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Pharmacotherapy

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Ever since the discovery of antipsychotic drugs in the 1950s, pharmacotherapy has been common in people with mental retardation. Surveys differ greatly in reported prevalences, but most of the recent drug surveys within institutions have reported psychotropic drug rates between 30 and 40% (Rinck, 1998). Studies of adults living in community settings often report rates between 25 and 35% (Rinck, 1998). Prevalence of psychotropic medicines among individuals with autism (across the life span) is currently around 45% (Aman, Lam, & Collier-Crespin, 2003; Langworthy-Lam, Aman, & Van Bourgondien, 2002). It is clear that drug therapy is common among people with mental retardation and developmental disabilities, and hence workers interested in this field cannot afford to be uninformed about pharmacotherapy.

In the interests of brevity, we shall be summarizing the evidence from an authoritative text (Reiss & Aman, 1998; The International Consensus Handbook) and from the recent Expert Consensus guideline Series: Treatment of psychiatric and behavioral problems in mental retardation (Rush & Frances, 2000). The latter was derived from a scientific survey of approximately 100 prominent researchers and clinicians in the field. Other evidence presented here comes directly from the scientific literature.

Historically, the use of medicines in this field has been driven by two considerations. Some patients have been treated because of behavioral excesses, such as prominent aggression. Others have been treated because they present with a Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2000) or International Classification of Diseases (ICD) (World Health Organization, 1992) psychiatric diagnosis, such as manic disorder. Most clinicians accept the use of pharmacotherapy for treating clear-cut psychiatric disorders, especially more severe ones like schizophrenia, major depressive disorder, and manic

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disorder. However, many workers (especially those espousing the use of behavior therapy) may oppose the use of medicine to manage non-DSM behavioral excesses. Nevertheless, the medication experts responding to the Expert Consensus questionnaire did endorse the use of medication for managing certain behavioral excesses, such as self-injurious behavior, interpersonal aggression, and hyperactivity.

Our personal position is that pharmacotherapy is justified for managing certain behavioral excesses, provided that hard data show clear benefit from use of medicine and that a proper cost-benefit analysis is conducted before and during treatment. These are the same standards that should be applied for the use of *any* therapy. It is a fact that it can be exceptionally difficult (if not impossible) to establish many diagnoses (e.g., schizophrenia, major depressive disorder) in people with severe or profound retardation. Nevertheless, these individuals should not be denied access to potentially therapeutic agents just because we have not learned to identify possible underlying conditions. It is also possible that there is no underlying DSM condition but that, for reasons that are not understood, the behavior problem is responsive to drug treatment. In keeping with this view, we shall discuss the use of psychotropic medicines in well-established DSM and ICD conditions. Following this, we shall discuss use of pharmacotherapy of other conditions—not otherwise specified (NOS) (i.e., behavioral excesses).

DSM OR ICD MENTAL DISORDERS

Diagnosing psychiatric disorders in individuals with intellectual disability is a challenging task for clinicians and requires a developmental approach. This is ordinarily based on the patient's intellectual or developmental age, rather than chronological age. The greatest obstacle in diagnosing psychiatric disorders in people with severe or profound intellectual disability is a diminished ability to communicate adequately with the individual; therefore collateral information from the primary caregiver, school, and counselor is usually very helpful for evaluation and assessment.

The most frequently made diagnoses following a psychiatric consultation of individuals with intellectual disability are (a) impulse control disorder, (b) anxiety disorder, and (c) mood disorders. Others include (d) schizophrenia, (e) ADHD, and (f) conduct disorder or oppositional defiant disorder. For this reason, we structure our review of the available research around these conditions. To assist readers with the discussions that follow, we have summarized the most common psychotropic drugs in the Appendix that follows this chapter. We also offer a brief note about recent pharmaceutical developments. In the 1990s, the selective serotonin reuptake inhibitors (SSRIs) and the atypical antipsychotics were ushered in. In general, the SSRIs are safer than the older heterocyclic antidepressants (e.g., amitriptyline, doxepin, nortriptyline, etc.), which can cause ECG changes, drowsiness, and (uncommonly) epileptic seizures. The newer atypical antipsychotics are generally safer than the classical antipsychotics and are less likely to cause extrapyramidal side effects (dystonias, Parkinsonism, akathisia) or tardive dyskinesia (a neurological movement condition that

may follow long-term exposure to antipsychotics). However, some atypical antipsychotics may be more likely to cause weight gain than classical antipsychotics. Both the SSRIs and the atypical antipsychotics appear to have certain therapeutic advantages as well over their predecessors.

Mood Disorders

Mood in individuals with intellectual disability (mental retardation) may be normal, elevated, or depressed; usually a sense of control is lost, and the client may experience great distress. The coexistence of mood disorders and mental retardation was not fully recognized until the early 1970s. Today, a consensus has been reached that individuals with intellectual disability are vulnerable to mood disorders, with an overall prevalence rate as high as in the general population (Reiss, 1994, p. 82).

Poindexter et al. (1998) conducted a helpful review of the available evidence on mood stabilizers in people with mental retardation. Lithium (Lithane, Lithobid) has been assessed in a few small-scale studies, some involving participants with manic depression and some with aggression but without manic disorder. Modest benefits were seen in both manic and in aggressive behavior. In general, these were poorly controlled studies; some were based on retrospective chart reviews. There have been relatively few studies of other agents for managing manic symptoms in people with mental retardation. One poorly controlled study did show a favorable response to valproic acid (Depakene) in 18 adults, especially among those with a history of epilepsy (see Poindexter et al., 1998). Only case reports are available for clonazepine (Klonopin) and, on balance, these were somewhat positive. One study comparing lithium only with lithium-plus-carbamazepine (Tegretol) reported better outcomes with the latter.

The Expert Consensus guideline recommendations for treating mood disorders in individuals with mental retardation are the same as for in the general population. For treating bipolar disorder, depressive episode without psychotic features, the Expert Consensus guidelines recommended treatment with lithium or valproic acid plus one of the following antidepressants (SSRI, bupropion [Wellbutrin], or venlafaxine [Effexor]). For bipolar disorder with psychotic features, the Expert Guidelines recommended lithium or divalproex plus an antidepressant (SSRI, bupropion, or venlafaxine), plus a newer atypical antipsychotic.

Sovner et al. (1998) conducted a very good review of the research on antidepressant medicines in people with mental retardation. They summarized nine reports of adults with either major depression or atypical depression who were treated with a monoamine oxidase inhibitor ($n = 27$), tricyclic antidepressant ($n = 7$), amoxapine (Asendin) ($n = 2$), or SSRI ($n = 10$; total $N = 46$). Two or three of these studies were properly controlled. All but one indicated improvement, but the sole negative report was one of the controlled investigations. Another of the controlled investigations was a single-subject study. Hence, most of the positive reports for adults were case reports or case series. Sovner et al. (1998) also summarized three reports involving children with mental retardation. These addressed the effectiveness of tricyclic antidepressants ($n = 14$),

tryptophan-plus-nicotinamide ($n = 2$), or fluoxetine (Prozac) ($n = 4$; total $N = 20$). All three reports indicated some improvement. We could not determine if two of the studies (written in Dutch) were controlled; the third was not. Thus the empirical support for efficacy of all of the antidepressants in patients with mental retardation is weak, although the uncontrolled literature is largely positive. The problem with this is that workers may not be inclined to report their failures, so that there is often a bias in the type of reports that are published. For major depressive disorders, the Expert Consensus guidelines recommended starting treatment with an SSRI, but also to consider using venlafaxine.

Recently it has been reported that SSRIs are often (although certainly not always) helpful in the treatment of ritualistic, stereotyped, or compulsive behaviors in individuals with mental retardation (Aman, Arnold, & Armstrong, 1999; Branford, Bhaumik, & Naik, 1998 ; see in section "self-injury"). However several researchers working with children have had limited success managing ritualistic and other perseverative behaviors with SSRIs (L. E. Arnold, March 2003; C. McDougle, March 2003; L. Scahill, March 2003; all personal communications). It is possible that SSRIs are helpful for managing perseverative behavior in adults but that, for reasons yet to be determined, their role in children is more limited.

Schizophrenia

There is very little research on the use of antipsychotic drugs to manage schizophrenia in people with mental retardation. The reason is fairly obvious, namely the significant difficulty compiling samples (with both mental retardation and schizophrenia) large enough for meaningful statistical analyses.

Menolascino, Ruedrich, Golden, and Wilson (1985) carried out a comparison of thioridazine (Mellaril) and thiothixene (Navane) in 31 patients with mental retardation and schizophrenia and 30 with normal range IQ and schizophrenia. There was no placebo control. Both the subjects with mental retardation and those with normal range IQ ($\geq$90) showed significant improvement with medication. However, no data were actually presented to show improvement. Those with mental retardation responded significantly more quickly to thiothixene, whereas those with normal range IQ responded faster (but not significantly so) with thioridazine. The clients with mental retardation required lower doses than the normal range IQ sample, although it was not clear if this difference was significant.

Craft and Schiff (1980) also reported an uncontrolled study of fluphenazine decanoate (Prolixin) in residents having both psychotic and nonpsychotic conditions; global improvements were reported. Sajatovic, Ramirez, Kenny, and Meltzer (1994) reported an open study of five adults with borderline IQ who met research diagnostic criteria for schizophrenia. Clozapine (Clozaril) in doses of 225–400 mg/day produced statistically significant improvement on several clinical rating scales.

Of course, the usefulness of antipsychotics for managing schizophrenia is well established in the general population, with about 75–80% of such patients showing a positive response (Baumeister, Sevin, & King,

1998). In the Expert Consensus survey, the experts most frequently chose (a) newer atypical antipsychotics (e.g., risperidone [Risperdal], olanzapine [Zyprexa]); (b) clozapine (in the case of numerous failed trials with other antipsychotics); and (c) long-acting depot antipsychotics (for patients who are noncompliant with oral medication—Rush & Frances, 2000). At this stage, it is safe to say that management of schizophrenia in individuals with mental retardation needs to be guided by researchers' and clinicians' experience in the general population.

Other Psychotic Disorders

There are other psychotic syndromes that do not meet the diagnostic criteria for schizophrenia, the major ones being schizophreniform disorder, schizoaffective disorder, delusional disorder, and brief psychotic disorder. To the best of our knowledge, none of these disorders has been the subject of proper controlled drug studies (Reiss & Aman, 1998).

The treatment for this group of psychotic disorders usually entails a comprehensive treatment plan, which involves bio-psycho-social aspects of the disorder. The use of antipsychotics is usually a major part of treatment. Clinically, antipsychotic drugs appear to be effective for treating many symptoms, including hyperactivity, aggression, tantrums, agitation, insomnia, and self-injury. Again, however, we are not aware of research data on antipsychotic management of other psychotic disorders in this population (Reiss & Aman, 1998). Despite the controversy that has surrounded the use of antipsychotic drugs in people with mental retardation over the years, they are widely prescribed for people with mental retardation and other psychotic disorders. The most highly recommended antipsychotics in the Consensus Survey for psychotic syndrome were risperidone and olanzapine (Rush & Frances, 2000).

Anxiety Disorders

Anxiety disorders are probably the most commonly undiagnosed psychiatric disorders in the general population. Obviously in individuals with mental retardation, the diagnosis will be more difficult due to lack of communication and altered expression of the common signs and symptoms of anxiety. The clinician's experience in observing signs or symptoms of anxiety is the cornerstone of diagnosis of anxiety in this population.

The DSM-IV lists 11 subtypes of anxiety disorder. Phobia is the most common type of anxiety disorder seen in people with mental retardation, whereas panic disorder is relatively uncommon and has only recently been reported for people with mental retardation (Szymanski et al., 1998). Posttraumatic stress disorder is indicated by a persistent tendency to re-experience a traumatic event in several ways. McNally and Shin (1995) found a negative correlation between the severity of PTSD symptoms over time and the IQ of combat soldiers. Reports of PTSD in people with ID have frequently focused on victims of physical and sexual abuse.

The actual research on anxiolytics in this field is extraordinarily limited. Werry (1998) reviewed the work on benzodiazepines (such as diazepam

[Valium]) and found that most of the published work has been done with children. Symptoms reflecting high-anxious behaviors were more responsive than symptoms of acting out, which often became *worse* with benzodiazepines. Furthermore, there are some data suggesting that individuals with conspicuous stereotypy and self-injury may respond paradoxically (i.e., with excitability and combativeness) to anxiolytics; lower IQ has also been a predictor of a paradoxical response. There are no research data on the effects of antihistamines on anxiety or sleep disorders in patients with mental retardation, and the very limited evidence for buspirone (BuSpar) is equivocal (Werry, 1998).

Faced with this lack of experimental evidence, clinicians are probably most likely to provide treatment based on symptoms present, symptom severity, and the clinician's own experience with various treatment modalities. The Expert Consensus guideline recommendations (Rush & Frances, 2000) for anxiety disorders in individuals with mental retardation consist of two categories of therapy, namely behavior therapy and medication therapy. Behavior therapy includes client and family education, applied behavior analysis, and managing the environment with cognitive and classical behavioral therapies. The preferred pharmacotherapy for anxiety disorders is to start with an SSRI or other agents such as venlafaxine, buspirone, and (in some cases) benzodiazepines.

ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the more common conditions among children with mental retardation (Benson & Aman, 1999). The mainstay of treatment for ADHD in typically-developing children is psychostimulant medication (such as methylphenidate [Ritalin], dextroamphetamine [Dexedrine], and amphetamine salts [Adderall]). Reviews of research in young people with mental retardation clearly show that these children also benefit with these medicines, although the response rate is lower (Aman, 1996; Arnold, Gadow, Pearson, & Varley, 1998). Aman (1996) calculated that 54% of participants in these studies were responders, as compared with approximately 75% in the general population.

Whereas stimulants may be the most thoroughly studied drug group for any specific DSM condition (i.e., ADHD) in mental retardation, many important questions remain unanswered. For example, Arnold et al. (1998) pointed out that the course of ADHD, duration of treatment effect, long-term side effects, and any development of tolerance all remain unstudied. Furthermore, there are now several relatively new and longer-acting preparations on the market such as Adderall and long-acting methylphenidate (Concerta, Metadate, Methypatch). We are not aware of any data on the efficacy of these newer agents in mental retardation.

Finally, a new agent, atomoxetine (Strattera), was recently approved by the FDA for the treatment of typically-developing children with ADHD. Arnold et al. (in press) conducted a crossover, placebo-controlled study with 16 children with autism spectrum disorders; six of the children (38%) also had mental retardation. Statistically significant improvement was

observed on the Hyperactivity subscale of the Aberrant Behavior Checklist and on DSM-IV ADHD hyperactive/impulsive symptoms. No changes were seen on cognitive measures, including on a test of vigilance (attention span). We are not aware of any studies that have assessed atomoxetine for management of ADHD in children chosen exclusively for ADHD and mental retardation.

In the Expert Consensus guidelines, the following medicines were endorsed, in this order, for ADHD: (a) psychostimulants (first line treatment), (b) alpha-2-agonists (clonidine [Catapres] or guanfacine [Tenex]—second line), (c) bupropion (Wellbutrin), and (d) tricyclic antidepressants. We are not aware of any controlled studies among children with mental retardation that support (or contest use of) drug groups (b) through (d), above. Given that ADHD is perhaps the best studied disorder within mental retardation, this gives some idea of the challenges before us and the gaps in knowledge that currently exist.

Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD)

CD and ODD are the main conditions comprising disruptive behavior disorders in children. CD with aggression has been found to have a higher prevalence in people with mental retardation than in the general population, with one survey giving a rate of 12.6% (Benson & Aman, 1999). CD, in particular, has a poor prognosis, with a high percentage of such individuals eventually engaging in substance abuse, criminal offenses, or eventually developing antisocial personality disorder.

There is a small literature on the effects of psychostimulants (e.g., methylphenidate, dextroamphetamine) on aggression in children of average IQ (Aman & Lindsay, 2002). For the most part, the literature suggests modest to moderate effects in reducing aggression. Presumably, the mechanism of effect is via reduction of impulsive acting out in such individuals. We are not aware of any literature on stimulant effects in aggressive children with mental retardation, although we assume that the effect would be similar and perhaps more modest.

Historically antipsychotic medicines have sometimes been used to manage aggression in children. Of the older (classical) antipsychotics, haloperidol (Haldol) is the best studied in this respect (Aman & Lindsay, in press). However, the tendency of the traditional antipsychotics to cause extrapyramidal effects or tardive dyskinesia probably makes them a suboptimal choice.

Recently, two controlled reports were published of the use of risperidone in children with either CD or ODD, prominent hostility, or aggression, and borderline IQ or mental retardation (Aman et al., 2002; Snyder et al., 2002). Both studies showed reductions in ratings of conduct problems by about 47% as compared with about 18% for placebo. These children were followed for nearly one year, and their behavior was found to remain stable, usually with mild to moderate side effects (Aman & Lindsay,

2003). We are not aware of similar controlled research with other atypical antipsychotics, although one report of clozapine indicated less aggression (Aman & Madrid, 1999).

Mood stabilizers (lithium carbonate, carbamazepine, sodium valproate, and others) have been assessed with clients having aggressive behavior and mental retardation and in aggressive individuals from the general population (Aman & Lindsay, 2003; Poindexter et al, 1998). These agents appear to reduce aggressive behavior to variable degrees, with the best results occurring with valproate (Depakote). However, most of this work is done with typically developing children.

In the Expert Consensus survey, practitioners were asked for their recommendations when a specific DSM-IV diagnosis could not be made and where the target symptom was physical aggression to people or property. The experts chose (a) newer atypical antipsychotics and (b) anticonvulsant/mood stabilizers as the first-line choices. They also chose (c) SSRIs and (d) beta blockers as second-line treatments. Whereas there are case series and uncontrolled reports of these latter agents (c and d), there is little or no controlled research on their value for this purpose in mental retardation (Fraser, Ruedrich, Kerr, & Levitas, 1998; Sovner et al., 1998).

Other Behaviors Not Otherwise Specified

Personality Disorder

Some investigators have identified several extreme personality characteristics that may occur in individuals with mental retardation (Zigler & Burack, 1989). They include over-dependency, low ideal self-image, limited aspirations, and an outer-directed style of problem solving. During the early developmental years, a combination of parental restrictiveness and overprotection, peer pressure and rejection, and low self-esteem and low confidence can lead to major problems with one's self-identity. The diagnosis and treatment of personality disorders in individuals with mental retardation is still controversial, but it seems that these individuals may have a higher rate of severe personality disorders than other groups.

The treatment of personality disorder in individuals with mental retardation is not different from the general population. It consists of psychotherapy or behavior therapy and pharmacotherapy. The latter depends on the IQ of the individual with mental retardation. In dealing with agitation, pharmacotherapy with an anti-anxiety agent such as diazepam (Valium) is usually sufficient, although sometimes it is necessary to use an antipsychotic; recently the atypical antipsychotics have become standard treatments when stronger agents are needed. We are not aware of any drug research involving personality disorders in this field (Reiss & Aman, 1998).

Aggression

This category was addressed above when CD and ODD were discussed. Suffice it to say that aggression (without a co-existing DSM disorder) has been a frequent target of treatment since the first psychotropic agents

were synthesized. Much of this work was with the classical antipsychotics, which are now superseded by the atypical antipsychotics. In their review of antidepressants, Sovner et al. (1998) identified seven case reports and case series ($n = 9$ participants) showing improvement when treated with a variety of drugs. One patient had organic personality disorder and another had intermittent explosive disorder, but the remainder did not have DSM diagnoses normally considered to cause aggression. The antidepressants used included trazodone (Desyrel), fluoxetine (Prozac), and fluvoxamine (Luvox).

As noted above, the Expert Consensus guidelines identified atypical antipsychotics, antipsychotics in combination with mood stabilizers, SSRIs, and beta blockers as the most likely to be helpful for aggressive behavior in the absence of a DSM diagnosis (Rush & Frances, 2000). This statement is based on expert *opinion* and awaits confirmation in rigorous controlled studies.

Pica

Eating inedible substances is fairly common in people with severe or profound mental retardation. In the Expert Consensus survey, the respondents most commonly recommended the following: (a) no medication ("first-line"), (b) SSRI, and (c) mineral or nutritional supplement (e.g., zinc, iron) (Rush & Frances, 2000). We do not know the rationale for using SSRIs and we are not aware of any research on this. The use of vitamin or mineral supplements makes sense if the pica reflects some sort of compensatory need and if it can be shown by laboratory tests that the individual has a vitamin or mineral deficiency.

Self-Injury

Self-injury of a repetitive nature is somewhat common in people with developmental disabilities, and its prevalence seems to increase with functional impairment. Approximately 10–15% of institutional residents display self-injury as compared with 1–2.5% in the community (Aman, 1993).

Virtually every type of psychotropic agent has been tried in the past in the hopes of reducing self-injury. In one review, the evidence seemed strongest for certain classical antipsychotics, lithium carbonate, and the opiate blocker naltrexone (Trexan—Aman, 1993). Among the atypical antipsychotics, risperidone, clozapine, and olanzapine have all been shown to reduce self-injury, although the methodology in most of the reports was found to be wanting (Aman & Madrid, 1999).

In the 1980s and 1990s there was considerable interest in the notion that self-injury might reflect a dysfunction in the patient's opiate system, and this generated a number of studies of naltrexone, a relatively pure opiate blocker (Sandman et al., 1998). Our reading of this literature is that naltrexone has not lived up to its initial promise, although a few patients do appear to get benefit from it. There has also been speculation that self-injury may reflect an underlying form of obsessive compulsive disorder or

that it may be a symptom of underlying major depression, both of which could implicate serotonergic antidepressants as therapeutic agents. A review of SSRI reports identified 12 that were positive in outcome, one that was mixed, and two that were negative (Aman et al., 1999). The same review identified two positive studies with clomipramine (Anafranil) and one negative one. Thus, overall, the literature suggests some benefit with SSRIs, atypical antipsychotics, lithium carbonate, and natrexone, although sample sizes were often small and research methodology frequently weak. Some clinicians try to tailor treatment to patient characteristics by prescribing (a) antidepressants when there is a bout of depression, OCD, or evidence of affective disorder in family members; (b) antipsychotics when behavior presents as bizarre or there is a family history of psychosis; and (c) naltrexone when the self-harm is very repetitive with no apparent reinforcement to maintain it.

In the Expert Consensus survey, the respondents chose the following therapies in this order when asked how they would treat self-injury in the absence of a DSM diagnosis: (a) newer atypical antipsychotic, (b) anticonvulsant in combination with a mood stabilizer (a and b: "first-line" treatments), (c) serotonergic antidepressant, and (d) naltrexone ("second line" treatments). Conventional antipsychotics, beta blockers, and buspirone (an anxiolytic) were also mentioned.

Symptoms Accompanied by a General Medical Condition

The most common general medical condition associated with mental retardation is seizure disorder, which can present as generalized or partial seizures. The most common generalized seizures in adults are tonic-clonic seizures ("grand mal" convulsions). Partial seizures are either complex or simple partial seizures; seizures are associated with alterations of consciousness or somatosensory, autonomic, or mixed symptoms. Clinicians often treat combined mood disorder with seizures with divalproex sodium (Depakote) or carbamazepine (Tegretol), both of which are approved by the U.S. Food and Drug Administration for this purpose. It is widely accepted that higher doses of these two antiepileptic mood stabilizers are needed to treat combined mood and seizure disorders. Lithium, a mood stabilizer without antiepileptic properties, would not ordinarily be used to manage combined mood and seizure disorders.

DISCUSSION

State of the Field

There has been a proliferation of new psychotropic agents in the recent past. Examples include the atypical antipsychotics (with the recent addition of aripiprazole [Abilify] and ziprasidone [Geodon]), SSRIs (with citalopram [Celexa] and escitalopram [Lexapro] recently introduced to the U.S. market), several new anticonvulsants (e.g., lamotrigine, topiramate,

gabapentin; many of which have found a place as mood stabilizers), and certain over-the-counter agents (e.g., St. John's Wort, melatonin). Suffice it to say that good research has not been able to keep pace with this rate of development. There are several major challenges that confront researchers in this field including the following. First, the numbers of individuals with mental retardation and a psychiatric problem are far smaller than in the general population, making recruitment for research very difficult. Second, this is an "orphan population," sufficiently small that many pharmaceutical companies may lack incentive for grooming new psychoactive agents. Third, it can be exceptionally difficult to make psychiatric diagnoses with confidence in this population, especially with people having severe or profound retardation, which further compounds difficulties in defining research samples. Fourth, by the very nature of mental retardation, many participants may find it difficult to cooperate with test procedures (e.g., perform cognitive tests) or provide valuable subjective feedback regarding sensation or emotion.

Consequently, it is exceptionally difficult to conduct research in this field. It is still true today, as it was 35 years ago (Sprague & Werry, 1971), that investigators often rush to assess the latest sexy drug. Scientific journals often publish such reports, even when the research methods are inferior. The reality is that we do not have much evidence for the efficacy of most agents based on research with patients having mental retardation. Much of the literature that is available is either poorly controlled or uncontrolled. Consequently, we do not have much hard evidence for the efficacy of most agents based on research with patients having mental retardation. Hence, many (perhaps most) practitioners try to work by inference or analogy from what is known in the general population. Having said that, we do have certain directions from past experience. For instance, clinicians are becoming more sophisticated in making dual diagnoses of developmental and mental disorders. In addition, many prescribers seem to appreciate important challenges posed by clients having mental retardation. For example, most experts appreciate that it is often necessary to start with lower doses (presumably because of central nervous system [CNS] dysfunction) and to titrate dosage more slowly when medicating patients with mental retardation (Rush & Frances, 2000).

Directions for the Future

In the short term, we cannot possibly assess all novel agents for all psychiatric conditions and target symptoms in this field. At the very least, then, we should strive for some sound investigations with at least a *prototype* of each medication class and for each major indication for these agents. For example, it would be rational to attempt to assess good candidates from among the atypical antipsychotics (currently numbering at least 7) and from the SSRIs (numbering 5 at time of this writing). The National Association for the Dually Diagnosed (NADD) and the American Psychiatric Association are working together to develop modified symptom criteria in people with mental retardation that are equivalent to symptoms

among psychiatric patients in the general population (R. Fletcher, personal communication, February 2003). It is hoped that the guidelines will help future investigators to achieve better reliability when choosing study participants.

New imaging techniques are becoming more sophisticated and (perhaps) less invasive. Examples are functional MRI, SPECT and PET scan, which can locate areas of brain with metabolic hyperactivity. Both CT and MRI have been used successfully in identifying specific congenital disorders. It is likely that these tools will help us both to identify more appropriate participants and to understand the central nervous system effects that make a given drug therapeutic. We also have much greater sophistication than in the past in identifying metabolically (and genetically) determined etiological subgroups and behavioral phenotypes among people with mental retardation. If we conduct our research carefully, with documentation of such subgroups and attention to rational matches between conditions and pharmacological agents, we may be able to achieve breakthroughs in pharmacotherapy.

APPENDIX

Common Psychotropic Medicines Grouped by Class

Drug groups and examples	Brand names
Antipsychotics	
(Classical antipsychotics)	
chlorpromazine	Largactil, Thorazine
flupenthixol	Depixol
fluphenazine	Prolixin, Modecate
thioridazine	Mellaril
haloperidol	Haldol
loxapine	Loxitane
molindone	Moban
prochlorperazine	Compazine
(Atypical antipsychotics)	
aripiprazole	Abilify
clozapine	Clozaril
olanzapine	Zypreza
quetiapine	Seroquel
risperidone	Risperdal
sertindole	Serlect
ziprasidone	Geodon
Antidepressants	
(Heterocyclics)	
amitriptyline	Elavil
clomipramine	Anafranil
desipramine	Norpramin
doxepin	Sinequan
imipramine	Tofranil
nortriptyline	Aventyl, others

(Continued)

Drug groups and examples	Brand names
(Atypical antidepressants)	
amoxapine	Asendin
bupropion	Wellbutrin
maprotiline	Ludiomil
nefazadone	Serzone
trazodone	Desyrel
Selective serotonin reuptake inhibitors (SSRIs)	
citalopram	Celexa
escitalopram	Lexapro
fluoxetine	Prozac
fluvoxamine	Luvox
paroxetine	Paxil
sertraline	Zoloft
(Monoamine oxidase inhibitors)	
moclobemide[a]	Aurorix
phenelzine	Nardil
tranylcypromine	Parnate
Mood stabilizers	
carbamazepine[b]	Tegretol
clonazepam[b]	Klonopin, Rivotril
gabapentin[b]	Neurontin
lamotrigine[b]	Lamictal
lithium carbonate	Eskalith, others
valproic acid[b]	Depakote, Depakene
Psychostimulants	
amphetamine salts	Adderall
D-amphetamine	Dexedrine
methylphenidate	Ritalin, Metadate, Concerta, Methypatch
D-methylphenidate	Focalin
Norepinephrine reuptake inhibitor	
atomoxetine	Strattera
Alpha 2 adrenergic agonists	
clonidine	Catapres
guanfacine	Tenex
Anxiolytics/sedatives	
(Benzodiazepines and benzodiazepine analogue)	
alprazolam	Xanax
diazepam	Valium
flurazepam	Dalmane
lorazepam	Ativan
nitrazepam	Mogadon
temazepam	Restoril
zopiclone	Ambien
(Atypical anxiolytic)	
buspirone	BuSpar
(Antihistamines)	
diphenhydramine	Benedryl
hydroxyzine	Atarax
promethazine	Phenergan

[a] Not available in the United States.
[b] Main indication is as antiepileptic agent.

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