



# The Pharmacological Management of Depression in the Adult Person with Mental Retardation and Developmental Disabilities (MR/DD)

## 1. Overview

Multiple classes of medications are available for treatment of depression in the patient with MR/DD. Despite the availability of sophisticated structural and functional brain imaging, clinicians must choose antidepressants using clinical judgment and past experience (1). Available technology does not allow the clinician to determine which class of medications is most effective for a particular patient. Antidepressant medications can be chosen for effectiveness, toxicity, expense, and ease of administration (2), (3).

The pharmacological treatment of depression in the patient with MR/DD begins with a careful assessment to determine the cause of depression and identification of potential target symptoms for medications (4). Medical problems that mimic depression should be corrected prior to treatment with medication (5). Depressive symptoms in the patient with MR/DD can include cognitive, functional, and behavioral manifestations (6), (7). The choice of medications is partially determined by the type of depression and comorbid psychiatric symptoms such as anxiety, anergy, etc. All women with MR/DD of childbearing age require pregnancy testing prior to initiation of pharmacological agents.

This section deals with the pharmacological management of depression in adult and elderly populations with mental retardation or developmental disorders (MR/DD). Psychiatric and behavioral problems are common in children; however, this section does not contain material that is appropriate to this age population. The assessment and management of psychiatric or behavioral problems in a child or young teenager requires the attention of a child psychiatrist and a pediatrician.

## 2. Types of Antidepressants

Antidepressant medications can be divided into three broad classes: 1) first generation, 2) second generation, and 3) third generation medications (8). The first generation drugs include older medications such as tricyclic antidepressants and monoamine oxidase inhibitors, while the second generation drugs include many selective serotonin reuptake inhibitors. The third generation medications include drugs that alter both the serotonin and norepinephrine systems (See Table 1). Each medication class includes multiple drugs with specific therapeutic windows and side effect profiles. The average clinician cannot be familiar with all of these medications; therefore, the practitioner should familiarize themselves with one or two drugs from each generation. Most clinicians begin therapy with a second or third generation medication.

### 3. Selective Serotonin Reuptake Inhibitors (SSRI's)

The national consensus guidelines suggest second generation antidepressants as the first drug of choice for depressed patients with MR/DD (8). The second generation antidepressant medications include multiple selective serotonin reuptake inhibitors (SSRI's). The SSRI's are a class of medication that includes drugs such as sertraline, citalopram, fluoxetine, paroxetine, and others. These medications are specific for the serotonergic system by blocking the reuptake of serotonin at the transporter level (8), (9). The SSRI's are effective in the treatment of depression and these drugs are also beneficial for persons with anxiety disorders, bulimia, and obsessive-compulsive disorder (10), (11). The SSRI's require 6 weeks of effective dosing to determine efficacy. Several SSRI's have clinical data in the person with MR/DD that demonstrate efficacy and safety.

The SSRI's are particularly effective for the anxious, depressed patient. The SSRI medications include titration drugs and standard dose medications. Drugs such as Prozac and Paxil have a relatively narrow dosing range that allows the clinicians to prescribe consistent set amounts. Sertraline has a wide dosing range that requires titration and symptom monitoring (See Table 1). The standard side effects of the SSRI's include sleep disturbance, anxiety termed "akathisia", sexual dysfunction, and stomach upset. The anxiety and akathisia are related to 5HT2 receptor system in the basal ganglia while the GI upset is related to alteration of the 5HT3 receptor system. Each drug exerts a variable mixture of effects on the individual. Serotonin receptor activation produces a variable picture of toxicity (1), (2).

### 4. Third Generation Medications

Third generation medications include some of the newest drugs including mirtazapine, duloxetine and venlafaxine. The third generation drugs act by enhancing both norepinephrine and serotonin in the synapse or by exerting a direct agonist effect on the noradrenergic and serotonergic receptors. These drugs can also alter other transmitter systems such as the alpha adrenergic and the histaminergic systems and produce blood pressure changes or drowsiness. The third generation drugs can be quite expensive. Limited published clinical data is available on efficacy or safety for these drugs for patients with MR/DD (9).

Wellbutrin is a unique antidepressant because its pharmacology involves multiple transmitter systems. Wellbutrin is distinct from other first and second generation drugs. This medication may improve depression and addictive behaviors. Wellbutrin has almost no sexual, sleep, or appetite problems; however, this medication can lower seizure threshold. In general, Wellbutrin should be avoided in persons with epilepsy or a past history of seizures (9), (12).

### 5. Tricyclic Antidepressants

The tricyclic antidepressants, e.g., nortriptyline, are an old, well-studied first generation class of medication with high efficacy for person with severe depression. These drugs have significant side effects including orthostasis, tachycardia, urinary retention and other symptoms of anticholinergic side effects including confusion. The limited available data on the use of tricyclic antidepressants in the population with MR/DD suggests that these medications are effective (8). Clinicians should avoid tricyclics with high anticholinergic side effects such as amitriptyline and imipramine. Nortriptyline is one of the safest, first generation medications for use in the population with MR/DD (See Table 1). This drug should be started at 25mg per day

and slowly increased in 25mg increments to a blood level between 60 to 100. Orthostatic blood pressure should be monitored. Patients should receive a 6-week trial of adequate doses of tricyclic antidepressants to determine their efficacy. The tricyclic antidepressants are not recommended as a first line choice in frail patients or those with moderate to severe MR. These medications can be quite helpful in melancholic depression and may be used as a first choice in healthy, mildly retarded persons. The tricyclic antidepressants are beneficial for chronic pain syndromes. Although Elavil is often described as the drug of choice for neuropathic pain, nortriptyline works with equal effectiveness.

The tricyclic antidepressants affect both the noradrenergic and serotonergic systems. The one exception is clomipramine, i.e., Anafranil, which has a highly specific effect on the serotonergic system. This medicine is often used for obsessive-compulsive disorder with some significant success (13).

Table 1

**A Summary of Common Antidepressant Medications Prescribed for Adult Populations with MR/DD (1), (2), (9)**

<b>Drug</b>	<b>Healthy/Adult (Daily Dose Range)</b>	<b>Frail/Elderly (Daily Dose Range)</b>	<b>Comments (See PDR for Full Description)</b>
<b>1<sup>st</sup> Generation (TCA's)</b>			
Nortriptyline	25-150mg	10-100mg	Therapeutic Level (50-150ng/ml)
<b>2<sup>nd</sup> Generation (SSRI's)</b>			
Fluoxetine	10-80mg	5-40mg	Generic Available. May be Activating
Paroxetine	10-60mg	5-30mg	Generic Available. ↑ Anticholinergic
Sertraline	50-200mg	25-200mg	GI Side Effects. Take With Food
Citalopram	20-60mg	10-20mg	Few Significant Drug Interactions
Escitalopram	10-30mg	5-20mg	Few Significant Drug Interactions
<b>3<sup>rd</sup> Generation (SNRI's, Others)</b>			
Bupropion	75-450mg	75-300mg	Use Caution With Seizure Disorders
Mirtazapine	15-45mg	7.5-45mg	Weight Gain/Sedate at Lower Doses (<30)
Trazodone	50-300mg	25-150mg	Monitor Priapism and Orthostasis
Venlafaxine	75-375mg	25-225	Monitor for Hypertension
Duloxetine	40-60mg	20-40mg	Dual Re-uptake Inhibitor, All Doses
<p>This table contains doses of antidepressant medications that are commonly prescribed for persons with MR/DD. Each patient requires careful assessment and individualized prescription based on medical and psychiatric features. This information provides a general overview and <b>does not</b> represent prescriptive guidance. See PDR for additional information. Consult an appropriate child psychiatrist for pharmacology in children and adolescents.</p>			

## 6. Monoamine Oxidase Inhibitors

The monoamine oxidase inhibitors are the second major group within the first generation of medications. These drugs have significant toxicity when used in combination with other cardiovascular drugs resulting in serious problems, such as hypotension (1), (2). Avoiding certain medications such as Demerol, sympathomimetic agents, as well as specific dietary restrictions, e.g., low tyramine, are essential to avoid serious complications with these drugs. There is no specific advantage for monoamine oxidase inhibitors over other medicines presently available for the treatment of depression and clinicians are encouraged to avoid use of these drugs, unless required by a specific clinical indication. The dietary restrictions are difficult for a retarded person to follow and the complex drug-drug interaction make these medications a distant choice in the treatment of depression (12).

## 7. Therapeutic Sequencing of Medications

The clinician may consider initiating therapy with whatever medication has worked in the past for the patient. Medications should be prescribed on the basis of desired effect, target symptoms, and potential drug-drug interactions for the patient. In general, the SSRI's are considered first-line medications in treatment of depression (8). A chosen SSRI medication should be prescribed at therapeutic doses for at least 6 weeks to determine efficacy. If the patient seems improved but not completely recovered, then the clinician should extend the clinical trial for another 6 weeks to determine efficacy. Failure to show improvement at 6 weeks or incomplete remission at 12 weeks may warrant a trial with a second medication (1), (9).

If the patient is not improved with the first medication, the clinician may then choose a different SSRI or a third generation drug with significant mixed noradrenergic/serotonergic activity or the patient may be prescribed a tricyclic antidepressant. The dosage of the first drug can be reduced while the second medication is increased. The clinical trial should be repeated as before and a re-evaluation should occur after an additional 12 weeks. Failure to respond to the second drug should trigger a re-evaluation to exclude some other causes of the depressive symptoms. The clinician has several options including a trial with a third agent, referral to a specialist for consideration of ECT or augmentation with lithium. Lithium in conjunction with a tricyclic antidepressant has been shown to be as effective as ECT in many patients (1), (2). Psychostimulants such as Ritalin can be used for depressed patients to improve energy and activity. The long-term effectiveness of stimulants for depression in persons with MR/DD is unknown.

Polypharmacy is discouraged in the mentally retarded because these individuals are quite sensitive to CNS and other toxicities associated with antidepressant therapy. The objective data on efficacy of combined antidepressant therapy is scant and the potential for drug-drug interaction is great. The use of two medications that alter the serotonergic system produces the risk for serotonin syndrome (8), (10), (15).

The dosing schedule and range for medications depend upon the age of the patient, comorbid medical problems, and the level of physical frailty (See Table 1). Young, healthy patients with mild to moderate mental retardation can tolerate full adult doses. Frail or elderly patients require a geriatric dosing schedule.

## 8. Antidepressant Medications to Manage Abnormal Behavior

The consensus guidelines recommend the prescription of SSRI medication for specific severe or dangerous behaviors that fail behavioral interventions (8). Monoamine oxidase inhibitors have not been demonstrated as effective for behavioral problems and should not be prescribed for this purpose. The SSRI antidepressants have the best literature for specific behavioral problems such as impulsivity, aggression, and self-injurious behavior (10), (14), (16), (17), (18). Tricyclic antidepressants have not been consistently demonstrated as effective for reduction of behavioral problems.

## 9. Therapy for Psychotic Depression

Psychotic symptoms occur in significant numbers of depressed persons with normal intellect. The rate of psychotic depression in the depressed patient with mental retardation is unknown although this symptom is probably common. The presence of psychotic symptoms suggests greater risk for therapy resistant depression (1). The treatment of psychotic depression may require the combined prescription of antipsychotic and antidepressant medications. The new second or third generation antipsychotics have mood stabilization qualities that make them superior to the older, first generation medicines that have many side effects. Most second or third generation antipsychotic medications are effective in the treatment of psychosis associated with depression. The antipsychotic should be titrated to the lowest dose necessary to control symptoms and continued until the patient is stable (See DDMED 39). The antipsychotic can be tapered after the patient has returned to a normal mood and the patient has remission of psychotic symptoms (8). Long-term use of antipsychotic medications in persons with MR/DD and mood disorders may increase the risk of tardive dyskinesia (19).

## 10. Co-administration of Benzodiazepines

The use of benzodiazepines in the depressed patient with MR/DD with anxiety or impulsivity carries a significant risk for side effects including confusion, disinhibition, reduced appetite and apathy (8), (20). Reversal of the depression will reduce most symptoms of anxiety in a depressed patient. Benzodiazepines should be used in the lowest possible dose for the briefest period of time to avoid significant drug toxicity, falls or confusion.

## 11. Therapeutic Endpoints

The therapeutic endpoint is reduction of symptoms as described by the patient and caregiver or as measured by behavioral monitoring. Most mildly retarded patients have sufficient communication skills to describe symptoms of depression. The clinician must depend on behavioral symptoms to determine efficacy in severely retarded persons. Minimal behavioral monitoring requires consistent measurements over a minimum of several days of observation (See Table 2).

**Table 2**  
**Methods of Assessing Therapeutic Benefit of Antipsychotic Medications**

Severity of Mental Retardation	Self-Reporting	Caregiver Reporting	Behavioral Monitoring
Mild	R	R	H
Moderate	H	R	R
Severe/Profound	U	R	R

R=Required

H=Helpful, but not always required

U=Unreliable

Individuals with depression are more likely to have behavioral manifestations of psychiatric symptoms when they occur and are less likely to be able to verbalize in a sophisticated way about what they are experiencing. Some assessment tools designed for aiding in the identification of psychiatric symptoms in individuals with intellectual disabilities include the DASH-II (Diagnostic Assessment for the Severely Handicapped – II), the ADD (Assessment of Dual Diagnosis), and the REISS Screen. These instruments have taken symptoms for the various diagnostic categories in the DSM and translated them into descriptions of behaviors that have been associated with particular diagnostic categories. This kind of assessment can also help sort out which behaviors are manifestations of depression and which behaviors are a result of learning. Functional behavioral assessments need to be conducted for the latter when identified.

## **12. Comprehensive Therapy**

Antidepressant medications should be combined with psychological or behavioral interventions to optimize outcome. Behavior analytic procedures can be included with other treatment modalities for a person who has both a psychiatric diagnosis and intellectual disabilities. Behavioral specialists can determine appropriate training strategies to assist a person with intellectual disabilities to gain better coping skills for dealing with their psychiatric symptoms. Triggers for the symptoms can be identified and strategies taught to staff, family members, and the individual to prevent escalation of the behavioral symptom. Counseling can be provided, keeping in mind that discussions need to be geared toward the level of understanding of the individual. Most counseling should take the form of skill-building and include the chance for positive reinforcement during the learning process. For example, if an individual becomes angry easily due to an impulse control problem, anger management training may be successful when presented in simplistic terms, modeled by the clinician, and practiced repeatedly by the individual in more than one or two sessions. As the person learns the management techniques, positive reinforcement should be delivered to assist with the acquisition and maintenance of the skills.

## **Conclusion**

Depression is a common problem in persons with MR/DD and this medical condition responds best to a biomedical, psychosocial intervention that combines accurate diagnosis, exclusion of medical problems, judicious prescription of antidepressant medications, and psychological or behavioral interventions.

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