Health Monitor®

Clinician Update

Schizophrenia Management

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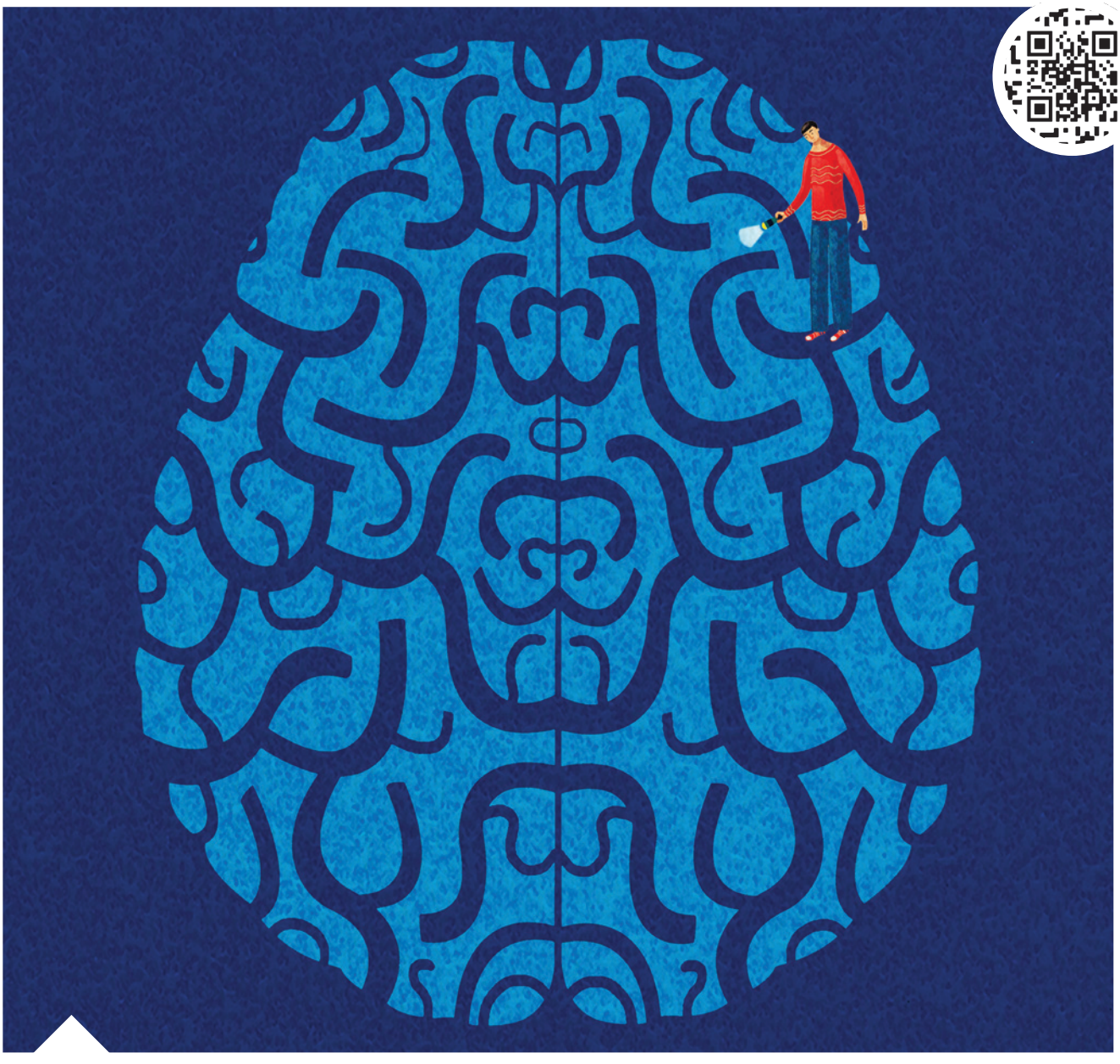

STRATEGIES FOR SWITCHING TO LONG-ACTING INJECTABLES

Think it's too early to consider a long-acting injectable antipsychotic (LAI) in recently diagnosed patients? It's not, say experts. Here's why.

LAIs, long regarded as a strategy for counteracting antipsychotic nonadherence and ensuring constant steady-state medication levels, traditionally have been reserved for later-stage patients who struggle to follow an oral regimen or who pose a potential danger to themselves or others.

However, as recent studies have shown the effectiveness of LAIs in reducing schizophrenia-related morbidity, and as more injectable formulations of second-generation antipsychotics have become available, physicians are focusing on their use earlier in the disease course. In fact, data show that LAIs, administered solely by a healthcare provider, can prevent relapses in early-stage schizophrenia and after a first relapse.[1,2]

"Starting an LAI early on in patients, who arguably have the most to gain and the most to lose, will enable them to benefit from not being destabilized by insufficient medication-taking, to not have relapses, and to pursue their goals while they are still able to function," explains Christoph U. Correll, MD, Professor of Psychiatry and Molecular Medicine at the Zucker School of Medicine at Hofstra/Northwell (Hempstead, NY). "Together with ongoing psychosocial support, LAIs enhance patients' chances of remaining stable and pursuing the goals that matter to them."

Continued on p. 4 ►

Illustration by Keith Negley

Who should get an LAI and who shouldn't?

Almost any patient with schizophrenia who requires a regular antipsychotic regimen should be considered for an LAI, Dr. Correll advises. "Nonadherence is part of the human condition. Anyone who is currently adherent has a high likelihood of not being adherent in the future," he notes, citing nonadherence drivers such as cognitive disability, inadequate social support, lack of insight into illness, perceived lack of need for the medication and adverse side effects.

But while preemptive schizophrenia treatment is strongly preferred over a reactive strategy, LAIs also can help establish control in patients grappling with acute symptoms. "Consider suggesting an LAI to any patient with schizophrenia for whom there is reason to suspect poor adherence," adds Joseph F. Goldberg, MD, clinical professor of psychiatry at Icahn School of Medicine at Mount Sinai (New York, NY). He says this includes patients who:

- Have a history of relapse or hospitalization
- Posed a danger to themselves or others at last relapse
- Report difficulty with following a prescribed antipsychotic regimen
- Demonstrate poor insight toward their illness or treatment
- Have little or no social support
- Have a comorbid substance use disorder
- Remain symptomatic on an oral antipsychotic with an LAI equivalent. This could signal "pseudo resistance."

LAIs, however, are not suitable for some patients with schizophrenia, Drs. Correll and Goldberg note. This includes patients who are well controlled on their current oral antipsychotic and unwilling to consider switching to an LAI; well controlled on clozapine, a "last-resort" oral second-generation antipsychotic for which no injectable formulation exists; or not responding to any antipsychotic with an injectable equivalent.

> "TOGETHER WITH ONGOING PSYCHOSOCIAL SUPPORT, LAIs ENHANCE PATIENTS' CHANCES OF REMAINING STABLE AND PURSUING THE GOALS THAT MATTER TO THEM."
>
> —*Christoph U. Correll, MD*

Making the switch

As with other treatments, switching from an oral antipsychotic to an LAI equivalent is a multistep process that requires constant communication between clinician and patient, Drs. Correll and Goldberg note. A frank discussion with the patient about the disease's personal impact, what the patient wants to achieve and motivating the patient to achieve those goals is critical to successfully resetting treatment.

While there are several motivational interviewing techniques, the GAIN method is associated with high rates of patient acceptance of, and adherence to, an LAI.[3] It includes:

- **G**oal setting
- **A**ction planning
- **I**nitiating treatment
- **N**urturing motivation

Ask patients to discuss recent setbacks, such as an arrest or job loss, then ask about future goals. Consider their point of view, offer sensitive feedback and identify areas where you agree, but also use the disparity between the patient's recent troubles and future goals to establish the need for a treatment change.[3] Also discuss current treatment and ask about issues that could be contributing to nonadherence.[3] "It's important to identify and understand what's important to patients and their lives, and then link this to medication stability and to the data pointing to LAI effectiveness," Dr. Correll says.

Next, help the patient set positive but attainable goals. Find out what is most important to the patient's life (e.g., holding a job, living independently), then help the patient identify 1 or 2 "SMART" goals that are:

- **S**pecific
- **M**easurable
- **A**ttainable
- **R**elevant
- **T**ime-bound

This involves setting reachable, short-term goals (e.g., walking with a family member twice weekly, medication adherence) that can help the patient achieve the larger, longer-term goals of staying connected, being active and remaining stable. The short-term goals need to be attainable based on the patient's life situation and the severity of the disease. "If the goal is something like building a castle in the sky, the patient will never get there and will become discouraged," Dr. Correll says. "When some patients have unrealistic goals, such as 'I want a girlfriend,' I'll say, 'First, let's get you stable, and then we'll see how we can achieve that.' "

In the process, recommending an LAI and discussing adherence should include shared decision-making and motivating the patient. "Don't say, 'Take this drug, so that you don't hear voices,' which patients may not see as their main concern," Dr. Correll says. "Instead, tell the patient: 'The last time you didn't take your medication, you had to be admitted to the hospital; you were very unhappy about this, and your parents had to call the police. Maybe taking your medication more regularly can help you stay with your parents and even help you get back to school—two goals that you have told me are important.' "

Getting family members or other people in the patient's life involved in the switching process also is critical, Drs. Correll and Goldberg stress. Because schizophrenia is chronic and LAI treatment likely is long-term, social support is critical to ensuring that the patient keeps reporting for regular injections, Dr. Correll says.

"Support from peers or immediate family members can be crucial, not only for promoting adherence and influencing attitudes about medication, but also for more comprehensively monitoring how well the patient is functioning in everyday life," Dr. Goldberg adds. "Absence of social support can drive isolation and leave patients feeling more disengaged with the world around them. Negative social support, such as criticism about taking medications or having side effects, can drive stigma, denial of symptoms or the need for treatment, and contribute to poorer patient self-care."

Once you've had the dialogue, data suggest that most patients will agree to the LAI if it's offered appropriately.[1] Of 576 patients with first-episode and early-phase schizophrenia who were invited to the Prevention of Relapse in Schizophrenia (PRELAPSE) study in which they were offered a switch to an LAI, only 83 (14.4%) declined to participate because they would not consider LAI therapy; 91% of the remaining patients accepted and received LAI treatment.[2]

Prescribing LAIs

If the patient agrees to try an LAI, then either prescribe the injectable equivalent of the patient's current antipsychotic or switch to an oral antipsychotic with an injectable equivalent, Dr. Correll notes. If starting a new antipsychotic, ensure that at least two oral doses 24 hours apart are administered to ensure the patient can tolerate the medication before

Choosing an LAI: Which option is best?

Nearly all patients with schizophrenia are candidates for long-acting injectable (LAI) therapy at any time during the course of disease, says Leslie Citrome, MD, MPH, Clinical Professor of Psychiatry and Behavioral Sciences, New York Medical College, Valhalla, NY. The only patients who should *not* receive an LAI are 1) those who require clozapine after all other drug options have failed; 2) those who are responding to an oral antipsychotic that is not available in injectable form; or 3) those who cannot tolerate any available LAI.

When deciding on which agent to use, it's important to consider the patient's medical history and preferences. The availability of different forms of LAI antipsychotic medication makes it easier than ever to customize therapy, notes Dr. Citrome. "Having the same active molecule available in different formulations allows for greater choice in terms of different features," he says, adding that the following should be considered:

- How often are the injections administered?
- What is the needle gauge?
- What is the injection volume?
- Is there a choice of injection site?
- Does this product require reconstitution?
- Is oral supplementation required?
- Does storage of this product require refrigeration?
- Are there any special requirements for post-injection observation?
- Are there any important drug-drug interactions and can they be remedied?
- Missed doses: What is the "grace period?"
- Is reimbursement an issue if used "off-label"?
- In case of reimbursement obstacles, can I easily access a patient assistance program?

starting the injectable version in an acute setting. In many instances, clinicians and patients may prefer a longer treatment interval (e.g., several weeks) with the oral medication to ensure the patient is tolerating and responding to the agent as desired before switching to the LAI.

Depending on which LAI is prescribed, the patient may need to take both the oral and injectable antipsychotic formulations for 2 to 3 weeks until adequate levels of the drug are reached; in some cases, a second injection is needed when starting the LAI or 7 days later, Dr. Correll notes. One exception is when switching to a subcutaneous risperidone formulation that reaches adequate blood levels in 6 to 24 hours. "In that case, you can stop the oral risperidone and move over," he adds. Another exception is an intramuscular aripiprazole formulation that requires only a 1-day overlap for both the oral and injectable versions but requires two injections on the first day.

FDA-approved, long-acting forms of the second-generation antipsychotics aripiprazole, olanzapine, paliperidone and risperidone are available, as are injectable forms of the first-generation antipsychotics haloperidol and fluphenazine. The routes of administration (intramuscular vs. subcutaneous injection) differ among the LAIs, as do the injection schedules, which range from biweekly to once every 6 months.[1,4]

Ultimately, choosing a specific LAI comes down to patient preference. "Does the patient want a subcutaneous or deep intramuscular injection?" Dr. Correll says. "And what dosing interval is preferred?" (For more considerations, see box on p. 5).

Note: Intramuscular LAI formulations are contraindicated in patients taking anticoagulants due to the risk of bleeding, Dr. Correll notes. Offer these patients a subcutaneous LAI instead.

Following up

Once an LAI is started, maintaining the therapeutic alliance is critical to keeping the patient motivated and on track, says Dr. Correll. Upon seeing patients after their first injection, ask them if they're noticing positive lifestyle changes. If they don't answer, take the lead or ask a family member or friend for feedback. "You might say, 'Since you're taking this medication, you're not as irritable and you're not using as many substances. You're even now participating in family activities. Your parents really like that. Do you like that, too?'"

Importantly, clinical necessity and severity of illness—not LAI dosing intervals—should determine follow-up visit frequency to ensure continued treatment success and adherence. "The more unstable the patient is, the more psychosocial support or medication renewals are needed, the more frequent the visits need to be," Dr. Correll stresses.

Although LAIs have been shown to improve antipsychotic adherence,[1] nonadherence to an LAI still can happen, Dr. Goldberg says. "If a patient misses an LAI injection and the prescriber is not doing the injection, the prescriber usually is notified by whomever is performing the injections," he says. "This makes it easy to address missed doses directly with the patient. From there, you can approach the patient about formulating a strategy to help with keeping appointments." ●

—by Pete Kelly

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Illustration by Keith Negley

IMPROVING ADHERENCE TO PHARMACOTHERAPY

Illustration by Jeannie Phan

Treatment failure in patients with schizophrenia is common, and inadequate adherence or nonadherence is often the cause.[1] As many as 3 out of 4 patients with schizophrenia stop taking their antipsychotics, often within 1 year of starting them—which subsequently increases their risk of relapse, hospitalization and the potentially catastrophic consequences of an acute episode.[2-5]

Of course, adherence problems are widespread throughout medicine: Approximately half of patients with chronic conditions skip doses or cease medications without telling their clinicians, some of which may be attributed to human nature.[6] "People, in general, don't want to take a medication unless they sense a significant benefit with no side effects, and that's true of very few medications," says Erik Messamore, MD, PhD, Associate Professor, Department of Psychiatry, Northeast Ohio Medical University in Rootstown. Factor in the negative self-perceptions that often come with schizophrenia, and convincing newly diagnosed patients to start an antipsychotic can be difficult. Anosognosia, or lack of awareness or insight of their condition, is also common. "First of all, the patient has to come to terms with their diagnosis, and stigma often gets in the way of that," Dr. Messamore says. "Second, you have to convince the patient to start a medication that comes with potentially serious or disfiguring [e.g., extrapyramidal] side effects. Taken together, that's a lot to ask of anyone."

Laying the foundation

To head off potential adherence problems, experts advise setting patients up for success with these approaches:

Build trust and discuss goals.
Gaining the patient's trust from the start is crucial to promoting medication adherence. "The initial conversation needs to focus on the patient's strengths and goals and not just the illness," Dr. Messamore says. "Medication should be framed as a tool toward reaching the goal of remission."

Involve family members—and make sure they're on board.
When possible, family members should be present at the patient's appointment. "I'm a strong believer in having whoever is involved with the patient's life at the meeting," says Ralph Aquila, MD, a New York-based psychiatrist and Medical Director of Fountain House, which helps adults with serious mental illness re-enter society. "I want to be part of a team that is moving the patient forward." He says this allows you to gauge whether the patient's family understands the need for medication. "The family's attitude likely will be your patient's attitude."

Start patients who are antipsychotic-naive at a lower dosage to reduce the risk of side effects.
Dr. Messamore notes that dosage recommendations on antipsychotic labeling are based on data from clinical trials that have enrolled volunteers with long-standing schizophrenia who have received multiple prior medications. But in real-world practice, he says, many newly diagnosed patients respond well to an antipsychotic agent given at a lower dosage.

Ask about adherence at every visit.
Some patients may be reluctant to disclose their nonadherence, either because they don't want to disappoint their physician or fear being switched to a more intolerable agent. "The simple question, 'Are you taking your medication?' is crucial to keeping the adherence conversation going," says Dr. Aquila. It's also helpful to ask for specifics since patients may perceive they're taking their medication but are missing doses. For example: "How many doses of medication do you take every day? About how many doses do you miss? Is it hard to remember to take it at the right time?"

> "RECEIVING AN ANTIPSYCHOTIC INJECTION EVERY 1 TO 3 MONTHS IS CONSIDERABLY MORE CONVENIENT, AND LESS STIGMATIZING, THAN REMEMBERING TO TAKE A PILL EVERY DAY."
> —*Jose M. Rubio, MD*

Overcoming barriers to adherence

By maintaining a strong therapeutic alliance with patients and their family members, you'll be in a better position to help patients overcome these common causes of nonadherence:

Adverse effects.
Urge patients to contact you as soon as they feel anything

unusual after starting an antipsychotic, says Dr. Aquila. He points out that sometimes patients experience a side effect from a medication but don't attribute it to the agent. On the other hand, patients who experience a reduction in symptoms may assume they just "have to live with" troublesome side effects, such as anticholinergic effects, which range from constipation, dry mouth and urinary retention to blurred vision and cognitive impairment.[7-11] "Stress to patients you will work together to find agents and dosages that maximize efficacy and minimize adverse effects," emphasizes Jose M. Rubio, MD, who specializes in schizophrenia treatment at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell and The Zucker Hillside Hospital in Glen Oaks, NY.

Perceived lack of need.
Too often, when an antipsychotic improves positive symptoms, patients believe they are "cured" and stop taking the medication. "I've never met a patient who doesn't stop taking a medication prematurely because he feels better," says Dr. Messamore, who suggests reviewing treatment goals at each visit, and then discussing the long-term plan to help the patient achieve those goals. "Explain that dopamine signals are usually too intense during psychosis and can cause the brain to generate misperceptions, and medications are designed to normalize or rebalance these signals. Also, explain that we will use the lowest effective dose to achieve symptom remission and help patients get their lives back on track."

In addition, Dr. Rubio suggests reviewing the treatment history with patients. During this review, the patient may see a pattern of relapsing every time treatment is stopped, reinforcing the need to continue or resume medication. "Many patients taking an antipsychotic may not feel it is working, when in fact it is."

Stigma.
Some patients who have schizophrenia may harbor negative self-perceptions of how others will view them. This self-stigma often worsens the disease course, negatively affects overall treatment and increases the risk of nonadherence.[12] The initial treatment conversation is crucial to helping break the stigma. Frame schizophrenia as a problem to overcome, rather than as a strange and disabling disease, Dr. Messamore says. Also, effective treatment may reduce stigma by controlling symptoms, adds Dr. Rubio, so point out this benefit of adherence as well.

Inability to follow their oral regimen.
Positive symptoms of schizophrenia discourage adherence.[2] Disorganized thinking or memory loss can cause patients to forget doses, and medication may be the farthest thing from an agitated patient's mind. Or patients may have a work or school schedule that makes it difficult to take their medication as prescribed.

In such cases, consider switching to a long-acting injectable (LAI) antipsychotic. Research shows improved adherence among patients receiving an LAI compared with oral agents, as well as a lower risk of relapse and significantly longer time to relapse compared with oral antipsychotics.[13-15] "At the very least, I can see whether the patient is taking the medication," says Dr. Aquila, noting that LAIs must be administered in-office by a healthcare professional. Dr. Rubio adds, "Receiving an antipsychotic injection every 1 to 3 months is considerably more convenient, and less stigmatizing, than remembering to take a pill every day." In addition, Dr. Messamore says, "Part of the problem is that taking an oral antipsychotic each day is like a ritual in which the person must be reminded they have a problem with their brain," he says. "Getting the medication out of sight and out of mind most days will improve the patient's quality of life."

Co-occurring depression or substance use disorder.
Either disorder can thwart maintenance therapy, and both are common in people who have schizophrenia:

- Nearly half of patients with schizophrenia develop an alcohol or illicit narcotic use disorder and a majority use nicotine, at a rate of approximately three times that of the general population.[9] Any of these substances can worsen the patient's disease course.
- Approximately 40% of schizophrenia patients develop a depressive disorder.[10] Depression worsens schizophrenia outcomes, increases the risk of relapse, can impair functional recovery and quality of life and raises an already heightened risk of suicide.[5,10]

Therefore, it's crucial to address these disorders up front if schizophrenia treatment is to be effective, Dr. Rubio says. For depression, standard treatments, such as cognitive behavioral therapy and antidepressants, should be initiated. In addition, certain antipsychotics are approved for treating major depressive disorder.

If substance use is present, refer the patient to a treatment center that specializes in helping patients with substance use and comorbid mental illness, says Dr. Messamore. Also, ask if the patient is using a substance to solve a problem, then explore alternatives. For example, if a patient uses amphetamines or nicotine to counteract a side effect such as somnolence, discuss switching to another antipsychotic medication. In addition, peer support or social skills training

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The key to getting patients on board: a positive approach

When treating individuals with schizophrenia, it's important to remember that nonadherence is neither a moral failing nor the mark of incompetence or apathy. "Many people have trouble regularly taking their medicines as prescribed," says Joseph F. Goldberg, MD, MS, clinical professor of psychiatry at Icahn School of Medicine at Mount Sinai in New York City. Engaging patients with a positive attitude can empower them to adhere to their regimen. To do this, Dr. Goldberg suggests the following:

1. **Encourage them to take ownership.** Ask them to express their opinions and to assume at least partial responsibility for risk-benefit decisions about medication. "This is harder to do when patients may have diminished capacity to understand the nature of their condition and the need for treatment," he says, "but clinicians should not assume that patients with psychotic disorders lack that awareness." Urge patients to identify the goals they consider most important, then devise a strategy for meeting those goals with a medication trial. "Promise that if the patient does not perceive a benefit within a reasonable period, you can switch them to a more effective regimen," he adds.
2. **Normalize nonadherence.** Without sounding "judgy," Dr. Goldberg says, "Ask the patient, 'How often do you run into difficulty with taking your medication?' or 'How can we help you take your medications more consistently?' This opens the door to a discussion about simplifying dosing frequencies, unrecognized side effects or discontinuing medicines that may not be having a clear benefit," he says.
3. **Forge an alliance.** Point out ways in which distress, adversity and suffering are consequences of undertreated mental illness, as patients may not make the connection. Then suggest ways in which collaborating with you can help patients identify and achieve their stated treatment goals. "The mindset really needs to be 'You and me against the illness' rather than 'Me and the illness against you,' " Dr. Goldberg says.

Illustration by Jeannie Phan

INDICATION AND USAGE

UZEDY (risperidone) extended-release injectable suspension for subcutaneous use is indicated for the treatment of schizophrenia in adults.

IMPORTANT SAFETY INFORMATION

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. UZEDY is not approved for use in patients with dementia-related psychosis and has not been studied in this patient population.

CONTRAINDICATIONS: UZEDY is contraindicated in patients with a known hypersensitivity to risperidone, its metabolite, paliperidone, or to any of its components. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone or paliperidone.

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions: In trials of elderly patients with dementia-related psychosis, there was a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in patients treated with oral risperidone compared to placebo. UZEDY is not approved for use in patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS is suspected, immediately discontinue UZEDY and provide symptomatic treatment and monitoring.

Tardive Dyskinesia (TD): TD, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause TD is unknown.

The risk of developing TD and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the cumulative dose. The syndrome can develop, after relatively brief treatment periods, even at low doses. It may also occur after discontinuation. TD may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for UZEDY, including Boxed WARNING, on the following pages.

UZEDY™ 50 mg 75 mg 100 mg 125 mg 150 mg 200 mg 250 mg
(risperidone) extended-release injectable suspension

AN LAI THAT CLINICIANS AND PATIENTS AGREE ON[1]*

RAPID ABSORPTION

UZEDY rapidly achieves therapeutic levels† in plasma within 6 to 24 hours of administration with a single dose[1,2]

DEMONSTRATED EFFICACY‡

UZEDY demonstrated significant reductions in the risk of relapse vs placebo[1,2]

STREAMLINED INITIATION

No loading dose or oral supplementation is required[2]

SUBCUTANEOUS INJECTION

UZEDY is for subcutaneous injection administered only by a healthcare professional and comes in a single-dose, prefilled syringe with a short, 5/8-inch needle[2]

FLEXIBLE 1- AND 2-MONTH DOSING INTERVALS

With 2 dosing intervals and 8 dosing options, you can tailor the dosing regimen to the individual patient needs[2]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Tardive Dyskinesia (TD) (Continued):
If signs and symptoms of TD appear in a patient treated with UZEDY, drug discontinuation should be considered. However, some patients may require treatment with UZEDY despite the presence of the syndrome. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and diabetes mellitus (DM), in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics, including risperidone. Patients with an established diagnosis of DM who are started on atypical antipsychotics, including UZEDY, should be monitored regularly for worsening of glucose control. Patients with risk factors for DM (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics, including UZEDY, should undergo fasting blood glucose (FBG) testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including UZEDY, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who

(continued on next page)

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for UZEDY, including Boxed WARNING, on the following pages.

LAI, long-acting injectable.

*Data were collected from 63 patients, 24 physicians, and 25 nurses in a prospective, cross-sectional companion survey assessing the perceptions regarding ease of use and satisfaction with UZEDY. The survey was administered after a minimum of 2 experiences prescribing, administering, or receiving UZEDY. Ninety-six percent of clinicians and 92% of patients reported that they were satisfied with UZEDY. Ninety-two percent of clinicians and 89% of patients reported that administration of UZEDY was easy. Eighty percent of clinicians and 94% of patients reported that if given a choice, they would choose a shorter needle over a longer needle.[1]

†The threshold for clinically relevant plasma concentrations of risperidone is defined as levels ≥10 ng/mL.[1]

‡The RISE phase 3 study was a randomized, double-blind, multicenter, placebo-controlled, relapse prevention study evaluating the safety and efficacy of UZEDY once monthly or once every 2 months vs placebo once monthly in 542 patients with schizophrenia.[2]

teva

UZEDY™ 50 mg 75 mg 100 mg 125 mg 150 mg 200 mg 250 mg
(risperidone) extended-release injectable suspension

IMPORTANT SAFETY INFORMATION (CONTINUED)

Metabolic Changes (Continued):

develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including UZEDY, should undergo FBG testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of risperidone.

Dyslipidemia has been observed in patients treated with atypical antipsychotics.

Weight gain has been observed with atypical antipsychotic use. Monitoring weight is recommended.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

Orthostatic Hypotension and Syncope: UZEDY may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope. UZEDY should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease, and conditions which would predispose patients to hypotension and in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral risperidone and antihypertensive medication.

Falls: Antipsychotics, including UZEDY, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other fall-related injuries. Somnolence, postural hypotension, motor and sensory instability have been reported with the use of risperidone. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Leukopenia, Neutropenia, and Agranulocytosis have been reported with antipsychotic agents, including risperidone. In patients with a pre-existing history of a clinically significant low white blood cell count (WBC) or absolute neutrophil count (ANC) or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of UZEDY at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue UZEDY in patients with ANC < 1000/mm^3) and follow their WBC until recovery.

Potential for Cognitive and Motor Impairment: UZEDY, like other antipsychotics, may cause somnolence and has the potential to impair judgement, thinking, and motor skills. Somnolence was a commonly reported adverse reaction associated with oral risperidone treatment. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that treatment with UZEDY does not affect them adversely.

RIS-40441 July 2023

Seizures During premarketing studies of oral risperidone in adult patients with schizophrenia, seizures occurred in 0.3% of patients (9 out of 2,607 patients), two in association with hyponatremia. Use UZEDY cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including UZEDY, should be used cautiously in patients at risk for aspiration.

Priapism has been reported during postmarketing surveillance for other risperidone products. A case of priapism was reported in premarket studies of UZEDY. Severe priapism may require surgical intervention.

Body temperature regulation. Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral risperidone use. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use UZEDY with caution in patients who experience these conditions.

ADVERSE REACTIONS

The most common adverse reactions with risperidone (≥5% and greater than placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain.

The most common injection site reactions with UZEDY (≥5% and greater than placebo) were pruritus and nodule.

DRUG INTERACTIONS

- Carbamazepine and other strong CYP3A4 inducers decrease plasma concentrations of risperidone.
- Fluoxetine, paroxetine, and other strong CYP2D6 inhibitors increase risperidone plasma concentration.
- Due to additive pharmacologic effects, the concomitant use of centrally-acting drugs, including alcohol, may increase nervous system disorders.
- UZEDY may enhance the hypotensive effects of other therapeutic agents with this potential.
- UZEDY may antagonize the pharmacologic effects of dopamine agonists.
- Concomitant use with methylphenidate, when there is change in dosage of either medication, may increase the risk of extrapyramidal symptoms (EPS)

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including UZEDY, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinicaland-research-programs/pregnancyregistry/.

Lactation: Infants exposed to risperidone through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and EPS.

Fertility: UZEDY may cause a reversible reduction in fertility in females.

Pediatric Use: Safety and effectiveness of UZEDY have not been established in pediatric patients.

Renal or Hepatic Impairment: Carefully titrate on oral risperidone up to at least 2 mg daily before initiating treatment with UZEDY.

Patients with Parkinson's disease or dementia with Lewy bodies can experience increased sensitivity to UZEDY. Manifestations and features are consistent with NMS.

Please see Brief Summary of full Prescribing Information for UZEDY on the following pages.

References: 1. Data on file. Parsippany, NJ: Teva Neuroscience, Inc. **2.** UZEDY™ (risperidone) extended-release injectable suspension Current Prescribing Information. Parsippany, NJ: Teva Neuroscience, Inc.

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR UZEDY (risperidone) extended-release injectable suspension, for subcutaneous use
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

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. UZEDY is not approved for the treatment of patients with dementia-related psychosis and has not been studied in this patient population *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE
UZEDY is indicated for the treatment of schizophrenia in adults.

4 CONTRAINDICATIONS
UZEDY is contraindicated in patients with a known hypersensitivity to risperidone, its metabolite, paliperidone, or to any of its components. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone or paliperidone.

5 WARNINGS AND PRECAUTIONS

5.1 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 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.
In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone when compared to patients treated with oral risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed.
UZEDY is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*.

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73 to 97 years) in trials of oral risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse reactions in patients treated with oral risperidone compared to patients treated with placebo. UZEDY is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome
Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.
If NMS is suspected, immediately discontinue UZEDY and provide symptomatic treatment and monitoring.

5.4 Tardive Dyskinesia
Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict, which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the cumulative dose. The syndrome can develop, after relatively brief treatment periods, even at low doses. It may also occur after discontinuation of treatment.
Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.
Given these considerations, UZEDY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.
If signs and symptoms of tardive dyskinesia appear in a patient treated with UZEDY, drug discontinuation should be considered. However, some patients may require treatment with UZEDY despite the presence of the syndrome.

5.5 Metabolic Changes
Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class

have been shown to produce some metabolic changes, each drug has its own specific risk profile.
Hyperglycemia and Diabetes Mellitus
Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including risperidone. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.
Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including UZEDY, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics, including UZEDY, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including UZEDY, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including UZEDY, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of risperidone.
Pooled data from three double-blind, placebo-controlled schizophrenia studies and four double-blind, placebo-controlled studies in another indication with oral risperidone are presented in *Table 2*.

Table 2: Change in Random Glucose from Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adults with Schizophrenia or Another Indication with Oral Risperidone

		Oral Risperidone	
	Placebo	1 mg to 8 mg per day	>8 mg to 16mg per day
		Mean change from baseline (mg/dL)	
	N=555	N=748	N=164
Serum Glucose	-1.4	0.8	0.6
		Proportion of Patients with Shifts	
Serum Glucose (<140 mg/dL to ≥200 mg/dL)	0.6% (3/525)	0.4% (3/702)	0% (0/158)

In longer-term, controlled and uncontrolled studies in adults, oral risperidone was associated with a mean change in glucose of +2.8 mg/dL at Week 24 (N=151) and +4.1 mg/dL at Week 48 (N=50).

Dyslipidemia
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Before or soon after initiation of antipsychotic medications, obtain a fasting lipid profile at baseline and monitor periodically during treatment.
Pooled data from 7 placebo-controlled, 3- to 8- week, fixed- or flexible-dose studies in adults with schizophrenia or another indication with oral risperidone are presented in *Table 3*.

Table 3: Change in Random Lipids from Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adults with Schizophrenia or Another Indication with Oral Risperidone

		Oral Risperidone	
	Placebo	1 mg to 8 mg per day	>8 mg to 16mg per day
		Mean change from baseline (mg/dL)	
Cholesterol	**N=559**	**N=742**	**N=156**
Change from baseline	0.6	6.9	1.8
Triglycerides	**N=183**	**N=307**	**N=123**
Change from baseline	-17.4	-4.9	-8.3
		Proportion of Patients with Shifts	
Cholesterol (<200 mg/dL to ≥240 mg/dL)	2.7% (10/368)	4.3% (22/156)	6.3% (6/96)
Triglycerides (<500 mg/dL to ≥500 mg/dL)	1.1% (2/180)	2.7% (8/301)	2.5% (3/121)

In longer-term, controlled and uncontrolled studies, oral risperidone was associated with a mean change in (a) non-fasting cholesterol of +4.4 mg/dL at Week 24 (N=231) and +5.5 mg/dL at Week 48 (N=86); and (b) non-fasting triglycerides of +19.9 mg/dL at Week 24 (N=52).
Weight Gain
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.
Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of 7% or greater of body weight from 7 placebo-controlled, 3- to 8- week, fixed- or flexible-dose studies in adults with schizophrenia or another indication with oral risperidone are presented in *Table 4*.

CONTINUED ON NEXT PAGE

Table 4: Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥7% Gain in Body Weight From Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adults With Schizophrenia or Another Indication with Oral Risperidone

		Oral Risperidone	
	Placebo (n=597)	1 mg to 8 mg per day (n=769)	>8 mg to 16mg per day (n=158)
Weight (kg) Change from baseline	-0.3	0.7	2.2
Weight Gain ≥7% increase from baseline	2.9%	8.7%	20.9%

In longer-term, controlled and uncontrolled studies, oral risperidone was associated with a mean change in weight of +4.3 kg at Week 24 (n=395) and +5.3 kg at Week 48 (n=203).

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This in turn may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia may lead to decreased bone density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

5.7 Orthostatic Hypotension and Syncope

UZEDY may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of patients treated with oral risperidone in Phase 2 and 3 studies in adults with schizophrenia.

UZEDY should be used with particular caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia and (2) in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral risperidone and antihypertensive medication.

5.8 Falls

Antipsychotics, including UZEDY, may cause somnolence, postural hypotension, motor and sensory instability which may lead to falls and, consequently, fractures or other fall-related injuries. Somnolence, postural hypotension, motor and sensory instability have been reported with the use of risperidone. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including risperidone. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and a history of drug-induced leukopenia/neutropenia. In patients with a pre-existing history of a clinically significant low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of UZEDY at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Discontinue UZEDY in patients with absolute neutrophil count <1000/mm^3 and follow their WBC followed until recovery.

5.10 Potential for Cognitive and Motor Impairment

UZEDY, like other antipsychotics, may cause somnolence and has the potential to impair judgement, thinking, and motor skills. Somnolence was a commonly reported adverse reaction associated with oral risperidone treatment, especially when ascertained by direct questioning of patients. This adverse reaction is dose-related, and in a study utilizing a checklist to detect adverse reactions, 41% of the high-dose patients (oral risperidone 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse reactions than spontaneous reporting, by which 8% of oral risperidone 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse reaction.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that treatment with UZEDY does not affect them adversely.

5.11 Seizures

During premarketing studies of oral risperidone in adult patients with schizophrenia, seizures occurred in 0.3% of patients (9 out of 2,607 patients), two in association with hyponatremia. Use UZEDY cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

5.12 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Antipsychotic drugs, including UZEDY, should be used cautiously in patients at risk for aspiration.

5.13 Priapism

Priapism has been reported during postmarketing surveillance for other risperidone products. A case of priapism was reported in premarket studies of UZEDY. Severe priapism may require surgical intervention.

5.14 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral risperidone use. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use UZEDY with caution in patients who may experience these conditions.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic changes *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions (5.7)]*
- Falls *[see Warnings and Precautions (5.8)]*
- Leukopenia/neutropenia and agranulocytosis *[see Warnings and Precautions (5.9)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Dysphagia *[see Warnings and Precautions (5.12)]*
- Priapism *[see Warnings and Precautions (5.13)]*
- Body temperature regulation *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of UZEDY for the treatment of schizophrenia in adults is based on adequate and well-controlled studies of oral risperidone in studies of patients with schizophrenia and other indications. The results of those adequate and well-controlled studies are presented below.

The data described in this section are derived from a clinical trial database consisting of 9,803 patients exposed to one or more doses of oral risperidone for the treatment of schizophrenia and other psychiatric disorders. Of these 9,803 patients, 2,687 were patients who received oral risperidone while participating in double-blind, placebo-controlled trials. The conditions and duration of treatment with oral risperidone varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 3 years) exposures. Safety was assessed by collecting adverse reactions and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Injection site reactions for UZEDY presented in this section (see "Injection Site Reactions with UZEDY" below) are based on a randomized withdrawal study in patients with schizophrenia consisting of a 12-week open-label oral risperidone (2 mg to 5 mg) stabilization phase, followed by a placebo-controlled phase in which patients were randomized to UZEDY (once monthly or once every 2 months) or placebo for a variable time until impending relapse or study completion.

The safety of UZEDY was evaluated in a total of 740 adult patients with schizophrenia who received at least 1 dose of UZEDY during the clinical development program. A total of 351 patients were exposed to UZEDY for at least 6 months, of which 221 patients were exposed to UZEDY for at least 12 months, which included 112 patients exposed to once monthly and 109 patients to once every 2 months dosing regimens. In addition, 32 patients were exposed to UZEDY for at least 24 months.

Adverse Reactions in Studies with Oral Risperidone

The most common adverse reactions in clinical trials of oral risperidone (>5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials –Adult Patients with Schizophrenia Treated with Oral Risperidone

Table 5 lists the adverse reactions reported in 2% or more of oral risperidone-treated adult patients with schizophrenia in three 4- to 8-week, double-blind, placebo-controlled trials.

Table 5: Adverse Reactions in ≥2% of Oral Risperidone-Treated Adult Patients (and greater than placebo) with Schizophrenia in Double-Blind, Placebo-Controlled Trials

	Percentage of Patients Reporting Reaction		
	Oral Risperidone		
System/Organ Class Adverse Reaction	2 mg to 8 mg per day (N=366)	>8 mg to 16 mg per day (N=198)	Placebo (N=225)
Cardiac Disorders			
Tachycardia	1	3	0
Eye Disorders			
Vision blurred	3	1	1
Gastrointestinal Disorders			
Nausea	9	4	4
Constipation	8	9	6
Dyspepsia	8	6	5
Dry mouth	4	0	1
Abdominal discomfort	3	1	1
Salivary hypersecretion	2	1	<1
Diarrhea	2	1	1
General Disorders			
Fatigue	3	1	0
Chest pain	2	2	1
Asthenia	2	1	<1
Infections and Infestations			
Nasopharyngitis	3	4	3
Upper respiratory tract infection	2	3	1
Sinusitis	1	2	1
Urinary tract infection	1	3	0
Investigations			
Blood creatine phosphokinase increased	1	2	<1
Heart rate increased	<1	2	0
Musculoskeletal and Connective Tissue Disorders			
Back pain	4	1	1
Arthralgia	2	3	<1
Pain in extremity	2	1	1
Nervous System Disorders			
Parkinsonism*	14	17	8
Akathisia*	10	10	3
Sedation	10	5	2
Dizziness	7	4	2
Dystonia*	3	4	2
Tremor*	2	3	1
Dizziness postural	2	0	0
Psychiatric Disorders			
Insomnia	32	25	27
Anxiety	16	11	11
Respiratory, Thoracic and Mediastinal Disorders			
Nasal congestion	4	6	2
Dyspnea	1	2	0
Epistaxis	<1	2	0
Skin and Subcutaneous Tissue Disorders			
Rash	1	4	1
Dry skin	1	3	0
Vascular Disorders			
Orthostatic hypotension	2	1	0

*Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, parkinsonism, cogwheel rigidity, akinesia, bradykinesia, hypokinesia, masked facies, muscle rigidity, and Parkinson's disease. Akathisia includes akathisia and restlessness. Dystonia includes dystonia, muscle spasms, muscle contractions involuntary, muscle contracture, oculogyration, tongue paralysis. Tremor includes tremor and parkinsonian rest tremor.

Other Adverse Reactions Observed During the Clinical Trial Evaluations of Oral Risperidone

The following is a list of additional adverse drug reactions that have been reported during the clinical trial evaluation of oral risperidone:

Blood and Lymphatic System Disorders: anemia, granulocytopenia, neutropenia

Cardiac Disorders: sinus bradycardia, sinus tachycardia, atrioventricular block first degree, bundle branch block left, bundle branch block right, atrioventricular block

Ear and Labyrinth Disorders: ear pain, tinnitus

Endocrine Disorders: hyperprolactinemia

Eye Disorders: ocular hyperemia, eye discharge, conjunctivitis, eye rolling, eyelid edema, eye swelling, eyelid margin crusting, dry eye, lacrimation increased, photophobia, glaucoma, visual acuity reduced

Gastrointestinal Disorders: dysphagia, fecaloma, fecal incontinence, gastritis, lip swelling, cheilitis, aptyalism

General Disorders: edema peripheral, thirst, gait disturbance, chest discomfort, chest pain, influenza-like illness, pitting edema, edema, chills, sluggishness, malaise, face edema, discomfort, generalized edema, drug withdrawal syndrome, peripheral coldness, feeling abnormal

Immune System Disorders: drug hypersensitivity

Infections and Infestations: pneumonia, influenza, ear infection, viral infection, pharyngitis, tonsillitis, bronchitis, eye infection, localized infection, cystitis, cellulitis, otitis media, onychomycosis, acarodermatitis, bronchopneumonia, respiratory tract infection, tracheobronchitis, otitis media chronic

Investigations: body temperature increased, blood prolactin increased, alanine aminotransferase increased, electrocardiogram abnormal, eosinophil count increased, white blood cell count decreased, blood glucose increased, hemoglobin decreased, hematocrit decreased, body temperature decreased, blood pressure decreased, transaminases increased

Metabolism and Nutrition Disorders: decreased appetite, polydipsia, anorexia

Musculoskeletal, Connective Tissue, and Bone Disorders: joint swelling, joint stiffness, musculoskeletal chest pain, posture abnormal, myalgia, neck pain, muscular weakness, muscle rigidity, rhabdomyolysis

Nervous System Disorders: balance disorder, disturbance in attention, dysarthria, unresponsive to stimuli, depressed level of consciousness, movement disorder, transient ischemic attack, coordination abnormal, cerebrovascular accident, speech disorder, syncope, loss of consciousness, hypoesthesia, tardive dyskinesia, cerebral ischemia, cerebrovascular disorder, neuroleptic malignant syndrome, diabetic coma, head titubation

Psychiatric Disorders: agitation, blunted affect, confusional state, middle insomnia, nervousness, sleep disorder, listlessness, libido decreased, anorgasmia

Renal and Urinary Disorders: enuresis, dysuria, pollakiuria, urinary incontinence

Reproductive System and Breast Disorders: menstruation irregular, amenorrhea, gynecomastia, galactorrhea, vaginal discharge, menstrual disorder, erectile dysfunction, retrograde ejaculation, ejaculation disorder, sexual dysfunction, breast enlargement

Respiratory, Thoracic, and Mediastinal Disorders: wheezing, pneumonia aspiration, sinus congestion, dysphonia, productive cough, pulmonary congestion, respiratory tract congestion, rales, respiratory disorder, hyperventilation, nasal edema

Skin and Subcutaneous Tissue Disorders: erythema, skin discoloration, skin lesion, pruritus, skin disorder, rash erythematous, rash papular, acne, hyperkeratosis, seborrheic dermatitis, rash generalized, rash maculopapular

Vascular Disorders: hypotension, flushing

Discontinuations Due to Adverse Drug Reactions with Oral Risperidone

Approximately 7% (39/564) of oral risperidone-treated patients in double-blind, placebo-controlled trials discontinued treatment due to an adverse reaction, compared with 4% (10/225) who were receiving placebo. The adverse reactions associated with discontinuation in 2 or more oral risperidone-treated patients were:

Table 6: Adverse Reactions Associated with Discontinuation in ≥2% of Oral Risperidone-Treated Adult Patients in Schizophrenia Trials

	Oral Risperidone		
Adverse Reaction	2 mg to 8 mg per day (N=366)	>8 mg to 16 mg per day (N=198)	Placebo (N=225)
Dizziness	1.4%	1%	0%
Nausea	1.4%	0%	0%
Vomiting	0.8%	0%	0%
Parkinsonism	0.8%	0%	0%
Somnolence	0.8%	0%	0%
Dystonia	0.5%	0%	0%
Agitation	0.5%	0%	0%
Abdominal pain	0.5%	0%	0%
Orthostatic hypotension	0.3%	0.5%	0%
Akathisia	0.3%	2%	0%

Discontinuation for extrapyramidal symptoms (including Parkinsonism, akathisia, dystonia, and tardive dyskinesia) was 1% in placebo-treated patients, and 3.4% in active control-treated patients in a double-blind, placebo- and active-controlled trial.

Dose Dependency of Adverse Reactions in Clinical Trials of Oral Risperidone

Extrapyramidal Symptoms

Data from two fixed-dose trials in adults with schizophrenia provided evidence of dose-relatedness for extrapyramidal symptoms associated with oral risperidone treatment. Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of oral risperidone (2, 6, 10, and 16 mg/day), including

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(1) a Parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Table 7: Extrapyramidal Symptoms Associated with Oral Risperidone-Treated Adult Patients in an 8-Week Fixed Dose Schizophrenia Trial

Dose Groups	Placebo	Oral Risperidone 2 mg	Oral Risperidone 6 mg	Oral Risperidone 10 mg	Oral Risperidone 16 mg
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	17%	21%	21%	35%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of oral risperidone (1, 4, 8, 12, and 16 mg/day):

Table 8: Extrapyramidal Symptoms Associated with Oral Risperidone-Treated Adult Patients in an 8-Week Fixed Dose Schizophrenia Trial

Dose Groups	Oral Risperidone 1 mg	Oral Risperidone 4 mg	Oral Risperidone 8 mg	Oral Risperidone 12 mg	Oral Risperidone 16 mg
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	17%	18%	20%

Changes in Body Weight

Weight gain was observed in short-term, controlled trials and longer-term uncontrolled studies in adults *[see Warnings and Precautions (5.5) and Adverse Reactions (6)]*.

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Other Adverse Reactions

Adverse reaction data elicited by a checklist for side effects from a large study comparing 5 fixed doses of oral risperidone (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse reactions: somnolence, vision abnormal, dizziness, palpitations, weight increase, erectile dysfunction, ejaculation disorder, sexual function abnormal, fatigue, and skin discoloration.

Changes in ECG

Between-group comparisons for pooled placebo-controlled trials of oral risperidone in adults revealed no statistically significant differences between oral risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all oral risperidone doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of oral risperidone were associated with a higher mean increase in heart rate compared to placebo (4 to 6 beats per minute).

Injection Site Reactions with UZEDY

Local tolerability assessments were administered to patients who reported injection site adverse reactions in a randomized withdrawal study with UZEDY in adult patients with schizophrenia. The injection site was assessed by appropriately trained personnel throughout the clinical development program.

All injection site reactions (nodule, pruritus, erythema, mass, and swelling) were mild to moderate in severity with the exception of 1 case of severe pruritus which resolved after 6 days. Injection site reactions were reported in 22 patients (13%) in the placebo group, 36 patients (20%) in the UZEDY once monthly group, and 37 patients (21%) in the UZEDY once every 2 months group. The most common injection site reactions were: nodule (7% in each UZEDY-treated group and 3% in the placebo group) and pruritus (5% and 3% in the UZEDY-treated once monthly and once every 2 months groups, respectively, and 2% in the placebo group).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of oral risperidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions include: alopecia, anaphylactic reaction, angioedema, atrial fibrillation, cardiopulmonary arrest, catatonia, diabetic ketoacidosis in patients with impaired glucose metabolism, dysgeusia, hypoglycemia, hypothermia, ileus, inappropriate antidiuretic hormone secretion, intestinal obstruction, jaundice, mania, pancreatitis, pituitary adenoma, precocious puberty, pulmonary embolism, QT prolongation, sleep apnea syndrome, somnambulism, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), sudden death, thrombocytopenia, thrombotic thrombocytopenic purpura, urinary retention, and water intoxication.

Postmarketing cases of extrapyramidal symptoms (dystonia and dyskinesia) have been reported in patients concomitantly taking methylphenidate and risperidone when there was an increase or decrease in dosage, initiation, or discontinuation of either or both medications.

7 DRUG INTERACTIONS

The interactions of UZEDY with co-administration of other drugs have not been studied. The drug interaction data provided in this section is based on studies with oral risperidone.

7.1 Drugs Having Clinically Important Interactions with UZEDY

Table 9 includes clinically significant drug interactions with UZEDY.

Table 9: Clinically Important Drug Interactions with UZEDY

Strong CYP2D6 Inhibitors	
Clinical Impact:	Concomitant use of UZEDY with strong CYP2D6 inhibitors may increase the plasma exposure of risperidone and lower the plasma exposure of a major active metabolite, 9-hydroxyrisperidone.
Intervention:	When initiation of strong CYP2D6 inhibitors is considered, patients may be placed on the lowest dose (50 mg once monthly or 100 mg once every 2 months) of UZEDY prior to the planned start of strong CYP2D6 inhibitors to adjust for the expected increase in plasma concentrations of risperidone. When strong CYP2D6 inhibitors are initiated in patients receiving UZEDY 50 mg once monthly or 100 mg once every 2 months, it is recommended to continue treatment with the same dose unless clinical judgment necessitates interruption of UZEDY treatment. The effects of discontinuation of strong CYP2D6 inhibitors on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied *[see Clinical Pharmacology]*.
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of UZEDY and a strong CYP3A4 inducer may cause decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone which could lead to decreased efficacy of UZEDY.
Intervention:	Changes in efficacy and safety should be carefully monitored with any dose adjustment of UZEDY. At the initiation of therapy with a strong CYP3A4 inducer, patients should be closely monitored during the first 4 to 8 weeks. In patients receiving UZEDY at a specific dose, consider increasing the dose to the next highest dose. In patients receiving UZEDY 125 mg once monthly or 250 mg once every 2 months, additional oral risperidone therapy may need to be considered. On discontinuation of a strong CYP3A4 inducer, the dosage of UZEDY or any additional oral risperidone therapy should be reevaluated and, if necessary, decreased to adjust for the expected increase in plasma concentration of risperidone and 9-hydroxyrisperidone. For patients treated with UZEDY 50 mg once monthly or UZEDY 100 mg once every 2 months discontinuing from a strong CYP3A4 inducer, it is recommended to continue treatment with the same dose unless clinical judgment necessitates interruption of UZEDY treatment.
Centrally-Acting Drugs and Alcohol	
Clinical Impact:	Due to additive pharmacologic effects, the concomitant use of centrally-acting drugs, including alcohol, may increase nervous system disorders.
Intervention:	Caution should be used when UZEDY is administered in combination with other centrally-acting drugs or alcohol.
Hypotensive Agents	
Clinical Impact:	Because of its potential for inducing hypotension, UZEDY may enhance the hypotensive effects of other therapeutic agents with this potential.
Intervention:	Caution should be used when UZEDY is administered with other therapeutic effects of other therapeutic agents with this potential.
Dopamine Agonists	
Clinical Impact:	Agents with central antidopaminergic activity such as UZEDY may antagonize the pharmacologic effects of dopamine agonists.
Intervention:	Caution should be used when UZEDY is administered in combination with levodopa and dopamine agonists.
Methylphenidate	
Clinical Impact:	Concomitant use with methylphenidate, when there is change in dosage of either medication, may increase the risk of extrapyramidal symptoms (EPS) *[see Adverse Reactions (6.2)]*.
Intervention:	Monitor for symptoms of EPS with concomitant use of UZEDY and methylphenidate.

7.2 Drugs Having No Clinically Important Interactions with UZEDY

Based on pharmacokinetic studies with oral risperidone, no dosage adjustment of UZEDY is required when administered concomitantly with amitriptyline, cimetidine, ranitidine, clozapine, topiramate, and moderate CYP3A4 inhibitors (erythromycin). Additionally, no dosage adjustment is necessary for lithium, valproate, topiramate, digoxin, and CYP2D6 substrates (donepezil and galantamine) when co-administered with UZEDY.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including UZEDY, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at *http://womensmentalhealth.org/clinicaland-research-programs/pregnancyregistry/*.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery (*see Clinical Considerations*). Overall, available data from published epidemiologic studies of pregnant women exposed to risperidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (*see Data*). There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including UZEDY, during pregnancy (*see Clinical Considerations*).

Oral administration of risperidone to pregnant mice caused cleft palate at doses 3- to 4-times the oral maximum recommended human dose (MRHD) of 16 mg/day with maternal toxicity observed at 4-times MRHD based on mg/m^2 body surface area. Risperidone was not teratogenic in rats or rabbits at doses up to 6-times the oral MRHD based on mg/m^2 body surface area. Increased stillbirths and decreased birth weight occurred after oral risperidone administration to pregnant rats at 1.5-times the oral MRHD based on mg/m^2 body surface area. Learning was impaired in offspring of rats when the dams were dosed at 0.6-times the oral MRHD and offspring mortality increased at doses 0.1- to 3-times the oral MRHD based on mg/m^2 body surface area.

The background risks of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

There is a risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including risperidone, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone demonstrated placental passage of risperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR = 1.26, 95% CI = 1.02 to 1.56) and of cardiac malformations (RR = 1.26, 95% CI = 0.88 to 1.81) in a subgroup of 1566 women exposed to risperidone during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal data

No developmental toxicity studies were conducted with subcutaneous risperidone suspension.

Oral administration of risperidone to pregnant mice during organogenesis caused cleft palate at 10 mg/kg/day which is 3-times the oral MRHD of 16 mg/day based on mg/m^2 body surface area; maternal toxicity occurred at 4-times the oral MRHD. Risperidone was not teratogenic when administered orally to rats at 0.6 to 10 mg/kg/day and rabbits at 0.3 to 5 mg/kg/day, which are up to 6-times the oral MRHD of 16 mg/day risperidone based on mg/m^2 body surface area. Learning was impaired in offspring of rats dosed orally throughout pregnancy at 1 mg/kg/day which is 0.6-times the oral MRHD and neuronal cell death increased in fetal brains of offspring of rats dosed during pregnancy at 1 and 2 mg/kg/day which are 0.6- and 1.2-times the oral MRHD based on mg/m^2 body surface area; postnatal development and growth of the offspring were also delayed.

Rat offspring mortality increased during the first 4 days of lactation when pregnant rats were dosed throughout gestation at 0.16 to 5 mg/kg/day which are 0.1- to 3-times the oral MRHD of 16 mg/day based on mg/m^2 body surface area. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams; a no-effect dose could not be determined. The rate of stillbirths was increased at 2.5 mg/kg or 1.5-times the oral MRHD based on mg/m^2 body surface area.

In a rat cross-fostering study the number of live offspring was decreased, the number of stillbirths increased, and the birth weight was decreased in offspring of drug-treated pregnant rats. In addition, the number of deaths increased by Day 1 among offspring of drug-treated pregnant rats, regardless of whether or not the offspring were cross-fostered. Risperidone also appeared to impair maternal behavior in that offspring body weight gain and survival (from Day 1 to 4 of lactation) were reduced in offspring born to control but reared by drug-treated dams. All of these effects occurred at 5 mg/kg which is 3-times the oral MRHD based on mg/m^2 and the only dose tested in the study.

8.2 Lactation

Risk Summary

Limited data from published literature reports the presence of risperidone and its metabolite, 9-hydroxyrisperidone, in human breast milk at relative infant dose ranging between 2.3 and 4.7% of the maternal weight-adjusted dosage. There are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to risperidone *(see Clinical Considerations)*.

There is no information on the effects of risperidone on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for UZEDY and any potential adverse effects on the breastfed child from UZEDY or from the mother's underlying condition.

Clinical Considerations

Infants exposed to UZEDY through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of risperidone (D_2 receptor antagonism), treatment with UZEDY may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.6)]*.

8.4 Pediatric Use

The safety and effectiveness of UZEDY have not been established in pediatric patients.

Juvenile Animal Toxicity Data

No juvenile animal studies were conducted with subcutaneous risperidone suspension.

Juvenile dogs were treated with oral risperidone from weeks 10 to 50 of age (equivalent to the period of childhood through adolescence in humans), at doses of 0.31, 1.25, or 5 mg/kg/day. Bone length and density were decreased with a no-effect dose of 0.31 mg/kg/day; this dose produced plasma AUC of risperidone plus its active metabolite paliperidone (9-hydroxyrisperidone) that were similar to those in children and adolescents receiving the oral MRHD of 6 mg/day. In addition, sexual maturation was delayed at all doses in both males and females. The above effects showed little or no reversibility in females after a 12 week drug-free recovery period.

Juvenile rats, treated with oral risperidone from days 12 to 50 of age (equivalent to the period of infancy through adolescence in humans) showed impaired learning and memory performance (reversible only in females), with a no-effect dose of 0.63 mg/kg/day which is 0.5 times the oral MRHD of 6 mg/day for children, based on mg/m^2 body surface area. This dose produced plasma AUC of risperidone plus paliperidone about half the exposure observed in humans at the oral MRHD. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest tested dose of 1.25 mg/kg/day which is 1 time the oral MRHD and produced plasma AUC of risperidone plus paliperidone that were about two thirds of those observed in humans at the oral MRHD of 6 mg/day for children.

8.5 Geriatric Use

Clinical studies of UZEDY in the treatment of schizophrenia did not include patients older than 65 years to determine whether or not they respond differently from younger patients. In general, dose selection for geriatric patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

UZEDY is substantially excreted by the kidneys, and the risk of reactions may be greater in patients with impaired renal function. Because geriatric patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Warnings and Precautions (5.7)]*.

Elderly patients with dementia-related psychosis treated with UZEDY are at an increased risk of death compared to placebo. UZEDY is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1, 5.2)]*.

8.6 Renal Impairment

In patients with renal impairment, titrate with oral risperidone (up to at least 2 mg daily) before initiating treatment with UZEDY.

UZEDY was not studied in patients with renal impairment.

8.7 Hepatic Impairment

In patients with hepatic impairment, titrate with oral risperidone (up to at least 2 mg daily) before initiating treatment with UZEDY*]*.

UZEDY has not been studied in patients with hepatic impairment; however, such effect has been investigated with oral risperidone.

8.8 Patients with Parkinson's Disease or Dementia with Lewy Bodies

Patients with Parkinson's disease or dementia with Lewy bodies can experience increased sensitivity to UZEDY. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

Manufactured for:
Teva Neuroscience, Inc.
Parsippany, NJ 07054

This Brief Summary is based on the full Prescribing Information for UZEDY UZE-002.

teva

RIS-40300 May 2023

might help patients who use substances as a tool to improve their ability to socialize.

Financial issues.
While many oral antipsychotics have generic equivalents, some newer agents may not appear on a patient's formulary. Even copays can be burdensome to a patient who is unemployed or on disability. As part of the ongoing dialogue, regularly ask if medication access is a problem, says Dr. Rubio, as formularies and copayment

"EXPLAIN THAT DOPAMINE SIGNALS CAN CAUSE THE BRAIN TO GENERATE MISPERCEPTIONS, AND MEDICATIONS ARE DESIGNED TO NORMALIZE OR REBALANCE THESE SIGNALS."
—Erik Messamore, MD, PhD

costs can change, often within the same year. If medication access is a problem, involve a social worker who can connect the patient with assistance programs. Also, The Medicine Program (*themedicineprogram.com*) can help patients and their caregivers or social workers sift through and enroll in assistance programs for prescription medication. Qualified patients can also get help from organizations such as the Partnership for Prescription Assistance (*pparx.org*), *NeedyMeds.org* and the Dispensary of Hope (*dispensaryofhope.org*). ●

–by Pete Kelly

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PATIENT: FRANK, 24, WAS DIAGNOSED WITH SCHIZOPHRENIA AFTER BEING HOSPITALIZED 2 YEARS AGO.

"The switch to an LAI helped him regain lasting stability"

PHYSICIAN:

Christoph U. Correll, MD

Professor of Psychiatry and Molecular Medicine, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY

Illustration by Juhee Kim

History:
Frank was working as a car mechanic and became increasingly withdrawn and noncommunicative. He refused to go to work, had decreasing hygiene, didn't leave the house, stopped interacting with friends and spent most of his time on the internet. When he visited his family, Frank refused to eat with them and had meals alone in his room. His parents brought him to the hospital after he attacked his brother, whom he accused of trying to sell his brain to the "medical mafia." In the hospital, Frank was given aripiprazole, which did not resolve his symptoms, and a higher dose made him restless. He was then switched to risperidone, on which Frank improved, and he was discharged back to his parents' home.

Over the next several weeks, Frank's hallucinations and delusions resolved, but he was notably depressed. An SSRI was added, which helped resolve the depression. Over the next few months, Frank's psychosis resurfaced intermittently, and he became paranoid and started hearing voices. This prevented him from returning to work or socializing. He refused to increase the risperidone dose, stating that he had been on a higher dose in the hospital and did not like the feeling. Frank also disclosed he had reduced the dose of risperidone and, at times, skipped it entirely because he was upset that he had gained 14 lbs. He was given metformin and titrated up weekly to the highest dose. This change, together with walking more outside with his brother, helped Frank lose weight, but his psychotic symptoms continued to resurface, and he was unable to return to psychosocial and vocational functioning.

Initiating treatment:
During an appointment, Frank voiced some ambivalence regarding his medication due to adverse effects and said he may forget to take it at times. Given this, we discussed the option of risperidone LAI with him and his parents, aiming for more stability and reliability of the medication levels. By addressing his personal goals to reconnect with friends, return to work and eventually live independently again, he agreed to try once-monthly risperidone LAI. We also discussed switching to twice-monthly risperidone LAI in the future, making it even easier to be on the medication without having to think about his illness.

With motivational interviewing and the help of his parents, he agreed to try risperidone LAI. After the change, his positive psychotic symptoms did not resurface. The symptomatic stability allowed Frank to start group therapy with patients his own age, providing support and social contact even outside of the therapy setting. He also entered a supported employment program, which helped him return to work. However, both he and his parents agreed that it was safer for him to live with them so they could help him with his daily needs, including getting to work on time.

Considerations:
Research shows LAIs are associated with a lower risk of relapse and hospitalization than oral agents. The switch to an LAI helped Frank regain lasting symptomatic stability that allowed him to take advantage of psychosocial treatments and make strides toward social and vocational autonomy. Not being reminded of his illness daily by needing to take oral medications, and the prospect of being able to move closer to achieving his life goals, were important factors for Frank when making his decision to try the LAI option. This change of course ultimately worked for him and made a big difference in his life. ●

NEW!
KOL ON DEMAND VIDEO
Scan here for more insight on Frank's case

Q&A

Expert insight on managing schizophrenia

Treating negative symptoms

Q: What are some strategies for treating social withdrawal and lack of motivation?

A: Negative symptoms of schizophrenia are notoriously hard to treat or even address. A recurring theme in all my discussions with patients and their families or caregivers is the importance of psychoeducation and their involvement in the patient's life. For example, patients and their caregivers must know what to expect when they are diagnosed—that is, their prognosis and the limitations of antipsychotic medications.

I'd first emphasize the importance of adhering to antipsychotic medications. Addressing negative symptoms such as social withdrawal and amotivation will be difficult without control of positive symptoms. In addition, connecting patients with social workers and/or social service organizations can help them navigate society after treatment and avoid the isolation that frequently accompanies schizophrenia. For patients who are even more impaired, I would advise that their family members encourage the person to join them in daily activities, such as grocery shopping or going to the gym, which could make a difference. Managing and monitoring medication side effects, including weight gain and sedation, can also indirectly decrease social withdrawal, amotivation and anergia.

—Ragy R. Girgis, MD, MS, *Associate Professor of Clinical Psychiatry, Department of Psychiatry, Columbia University, and New York State Psychiatric Institute*

Managing weight gain

Q: How can HCPs help patients avoid weight gain due to side effects of antipsychotics?

A: Weight gain, overweight and obesity are major problems in schizophrenia. First, providers must always monitor their patients' weight and medical status. Preventing weight gain is always easier than losing it. Fortunately, there are a number of strategies available for keeping weight gain in check. For example, there are data that show medications such as metformin, topiramate and GLP-1 agonists can minimize weight gain associated with antipsychotic medication.

Speaking with patients about healthy eating habits and exercise is always a good idea. Many do not understand concepts such as counting calories, avoiding processed foods and limiting fat and carbohydrates. Highly processed fast foods, which are cheap and readily available, tend to be high in fat, sugar and sodium. Teaching patients about the health risks of these sorts of foods is helpful.

In combination with diet, exercise is one of the most important preventive and therapeutic interventions available. It's important to emphasize that exercise does not necessarily mean doing 200-meter sprints or heavy weight lifting. Many individuals with schizophrenia are sedentary, and the only physical activity they get might be walking between rooms in their homes. Encouraging even slightly more physical movement, as medically indicated and safe, such as taking the stairs instead of an elevator, is a key strategy for preventing weight gain associated with treatment with antipsychotic medications.

—Ragy R. Girgis, MD, MS

Educating caregivers

Q: Is there any education you offer to family members apart from what you provide to patients?

A: Family members play a huge role in helping patients manage their schizophrenia. Patients often depend (consciously or unconsciously) on the insight that family members offer when it comes to taking their medications. Patients also often rely on them for motivation and energy if their own are lacking. For example, negative symptoms can cause patients to be uninterested in leaving their homes. Encouragement from family members may be all that is needed to motivate patients to get out of the house and engage in some sort of activity.

Again, psychoeducation about a patient's condition and its prognosis should always be given to patients and their family members. Many clinicians strongly recommend that family members join patients at appointments to hear the clinician's assessment and report on a patient's symptoms. This is particularly important for those with schizophrenia, who often lack insight and/or may be paranoid or embarrassed by their condition.

I would rarely offer specific education to family members apart from what I provide to patients. It is important for the therapeutic alliance, and to avoid becoming the object of paranoia, to remain open with patients with schizophrenia. This includes avoiding the appearance of hiding something from them, even if what is discussed, such as a prognosis, is discouraging to hear.

—Ragy R. Girgis, MD, MS

Revealing a diagnosis

Q: How do you help patients who are reluctant to reveal their diagnosis to other people?

A: This is tricky, and there is no easy answer. A lot depends on their symptom control, especially their level of negative symptoms, as patients with higher levels of negative symptoms don't overtly care as much about how they are perceived by others. For many patients, however, this is a real issue, and I recommend being open and honest early on in a relationship. That said, it's a good idea for patients to work with a therapist before revealing their diagnosis, including at work, so they can reason it out as clearly as possible and make the decision on when and how to approach these conversions.

In addition, many people with schizophrenia find comfort with others who are mentally ill, which limits the impact of stigma, and would benefit from joining a support group. More broadly, we as physicians should do our best to give people autonomy in their treatment choices.

—Joshua Kantrowitz, MD, *Director, Columbia University Schizophrenia Research Center, Associate Professor of Clinical Psychiatry, Department of Psychiatry, Columbia University*

Illustration by undrey

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Clinician Update

EXAM TOOL

Assessing adherence to antipsychotic medication

Nonadherence to antipsychotics is common among patients with schizophrenia—and is often the cause of relapse. Not only does this increase the risk of harmful behaviors and suicide, it also impacts every area of a patient's life, from their ability to work to the quality of their relationships. However, many patients who have trouble taking oral medication are not being offered long-acting injectable (LAI) antipsychotics, which can improve adherence and are recommended as an option by the American Psychiatric Association. To help gauge a patient's adherence and if their treatment is working, consider the following criteria.

Questions about symptoms[1]

	Rarely	Sometimes	Often
1. I feel the world around me is strange	☐	☐	☐
2. I hear or see things that are not there (e.g., voices)	☐	☐	☐
3. I can't concentrate or remember things	☐	☐	☐
4. I have trouble making decisions or doing chores (e.g., cleaning, shopping)	☐	☐	☐
5. I feel tired and sluggish	☐	☐	☐
6. I sleep too much or too little	☐	☐	☐
7. I feel sad or anxious	☐	☐	☐
8. I don't trust people	☐	☐	☐
9. I feel people don't understand me	☐	☐	☐
10. I have no interest in social activities	☐	☐	☐
11. I use things to feel better or deal with problems (e.g., smoke, drink alcohol, take something to feel alert)	☐	☐	☐

Questions about medication[2]

1. I don't like how my medication makes me feel	☐ True	☐ False
2. Sometimes I forget to take my medication, or can't remember if I took it	☐ True	☐ False
3. I only take my medication when I think I need it	☐ True	☐ False
4. I don't like taking daily medication because it reminds me I have an illness	☐ True	☐ False
5. Family and friends think my medication is good for me	☐ True	☐ False
6. I feel my medication is helping me	☐ True	☐ False
7. I feel the good things about taking my medication (e.g., staying out of the hospital, being able to work) are worth the effort	☐ True	☐ False

SOURCES: 1. Iancu I, et al. The Positive and Negative Symptoms Questionnaire: a self-report scale in schizophrenia. *Compr Psychiatry*. 2005;46(1):61-66.
2. Hogan TP, et al. A self-report scale predictive of drug compliance in schizophrenics (Drug Attitude Inventory). *Psychol Med*. 1983;13(1):177-183.