Treatment of Behavior Disorders in Mental Retardation: Report on Transitioning to Atypical Antipsychotics, With an Emphasis on Risperidone

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Background: Mental illnesses are more common in people with mental retardation and developmental disabilities than in the general population. Due to the difficulty of making specific psychiatric diagnoses in these patients, the target of medication is often a behavioral symptom. For many symptoms, antipsychotic medications are effective, but the serious side effect profile of conventional antipsychotics renders their use problematic. Recent findings concerning the safety and efficacy of atypical antipsychotics for control of certain disruptive behaviors in adults and children led a Special Topic Advisory Panel to draw up guidelines for transitioning patients with specific symptoms from classical antipsychotics to risperidone and, by extrapolation, to other atypical agents.

Participants: Participants were chosen by Janssen Pharmaceutica, based on individual achievements and lifetime experience. The Special Topic Advisory Panel on Transitioning to Risperidone Therapy in Patients With Mental Retardation and Developmental Disabilities comprised academic clinicians with at least 10 years' experience in the field of mental retardation and developmental disabilities. It included a clinical pharmacist, consultant pharmacists, a certified developmental disabilities nurse, psychiatrists, a family physician, and a psychologist.

Evidence: The Panel considered recent studies of the efficacy and tolerability of risperidone and other atypical antipsychotics in adults and children with mental retardation and developmental disabilities. MEDLINE searches were conducted using the name of each atypical antipsychotic and the following terms: *mental retardation, developmental disabilities,* and *behavior disorders*. Searches were conducted starting in July 2002 and done periodically through April 2004 to capture new additions to the literature. Searches were confined to English.

Guidelines Process: The Panel reviewed the available evidence, identified optimal doses and titration schedules, considered instruments and rating scales for assessing symptoms, and developed guidelines.

Conclusions: The guidelines set forth initial and target doses and titration schedules of risperidone therapy for some behavioral symptoms and provide recommendations concerning withdrawal of previous medications and for procedures and rating scales for assessing symptoms. In patients with severe retardation, the goal is often to identify specific target behaviors rather than to pursue an exact diagnosis, which may be unattainable.

(J Clin Psychiatry 2004;65:1197–1210)

Received March 18, 2003; accepted June 16, 2004. From The Nisonger Center, Ohio State University, Columbus (Dr. Aman); and Janssen Pharmaceutica, Titusville, N.J. (Dr. Gharabawi).

Supported by a grant from Janssen Research Foundation, Titusville, N.J.

Dr. Aman has received grant/research support from Janssen and Eli Lilly and has participated in speakers or advisory boards for Janssen. Dr. Gharabawi is an employee of Janssen Medical Affairs, LLC.

A complete list of the members of the Special Topic Advisory Panel appears at the end of this article.

This set of guidelines is intended to provide general suggestions for clinical practice. When treating individual patients, practitioners should use their own clinical judgment, taking into account that patient's unique health care needs. No claim is made for the appropriateness or validity of these guidelines for any given patient.

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Although it was once thought that people with mental retardation could not develop emotional disorders,[1] mental health professionals now recognize that such problems are much more common in this population than among people of normal intelligence. The pioneering Isle of Wight studies of Rutter et al.[2] revealed that although 7% of 10- to 12-year-old children had psychiatric disorders, such disorders were much more frequent in children with intellectual retardation, with one third of the latter exhibiting clinically significant antisocial behavior. The high rate of emotional or behavioral disturbance among people with mental retardation may arise from difficulty in functioning within their social settings.[3]

Estimates of the rate of psychiatric and behavioral disturbance among children with mental retardation have ranged from 10% to 80%.[1] This wide variation has been attributed by Borthwick-Duffy[1] to a number of factors: (1)

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definitions of intellectual retardation, (2) differences in disorders included, (3) difficulties in discerning psychiatric disturbance in the context of mental retardation, (4) differences in ability of informants to recognize psychopathology, and (5) use of different screening methods. This latter point is underscored by Reiss' study[4] of 205 mentally retarded people attending community-based day programs. Only 12% of the attendees had notations in their case files suggesting the presence of a psychiatric disorder, but a diagnostic screening test carried out by caregivers, teachers, and supervisors and interviews conducted by clinical psychiatrists indicated that 39% to 60% of attendees had such disorders.

One of the most prominent and consistent psychopathologies identified among people with mental retardation is "aggressive, antisocial, and self-injurious behavior."[5] Except for self-injurious behavior, this constellation of features seems analogous to DSM-IV–defined disruptive behavior disorders.[6] Disruptive behavior disorders are subdivided into (1) conduct disorder, characterized by physical aggression, property destruction, theft, and lying; (2) oppositional defiant disorder, characterized by defiant, hostile, vindictive, or negativistic behavior; and (3) disruptive behavior disorder not otherwise specified.

Disruptive behaviors are among the most common mental health problems seen in people with mental retardation. Benson[7] reported that 40 of the first 130 patients referred to a mental health program for individuals with developmental disabilities exhibited conduct disorder; only the schizoid-unresponsive and psychotic disorders were equally common. In Reiss' study,[4] aggression was rated by informants as a problem in 21% of the people screened, and temper tantrums (usually considered a symptom of oppositional defiant disorder) were a problem in 14%.

As might be expected, the difficulty of diagnosis increases with severity of mental retardation. Respondents to the Expert Consensus Guidelines edited by Rush and Frances indicated that, in the presence of relatively severe mental retardation, they found it rather difficult to make any DSM-IV diagnosis except autism with confidence.[3]

MEDICATION USE IN PATIENTS WITH MENTAL RETARDATION/ DEVELOPMENTAL DISABILITIES

The use of psychotropic medication is very common among people with mental retardation. Frequency of medication use varies widely among settings including hospitals, intermediate-care facilities, community-based programs, and institutions. Rinck[8] noted that community-based antipsychotic use in 1993 varied from 5% to 42% depending on the particular study reported. Gauging rate of drug use is complicated by medication prescriptions that may vary over time in response to the availability of new drugs, changes in clinical thinking, and pressures resulting from societal perception that drugs were being overused.

Surveys of entire populations reduce these problems. Lund[9] found that 19% of the 302 Danish people with retardation he studied were being treated with psychotropic medications. The highest rate of usage (42%) was in long-stay hospitals. Specialized institutions for residents with mental retardation and halfway houses had psychotropic medication usage rates of around 20%, while among those living in the community, usage was less than 5%. Lund[9] also found a positive correlation between frequency of drug use and severity of retardation. Spreat et al.[10] found a somewhat higher overall prevalence of medication use (33%) among 3789 individuals receiving services from the Oklahoma mental retardation system. The highest usage occurred in intermediate-care facilities for patients with mental retardation, with next highest usage in nursing homes, while use in community-based settings was lower.

Historically, the majority of psychotropic drugs prescribed for people with mental retardation have been antipsychotics. Spreat et al.[10] found that two thirds of the medicines prescribed for this population were antipsychotics. Most studies supporting the labeling of antipsychotics as effective treatment for schizophrenia and other psychoses, including psychosis associated with mood disorders, have been conducted in people of normal intelligence. There have been only 4 positive reports in people with mental retardation.[11–14] In this population, antipsychotics are often used to control symptoms of aggression, self-injury, and destructive behavior. Although these aberrant behaviors are effectively suppressed by antipsychotic drugs,[15] many of the studies used to make these conclusions about the efficacy of antipsychotic drugs in controlling certain aberrant behaviors were flawed.

Baumeister et al.[15] reviewed data from 21 studies on the effect of antipsychotics on self-injurious behavior in individuals with mental retardation. Nineteen of the 21 studies found that antipsychotic agents decreased self-injury. A decrease in stereotypic behavior was observed in 12 of 14 studies reviewed, including 11 of the 12 studies the reviewers considered methodologically sound. Results for aggression were more mixed; of 17 studies, 14 showed a decrease in aggressive behavior. However, of 3 studies that the authors judged to be methodologically sound, 1 showed an increase in aggression, 1 showed a decrease, and 1 showed no effect. Of 26 studies on hyperactivity, 20 showed a decrease in hyperactivity in a majority of those treated or in the group as a whole.

Major limitations on the use of conventional antipsychotics include the risk of extrapyramidal symptoms in the short term and withdrawal or tardive dyskinesia in the long term. These risks are greatly reduced, although certainly not absent, with the newer, atypical antipsychotics,

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Table 1. Atypical Binding Profiles[a,b]

Drug and Effect	D_2	H_1	M_1	5-HT_{2A}	α_1	α_2
Drug						
Haloperidol	2.6 ± 0.5	260 ± 20	> 10,000	61 ± 3	17 ± 1	600 ± 100
Clozapine	210 ± 30	3.1 ± 0.5	9 ± 1	2.59 ± 0.01	6.8 ± 0.8	15.0 ± 0.6
Olanzapine	20 ± 3	0.087 ± 0.005	36 ± 5	1.48 ± 0.05	44 ± 4	280 ± 30
Quetiapine	770 ± 30	19 ± 1	1400 ± 200	31 ± 4	8.1 ± 0.9	80 ± 10
Risperidone	3.77 ± 0.04	5.2 ± 0.5	34,000 ± 3000	0.15 ± 0.02	2.7 ± 0.3	8 ± 1
Ziprasidone	2.6 ± 0.1	4.6 ± 0.4	2440 ± 80	0.12 ± 0.01	2.6 ± 0.3	154 ± 9
Effect of blockade	Positive symptom decrease EPS Endocrine effects	Sedation Weight gain	Memory dysfunction Anticholinergic effects Mitigate EPS	Negative symptom decrease Mitigate EPS	Postural hypertension Dizziness Reflex tachycardia	Antidepressant?

[a]Data from Richelson and Souder.[19]
[b]Equilibrium dissociation constants (K_d). Values are geometric means ± SEM in nM.
Abbreviation: EPS = extrapyramidal symptoms.

of which clozapine was the first. An important advantage of the atypical antipsychotics is their potential to offer greater efficacy against the negative symptoms of schizophrenia, such as social withdrawal, while providing comparable or improved efficacy against positive symptoms such as delusions and hallucinations.[16–18]

When compared with conventional antipsychotics, most atypical antipsychotics have higher affinities for the serotonin 5-HT_{2A} receptor than for the dopamine D_2 receptor,[16] which may account for some of the differences in pharmacologic action. Atypical antipsychotics may have great potential for treating behavioral disorders in people with mental retardation due to the drugs' improved safety/tolerability profile and unique neurochemical action.

Although the exact mechanism of action of atypical antipsychotics is unknown, much has been theorized about the relationship between receptor binding and clinical effects. Equilibrium dissociation constants, derived from in vitro radioligand binding assays, may provide clues about antipsychotic efficacy, safety, and tolerability.[19]

Many of the pharmacologic features of a drug can be predicted from its affinity for a particular type of receptor or receptors. Table 1 shows the affinities of currently available atypical antipsychotic drugs for a variety of receptors in postmortem normal human brain tissue (larger equilibrium dissociation constant [K_d] = less affinity of the drug for a particular receptor and less receptor inhibition[19]). Although the atypical antipsychotic aripiprazole was not included in the study on which Table 1 is based,[19] a recent study[20] using cloned human receptors indicates that aripiprazole has significant affinity for the 5-HT_{2A}, α_{1A}-adrenergic, and histaminic H_1 receptors. The functional actions of aripiprazole on cloned human D_2 receptors (agonism, partial agonism, or antagonism) appear to be cell-type selective.[20]

Antagonism of D_2 receptors is thought to cause an amelioration of the positive signs and symptoms of psychosis but may induce movement disorders and elevate serum prolactin levels. Blockade of serotonin 5-HT_{2A} receptors may be associated with an amelioration of negative, depressive, and anxiety symptoms and may help mitigate the risk of reversible movement disorders caused by increasing D_2-receptor occupancy.[21] Blockade of α_2-adrenergic receptors on serotonin neurons increases serotonin release, which may further contribute to the alleviation of negative, depressive, and anxiety symptoms. However, antagonism of α-adrenergic receptors, particularly α_1 receptors, may cause postural hypotension, dizziness, and a reflex form of tachycardia. It is theorized that antagonism of the histaminic H_1-receptor causes side effects such as sedation and weight gain, while antagonism of the muscarinic M_1 receptor may cause anticholinergic side effects such as confusion, delirium, dry mouth, blurred vision, and constipation.[19]

Aman and Madrid[16] identified 21 articles (4 clozapine, 1 olanzapine, and 16 risperidone studies) published between 1989 and 1999 on the use of atypical antipsychotics in patients with developmental disabilities including autism and pervasive developmental disorder. Six studies examined adults with mental retardation and a defined psychiatric disorder. Five of these (2 on clozapine and 3 on risperidone) found improvement in abnormal behavior, especially aggression, self-injury, and agitation. The sixth study, with risperidone, by Simon et al.,[22] showed that partial or complete substitution of risperidone for a conventional antipsychotic led to resolution of side effects with no change in behavior. Three other studies reviewed by Aman and Madrid[16] involved adults with mental retardation and behavior problems that were not associated with a specific psychiatric diagnosis. All 3 studies reported decreases in maladaptive behavior, including self-injury. Generally, the studies reviewed by Aman and Madrid[16] showed reductions in repetitive or compulsive behavior and self-injury. Individual studies reported reduced agitation, increased social awareness, and improved sleep hygiene.

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SPECIAL TOPIC ADVISORY PANEL ON TRANSITIONING TO RISPERIDONE THERAPY

The recent findings concerning the safety and efficacy of atypical antipsychotics for control of certain disruptive behaviors in adults and children led to a Special Topic Advisory Panel to draw up guidelines for transitioning patients with specific symptoms from classical antipsychotics to risperidone and, by extrapolation, to other atypical agents.

Participants: Janssen Pharmaceutica decided to convene a Special Topic Advisory Panel on Transitioning comprising academic clinicians with at least 10 years' experience in the field of mental retardation and developmental disabilities. It included a clinical pharmacist, consultant pharmacists, a certified developmental disabilities nurse, psychiatrists, a family physician, and a psychologist.

Evidence: The Panel considered recent studies of the efficacy and tolerability of risperidone and other atypical antipsychotics in adults and children with mental retardation and developmental disabilities.

Guidelines Process: The Panel reviewed the available evidence, identified optimal doses and titration schedules, considered instruments and rating scales for assessing symptoms, and developed guidelines.

Psychosocial treatment for children and adults with developmental disabilities, although beyond the scope of this article, is an important treatment modality that should be integrated with pharmacologic agents in a multidisciplinary care plan. (For a discussion of behavioral approaches to treatment for patients with mental retardation, see Reiss S., *Handbook of Challenging Behavior: Mental Health Aspects of Mental Retardation*. Worthington, Ohio: IDS Publishing Corporation, 1994:139–180.)

CURRENT GUIDELINES FOR ASSESSMENT, DIAGNOSIS, AND TREATMENT

Guidelines for the use of psychotropic medications in patients with mental retardation have been developed in response to the growing perception that these medications were being greatly overused.[23] While disruptive behaviors appear to be suppressed by antipsychotics, many health care workers are concerned that behaviors essential to the patient's habilitation and quality of life may also be suppressed.[23,24] In addition, the risk of developing tardive dyskinesia while being treated with conventional antipsychotics rendered treatment even more worrisome.

Recent guidelines indicate that health care practitioners are expected to identify a specific diagnosis or behavior as the target of treatment, use the most appropriate drug at the lowest effective dose, and monitor effectiveness. Most guidelines also encourage a detailed analysis of behavior with validated tools (see "Rating Scales" section below) to guide the choice and dose of drug treatment. Guidelines in most states encourage a multidisciplinary approach to treatment. Medication should ordinarily be used in conjunction with behavioral therapy.[3,23]

A Review of the Previously Published *Expert Consensus Guidelines for the Treatment of Psychiatric and Behavioral Problems in Mental Retardation*, Edited by A. John Rush and Allen Frances[3]

In addition to diagnostic and medication issues, these previously published guidelines[3] cover behavior therapy and acknowledge its importance in the overall treatment plan. However, such therapy lies outside the scope of this review.

Assessment and diagnosis.[3] All treatment must start with a thorough assessment of the patient, including a medical history and physical examination. Preferred methods of psychiatric and behavioral assessment included interviews with family or caregivers, direct observation, functional behavioral assessment, and evaluation of medication and side effects. Unstructured psychiatric interviews were recommended for patients with mild or moderate retardation. Use of standardized rating scales, other standardized tests, and laboratory tests are also appropriate. The Rush and Frances guidelines[3] also called for attention to environmental stressors, whether acute or chronic.

Psychotropic medication use: general principles. The Rush and Frances guidelines[3] recommend medication use if based on a psychiatric diagnosis or specific behavioral-pharmacologic hypothesis (i.e., reason to believe that a specific medication may help control an identified target behavior). In patients with mental retardation, initial doses of medication should be lower and escalation rates slower than in patients of normal intelligence. Maintenance and maximum doses should be no greater than for the general population. The possibility of dose reduction should be considered at regular intervals, but any reduction should be gradual. Drug trials should not be abandoned prematurely. The Rush and Frances guidelines[3] also recommend keeping the drug regimen as simple as possible.

Treatment effectiveness and side effects should both be evaluated rigorously. Treatment effectiveness is best evaluated by monitoring specific index behaviors using standard procedures such as direct observation or rating scales. Side effects should be monitored every 3 to 6 months or following any change in drug regimen. When antipsychotics are used, especially conventional antipsychotics, a standardized assessment instrument should be employed to check for tardive dyskinesia at intervals of 3 to 6 months (depending on the medication). The possibility of drug interactions should be considered whenever

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Table 2. Medications Recommended for Specific Disorders and Target Behaviors[a]

Condition	Recommended Medications
Schizophrenia	Newer atypical antipsychotics (e.g., risperidone, olanzapine), but clozapine becomes first-line following numerous failed trials of other antipsychotics; a long-acting depot antipsychotic may be considered (high second-line) when patient is noncompliant with oral medication.
Psychosis not otherwise specified	Newer atypical antipsychotic (e.g., risperidone, olanzapine)
Bipolar disorder, manic episode	Divalproex/valproic acid, with lithium also first-line for classic episodes
Bipolar disorder, depressive episode	Divalproex or lithium plus a selective serotonin reuptake inhibitor (SSRI), bupropion, or venlafaxine For psychotic depression add a new atypical antipsychotic (e.g., risperidone, olanzapine)
Major depressive disorder	SSRI
Posttraumatic stress disorder	SSRI
Obsessive-compulsive disorder	SSRI
Attention-deficit/hyperactivity disorder	Psychostimulant, atomoxetine[b]
Pica	No medication recommended; nutritional management SSRI considered second-line
Self-injurious behavior	Newer atypical antipsychotic (e.g., risperidone, olanzapine), anticonvulsant/mood stabilizer (e.g., divalproex/valproic acid, carbamazepine)
Physical aggression to people or property	Newer atypical antipsychotic (e.g., risperidone, olanzapine), anticonvulsant/mood stabilizer (e.g., divalproex/valproic acid, carbamazepine)
Nonaggressive agitation	Anticonvulsant/mood stabilizer
Suicidal ideation/behavior	SSRI
Anxiety	SSRI, buspirone
Hyperactivity	Psychostimulant, atomoxetine[b]
Insomnia	Trazodone
Psychiatric or behavioral problems in patients with comorbid epilepsy	Divalproex/valproic acid, carbamazepine

[a]Adapted with permission from Rush and Frances.[3]
[b]Added by present authors; not available at time of Expert Consensus Survey.

more than 1 medication is being given. Finally, it is important to assess whether the drug may be interfering with the patient's functional status and activities of daily living. Based on these data, the medication regimen should be reviewed at least every 3 months to determine whether the medication is still necessary and whether the dose is the lowest that can improve or stabilize the problem.

The Rush and Frances guidelines[3] discourage long-term use of p.r.n. medication orders, benzodiazepines, short-acting sedative–hypnotics (or any use of long-acting sedative–hypnotics), and anticholinergic medications (or any use in the absence of extrapyramidal symptoms); higher-than-usual doses of antipsychotic medications; and use of older anticonvulsants as psychotropic medications.

Medication recommendations for specific disorders and target behaviors.[3] Table 2 indicates the drug classes and, within each class, the drugs that the Rush and Frances guidelines[3] recommend as first-line therapy for each disorder or behavior. Classes and drugs are listed in order of the support received from the surveyed experts. For many conditions, the guidelines also indicate second-line medications that may be considered when first-line choices prove ineffective.

Long-term medication use. Although the Rush and Frances guidelines[3] suggest that dose reduction or discontinuation should be periodically considered, DSM-IV diagnoses of schizophrenia, bipolar disorder, or frequently recurrent major depression may call for long-term maintenance therapy. Such is also the case in psychotic disorder not otherwise specified and in obsessive-compulsive disorder. In addition, dose reduction or withdrawal is usually inadvisable in the continued presence of symptoms such as psychosis or severe aggression, when the patient has relapsed during a previous attempt at discontinuation, or when there is a history of very severe symptoms, severe self-injurious behavior, or significant aggression. Other identified situations that might make it inadvisable to discontinue a drug include: (1) when the patient has responded to the drug and had previously failed to respond to other medications, (2) when there is concern that the patient may not respond as well if the treatment needs to be restarted later, or (3) when there is a history of a month or more of persistent symptoms or of failure to respond to psychosocial interventions.

Rating scales for diagnosis and efficacy assessment.[3] The Rush and Frances guidelines[3] identify rating scales primarily for use in monitoring treatment outcomes; the scales are described as a "second-line" choice for diagnosis, but 1 of the present authors (M.G.A.) disagrees. Rating scales almost always have an important place in monitoring treatment effects in patients with mental retardation, given the inability of many of these patients to introspect, report on their internal state, and communicate adverse effects of medicines. Twelve scales are ranked in the Rush and Frances guidelines.[3] Among those scales recommended by the Expert Consensus Guidelines, we, the Special Topic Advisory Panel on Transitioning, recommend the following rating scales: the Aberrant Behavior Checklist (ABC),[5,25] Nisonger Child Behavior Rating Form (N-CBRF),[31] revised Conners Parent Rating Scale and Conners Teacher Rating Scale,[26,27] Clinical Global Impressions scale (CGI),[28] Child Behavior Checklist,[29] Reiss Screen for Maladaptive Behavior,[5,30] and Diagnostic Assessment for the Severely Handicapped.[5,32]

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TREATMENT OF MENTAL RETARDATION/ DEVELOPMENTAL DISABILITIES: EVIDENCE FROM RECENT SHORT- AND LONG-TERM TRIALS

MEDLINE searches were conducted using the name of each atypical antipsychotic and the following terms: *mental retardation*, *developmental disabilities*, and *behavior disorders*. Searches were conducted starting in July 2002 and done periodically through April 2004 to capture new additions to the literature. Searches were confined to English. Upon extensive review of the literature, we determined that risperidone was the only atypical antipsychotic associated with recently published randomized controlled trials or with large trials of any type in subjects with mental retardation or autistic disorder. There have been several relatively small open-label studies with olanzapine; the 2 largest—those of Kemner et al.[33] in children (N = 25) and of Janowsky et al.[34] in adults (N = 20)—are discussed below. Additionally, 2 open-label studies of patients switched to ziprasidone from other atypical antipsychotics[43,44] have been published.

Olanzapine

Children with pervasive developmental disorder. Kemner et al.[33] studied 25 children with pervasive developmental disorder treated with olanzapine in a 3-month open-label, open-dosage trial. The children were 6 to 16 years of age and had a mean IQ (N = 17) of 98 (range, 55–144). Results were reported for 22 children (2 failed to complete the study and 1 failed to meet diagnostic inclusion criteria). Previous medications, if any, were discontinued at least 2 weeks prior to starting olanzapine, but subjects who experienced a significant worsening of symptoms during that period were excluded. The olanzapine dose was titrated upward to 15 mg/day for children weighing less than 55 kg and to 20 mg/day for heavier children.

On the ABC, olanzapine led to significantly lower scores for the irritability, hyperactivity, and excessive speech subscales. Data on social behavior collected during structured social interactions with observers showed improvement on 4 of the 6 variables measured. Likewise, scores on the parent-completed TARGET checklist showed improvement in behaviors considered socially inadequate. On the 7-point CGI-Severity of Illness (CGI-S) scale, 3 children showed at least a 2-point improvement, 9 showed a 1-point improvement, 9 were considered unchanged, and 1 was judged minimally worse. On the CGI-Improvement (CGI-I) scale, 3 children were rated as "much improved," 10 as "minimally improved," and 9 as "not improved." This limited global improvement led the authors to suggest that the clinical usefulness of olanzapine in this population may be questioned.

Institutionalized adults with mental retardation. Janowsky et al.[34] conducted a retrospective chart review of 20 institutionalized adults with mental retardation who had been treated with olanzapine from 1995–2000; retardation was moderate in 1 patient, severe in 4, and profound in 15. Target behaviors were aggression, self-injurious behavior, and destructive/disruptive behavior. Patients were placed on olanzapine therapy because previous treatment regimens had proven inadequate, unacceptable side effects had developed, or an agent less likely to cause extrapyramidal symptoms and/or tardive dyskinesia was desired. At the time olanzapine therapy was initiated, 17 patients were receiving conventional antipsychotic drugs and 1 was receiving quetiapine; 18 were receiving non-neuroleptic psychiatric and/or anticonvulsant agents. The final dose of olanzapine ranged from 2.5 to 22.5 mg/day (mean = 9.1 mg/day).

After olanzapine treatment was initiated, aggression decreased in 13 of 14, self-injurious behavior in 6 of 7, and disruptive behaviors in 8 of 11 individuals; all changes were statistically significant. In 16 (80%) of 20 individuals, global ratings of target behaviors were lower than they had been previously. The dose of previously administered antipsychotic medications was reduced for 7 patients and completely eliminated for an additional 5. Doses of non-neuroleptic medications were generally stable. Obviously, there were problems with lack of blinding and experimental control in this study.

Risperidone

There have been 7 recent large-scale studies of risperidone in people with mental retardation or developmental disabilities: 4 in children with mental retardation, 2 in adults with mental retardation, and 1 in children with autism.[35–41]

Two of the studies in children with mental retardation were 6-week, double-blind, placebo-controlled trials of identical design, carried out independently in the United States[35] and Canada.[36] Patients were 5 to 12 years old with IQs in the range of 36 to 84, a rating of ≥ 24 on the conduct problem subscale of the N-CBRF, a Vineland Adaptive Behavior Scale score ≤ 84, and a diagnosis of any of the 3 subcategories of DSM-IV disruptive behavior disorder. Treatment consisted of 0.02 to 0.06 mg/kg/day of risperidone or placebo. Use of some concomitant medications was permitted if they did not interfere with risperidone metabolism or with treatment or side effect evaluation. For example, psychostimulant medications were allowed to continue at levels unchanged from 30 days prior to baseline.

One hundred eighteen subjects in the U.S. study and 110 in the Canadian study were randomly assigned to medication. The primary outcome measure, the conduct problem subscale of the N-CBRF, showed a significantly greater improvement in the risperidone groups than in the placebo groups from week 1 onward ($p < .001$ in both studies). For the risperidone groups, there was a decline of

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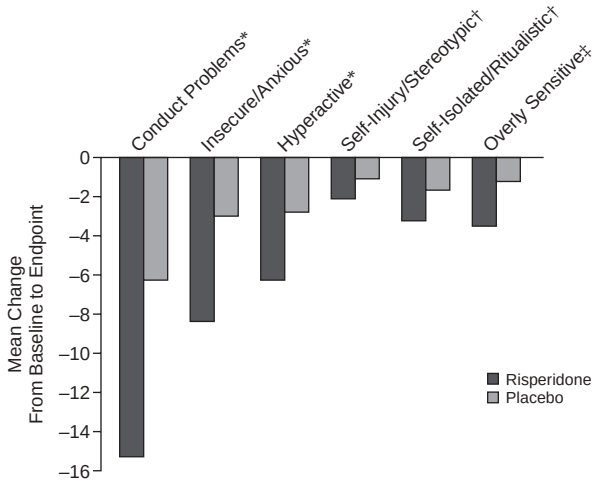
Figure 1. Mean Reductions in N-CBRF Problem Behavior Subscale Scores From Baseline to Endpoint in Children With Mental Retardation and Disruptive Behavior Symptoms Treated With Risperidone or Placebo (U.S. short-term trial)[a]



[a]Data from Aman et al.[35]
*p < .001.
†p < .02.
‡p = .002.
Abbreviation: N-CBRF = Nisonger Child Behavior Rating Form.

approximately 50% in the conduct problem subscale score from baseline.

There were significantly greater improvements in the risperidone group in both studies on the caregiver's Visual Analog Scale (VAS) rating of the most troublesome problem.

***U.S. study*.[35]** Risperidone produced significantly greater improvement than placebo on all N-CBRF subscales, with prosocial behavior increasing and problem behavior decreasing. Improvements occurred on the subscales of insecure/anxious ($p < .001$), hyperactive ($p < .001$), self-injury/stereotypic ($p < .02$), self-isolated/ritualistic ($p < .02$), and overly sensitive ($p = .002$) (Figure 1). Risperidone was superior to placebo on the following subscales of the ABC: irritability ($p < .001$), lethargy/social withdrawal ($p < .01$), and hyperactivity/noncompliance ($p < .001$).

By the end of the U.S. study, 40 patients (76.9%) in the risperidone group were rated "improved" on the CGI-I scale, while 21 (33.4%) in the placebo group were so rated. Twenty-eight (53.8%) of the patients in the risperidone group and 5 (7.9%) of the patients in the placebo group were rated "much to very much improved" ($p < .001$).

***Canadian study*.[36]** Statistically significant decreases occurred on all except 1 N-CBRF problem subscale for the risperidone treatment group. The conduct problem ($p < .001$), insecure/anxious ($p < .001$), hyperactive ($p < .01$), self-injury/stereotypic ($p < .05$), and self-isolated/ritualistic ($p < .01$) subscale scores were significantly lower in the risperidone group. Risperidone was superior to placebo on all ABC subscales. Significant improvement on the adaptive social subscale ($p < .01$) also occurred.

Forty-two (77.4%) of the risperidone patients were judged "improved" on the CGI scale at the end of the study, while 14 (24.6%) of the placebo group were so rated ($p < .001$). Eighteen (32.1%) of the patients in the risperidone group were rated "much to very much improved" as compared with 6 (10.6%) of the patients in the placebo group ($p < .001$).

***Long-term, open-label studies in children*.** There have been 2 long-term, open-label risperidone studies in children.[37,38] One was a 107-patient, 48-week extension of the short-term, placebo-controlled U.S. study described above.[35] As in the original study, previously administered psychostimulants for control of attention-deficit/hyperactivity disorder were continued. This study found that improvements achieved by patients treated with risperidone during the double-blind study were maintained over the 48-week extension. Initiation of risperidone treatment in those previously in the placebo group was accompanied by significant improvement comparable to that of the risperidone group in the double-blind trial. At the beginning of the open-label study, the insecure/anxious, hyperactive, self-injury/stereotypic, self-isolated/ritualistic, and overly sensitive N-CBRF subscale scores all decreased in the former placebo group so that the scores were similar to those of the risperidone group at 4 weeks.

The other long-term, open-label study in children was an extension of the double-blind Canadian study but also included patients initially enrolled on an open-label basis. The ultimate goal is to enroll a total of 500 subjects; the most recent report includes 319 subjects followed up to 498 days (mean = 261 days).[38] This report detailed an observed substantial reduction on the N-CBRF conduct problem subscale during the first 4 weeks ($p < .001$ vs. baseline) that was maintained through the remainder of the study. There was significant improvement in all other N-CBRF subscale scores ($p < .001$ vs. baseline). On the CGI scale, only 6.9% of the patients who entered the study were rated as having mild-to-absent symptoms; at endpoint, 65.6% had this rating.

***The Research Units on Pediatric Psychopharmacology (RUPP) Study*.[39]** This study, conducted in children with autism, was sponsored by the National Institute of Mental Health. It included both an 8-week, double-blind, placebo-controlled phase and a 4-month, open-label extension that were followed by a 2-month, placebo-controlled withdrawal phase. Only anticonvulsants were permitted to be continued during the study; all other previous medications, including psychostimulants, were phased out prior to the first administration of study medication. The study enrolled 101 children aged 5 to 17 years with autism and a score of at least 18 on the irritability subscale of the ABC. A positive response was defined as a 25% reduction in the irritability subscale score

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plus a CGI-I scale rating of "much improved" or "very much improved."

At the end of 8 weeks, the irritability subscale score of children in the risperidone group fell significantly ($p < .001$), and 34 (69.4%) of 49 were classed as responders ($p < .001$). By contrast, scores in the placebo group had minor drops, and 6 (11.5%) of 52 were scored as responders. There were also significant improvements in the stereotypic behavior and hyperactivity subscales of the ABC ($p < .001$) and on the CGI-I scale ($p < .001$). Treatment gains were maintained for 6 months in 23 (69.4%) of the 34 risperidone responders who entered the extension phase.

Studies in adults with mental retardation. Seventy-seven adults with mental retardation took part in a 4-week, double-blind trial of risperidone (1–4 mg/day) and placebo.[40,41] The intelligence criteria for entry were similar to those in the children's studies (IQ range 35–84). In addition to the 3 subcategories of disruptive behavior disorder, subjects were also eligible if they had a DSM-IV diagnosis of antisocial personality disorder or intermittent explosive disorder.

The primary efficacy outcome measure was ABC total score. The risperidone group differed from the placebo group on ABC total score. Although the risperidone group had better results on all ABC subscales, only the irritability subscale score reached statistical significance ($p < .05$) at endpoint. The Behavior Problems Inventory total score was also significantly greater for risperidone than for placebo at weeks 1 and 3. According to the CGI scales, severity of conduct disorder was substantially reduced in more risperidone than placebo patients. On the VAS for the most troublesome symptom, values fell from 67.9 to 36.6 in the risperidone group and from 70.8 to 57.9 in the placebo group ($p < .001$).

Fifty-eight patients from this short-term adult study entered an open-label extension of 12 months' duration.[42] Total ABC scores in patients originally treated with risperidone fell significantly. At endpoint, there was little difference between groups initially treated with risperidone or placebo. An increase in the proportion of patients in the category of "not ill" to "mild" on the CGI-I scale and an improvement on VAS for the most troublesome symptom occurred.

Conclusions. Low-dose risperidone was effective in reducing disruptive behaviors. Risperidone appears to retain its effectiveness for at least 1 year. The main evidence applies to people with IQs of at least 35, but there is no a priori reason to believe the drug would not be equally effective in appropriately selected patients of lower IQ.

Ziprasidone

Two recent studies by Cohen et al. have reported the effects of switching to ziprasidone from other atypical antipsychotics in, respectively, 40 adults with mental retardation and maladaptive behaviors[43] and 10 adults with autism.[44] Among the latter group, 9 patients were profoundly retarded and 1 had borderline intellectual function. Both studies were retrospective chart reviews, covering a 6-month period, with patients who discontinued ziprasidone prior to 6 months being excluded. Seventy percent of the patients in the first study and 80% in the second had previously been treated with risperidone. Excessive weight gain was the most common reason for switching to ziprasidone, although other reasons were noted as well.

Among the mentally retarded patients, scores on the Maladaptive Behavior Scale were available for 25 of the 30 institutionalized patients and none of the 10 outpatients.[43] Among those for whom scores were available, 12 improved following the switch, 6 remained the same, and 7 worsened; there was no significant change for the group as a whole. Among the autistic patients, maladaptive behavior scores improved in 6, remained the same in 1, and worsened in 3.[44] Again, there was no significant change for the group as a whole.

SAFETY PROFILE OF ATYPICAL ANTIPSYCHOTICS IN PATIENTS WITH MENTAL RETARDATION OR AUTISM

Reversible movement disorders (including extrapyramidal syndrome) occur as a function of dose and dopamine D_2-receptor occupancy. Increased occupancy of the D_2 receptor may be associated with a higher rate of reversible movement disorders, but the exact mechanism is unknown. Some atypical antipsychotics, including risperidone and olanzapine, occupy serotonin 5-HT_2 receptors faster and at lower doses than they do D_2 receptors.[45] At therapeutic and low doses of these antipsychotics, there is minimal risk for reversible movement disorders, as they may be prevented by the preferentially increased serotonin activity associated with 5-HT_2-receptor occupancy.

For the 7 risperidone trials described in a previous section of this article, extrapyramidal symptoms in people with mental retardation, as judged by the Extrapyramidal Symptom Rating Scale (ESRS)[69] and the Simpson Angus Rating Scale,[46] remained consistently low with no between-group (i.e., drug) differences.[35–38,40–42] Mean doses in the studies ranged from 0.98 mg/day to 1.81 mg/day. In the U.S. 6-week, double-blind trial in children,[35] 2 children in the risperidone group experienced extrapyramidal symptoms; neither required medication for the symptoms. In the long-term (1-year) U.S. extension study,[37] the mean total ESRS scores, based on a scale ranging from 0 (complete absence) to 5 (severe), declined at the end of the study. One patient required medication for extrapyramidal symptoms; there were no reported cases of tardive dyskinesia. In the 6-week Canadian double-blind trial,[36] extrapyramidal symptoms were reported in 7 patients receiving risperidone and 3 receiving placebo. One child rated as

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having emergent tardive dyskinesia was in the placebo group. In the international, long-term extension of the Canadian study,[38] 2 subjects reported symptoms resembling tardive dyskinesia; these resolved when the medication was discontinued. The mean total ESRS scores also declined at the end of the study.

In the RUPP study with autistic children,[39] clinician assessment revealed few extrapyramidal symptoms, but parent-reported tremor was significantly more common in the risperidone group than in the placebo group (7 subjects versus 1).

Extrapyramidal disorder occurred in 1 adult taking risperidone in the short-term mental retardation study.[41] There were no reports of extrapyramidal symptoms or changes in ESRS in the long-term adult study.[42]

Three of 25 children with autism treated with olanzapine developed clinician-observed extrapyramidal symptoms.[33] All symptoms resolved following dose reduction. Tremor was also reported as an adverse effect in 5 children. One of 20 adults with mental retardation treated with olanzapine developed a gait problem.[34] There were no reports of clinically observed extrapyramidal symptoms in the open-label studies with ziprasidone.[43,44]

Risperidone significantly elevated prolactin levels in both boys and girls (adult studies did not address prolactin levels). In the 2 long-term studies of children,[37,38] prolactin levels peaked approximately 4 weeks after initiation of risperidone dosing, then slowly declined but remained significantly above baseline. In the long-term U.S. extension study,[37] boys previously treated with placebo had mean values at baseline of 8.3 ng/mL; mean values peaked at 29.8 ng/mL (upper limit of normal, 18.0 ng/mL), then declined toward normal range to a mean of 16.4 ng/mL at the conclusion of the study ($p = .007$ vs. baseline). For boys previously treated with risperidone during the double-blind study, mean values were 29.0 ng/mL at extension-study baseline and 18.4 ng/mL at the end ($p = .009$ vs. baseline). For girls previously treated with placebo, values increased from a baseline of 8.9 ng/mL to 22.5 ng/mL (upper limit of normal 30 ng/mL) and then fell to 14.6 ng/mL ($p < .05$ vs. baseline). Girls previously treated with risperidone entered the extension study at 18.1 ng/mL and had values of 17.3 ng/mL at the end.[37]

The dopaminergic neurons of the tuberoinfundibular system (TS) of the hypothalamus produce a continuous inhibitory tone that inhibits prolactin release. Any reduction in this tone produces an increase in prolactin release.[47] As all currently available antipsychotics block D_2 receptors in the TS, their long-term administration leads to inhibition of this hypothalamic tone, thereby producing an increase in serum prolactin concentration. This has led to a class-labeling of all antipsychotics. No clear threshold exists for the development of clinical symptoms mediated by prolactin[47,48]; therefore, it may not be clinically meaningful to treat a prolactin laboratory value in isolation. Instead, physicians should ordinarily focus on the presentation of clinical symptoms.

In the short-term U.S. study,[35] there was 1 instance of transient gynecomastia, which resolved without treatment after 15 weeks. In the larger, international long-term study,[38] prolactin levels followed the same pattern. Symptoms related to hyperprolactinemia included 10 cases of mild-to-moderate gynecomastia, 1 of galactorrhea, 1 of amenorrhea, and 1 of menorrhagia. All resolved; only the patient with amenorrhea required treatment.

Prolactin levels were not measured in the studies on olanzapine[33,34] or ziprasidone.[43,44] No clinically observed symptoms possibly related to hyperprolactinemia were reported.

The most frequent adverse event in the short- and long-term studies of children with mental retardation was mild, transient somnolence, reported by 51% of risperidone patients in the U.S. short-term children study (placebo rate = 10%),[35] 41.5% in the Canadian short-term children study (placebo rate = 14%),[36] 32.7% in the U.S. children long-term study,[37] 28.2% in the international children long-term study,[38] 23.1% in the short-term adult study (placebo = 15.8%),[49] 41.4% in the long-term adult study,[42] and 49% in the study of children with autism (placebo rate = 12%).[39] Two patients withdrew from the U.S. short-term children study and 2 from the long-term adult study due to somnolence.

Somnolence was reported in 6 of 25 autistic children[33] and sedation in 4 of 20 mentally retarded adults[34] treated with olanzapine. Asthenia appeared to be a more significant adverse effect among the children, however, being reported in 14 of the autistic children. By contrast, there were no reports of asthenia among adults with mental retardation treated with olanzapine. Cohen et al. did not discuss adverse effects among adults with mental retardation switched to ziprasidone[43] and stated that there were none of significance among the 10 autistic adults so switched.[44]

Cognitive function was assessed in the disruptive behavior disorder studies using the Continuous Performance Task, which measures vigilance, and a modification of the California Verbal Learning Test for Children adapted for use with people of subaverage IQ. Results indicated no decline in cognitive function in the 2 short-term trials in children with mental retardation.[35,36]

Weight gain was seen in all risperidone studies. Weight gain in the smaller U.S. open-label extension in children[37] amounted to 5.5 kg over the course of a year; normal childhood growth was reported to account for 4.9 kg of this weight gain.[50] Similarly, children in the larger international long-term study gained 6.3 kg,[38] and subjects in the adult long-term study[42] gained 3.8 kg. Weight gain beyond that which occurred with placebo in the short-term studies was reported to be 1.3 kg (U.S. children),[35] 2.0 kg (Canadian children),[36] 1.0 kg (adults),[40,41] and 1.9 kg (autistic

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children).[39] A few patients discontinued treatment because of the weight gain.[35–42,50]

Children with autism treated with olanzapine gained an average of 4.7 kg over a 12-week period,[33] while adults with mental retardation gained a mean of 3.4 kg over a 6-month period of treatment.[34] By contrast, the 2 studies of adult patients switched to ziprasidone from other atypical antipsychotics[43,44] reported weight losses of, respectively, 3.6 kg and 4.3 kg. These results are in reasonable accord with a series of reviews[51–57] concluding that weight gain is greatest with clozapine and olanzapine, intermediate with quetiapine and risperidone (although authors disagree about the risk with quetiapine), and lowest with ziprasidone and the newer atypical antipsychotic aripiprazole.

Metabolic disturbances, including hyperglycemia/insulin resistance and hyperlipidemia, are serious and potentially fatal consequences of weight gain. However, weight gain need not be a prerequisite for the development of metabolic disturbances. For example, an analysis of 45 published cases of adult patients with schizophrenia[58] who developed new-onset diabetes mellitus or diabetic ketoacidosis following the initiation of atypical antipsychotics including clozapine (N = 20), olanzapine (N = 19), quetiapine (N = 3), and risperidone (N = 3) revealed that 50% of patients had gained no weight at the time of presentation with diabetes mellitus or diabetic ketoacidosis. Results from this study suggest that weight gain is not necessary for patients to develop diabetes during treatment with atypical antipsychotics, although obesity may be an important diabetes mellitus risk factor to consider prior to implementing antipsychotic therapy.

Nevertheless, the likelihood that a given atypical antipsychotic will lead to metabolic disturbance appears to correlate with the frequency and severity of weight gain. Thus, Melkersson and Dahl,[59] after an extensive review of the literature, concluded that "the relative risk of glucose intolerance/diabetes mellitus, hyperlipidaemia, and hyperleptinaemia is highest for clozapine and olanzapine, moderately high for quetiapine, rather low for risperidone, and lowest for ziprasidone."(p702) Janowsky et al. saw no increased glucose levels,[34] and there was no change in glucose levels (together with significant reductions in total cholesterol and triglyceride levels) among adults with mental retardation switched to ziprasidone.[43] The 4 placebo-controlled studies of risperidone[35,36,39,41] all reported no significant differences in laboratory values between active-treatment and control groups. In the long-term, open-label extension of the U.S. study,[37] there were no clinically relevant changes in clinical chemistry values.

Overall, risperidone was well tolerated by children and adults with mental retardation and/or borderline IQ. There was no evidence of adverse effects on cognitive function, and extrapyramidal effects were uncommon. Over time, elevated prolactin levels fell toward normal, with clinical symptoms uncommon or absent. Somnolence was mild and transient in most cases and may have benefited some patients experiencing sleep problems. Weight gain was moderate. To the extent that data are available, results appeared similar for olanzapine and ziprasidone, except that weight gain was more severe with olanzapine, while ziprasidone-treated patients experienced a fall in weight from levels reached on previously used atypical antipsychotics.

SPECIAL TOPIC ADVISORY PANEL'S CONSENSUS ON TRANSITIONING TO RISPERIDONE OR OTHER ATYPICAL ANTIPSYCHOTICS IN THE CONTEXT OF MENTAL RETARDATION

It is unknown how many people with mental retardation and behavioral disorders continue to be treated with conventional antipsychotics. However, in view of the risks of elevated extrapyramidal symptoms and tardive dyskinesia, physicians may choose to move many of their patients from conventional antipsychotics to risperidone (or perhaps to another atypical antipsychotic). The best way to make the change may not always be obvious, however. These guidelines are intended to help clinicians make this transition. Since the Panel was asked only to provide guidelines for the transition to risperidone, the recommended dosages and schedules are specific to that medication. However, the general principles are applicable to transitions to other atypical antipsychotics as well.

Defining Patient Characteristics

In the Panel's opinion, the optimal transition pathway may be determined by target behavior, degree of cognitive impairment (which may affect assessment methods), severity of symptoms, and type of previous antipsychotic medication. Accordingly, the Panel's recommendations are divided by symptom severity, and recommendations for withdrawal of the previous medication depend on whether it was a conventional or an atypical antipsychotic. The Panel enumerated several target symptoms and subcategories. These included aggression, irritability, impulse control, and psychosis.

Behavior Problems and DSM-IV Diagnosis

As noted, behavioral problems in people with mental retardation may be severe and persistent but difficult to diagnose as specific DSM-IV disorders. As a result, deciding on a specific DSM-IV diagnosis may not be possible. Even if a diagnosis is made, it may be too uncertain to be useful. The Rush and Frances Expert Consensus respondents felt that only autism could usually be reliably diagnosed in the presence of more severe mental retardation.[3] The Rush and Frances Expert respondents had serious reservations concerning structured diagnostic interviews in this population. While a specific DSM-IV diagnosis re-

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mains the ideal when it can be made with confidence, there will be many instances—especially in patients with severe or profound mental retardation—when an identified behavioral symptom is the target of treatment.

Assessment Methods

The Panel identified the following preferred methods for identifying specific problems in people with mental retardation and deciding which are appropriate for risperidone treatment: interview with family or caregivers, direct observation of behavior, medical history and physical examination (a sudden change in behavior often indicates a medical rather than a psychiatric problem), functional and behavioral assessment, evaluation of medication and side effects, and unstructured psychiatric diagnostic interview.

Rating Scales That Can Be Used to Assess Psychiatric and Behavioral Problems in People With Mental Retardation

With 1 exception, the Panel identified as potentially useful the same instruments identified by the Rush and Frances Expert Consensus Panel. Rather than recommending the Psychopathology Inventory for Mentally Retarded Adults (PIMRA),[70] our group chose the Assessment of Dual Diagnosis,[60] which has replaced the PIMRA. In the Panel's opinion, the Reiss Screen and the Assessment of Dual Diagnosis may be helpful for diagnostic purposes, whereas the following can be helpful for monitoring effectiveness of treatment: Aberrant Behavior Checklist (adults and children), CGI (all ages), Nisonger Child Behavior Rating Form (children and adolescents), and Diagnostic Assessment of the Severely Handicapped (adults).

Recently, the National Association for Dual Diagnosis (NADD), in association with the American Psychiatric Association, has been developing a diagnostic system that will be made available to researchers and clinicians in the field. This system will very likely provide a list of symptoms in the population dually diagnosed and the equivalent symptoms in patients of normal intelligence (oral communication, February 2003; Robert Fletcher, Ph.D., president of NADD).

Drug-Drug Interactions

After oral administration, risperidone is completely absorbed, and the extent of absorption is unaffected by the presence of food.[61] Risperidone is primarily metabolized via the hepatic enzyme cytochrome P450 2D6 (CYP2D6) and may also be metabolized to a minor extent by CYP3A4.[62] The action of CYP2D6 leads to the formation of 9-hydroxyrisperidone, the main metabolite of risperidone, which has a similar pharmacologic profile as the parent drug. Hence, the sum of risperidone and 9-hydroxyrisperidone is responsible for the antipsychotic activity and constitutes the active moiety.[61]

Table 3. Drugs That May Have Clinically Significant Interactions With Risperidone[a]

Drugs that may increase concentration, reduce clearance, increase half-life of risperidone (cytochrome P450 [CYP] and CYP2D6 inhibitors)
Fluoxetine[63]
Paroxetine[63,64]
Sertraline[63]
Clozapine[62]
Ritonavir[67]
Indinavir[67]
Drugs that may decrease concentration, increase clearance, decrease half-life of risperidone (CYP450 and CYP3A4 inducers)
Carbamazepine[62,65,68]
Barbiturates including phenobarbital[65,68]
Phenytoin[68]
Nefazodone[62]

[a]Risperidone may antagonize the effects of levodopa and dopamine agonists. It may increase the antihypertensive effects of antihypertensive agents (due to its α-adrenergic agonist properties) and would be expected to increase the sedative effects of other CNS depressant agents, such as alcohol, barbiturates, chloral hydrate, and benzodiazepines.[66] Risperidone may also increase blood concentrations of indinavir and ritonavir.

Potent inhibitors of CYP2D6 (e.g., fluoxetine) do increase the plasma concentrations of risperidone.[63] However, as this is associated with lower levels of 9-hydroxyrisperidone, the pharmacokinetics of the active moiety are much less affected. Nevertheless, when concomitant fluoxetine is initiated or discontinued, the physician should reevaluate the dosing of risperidone.

Carbamazepine, a potent inducer of CYP3A4, was shown to influence the metabolism of risperidone and 9-hydroxyrisperidone. Concurrent intake of carbamazepine decreased the plasma concentrations of the active moiety in vivo by about 70%.[64] Therefore, on discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of risperidone should be reevaluated and, if necessary, decreased.[65] Table 3 lists commonly used drugs that metabolically interact with risperidone.

Target Symptoms and Guidelines for Their Treatment

The target symptoms these recommendations address are aggression, irritability, impulse control, and psychotic behavior. Recommendations for risperidone treatment of these symptoms are found in Table 4. These are based in part on published scientific studies and in part on clinical experiences of the Panel members. Recommended dosing may have to be reduced for children and/or elderly patients.

Withdrawing Previous Antipsychotics

The time frame for withdrawal of previous antipsychotics should be based on tolerability and control of symptoms. Withdrawal should be slow to avoid the false impression that transition has failed. This withdrawal should begin as soon as control of symptoms is achieved

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Table 4. Special Topic Advisory Panel Consensus Guidelines for Risperidone Dosing for Adults in Target Symptoms

Target Symptom	Severity	Initial Dose	Titration	Target Dose	Other Recommendations
Psychotic (delusions, paranoia, hallucinations, hostility, withdrawal, deficit syndrome)	Severe	0.5–1.0 mg bid	Increase dose 0.5 mg/d every 1–3 days; after 4.0 mg/d, make adjustments in 0.25–0.5 mg/d increments.	4.0–6.0 mg/d	Consider use of short-acting benzodiazepine.
	Less severe	0.5 mg/d	Increase by 0.5 mg/d every 2–4 weeks; after 4.0 mg/d, make adjustments in 0.25–0.5 mg/d increments.	4.0–6.0 mg/d	
Aggression (against property, self-injurious behavior, verbal, against others, predatory/calculated, protective [boundary])	Very severe	0.5–1.0 mg bid; begin with 0.5 mg/d and add second 0.5 mg dose if necessary; start with 0.25 mg if orthostasis is a concern.	Increase dose 0.5 mg every 1–3 days.	2.0–4.0 mg/d	Assume hospitalization. Emergent, very severe = more rapid dose escalation Do not change existing medications until new medication is titrated up. Once stabilized, emphasize psychosocial behavioral interventions.
	Less severe or moderate	0.25–0.5 mg/d	Increase by 0.5 mg/d over 2–4 weeks.	2.0–4.0 mg/d	
Irritability (mood swings/ sensitivity, tantrums, screaming, intolerance to stimulus change)	Very severe	0.25–0.5 mg/d	Increase 0.5 mg/d over 1–3 days per tolerability and symptom control.	2.0–4.0 mg/d	Severe = tantrums, screaming, mood swings
	Less severe	0.25–0.5 mg/d	Increase 0.25 mg/d over 24 weeks.	1.0–3.0 mg/d	Optimize/bring to forefront psychosocial/behavioral interventions.
Impulse control (boundary, sexual aggression, reactionary rage, frustration intolerance)	Very severe	0.5–1.0 mg bid; begin with 0.5 mg/d dose and add second 0.5 mg dose if necessary; start with 0.25 mg if orthostasis is a concern.	Increase dose 0.5 mg/d every 1–3 days.	2.0–4.0 mg/d	Anticonvulsants are first-line, risperidone adjunctive. Strongly consider adjunctive mood stabilizers, possibly single-dose benzodiazepine. Limit risperidone dose if anxiolytics are used.
	Less severe	0.5 mg/d	Increase 0.25–0.5 mg/d over 2–4 weeks depending on symptom control.	1.0–3.0 mg/d	Anticonvulsants are first-line, risperidone adjunctive. Consider mood stabilizers.

or after the maximum target dose of risperidone has been administered for 1 week. Withdrawal should be continuously monitored for either the reappearance of psychiatric symptoms or withdrawal symptoms such as cachexia (physical wasting, malnutrition), motor effects (e.g., dyskinesias and dystonias), cholinergic rebound effects, or eating disorders. These events may signal a need to delay or cease withdrawal. If no contraindication appears, conventional antipsychotics should be withdrawn at the rate of 10% a month, atypical antipsychotics at the rate of 25% to 50% a month.

SUMMARY

The Special Topic Advisory Panel on Transitioning to Risperidone Therapy in Patients With Mental Retardation and Developmental Disabilities concluded with some general considerations physicians should keep in mind when prescribing psychotropic medication for patients with mental retardation.

The physician should be aware not only of the history of a particular patient's mental illness, but also of the general prevalence of mental illness in people with mental retardation. This information may help refine diagnostic and treatment approaches. Practitioners should always be aware of the latest developments in psychopharmacology—newly available trial data and drugs may guide the clinician to make the best treatment choices for patients. An accurate diagnosis of mental illness in patients with mental retardation is desirable, although the guided treatment of target symptoms may be as important as obtaining the diagnosis.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril, Fazaclo, and others), divalproex (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), indinavir (Crixivan), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil and others), phenytoin (Cerebyx, Dilantin, and others) quetiapine (Seroquel), risperidone (Risperdal), ritonavir (Norvir), sertraline (Zoloft), trazodone (Desyrel and others), valproic acid (Depakene and others), venlafaxine (Effexor), ziprasidone (Geodon).

Acknowledgment: In addition to the authors of the present article, the Special Topic Advisory Panel on Transitioning to Risperidone Therapy in Patients with Mental Retardation and Developmental Disabilities included William Benefield, Pharm.D., B.C.P.P., University of Texas at Austin; Kathleen Brown, R.N., C.D.D.N., Enloe Drugs, South Elgian, Ill.; Brian Chicoine, M.D., University of Illinois, Chicago; Katherine Fischer, R.Ph., Omnicare of Minnesota, Crystal, Minn.; Ronald Hardrict, M.D., University of Minnesota, Minneapolis; Thomas Lee, M.D., Loyola University Medical Center, Maywood, Ill.; Carole Rosanova, M.D., Psychiatric Institute, Chicago, Ill.; and Nanette Wrobel, R.Ph., Enloe Drugs, South Elgian, Ill.

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