25 to ≥ 25 or from 25-29.9 to ≥ 30. Check Yes/No to indicate that this prompted nutritional consultation.
- Check left box when fasting glucose ≥ 100 mg/dl. Check Yes/No to indicate that this prompted nutritional consultation.
- Check left box when lipid levels become abnormal. Check Yes/No to indicate that this prompted nutritional consultation.
### Appendix 7. (Continued)

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL PALIPERIDONE</strong></td>
<td>YES NO NA</td>
</tr>
</tbody>
</table>

*Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.*

<table>
<thead>
<tr>
<th>10. Actions in relation to the development of high prolactin levels and/or related symptoms due to paliperdone:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Check left box when menstrual cycle changes, or when galactorrhea, gynecomastia or sexual dysfunction occur. Check Yes/No to indicate that this prompted appropriate consideration of risk/benefits.</td>
</tr>
<tr>
<td>□ Check left box when prolactin &gt; 200 ng/ml. Check Yes/No to indicate that this prompted brain MRI and consultation with expert, if needed.</td>
</tr>
</tbody>
</table>

*Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.*

<table>
<thead>
<tr>
<th>11. Other adverse drug reactions (ADRs) due to paliperdone: Check left boxes to indicate which ADRs are present</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Long QTc □ Extrapyramidal symptoms</td>
</tr>
<tr>
<td>□ Sedation □ Activation</td>
</tr>
<tr>
<td>□ Orthostatism □ Sexourinary</td>
</tr>
<tr>
<td>□ GI/Nausea or worsening dysphagia □ Seizure</td>
</tr>
<tr>
<td>□ ↑ AST/ALT □ Other</td>
</tr>
</tbody>
</table>

*Answer Yes (intervention or benefit/risk discussion after ADRs developed) or No (neither intervention nor benefit/risk discussion after ADRs developed). If no ADRs are present check NA.*
### Appendix 8. Drug utilization review: oral quetiapine

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL QUETIAPINE</strong></td>
<td></td>
</tr>
<tr>
<td>1. Indications: Check one of the following indications for use</td>
<td>YES NO NA</td>
</tr>
<tr>
<td>DSM-IV-TR diagnosis of schizophrenia</td>
<td></td>
</tr>
<tr>
<td>DSM-IV-TR diagnosis of bipolar disorder</td>
<td></td>
</tr>
<tr>
<td>Severe persistent aggressive or self-injurious behaviors with evidence that behavioral treatment was ineffective</td>
<td></td>
</tr>
<tr>
<td>An explanatory note in the chart justifying the off-label use for another psychosis including schizoaffective disorder, dementia, depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders or Tourette’s syndrome</td>
<td></td>
</tr>
<tr>
<td>To meet indication criteria at least one indication is present</td>
<td></td>
</tr>
<tr>
<td>2. Dose:</td>
<td></td>
</tr>
<tr>
<td>Oral quetiapine is administered on a BID schedule (unless justification is provided)</td>
<td></td>
</tr>
<tr>
<td>Seroquel XR is administered once a day in the evening, without food or with a light meal, and the tablets were not split or crushed.</td>
<td></td>
</tr>
<tr>
<td>The initial dose was ≤ 25 mg BID or justification was provided.</td>
<td></td>
</tr>
<tr>
<td>Seroquel XL initial dose was ≤ 300 mg/day.</td>
<td></td>
</tr>
<tr>
<td>Patients on quetiapine were switched to the equivalent total daily dosage of Seroquel XR taken once daily.</td>
<td></td>
</tr>
<tr>
<td>Dose titration took into account orthostatic changes. Orthostatic pulse and blood pressure were monitored prior to oral dose administration for one week after starting or increasing the dosage and until the psychiatrist decided that the dose was stable.</td>
<td></td>
</tr>
<tr>
<td>The highest dosage for quetiapine or Seroquel XL was ≤ 800 mg/day. If the highest dosage is &gt; 800 mg/day, to meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.</td>
<td></td>
</tr>
<tr>
<td>To meet dose criteria all are Yes or NA.</td>
<td></td>
</tr>
<tr>
<td>3. Relative contraindications: Check any present</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome or its components are present or there is a high risk for them</td>
<td></td>
</tr>
<tr>
<td>Concomitant use of medications known to cause elevated blood glucose (e.g., steroids, niacin, thiazide diuretics)</td>
<td></td>
</tr>
<tr>
<td>Dementia, cerebrovascular disease and conditions that would predispose individuals to hypotension</td>
<td></td>
</tr>
<tr>
<td>Severe cardiovascular disease, history of myocardial infarction or ischemia, or heart failure</td>
<td></td>
</tr>
<tr>
<td>History of prolactin-sensitive breast cancer</td>
<td></td>
</tr>
<tr>
<td>Liver disease, history of hepatitis or treatment with potentially hepatotoxic drugs</td>
<td></td>
</tr>
<tr>
<td>Patient is predisposed to hypotension, taking medication with potential to induce hypotension, including some antihypertensives or those with underlying heart disease.</td>
<td></td>
</tr>
<tr>
<td>If any of the above are checked, rationale is documented in chart to meet relative contraindication criteria. If none are present check NA.</td>
<td></td>
</tr>
<tr>
<td>4. Baseline information: Check all documented baseline information</td>
<td></td>
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</tbody>
</table>
Appendix 8. (Continued)

<table>
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<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL QUETIAPINE</td>
<td>YES NO NA</td>
</tr>
</tbody>
</table>

- Weight and height (with ideal body weight noted)
- Waist circumference
- Personal history of high BMI, diabetes mellitus and hyperlipidemia
- Family history of diabetes mellitus

Answer Yes (all documented) or No.

5. Baseline monitoring studies:
- Glycosylated hemoglobin level (Hgb A1C)
- Fasting serum glucose
- Lipid panel
- Electrolytes
- Liver function tests
- Serum prolactin
- DISCUS rating
- EKG
- Vital signs

Answer Yes (all completed) or No.

6. Monthly monitoring:
- Monthly weights

Answer Yes (all monthly weights completed) or No.

7. Semiannual monitoring:
- Fasting serum glucose
- Lipid panel
- DISCUS rating

Answer Yes (all completed semiannually) or No.

8. Annual monitoring:
- Serum prolactin level
- Breast examination
- Sexual/menstrual changes were assessed or was not appropriate to do it
- Waist circumference
- EKG

Answer Yes (all completed annually) or No.

9. Actions after metabolic abnormalities develop due to quetiapine:
- Check left box when weight increases > 5% in 1m, 7.5% in 3 m or 10% in 6 m, or waist circumference increases to > 35 (females) / 40 inches (males) or BMI increases from < 25 to ≥ 25 or from 25-29.9 to ≥ 30. Check Yes/No
### Appendix 8. (Continued)

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL QUETIAPINE</td>
<td>YES NO NA</td>
</tr>
<tr>
<td>to indicate that this prompted nutritional consultation.</td>
<td></td>
</tr>
<tr>
<td>☐ Check left box when fasting glucose ≥ 100 mg/dl. Check Yes/No to indicate that this prompted nutritional consultation.</td>
<td></td>
</tr>
<tr>
<td>☐ Check left box when lipid levels become abnormal. Check Yes/No to indicate that this prompted nutritional consultation.</td>
<td></td>
</tr>
<tr>
<td>Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.</td>
<td></td>
</tr>
<tr>
<td>10. Actions in relation to the development of high prolactin levels and/or related symptoms due to quetiapine:</td>
<td></td>
</tr>
<tr>
<td>☐ Check left box when menstrual cycle changes, or when galactorrhea, gynecomastia or sexual dysfunction occur. Check Yes/No to indicate that this prompted appropriate consideration of risk/benefits.</td>
<td></td>
</tr>
<tr>
<td>☐ Check left box when prolactin &gt; 200 ng/ml. Check Yes/No to indicate that this prompted brain MRI and consultation with expert, if needed.</td>
<td></td>
</tr>
<tr>
<td>Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.</td>
<td></td>
</tr>
<tr>
<td>11. Other adverse drug reactions (ADRs) due to quetiapine: Check left boxes to indicate which ADRs are present</td>
<td></td>
</tr>
<tr>
<td>☐ Long QTc</td>
<td>☐ Extrapyramidal symptoms</td>
</tr>
<tr>
<td>☐ Sedation</td>
<td>☐ Activation</td>
</tr>
<tr>
<td>☐ Orthostatism</td>
<td>☐ Sexourinary</td>
</tr>
<tr>
<td>☐ GI/Nausea or worsening dysphagia</td>
<td>☐ Seizure</td>
</tr>
<tr>
<td>☐ ↑ AST/ALT</td>
<td>☐ Other _____</td>
</tr>
<tr>
<td>Answer Yes (intervention or benefit/risk discussion after ADRs developed) or No (neither intervention nor benefit/risk discussion after ADRs developed). If no ADRs are present check NA.</td>
<td></td>
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</tbody>
</table>
## Appendix 9. Drug utilization review: oral risperidone

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL RISPERIDONE</strong></td>
<td>YES</td>
</tr>
</tbody>
</table>

### 1. Indications: Check one of the following indications for use

- [ ] DSM-IV-TR diagnosis of schizophrenia
- [ ] DSM-IV-TR diagnosis of bipolar disorder
- [ ] Severe persistent aggressive or self-injurious behaviors with evidence that behavioral treatment was ineffective
- [ ] An explanatory note in the chart justifying the off-label use for another psychosis including schizoaffective disorder, dementia, depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders or Tourette’s syndrome

*To meet indication criteria at least one indication is present*  

- [ ]
- [ ]

### 2. Dose:

- The initial doses were ≤ 1-2 mg/d or justification was provided.  
  - [ ]
  - [ ]
  - [ ]

- Dose titration took into account orthostatic changes. Orthostatic pulse and blood pressure was monitored prior to oral dose administration for one week after starting or increasing the dosage and until the psychiatrist decided that the dose was stable.  
  - [ ]
  - [ ]

- The highest dosage was ≤ 8 mg/day. If the highest dosage is > 8 mg/day, to meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.  
  - [ ]
  - [ ]

- Doses account for the need for decreased doses when co-administered with other drugs that inhibit CYP2D6 (paroxetine, bupropion or fluoxetine) or CYP3A (ketoconazole, erythromycin, or fluvoxamine).  
  - [ ]
  - [ ]
  - [ ]

- Doses account for the need for increased doses when co-administered with other drugs that induce CYP3A (carbamazepine, phenytoin, phenobarbital, primidone, some glucocorticoids or rifampin).  
  - [ ]
  - [ ]
  - [ ]

- Doses account for the need for decreased doses in elderly or debilitated patients, patients with severe renal or hepatic impairment, and in patients predisposed to hypotension or for whom hypotension would pose a risk.  
  - [ ]
  - [ ]

*To meet dose criteria all are Yes or NA.*

### 3. Relative contraindications: Check any present

- [ ] Metabolic syndrome or its components are present or there is a high risk for them.
- [ ] Concomitant use of medications known to cause elevated blood glucose (e.g., steroids, niacin, thiazide diuretics).
- [ ] Dementia, cerebrovascular disease and conditions that would predispose individuals to hypotension.
- [ ] Severe cardiovascular disease, history of myocardial infarction or ischemia, or heart failure.
- [ ] History of prolactin-sensitive breast cancer
- [ ] Liver disease, history of hepatitis or treatment with potentially hepatotoxic drugs.
- [ ] Patient is predisposed to hypotension, taking medication with potential to induce hypotension, including some antihypertensives or those with underlying heart disease.
<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL RISPERIDONE</strong></td>
<td>YES NO NA</td>
</tr>
<tr>
<td>If any of the above are checked, rationale is documented in chart to meet relative contraindication criteria. If none are present check NA.</td>
<td>☐ ☐ ☐</td>
</tr>
</tbody>
</table>

### 4. Baseline information: Check all documented baseline information

- ☐ Weight and height (with ideal body weight noted)
- ☐ Waist circumference
- ☐ Personal history of high BMI, diabetes mellitus and hyperlipidemia
- ☐ Family history of diabetes mellitus

*Answer Yes (all documented) or No.*

- ☐ ☐

### 5. Baseline monitoring studies:

- ☐ Glycosylated hemoglobin level (Hgb A1C)
- ☐ Fasting serum glucose
- ☐ Lipid panel
- ☐ Electrolytes
- ☐ Liver function tests
- ☐ Serum prolactin
- ☐ DISCUS rating
- ☐ EKG
- ☐ Vital signs
- ☐ When patient has low renal function: creatinine clearance

*Answer Yes (all completed) or No.*

- ☐ ☐

### 6. Monthly monitoring:

- ☐ Monthly weights

*Answer Yes (all monthly weights completed) or No.*

- ☐ ☐

### 7. Semiannual monitoring:

- ☐ Fasting serum glucose
- ☐ Lipid panel
- ☐ DISCUS rating

*Answer Yes (all completed semiannually) or No.*

- ☐ ☐

### 8. Annual monitoring:

- ☐ Serum prolactin level
- ☐ Breast examination
- ☐ Sexual/menstrual changes were assessed or was not appropriate to do it
- ☐ Waist circumference
- ☐ EKG
### Appendix 9. (Continued)

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL RISPERIDONE</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Answer Yes (all completed annually) or No.**

9. Actions after metabolic abnormalities develop due to risperidone:

- Check left box when weight increases > 5% in 1m, 7.5% in 3 m or 10% in 6 m, or waist circumference increases to > 35 (females) / 40 inches (males) or BMI increases from < 25 to ≥ 25 or from 25-29.9 to ≥ 30. Check Yes/No to indicate that this prompted nutritional consultation.

- Check left box when fasting glucose ≥ 100 mg/dl. Check Yes/No to indicate that this prompted nutritional consultation.

- Check left box when lipid levels become abnormal. Check Yes/No to indicate that this prompted nutritional consultation.

**Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.**

10. Actions in relation to the development of high prolactin levels and/or related symptoms due to risperidone:

- Check left box when menstrual cycle changes, or when galactorrhea, gynecomastia or sexual dysfunction occur. Check Yes/No to indicate that this prompted appropriate consideration of risk/benefits.

- Check left box when prolactin > 200 ng/ml. Check Yes/No to indicate that this prompted brain MRI and consultation with expert, if needed.

**Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.**

11. Other adverse drug reactions (ADRs) due to risperidone:

*Check left boxes to indicate which ADRs are present*

- Long QTc
- Sedation
- Orthostatism
- GI/Nausea or worsening dysphagia
- ↑ AST/ALT
- Extrapyramidal symptoms
- Activation
- Sexuinary
- Seizure
- Other

**Answer Yes (intervention or benefit/risk discussion after ADRs developed) or No (neither intervention nor benefit/risk discussion after ADRs developed). If no ADRs are present check NA.**
Appendix 10. Drug utilization review: long-acting risperidone

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>LONG-ACTING RISPERIDONE INJECTION</td>
<td>YES NO NA</td>
</tr>
</tbody>
</table>

1. Dose:
- Tolerability is established with an oral dose prior to initiating treatment with intramuscular injections (indications, relative contraindications and baseline laboratory studies were considered when starting oral risperidone).
- Injections in the gluteal muscle were ordered.
- If patient can tolerate 2 mg/day of oral risperidone, the initial dose was ≤25 mg every two weeks. If patient was taking < 2 mg/day of oral risperidone, the initial dose was ≤12.5 mg every two weeks.
- Oral risperidone was continued for three weeks after the first injection.
- There was an attempt to monitor orthostatic changes for the first 3 weeks after adding the first injection and, if there were signs of hypotension, the oral dose was decreased to compensate for the progressive increase of blood levels released from long-acting injection.
- The highest dosage was 50 mg q 2 weeks. If the highest dosage is 50 mg q 2 weeks. To meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.
- Doses account for the need for decreased doses when co-administered with other drugs that inhibit CYP2D6 (paroxetine, bupropion or fluoxetine) or CYP3A (ketoconazole, erythromycin, or fluvoxamine).
- Doses account for the need for increased doses when co-administered with other drugs that induce CYP3A (carbamazepine, phenytoin, phenobarbital, primidone, some glucocorticoids or rifampin).
- Doses account for the need for decreased doses in elderly or debilitated patients, patients with severe renal or hepatic impairment, and in patients predisposed to hypotension or for whom hypotension would pose a risk.

*To meet dose criteria all are Yes or NA.*

2. Monthly monitoring:
- ☐ Monthly weights

*Answer Yes (all monthly weights completed) or No.*

3. Semiannual monitoring:
- ☐ Fasting blood glucose
- ☐ Lipid panel
- ☐ DISCUS rating

*Answer Yes (all completed semiannually) or No.*

4. Annual monitoring:
- ☐ Serum prolactin level
- ☐ Breast examination
- ☐ Sexual/menstrual changes were assessed or was not appropriate to do it
- ☐ Waist circumference
### Appendix 10. (Continued)

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LONG-ACTING RISPERIDONE INJECTION</strong></td>
<td>YES</td>
</tr>
<tr>
<td>□ EKG</td>
<td></td>
</tr>
</tbody>
</table>

*Answer Yes (all completed annually) or No.*

5. **Actions after metabolic abnormalities develop due to long-acting risperidone injections:**

- Check left box when weight increases ≥ 5% in 1m, 7.5% in 3m or 10% in 6m, or waist circumference increases to ≥ 35 (females) / 40 inches (males) or BMI increases from < 25 to ≥ 25 or from 25-29.9 to ≥ 30. Check Yes/No to indicate that this prompted nutritional consultation.

- Check left box when fasting glucose ≥ 100 mg/dl. Check Yes/No to indicate that this prompted nutritional consultation.

- Check left box when lipid levels become abnormal. Check Yes/No to indicate that this prompted nutritional consultation.

*Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.*

6. **Actions in relation to the development of high prolactin levels and/or related symptoms due to long-acting risperidone injections:**

- Check left box when menstrual cycle changes, or when galactorrhea, gynecomastia or sexual dysfunction occur. Check Yes/No to indicate that this prompted appropriate consideration of risk/benefits.

- Check left box when prolactin > 200 ng/ml. Check Yes/No to indicate that this prompted brain MRI and consultation with expert, if needed.

*Answer Yes (intervention after abnormality developed) or No (no intervention after abnormality developed). If no abnormality developed check NA.*

7. **Other adverse drug reactions (ADRs) due to long-acting risperidone injections:** Check left boxes to indicate which ADRs are present

- Long QTc
- Sedation
- Orthostatism
- GI/Nausea or worsening dysphagia
- ↑ AST/ALT

- Extrapyramidal symptoms
- Activation
- Sexuinary
- Seizure
- Other

*Answer Yes (intervention or benefit/risk discussion after ADRs developed) or No (neither intervention nor benefit/risk discussion after ADRs developed). If no ADRs are present check NA.*
Appendix 11. Drug utilization review: oral ziprasidone

<table>
<thead>
<tr>
<th>TARGET DRUG REVIEW CRITERIA</th>
<th>CRITERIA MET</th>
</tr>
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<tbody>
<tr>
<td>ORAL ZIPRASIDONE</td>
<td>YES NO NA</td>
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</tbody>
</table>

1. Indications: Check one of the following indications for use

☐ DSM-IV-TR diagnosis of schizophrenia
☐ DSM-IV-TR diagnosis of bipolar disorder
☐ Severe persistent aggressive or self-injurious behaviors with evidence that behavioral treatment was ineffective
☐ An explanatory note in the chart justifying the off-label use for another psychosis including schizoaffective disorder, dementia, depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders or Tourette’s syndrome

To meet indication criteria at least one indication is present ☐ ☐ ☐

2. Dose:

☐ Oral ziprasidone is administered with food and on a BID schedule (or justification is provided)
☐ The initial doses were ≤ 20 mg BID or justification was provided.
☐ Dose titration took into account orthostatic changes. Orthostatic pulse and blood pressure was monitored prior to oral dose administration for one week after starting or increasing the dosage and until the psychiatrist decided that the dose was stable.
☐ The highest dosage was ≤ 200 mg/day. If the highest dosage is > 200 mg/day, to meet the criteria the psychiatrist needs to document in the chart the explanation for using higher doses.

To meet dose criteria all are Yes or NA. ☐ ☐ ☐

3. Relative contraindications: Check any present

☐ Metabolic syndrome or its components are present or there is a high risk for them.
☐ Concomitant use of medications known to cause elevated blood glucose (e.g., steroids, niacin, thiazide diuretics)
☐ Dementia, cerebrovascular disease and conditions that would predispose individuals to hypotension
☐ Severe cardiovascular disease, history of myocardial infarction or ischemia, or heart failure
☐ History of prolactin-sensitive breast cancer
☐ Liver disease, history of hepatitis or treatment with potentially hepatotoxic drugs
☐ History of sudden death in the family, personal history of syncope, cardiovascular disease or electrolyte abnormalities that may contribute to QTc prolongation. Serum electrolyte abnormalities (e.g., low potassium) should be corrected before starting ziprasidone.
☐ Patient is predisposed to hypotension, taking medication with potential to induce hypotension, including some antihypertensives or those with underlying heart disease.

If any of the above are checked, rationale is documented in chart to meet relative contraindication criteria. If none are present check NA. ☐ ☐ ☐

4. Baseline information: Check all documented baseline information
### Appendix 11. (Continued)

<table>
<thead>
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<td></td>
</tr>
</tbody>
</table>

- [ ] Weight and height (with ideal body weight noted)
- [ ] Waist circumference
- [ ] Personal history of high BMI, diabetes mellitus and hyperlipidemia
- [ ] Family history of diabetes mellitus

*Answer Yes (all documented) or No.*

#### 5. Baseline monitoring studies:

- [ ] Glycosylated hemoglobin level (Hgb A1C)
- [ ] Fasting serum glucose
- [ ] Lipid panel
- [ ] Electrolytes
- [ ] Liver function tests
- [ ] Serum prolactin
- [ ] DISCUS rating
- [ ] EKG
- [ ] Vital signs

*Answer Yes (all completed) or No.*

#### 6. Monthly monitoring:

- [ ] Monthly weights

*Answer Yes (all monthly weights completed) or No.*

#### 7. Semiannual monitoring:

- [ ] Fasting serum glucose
- [ ] Lipid panel
- [ ] DISCUS rating
- [ ] EKG (or completed at maximum ziprasidone dose)

*Answer Yes (all completed semiannually) or No.*

#### 8. Annual monitoring:

- [ ] Serum prolactin level
- [ ] Breast examination
- [ ] Sexual/menstrual changes were assessed or was not appropriate to do it
- [ ] Waist circumference
- [ ] EKG

*Answer Yes (all completed annually) or No.*

#### 9. Actions after metabolic abnormalities develop due to ziprasidone:

- [ ] Check left box when weight increases > 5% in 1m, 7.5% in 3 m or 10% in 6
### References


