Atypical Antipsychotic Medications: Use in Adults

The Centers for Medicare & Medicaid Services (CMS) Medicaid Integrity Group (MIG) has identified issues with the utilization of the atypical antipsychotic, or second-generation antipsychotic (SGA), drug therapy class. The U.S. Food and Drug Administration (FDA) approves product labeling for prescription drugs. The MIG has identified that some providers may have prescribed atypical antipsychotics outside of FDA-approved product labeling for indication, age, dosage, or duration of therapy. Therefore, CMS' goal is to improve quality of care and enhance patient safety by educating providers on the proper use of atypical antipsychotics in adults.

This fact sheet summarizes the current FDA-approved product labeling for the use of atypical antipsychotic medications in adults. After reading this fact sheet, the provider should be able to accurately:

- Describe the FDA-approved indications for the use of atypical antipsychotics in adult patients;
- Formulate treatment regimens that comply with FDA-approved product labeling; and
- Describe the adverse reactions and risks associated with atypical antipsychotic therapy in adult patients.

First generation and atypical antipsychotics are dopamine receptor antagonists. The main difference between the two classes is that atypical antipsychotics also antagonize norepinephrine and serotonin (5-HT) receptors to varying degrees, which may help reduce the likelihood of extrapyramidal symptoms.

FDA-Approved Indications for Atypical Antipsychotic Medications in Adults

The FDA-approved adult indications for atypical antipsychotics are summarized in Table 1. The FDA-approved adult indications and dosages for atypical antipsychotics are provided in the document "Atypical Antipsychotics: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults" available at https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/atyp-antipsych-education.html on the CMS website.

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Table 1. FDA-Approved Adult Indications for Atypical Antipsychotics

Indications	Atypical Antipsychotics
bipolar I disorder	aripiprazole,[1, 2] asenapine,[3] olanzapine,[4] quetiapine,[5] quetiapine extended-release (XR),[6] risperidone,[7] ziprasidone[8]
bipolar depression	lurasidone,[9] olanzapine, quetiapine, quetiapine XR
schizophrenia	aripiprazole, asenapine, brexpiprazole,[10] clozapine,[11, 12] clozapine oral suspension,[13] iloperidone,[14] lurasidone, olanzapine, paliperidone,[15] quetiapine, quetiapine XR, risperidone, ziprasidone
schizoaffective disorder	clozapine, paliperidone
major depressive disorder (MDD), adjunct	aripiprazole (Abilify®), brexpiprazole, olanzapine, quetiapine XR

Treatment Guidelines for the Use of Atypical Antipsychotics in Adults

The Agency for Healthcare Research and Quality (AHRQ) hosts a database of treatment guidelines. The AHRQ is a branch of the U.S. Department of Health and Human Services. For information on the available treatment guidelines, search "atypical antipsychotics" or any of the conditions for which an atypical antipsychotic is an indicated treatment in the AHRQ's National Guideline Clearinghouse at https://www.guideline.gov on the Internet. Links to some of the guidelines that provide information on the use of atypical antipsychotics in adults are provided in Table 2.

Table 2. Treatment Guidelines for the Use of Atypical Antipsychotics in Adults

Sponsoring Organization	Title of Guideline	Link to Guideline
American Psychiatric Association	Practice guideline for the psychiatric evaluation of adults. [2006]	https://www.guideline.gov/content.aspx?id=9317
Department of Veterans Affairs (VA), Department of Defense (DoD)	VA/DoD clinical practice guideline for management of bipolar disorder in adults. [2010]	https://www.guideline.gov/content.aspx?id=16314

Time to Symptom Improvement with an Atypical Antipsychotic Medication

Many patients will experience relief of some symptoms within a few days of starting treatment with an atypical antipsychotic, but the full effects of the medication may not be seen for up to 6 weeks. Agitation and hallucinations are typically relieved during the first few days of treatment, but it may take weeks for delusions to subside. Every patient responds differently to antipsychotic therapy, so it may take several trials of different antipsychotic medications to find the one that works best.[16] The titration schedule of the medication may also influence the length of time it takes to see symptom improvement: a medication that takes 2 weeks to reach the recommended dose may require a longer trial than a medication that takes less than 1 week to reach the recommended dose.

If a patient does not achieve the desired clinical response, the dose of the atypical antipsychotic may need to be increased or the medication may need to be changed to a different antipsychotic medication. Treatment guidelines can provide guidance about when a change in therapy is warranted. Factors for switching medication therapy include:

- Lack of efficacy;
- Lack of improvement in negative symptoms;
- Presence of extrapyramidal side effects (EPS) or adverse reactions impacting adherence to therapy; and
- Cost of therapy.

Patient adherence to therapy should also be assessed prior to increasing dosage, switching to a different antipsychotic, or prescribing an additional medication. If the patient has had trouble complying with treatment in the past, a long-acting injectable medication may be the best option. The patient should still be evaluated for symptom improvement during the effective duration of the long-acting injectable medication to assess its efficacy.

ACRONYMS

5-HT	serotonin
AHRQ	Agency for Healthcare Research and Quality
ANC	absolute neutrophil count
CDER	Center for Drug Evaluation and Research
CMS	Centers for Medicare & Medicaid Services
DoD	Department of Defense
EPS	extrapyramidal side effects
FDA	U.S. Food and Drug Administration
MDD	major depressive disorder
MIG	Medicaid Integrity Group
MPIE	Medicaid Program Integrity Education
NNRMF	Non-Rechallenge Master File
OTC	over the counter
REMS	risk evaluation and mitigation strategy
SGA	second-generation antipsychotic
VA	Department of Veterans Affairs
WBC	white blood cell

Off-Label Use of Atypical Antipsychotics in Adults

In September 2011, the AHRQ released "Off-Label Use of Atypical Antipsychotics: An Update."[17] After the initial 2007 version of the report was published, studies on off-label indications were published, and the FDA approved certain previously off-label indications. Safety and efficacy were evaluated and a summary of the findings for each off-label indication is provided in the 2011 update, which is available at http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=778&PCem=EN on the AHRQ website.

Pregnancy Registry

Some atypical antipsychotics did not include pregnant women in their clinical trials and indicate in the prescribing information that safety and efficacy for that population group has not been established. As a precaution, however, the prescribing information for a few atypical antipsychotic medications includes contact information for the Massachusetts General Hospital's National Pregnancy Registry for Psychiatric Medications. For more information, visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry on the Internet or call 866-961-2388.

Adverse Reactions and Risks of the Use of Atypical Antipsychotic in Adults

Patients should be made aware of the risks of taking an atypical antipsychotic prior to initiating therapy. Because atypical antipsychotic medications are associated with significant weight gain and metabolic changes, a baseline for weight, blood glucose level, and lipid panel should be established and then monitored.[18] Other common adverse reactions are:

- Drowsiness;
- Orthostatic hypotension;
- Tachycardia;
- Menstrual problems;
- Blurred vision;
- Sun sensitivity; and
- Skin rash.[19]

Risk of Suicidality

The atypical antipsychotics aripiprazole, brexpiprazole, lurasidone, olanzapine, quetiapine, and quetiapine XR are FDA approved for the treatment of depression episodes in bipolar I disorder or as adjunctive treatment for MDD. Antidepressant medications have been shown to increase the risk of suicidal thinking and behavior. In pooled analyses of short-term, placebo-controlled trials of nine antidepressant medications, patients taking an antidepressant had twice the risk of suicidality in the first few months of treatment than those taking placebo. The long-term risk is unknown. As a result of this analysis, a boxed warning was added to all antidepressant medications since the risk was not confined to one class of antidepressants.[20]

The boxed warnings for ariprazole and quetiapine are similar. Aripiprazole's boxed warning states:[21]

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS AND SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.2)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.2)]*.

The FDA also requires that a Medication Guide be provided with each aripiprazole, olanzapine, quetiapine, and quetiapine XR prescription to alert patients to the risk of suicidal thinking and behavior. Each Medication Guide includes information on precautions that may be taken. Links to the required Medication Guides can be found at http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm on the FDA website.

Use in Elderly Patients with Dementia

None of the atypical antipsychotic medications are FDA approved for treating behavioral disorders in elderly patients with dementia. A warning was added to product labeling for certain atypical antipsychotic drugs to describe this increased risk of mortality and to note that atypical antipsychotics are not approved for this indication.[22] Some labels for atypical antipsychotics have an abbreviated black box warning for this indication and, with one exception,[23] refer to the full text in the Warnings and Precautions section of the label.[24] The rest have the full text in the black box warning itself.[25]

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen [17] placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. [Established medication name] is not approved for the treatment of patients with dementia-related psychosis.

Risk of Serious Allergic Reactions with Asenapine

On September 1, 2011, the FDA published a Drug Safety Communication to alert the public to the risk of serious allergic reactions with asenapine. The allergic reactions are Type I hypersensitivity reactions that may include anaphylaxis, angioedema, difficulty breathing, hypotension, rash, swollen tongue, tachycardia, or wheezing. Patients should be counseled on the signs and symptoms of an allergic reaction and should be instructed to seek immediate medical attention if signs or symptoms occur.[26]

Post-Injection Delirium and Sedation with Olanzapine Pamoate Injection

Olanzapine pamoate injection is a long-acting atypical antipsychotic. It has been associated with delirium and sedation, typically seen in a patient with an olanzapine overdose. Because of the severity of this potential adverse reaction, olanzapine pamoate injection may only be given in a registered health care facility, is only available through a restricted distribution program, and may not be dispensed directly to the patient.

The boxed warning for olanzapine pamoate injection states:[27]

WARNING: POST-INJECTION DELIRIUM/SEDATION SYNDROME

Post-Injection Delirium/Sedation Syndrome—Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of ZYPREXA RELPREVV. ZYPREXA RELPREVV must be administered in a registered healthcare facility with ready access to emergency response services. After each injection, patients must be observed at the healthcare facility by a healthcare professional for at least 3 hours. Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment *[see Dosage and Administration (2.1), Warnings and Precautions (5.1, 5.2), Overdosage (10.2), and Patient Counseling Information (17.2)]*.

Clozapine Warnings

Clozapine has been associated with severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy. It has also been linked to respiratory arrest and cardiac arrest in patients taking benzodiazepines or other psychotropic drugs. To address these serious adverse reactions, the FDA requires boxed warnings for clozapine products, which state:[28, 29, 30]

WARNING: SEVERE NEUTROPENIA; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Severe Neutropenia

CLOZARIL treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/µL. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with CLOZARIL a baseline ANC must be at least 1500/µL for the general population; and must be at least 1000/µL for patients with documented Benign Ethnic Neutropenia (BEN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat) *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

Because of the risk of severe neutropenia, CLOZARIL is available only through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program. *[see Warnings and Precautions (5.2)]*.

Orthostatic Hypotension, Bradycardia, Syncope

Orthostatic hypotension, bradycardia, syncope, and cardiac arrest have occurred with CLOZARIL treatment. The risk is highest during the initial titration period, particularly with rapid dose escalation. These reactions can occur with the first dose, with doses as low as 12.5 mg per day. Initiate treatment at 12.5 mg once or twice daily; titrate slowly; and use divided dosages. Use CLOZARIL cautiously in patients with cardiovascular or cerebrovascular disease or conditions predisposing to hypotension (e.g., dehydration, use of antihypertensive medications) *[see Dosage and Administration (2.2, and 2.5) and Warnings and Precautions (5.3)]*.

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Seizures

Seizures have occurred with CLOZARIL treatment. The risk is dose-related. Initiate treatment at 12.5 mg, titrate gradually, and use divided dosing. Use caution when administering CLOZARIL to patients with a history of seizures or other predisposing risk factors for seizure (CNS pathology, medications that lower the seizure threshold, alcohol abuse). Caution patients about engaging in any activity where sudden loss of consciousness could cause serious risk to themselves or others *[see Dosage and Administration (2.2), Warnings and Precautions (5.4)]*.

Myocarditis and Cardiomyopathy

Fatal myocarditis and cardiomyopathy have occurred with CLOZARIL treatment. Discontinue CLOZARIL and obtain a cardiac evaluation upon suspicion of these reactions. Generally, patients with CLOZARIL-related myocarditis or cardiomyopathy should not be rechallenged with CLOZARIL. Consider the possibility of myocarditis or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur *[see Warnings and Precautions (5.5)]*.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CLOZARIL is not approved for use in patients with dementia-related psychosis *[see Warnings and Precautions (5.6)]*.

New Centralized Clozapine Registry

Due to the increased risk of neutropenia in patients treated with clozapine, the FDA recently approved major changes for prescribing clozapine. The FDA is replacing the six manufacturer registries with a shared clozapine registry as part of the new risk evaluation and mitigation strategy (REMS)[31, 32]. The new registry is known as the Clozapine REMS Program. Providers are responsible for monitoring neutropenia by only the absolute neutrophil count (ANC) and submitting that data to the Program. White blood cell (WBC) count will no longer be required. Prescribers and pharmacists must enroll with the registry. Patients on the manufacturer registries will be transferred automatically, and prescribers will enroll new patients in the registry. Prescribers and pharmacists must obtain certification in the Program to prescribe and dispense.[33]

Previously, Novartis had managed the National Non-Rechallenge Master File (NNRMF), a database of those who had stopped clozapine therapy due to concerns about agranulocytosis or neutropenia and could not have it prescribed again. The NNRMF will also be discontinued, and this function will be transferred to the Clozapine REMS Program. Patients who had previously been added to the NNRMF or could not be prescribed clozapine because of benign ethnic neutropenia may now be able to resume or begin treatment with clozapine, depending on ANC levels. The Clozapine REMS Program is available at https://www.clozapinerems.com on the Internet, or call 844-267-8678. The new registry is available beginning October 2015.[34]

Resources

Visit http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-State/By-State.html for links to State Medicaid program websites.

For up-to-date information about atypical antipsychotic drugs, visit the Postmarket Drug Safety Information for Patients and Providers page at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094303.htm on the FDA website.

For more information on the Clozapine REMS Program and participant responsibilities, refer to https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/WhatsNEWwithClozapine_An%20Overview.pdf on the Internet. For detailed instructions for this REMS, visit https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=351 on the FDA website.

The Center for Drug Evaluation and Research (CDER) hosts a website providing health professionals with current information on over-the-counter (OTC) and prescription drugs. Visit http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals to access drug-related databases, information on drug recalls and alerts, current information on new and generic drug approvals, and information on drug safety and availability.

Section 1927(g)(1)(B) of the Social Security Act identifies the predetermined standards that the State's drug use review program must use to assess data on drug use. Visit http://www.ssa.gov/OP_Home/ssact/title19/1927.htm for information on the compendia.

To see the electronic version of this fact sheet and the other products included in the "Atypical Antipsychotics" Toolkit, visit the Medicaid Program Integrity Education page at https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/pharmacy-ed-materials.html on the CMS website.

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References

1 Abilify® (aripiprazole) prescribing information. (2014, December 12). Retrieved August 7, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf

2 Aripiprazole prescribing information. (2015, April 28). Retrieved August 13, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202101s000lbl.pdf

3 Saphris® (asenapine) prescribing information. (2015, March12). Retrieved August 7, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022117s017s018s019lbl.pdf

4 Zyprexa® (olanzapine) prescribing information. (2015, July 23). Retrieved August 7, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020592s064,021086s042,021253s049lbl.pdf

5 Seroquel® (quetiapine) prescribing information. (2013, October 29). Retrieved August 10, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020639s061lbl.pdf

6 Seroquel XR® (quetiapine extended-release) prescribing information. (2013, October 29). Retrieved August 10, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022047s034lbl.pdf

7 Risperdal® (risperidone) prescribing information. (2014, April 28). Retrieved August 11, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020272s073,020588s062,021444s048lbl.pdf

8 Geodon® (ziprasidone) prescribing information. (2014, December 10). Retrieved August 11, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020825s053,020919s040,s021483s013lbl.pdf

9 Latuda® (lurasidone) prescribing information. (2013, September 3). Retrieved August 7, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/200603lbls10s11.pdf

10 Rexulti® (brexpiprazole) prescribing information. (2015, July 10). Retrieved August 11, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205422s000lbl.pdf

11 Clozaril® (clozapine) prescribing information. (2015, September 18). Retrieved September 24, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/019758s074lbl.pdf

12 FazaClo® (clozapine) prescribing information. (2015, September 15). Retrieved September 24, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021590s014s027lbl.pdf

13 Versacloz® (clozapine oral suspension) prescribing information. (2015, September 15). Retrieved September 24, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203479s007s008lbl.pdf

14 Fanapt® (iloperidone) prescribing information. (2014, April 21). Retrieved August 7, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022192s013lbl.pdf

15 Invega® (paliperidone) prescribing information. (2014, April 29). Retrieved August 10, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021999s029lbl.pdf

16 U.S. Department of Health and Human Services. National Institute of Mental Health. National Institutes of Health. (2009). Schizophrenia. [Click: "How is Schizophrenia Treated?" in the left menu]. [NIH Publication 09–3517]. Retrieved August 11, 2015, from http://www.nimh.nih.gov/health/publications/schizophrenia/index.shtml

17 U.S. Department of Health and Human Services. Agency for Healthcare Research and Quality. (2011, September). Off-Label Use of Atypical Antipsychotics: An Update. (AHRQ Publication No. 11-EHC087-EF). Retrieved August 11, 2015, from http://www.effectivehealthcare.ahrq.gov/ehc/products/150/778/CER43_Off-LabelAntipsychotics_20110928.pdf

18 U.S. Department of Health and Human Services. National Institutes of Health. National Institute of Mental Health. (2009). Schizophrenia. [Click: "How is Schizophrenia Treated?" in the left menu]. [NIH Publication 09–3517]. Retrieved August 11, 2015, from http://www.nimh.nih.gov/health/publications/schizophrenia/index.shtml

19 U.S. Department of Health and Human Services. National Institutes of Health. National Institute of Mental Health. (2009). Schizophrenia. [Click: "How is Schizophrenia Treated?" in the left menu]. [NIH Publication 09–3517]. Retrieved August 11, 2015, from http://www.nimh.nih.gov/health/publications/schizophrenia/index.shtml

20 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2009, February 25). Labeling Change Request Letter for Antidepressant Medications. Retrieved August 11, 2015, from http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096352.htm

21 Abilify® (aripiprazole) prescribing information. (2014, December 12). Retrieved August 7, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf

22 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2013, August 16). Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. Retrieved August 12, 2015, from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053171.htm

23 Abilify® (aripiprazole) prescribing information. (2014, December 12). Retrieved August 7, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf

24 Clozaril® (clozapine) prescribing information. (2015, September 18). Retrieved September 24, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/019758s074lbl.pdf

25 Zyprexa® (olanzapine) prescribing information. (2015, July 23). Retrieved August 7, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020592s064,021086s042,021253s049lbl.pdf

26 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2011, September 20). FDA Drug Safety Communication: Serious Allergic Reactions Reported with the Use of Saphris (asenapine maleate). Retrieved August 13, 2015, from: http://www.fda.gov/Drugs/DrugSafety/ucm270243.htm

27 Zyprexa® Relprevv® (olanzapine pamoate) prescribing information. (2015, July 23). Retrieved September 24, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022173s017lbl.pdf

28 Clozaril® (clozapine) prescribing information. (2015, September 18). Retrieved September 24, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/019758s074lbl.pdf

29 FazaClo® (clozapine) prescribing information. (2015, September 15). Retrieved September 24, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021590s014s027lbl.pdf

30 Versacloz®(clozapine oral suspension) prescribing information. (2015, September 15). Retrieved September 24, 2015, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203479Orig1s001Lbl.pdf

31 U.S. Food and Drug Administration. (2015, September 15). Approved Risk Evaluation and Mitigation Strategies (REMS): Clozapine Shared System REMS. Retrieved September 24, 2015, from https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=351

32 U.S. Food and Drug Administration. (2015, September 15). FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines. Retrieved September 24, 2015, from http://www.fda.gov/Drugs/DrugSafety/ucm461853.htm

33 Clozapine REMS. (2015, September). What's New with Clozapine: An Overview. Retrieved September 24, 2015, from https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/WhatsNEWwithClozapine_An%20Overview.pdf

34 Clozapine REMS. (2015, September). What's New with Clozapine: An Overview. Retrieved September 24, 2015, from https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/WhatsNEWwithClozapine_An%20Overview.pdf

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