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An examination of psychotropic medication prescription practices among individuals with mental retardation

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AN EXAMINATION OF PSYCHOTROPIC MEDICATION PRESCRIPTION PRACTICES AMONG INDIVIDUALS WITH MENTAL RETARDATION

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ABSTRACT

While there is an extensive literature on the use of psychotropic medications among individuals with mental retardation, little of it has focused on the reasons for these prescriptions. Researchers have shown that the prevalence of psychotropic medication use among individuals with mental retardation is relatively high when compared to people with other disabilities and that the reasons for these drug prescriptions may not be based on rational pharmacotherapy. Data is needed on the prescribing physician's adherence to consensus guidelines or algorithms developed to enhance rational psychopharmacotherapy. In order to do this, the rationales being used by physicians when they decide to prescribe a medication must first be examined. The current study examines the approaches to medication prescription taken by physicians at one state facility. The results of this study showed that physicians at this particular facility for individuals with developmental disabilities typically used a primary illness approach in prescribing psychotropic medication. The results also showed that, in general, the documentation in the charts regarding assessments, diagnostic formulation, differential diagnosis, and rationale of pharmacotherapy was not very clear or missing. The limitations of this study are discussed as well as implications for future research.

INTRODUCTION

Psychotropic medications are prescribed to treat a myriad of behavioral and psychiatric symptoms in both the general population and in individuals with mental retardation (Advocat, Mayville, & Matson, 2000; Singh & Winton, 1989; Young & Hawkins, 2002). In the field of mental retardation, psychotropic medications are typically used to reduce maladaptive behavior such as aggression, pica, property destruction, and self-injury (Aman, Singh, & Fitzpatrick, 1987; Aman, Singh, & White, 1987; Intagliata & Rinck, 1985). As such, individuals with mental retardation may be prescribed psychotropic medication for suppressing behavior rather than treating a psychiatric disorder (Aman & Singh, 1991).

As many individuals with mental retardation are non-verbal, they must find other means to communicate or control their environment. Researchers suggest that individuals with mental retardation who have limited communication skills use expressive behavior to communicate their wants and needs (Dura, 1997; Durand & Carr, 1991). In fact, limited communication skills can lead to communication in the form of aggression, self-injury, or self-stimulatory behavior (Menolascino, Levitas, & Greiner, 1986). Therefore, aggression, property destruction, self-injury and other socially inappropriate behaviors may serve a functional purpose for an individual (Carr & Durand, 1985). As psychotropic medications may cause side effects that cause some degree of behavioral or cognitive impairment, these drugs may be suppressing the individuals' ability to functionally communicate (Lowry & Sovner, 1991).

Research on the functional aspects of an individuals' behavior, determining what motivates an individual to engage in a particular behavior, has yielded several technologies designed for assessing an individual's behavior. Assessment techniques based on various operant procedures include functional analysis (Iwata, Dorsey, Slifer, Bauman, & Richman, 1982), functional assessment (Hile & Desrochers, 1993), functional communication training (Carr & Durand, 1985), and positive

behavior supports (Carr et al., 2002). The aim of these assessments is to determine the function of an individual's behavior and use this information to design interventions that teach the individual socially appropriate, functionally alternative replacement behaviors. The efficacy of these behavioral assessment methods has been documented in the literature. However, teaching an individual the new skills they need relies on the individual being able to learn. As mental retardation is primarily a learning disorder and psychotropic medications may impair learning, these medications may reduce an individual's chances for success and negatively impact on their quality of life (Lowry & Sovner, 1991). Given the existence of procedures that teach individuals skills that enable them to communicate appropriately and effectively, it may not be appropriate to treat problems that are behavioral and functional in nature with psychotropic medication.

Literature on psychotropic medication has strongly indicated a link to an increased risk of serious side effects; of particular concern to individuals with mental retardation are side effects that may interfere with learning (Advocat, Mayville, & Matson, 2000; Maxmen & Ward, 2002; Schatzberg, Cole & DeBattista, 2003). Some of these side effects include cognitive slowing, loss of creativity, memory problems, confusion, sedation, akathisia, akinesia, noncompliance and blurred vision (Baumeister, Sevin, King, 1998; Janicak, Davis, Preskorn, & Ayd, 2001; Schatzberg, Cole & DeBattista, 2003). Further, as individuals with mental retardation generally have more health problems than individuals without, the risk of side effects among individuals with mental retardation is greater and further reaching and the use of psychotropic medication needs to be approached more carefully (Janicki et al., 2002; Mulligan Ault, Guy, Rues, Noto, & Guess, 1994; Springer, 1987). However, this does not seem to be the case. For example, one study found that 62% of individuals in their sample were prescribed psychotropic medications without a valid documented psychiatric diagnosis (Bisconer, Sine, & Zhang, 1996). This case may not be an isolated one.

While a body of literature on the use of psychotropic medications among individuals with mental retardation exists, it is limited in that it has been focused primarily on prevalence rates and patterns of prescription rather than on the primary reasons for drug prescription (Young & Hawkins, 2002). Few studies have examined why individuals with mental retardation are prescribed psychotropic medications, and fewer have examined the legitimacy of these prescriptions. Unless a careful and thorough assessment indicates that an individual with mental retardation engages in behavior problems that are a feature of an underlying mental illness that may be responsive to psychotropic drug therapy, the use of these drugs should be considered inappropriate treatment to control an individual's behavior (Sovner, 1989). In fact, it may be considered a form of chemical restraint if the medication is prescribed solely for behavioral control and to such a point they cannot learn or function. For psychotropic medication prescription to be considered legitimate, it should target the behavioral end-point(s) of a specific psychiatric disorder as defined in the DSM-IV-TR (APA, 2000), or have a specific behavioral-psychopharmacologic hypothesis.

The practice of prescribing medication for behavioral control tends to ignore the bi-directionality of drug and psychosocial interventions. For example, self-injury has been shown to respond to both pharmacological and behavioral treatments (Mace, Blum, Sierp, Delaney, & Mauk, 2001). Behavioral treatments operate on the premise that the behavior is controlled and maintained by the environment. Pharmacological treatments are based on the hypothesis that the behavior may be caused by an underlying chemical imbalance. Thus, a bio-behavioral assessment and diagnostic system could be used to differentiate between conditions most likely to respond to behavioral treatments and those most likely to respond to pharmacological treatments. If the assessment reveals that an individual's self-injury is a mixed type, that is part behavioral and part biological, then treatment would consist of both behavioral and pharmacological components. Both behavioral and drug treatments produce changes in the individual. As these changes are reinforced in the

individual's environment, the need for medication can decrease and the need for skills training to maintain and continue the reduction of the behavioral aspect of self-injury could increase, or vice versa. This bi-directionality of the effects of interventions is rarely appreciated when psychopharmacological and non-psychopharmacological interventions are developed for people in general, let alone individuals with developmental disabilities (Napolitano et al., 1999). The lesson here is that the impact of all interventions must be constantly evaluated to account for and respond to changes in the individual and their environment.

The literature on current drug prescribing practices indicates that comprehensive process and outcome evaluations are rarely performed and the needs of individuals with mental retardation are not being fully met (Hellings, 1999; Sevin et al., 2001). It is evident that a closer look at the prescription patterns of psychotropic medications is warranted. Individuals with mental retardation depend on professionals to teach them the skills they need in order to have the highest quality of life possible (Matson, Bamburg, Smalls, & Smiroldo, 1997; Menolascino et al., 1986). Simply prescribing medication to treat behavioral symptomology ignores the fact that drugs do not target the cause of the behavior problem or the individual's vulnerability to it. That is, while medications may physiologically reduce behavioral symptoms, the individual has not learned anything and is still vulnerable to the internal and external environmental triggers of the particular problem behavior (Zuckerman, 1999). Using psychotropic medications among individuals with mental retardation needs to be carefully considered and, if their use is deemed appropriate, they should be monitored closely to ensure that the individuals are receiving the best possible treatment according to current best practice.

Ideally, the use of psychotropic medication involves matching specific label and clinically validated off-label uses of the medication to the specific signs and symptoms of a psychiatric disorder or a well-defined behavioral target (Reiss & Aman, 1998). Psychotropic medication

prescriptions should be specific as to what particular signs and symptoms of a disorder are being targeted. For example, for an individual with depression it is important to know if the medication is targeting weight loss, insomnia, lethargy, or mood; for ADHD, is the medication targeting symptoms such as difficulty sustaining attention, being easily distracted, or fidgeting. As psychotropic medications do not treat entire symptom profiles, it is important to know which symptoms are being targeted so that supplemental therapies may be introduced to treat other symptoms that may have a behavioral, or learned, component. In this manner, a clinician can properly monitor the individual's progress objectively and ensure that the prescribed treatments are appropriate. In order to examine how well a particular psychotropic medication fits the individual's diagnosis and target symptoms, we must first examine what approaches physicians are taking to prescribing medications to individuals with mental retardation.

There are three ways of conceptualizing psychopharmacotherapy in people with mental retardation, including (a) a target symptom approach, (b) a primary illness approach, and (c) a behavioral-pharmacologic hypothesis approach. The target symptom approach is based on the notion that if a clinician does not know or cannot unravel the biomedical or behavioral basis of a target behavior, the behavior can still be treated directly without knowing the underlying cause (Conner, 2002; Rush & Francis, 2000). For example, aggression that has an explosive and rageful quality to it and is often seen as a behavioral expression of several psychiatric disorders (e.g., conduct disorder in children, antisocial personality disorder in adults) is medication responsive. Regardless of the actual psychiatric diagnosis, the overt aggression can be treated with psychotropic medications. For example, overt aggression associated with explosive rage can be treated with atypical antipsychotic medications and lithium, aggression associated with affective lability can be treated with mood stabilizers, and those associated with autonomic nervous system (ANS) overarousal can be treated with adrenergics, Clonidine, Guanfacine and β - blockers. This approach

is analogous to palliative medical treatment when the underlying medical illness is not known or not treatable.

The primary illness approach assumes that we can treat the underlying condition, thereby taking care of the associated symptoms without directly treating them (Conner, 2002; Rush & Francis, 2000). That is, we can identify the psychiatric disorder that underlies the target behavior and the psychiatric illness itself is amenable to psychopharmacological treatment. For example, if the aggression is a behavioral manifestation of the underlying psychosis or mood disorder, then it will decrease when the underlying psychosis or mood is treated with medication. This treatment is not palliative, but focused on the underlying disorder.

The behavioral-pharmacologic hypothesis approach is based on the notion that there may be specific mechanisms that explain the probable genesis and maintenance of a target behavior (Conner, 2002; Rush & Francis, 2000). For example, aggression (e.g., self-injury) may occur as a result of an imbalance of endogenous opiates in the body and using naltrexone to restore this imbalance will reduce or eliminate the aggression.

PREVALENCE OF PSYCHOTROPIC MEDICATION USE

In 1966, Ronald Lipman undertook the first survey of drug usage among individuals with mental retardation in institutions. This seminal investigation examined 142 state and 31 private institutions across the country and found that 51% of residents were prescribed psychotropic medications. Interestingly, two drugs, specifically thioridazine and chlorpromazine, accounted for approximately 58% of all psychotropic drug prescriptions and were the two most frequently prescribed drugs in 91% of the institutions surveyed (Lipman, 1970). Overall, the drug classes that were prescribed most commonly were major tranquilizers, which accounted for 39.2% of prescriptions, minor tranquilizers (8.1%), and antidepressants (3.8%). Further, in the institutions surveyed, 25% of the residents' prescribed psychotropic medications typically received these drugs for four years up to an indefinite period of time. While this survey did not examine the issue of polypharmacy, the prescription of two or more psychotropic medications, Lipman (1970) did find that maximum dosages above recommendations set by drug manufacturers were common.

This landmark study was followed by several other investigations, with most reporting similar findings (Singh, Ellis, & Wechsler, 1997). In an effort to update Lipman's survey Singh, Ellis, and Wechsler (1997) reviewed drug prevalence studies between 1966 and 1995. This review split the sample of drug prevalence studies into two time periods, one from 1966 to 1985 and the other from 1986 to 1995. Research performed from 1966 to 1985 had been summarized by other authors, so Singh et al. (1997) only briefly summarized previous findings. During the first time period, 1966 to 1985, the prevalence of psychotropic drug use in institutions ranged from 19% to 86% with most studies reporting between 30% and 50%. In the community samples, the prevalence of psychotropic drug use in adults ranged from 26% to 36%. During the second time period, 1986 to 1995, Singh et al. found that the prevalence of psychotropic drug use in institutions ranged from

12% to 49%. In community studies, the typical prevalence rate of psychotropic drugs ranged from 19% to 29%.

Since the Singh et al. (1997) review, several studies have been published which examine the prevalence rates of psychotropic medication use among individuals with mental retardation and have reported similar findings (e.g., Nottestad & Linaker, 2003; Roberson et al., 2000; Stolker, Koedoot, Heerdink, Leufkens, & Nolen, 2002). The prevalence of psychotropic drug use in institutions has been found to range from 25% to 60% (Roberstson et al., 2000). In community settings, the prevalence rate of psychotropic medication use has been found to range from 20% (Emerson et al., 1997) to 56% (Roberstson et al., 2000).

As the literature demonstrates, there has not been a significant change in the use of psychotropic medications among individuals with developmental disabilities since Lipman's survey in 1966. This situation is surprising considering the emergence of literature indicating that the use of such medication in this population is often unnecessary and inappropriate. Further, research has shown that most of the medications being prescribed to individuals with developmental disabilities can have serious side effects and cause long term harm. While guidelines for the prescription of psychotropic medications exist (e.g., American Journal on Mental Retardation, Vol. 105, No. 3; Reiss & Aman, 1998) the prevalence of these medications suggests that these guidelines are not be being followed and individuals with mental retardation may be overmedicated.

PSYCHOTROPIC MEDICATIONS

Psychotropic medications affect specific brain functioning by increasing or decreasing the activity of neurotransmitters, the chemical messengers of the brain (Diamond, 2002). Some neurotransmitters trigger the firing of nerve cells and are known as excitatory while others block the firing of a nerve cell and are known as inhibitory. Medications are designed to either increase or decrease the activity of specific neurotransmitters. Change in the neurotransmitter pathways cause changes in brain functions that ultimately lead to changes in an individual's behavior. As previously noted, psychotropic medications are used to target behavioral and psychiatric symptoms of mental illness.

History

The historical origin of the antipsychotic known as Chlorpromazine (CPZ) dates back to 1883 and the synthesis of its parent compound phenothiazine by a German chemist named August Heinrich (Swazey, 1974). Interestingly, Heinrich was investigating the structural properties of methylene blue compounds, valuable dye products. In 1883 he published a paper in which he described the nucleus of methylene blue and its synthesis; the nucleus he described was phenothiazine. The identification of and synthesis of methylene blue would have effects far beyond the dye industry (Swazey, 1974).

The advent of CZP in 1950 was the result of the combination of two lines of research. One line was concerned with the production of synthetic antihistamines that were powerful and nontoxic enough to be used in the treatment of allergies. The other was phenothiazine chemistry that was aimed at creating drugs that could be used to fight malaria, African sleeping sickness, and worm infestations. In 1945, these lines of research merged when chemists at the French laboratory Rhone-Poulenc discovered that a phenothiazine amine compound named 3015 RP, synthesized by Paul Charpentier, had strong antihistamine properties (Swazey, 1974). Research into phenothiazine

amines was further advanced in 1946 when it was reported to be useful in the treatment of Parkinson's disease. These clinical effects of the phenothiazine amine, namely sedation, led researchers to believe that these drugs had some type of unknown central nervous system effects.

Concurrent with the research being conducted at Rhone-Poulenc, French navy surgeon Henri Laborit was using synthetic antihistamines to fight circulatory shock after surgery. While using antihistamines, Laborit noted secondary qualities beneficial to the prevention and treatment of surgical shock: hypothermic and gangliopalegic properties. This, coupled with other clinical findings were factors in Rhone-Poulenc's decision to begin research into the development of a phenothiazine amine that displayed a high degree of central nervous system activity regardless of it antihistaminic activity (Koetschet, 1955). In 1950, Rhone-Poulenc began intensive studies of CPZ's pharmacological properties; the results of these initial studies indicated strong central action and clinical trials.

Laborit, who wanted an alternative to the drug he was using at the time, began using CPZ to relax patients and reduce the likeliness of surgical complications and shock. He reported that patients who received 50-100 mg intravenously had some drowsiness but were indifferent to the surgical procedure; in fact, he reported that his patients had a broader indifference and seemed not to care about anything at all (Laborit, Huguenard, & Alluaume, 1952). Labroit's results led him to suggest to a number of psychiatrists that the use it with psychiatric patients. However, not many of his colleagues were interested.

CPZ's efficacy as an antipsychotic was not clinically established until 1952. Until this time, a small series of publications had been reporting the use of CPZ in French psychiatric patients, with some success. These papers showed that CPZ was being used in four major ways: 1) as a barbiturate potentiator in manic agitation; 2) in conjunction with shock treatment in anxiety states and manic depressive states; 3) the potentiation of other drugs in sleep therapy; and 4) administered alone. It

was this last area of research, used alone, that is historically the most significant (Swazey, 1974). In 1952, John Delay and Pierre Deniker presented a report to the Societe Medico-Psychologique that, while not a permanent cure, CPZ was effective in reducing manic states in psychiatric patients (Delay & Deniker, 1952). This report is often cited as being the first public presentation of an effective drug treatment for a mental disorder (Marder & Van Putten, 1995).

News of this discovery spread quickly, and within two years CPZ was used around the world to help individuals with agitation associated with mania and nausea. CPZ's rapid and widespread increase in usage can be attributed to several factors. The foremost of which was that until CPZ, there was no other effective treatment for schizophrenia or any other form of psychosis (Marder & Van Putten, 1995). Another factor was that CPZ was inexpensive to administer and was considered relatively safe, despite it side effects. Further, CPZ was effective for a large number of individuals, leading to a decrease in the use of restraint devices, seclusion, and locked units. Unfortunately, many individuals have residual symptoms and continue to relapse.

However, the advent of CPZ for use in psychiatric populations was not the only precipitating factor to spark research into the biological basis of psychotic disorders and drug that could be used to treat them. Several decades' earlier, Indian researchers began scientific investigations of R. serpentina, a tropical species of shrub that grows in regions of India. In the early 1930's, researchers isolated several of R. serpentina's alkaloids and began documenting their physiological activity and noted that the compound was useful in treating violent manic symptoms associated with insanity (Baumeister & Francis, 2002). Shortly after the publication of these results, Ciba laboratories identified the sedative aspect of R. serpentina, which they named reserpine and marketed as an antihypertensive-sedative called Serpasil. (Baumeister, Hawkins, & Uzelac, 2003). Clinical trials soon established that the clinical profile of reserpine was close to that of CPZ, that is, both drugs were sedating without producing a clouding of consciousness as found in barbiturates

(Swazey, 1974). These new drugs were labeled neuroleptics, a term arising from the Greek works neuron and leptos meaning to "take hold of the nervous system" (Deniker, 1983).

While the discovery of CPZ was paramount in the beginning stages of psychopharmacology and neuroleptic drug development, it was not a cure all and not without problems. Shortly after CPZ's introduction in 1952, side effects that included induced Parkinsonism and other extrapyramidal side effects (EPS), such as tardive dyskinesia, were being reported (Lehmann & Hanrahan, 1954). The ability of neuroleptic drugs to produce antipsychotic as well as extrapyramidal effects has been attributed to their ability to block the D_2 dopamine receptor subtype. Because typical antipsychotics often do not result in a full remission of symptoms and produce unwanted side effects, researchers have been searching for better antipsychotic drugs. Researchers have been focusing on compounds with an improved efficacy on both positive symptoms (an excess or distortion of normal functioning such as delusions, hallucinations, and disorganized speech) and negative symptoms (restrictions in the range and intensity of emotional expression, fluency and productivity of speech and thought, and initiation of goal oriented behavior) and side effects profiles (APA, 2000; Owens & Risch, 1995).

Second-generation antipsychotics have been termed atypical, as they tend to produce fewer extrapyramidal side effects and improved efficacy at therapeutic doses (Owens & Risch, 1995). While unclear, the mechanism of action of the atypical drugs is considered to be through either differential actions in various dopamine neurons and/or binding to different dopamine receptor subtypes, or additional binding to other neurotransmitter receptors (Owens & Risch, 1995). Studies have shown atypical drugs to be relatively weaker D_2 antagonists and that they possess relative mesolimbic dopaminergic specificity compared to nigrostriatal dopamine neurons. This selective targeting may explain why atypical antipsychotics have fewer EPS side effects and tardive dyskinesia

liability. Six second-generation atypical antipsychotic medications have been introduced since the late 1980's and include olanzapine, risperidone, sertindole, and ziprasidone.

Clinically, neuroleptics are generally effective in controlling psychomotor agitation and excitement, in the management of psychosis, and the treatment of schizophrenia and mania (Lieberman & Mendelowitz, 2000). Antidepressants are useful in the treatment of depressive disorders and anxiety disorders such as obsessive-compulsive and panic disorders (Ban, 2001). Minor tranquilizers relieve tension and are used to treat panic attacks and generalized anxiety disorder, and hypnotics-sedatives are used in the treatment of insomnia (Diamond, 2002). Mood stabilizers are used to treat manic-depressive and bipolar disorders (Hopkins & Gelenberg, 2000). Stimulant medications are used to treat attention deficit hyperactivity disorder and narcolepsy (Fawcett & Busch, 1995). Cholinesterase inhibitors have shown promise in the treatment of Alzheimer's disease (Ban, 2001).

Determining which medication is best suited for an individual is a complex task. To aide clinicians in this task, several expert consensus guidelines have been developed (Rush & Frances, 2000; Reiss & Aman, 1998), along with medication algorithms such as the Texas Medication Algorithm Project (Gilbert et al., 1998; Rago & Shon, 2001). These guidelines and algorithms provide clinicians with step-by-step procedures for the implementation of medication regimens based on the characteristics of an individual and their presenting symptomology. In addition, they provide clinicians with alternative drug therapies if the first line does not have a significant positive impact. Therefore, these guidelines also serve to inform clinicians about the multiple uses and combinations of various medications to safely reach a desired therapeutic effect and how to effectively monitor their clients progression. The following is a review of the most common classes of medications shown to be useful among individuals with mental retardation including drug mechanisms, clinical effects, and side effects.

Antipsychotic Medications

Antipsychotic drugs are used to treat nearly all forms of psychosis and psychoses associated with organic mental disorders (Marder & Van Putten, 1995). First generation antipsychotics are classified as a neuroleptic; a term arising from the Greek works neuron and leptos, meaning to "take hold of the nervous system" and used to describe the adverse motor slowing effects of these drugs (Lieberman & Mendelowitz, 2000). The implication was that the motor side effects were a fundamental part of the therapeutic aspects of the drugs and could not be separated out. Thus, typical antipsychotic drugs developed until the late 1980's were considered to be neuroleptics. However with the introduction of clozapine, the first of the second-generation medications to have antipsychotic properties without EPS, the term neuroleptic was no longer appropriate (Lieberman & Mendelowitz, 2000). As such, second-generation neuroleptics were termed atypical antipsychotics. Although drug classes are based on biochemical structure, a more meaningful classification within antipsychotic medications is whether they are EPS-producing neuroleptics or non-EPS-producing antipsychotics (Stahl, 1996).

Mechanism

The traditional, or older, typical antipsychotic medications typically exerted their effects by blocking the D_2 dopamine receptor in the brain. There are four major dopamine pathways in the brain and typical antipsychotics block all four of these pathways. However, the dopamine pathway located in the limbic system, specifically the mesolimbic dopamine pathway is considered responsible for psychotic symptoms. Generally, chemicals that decrease activity in this pathway decrease psychotic symptoms while chemicals that increase activity increase, or cause, psychotic symptoms (Diamond, 2002). Another dopamine pathway located in the frontal cortex that stimulates behavior, thought, expression, and motivation is the mesocortical dopamine pathway. Blocking dopamine in this pathway decreases these aspects of an individual's personality and can

exacerbate the negative symptoms of schizophrenia. The third dopamine pathway is located in the nigrostrital pathway, an area responsible for the control of the extrapyramidal motor system. Blocking dopamine in this pathway causes a loss in voluntary muscle movement resulting in parkinsonism-like extrapyramidal side effects (EPS) (Stahl, 1996). The fourth pathway is the tuberoinfundibular dopamine pathway responsible for the secretion of prolactin, a sex-related hormone produced by the hypothalamus. When this pathway is blocked, the individual's prolactin level increases and can result in breast enlargement, secretion of a milk-like substance from the breasts in both men and women, and other sexual side effects. As the typical antipsychotics are not selective with respect to which pathway dopamine is blocked.

New atypical antipsychotic medications leave dopamine receptors in other parts of the brain largely unaffected by using the brain's own self-regulation system (Diamond, 2002). One hypothesis is that serotonin blocks the release of dopamine in some brain pathways. As such, blocking serotonin receptors causes nerve cells to release more dopamine. If both serotonin and dopamine receptors are blocked at the same time, the result is a net increase in the amount of dopamine released. However, as only some of the dopamine receptors are blocked, the dopamine system is less sensitive to the increased amount of dopamine and the overall response to dopamine remains about the same. Thus, the increased amount of dopamine released has relatively no effect in those areas that have a serotonin control system. Interestingly, there is no serotonin control system in the mesolimbic dopamine pathway, the pathway responsible for the expression of psychotic symptoms. By blocking dopamine and serotonin at the same time, atypical antipsychotic medications selectively block dopamine in only one part of the brain. However, reaching a balance between blocking serotonin and dopamine is not easy and there is more than one type of serotonin receptor.

Side Effects

All antipsychotic medication side effect profiles can be grouped into four broad categories: 1) muscle related, or extrapyramidal, 2) non-muscle related, 3) dangerous or rare, and 4) weight gain and diabetes. These categories represent a wide range of potential side effects that correspond to each drugs pharmacological properties (Lieberman & Mendelowitz, 2000). Further, typical and atypical antipsychotic medications vary widely in their side effect profiles both between and within each drug classification.

All of the typical antipsychotic medications reduce psychotic symptoms by blocking dopamine receptor sites in the brain. However, each of the typical antipsychotic medications varies in potency. That is, different amounts of each medication are required to be equally effective. High potency medications are relatively less sedating, cause less postural hypotension, and cause fewer anticholinergic side effects such as blurred vision, constipation or dry mouth (Stahl, 1996). However, high potency typical antipsychotic medications also have a higher incidence of extrapyramidal side effects (EPS) such as tremors, motor restlessness, and tardive dyskinesia. New atypical antipsychotic medications also produce extrapyramidal side effects but with far less incidence and severity than the typical antipsychotic medications.

The first category of side effects is extrapyramidal effects. Pyramidal nerve cells are those cells in the brain that control voluntary muscle movement. Extrapyramidal refers to those areas in the central nervous system that are not part of the main pyramidal tract and are concerned with control and coordination of muscle movements. While not typically dangerous, this category of side effect is uncomfortable and cause many individuals to discontinue the use of their antipsychotic medication. Most of the EPS's, with the exception of tardive dyskinesia and akathisia, are usually treatable with other medications such as anticholinergic agents and disappear with the discontinuation of the antipsychotic medication. Each EPS has a time course, except for tardive

dyskinesia) and may not require medication treatment. Tardive dyskinesia, a set of hyperkinetic movements that especially effects the face, neck, and extremities and can include movements such as lip smacking, chewing, tongue protrusions, facial grimacing, and rapid limb movements has no reliable treatment and persist even after antipsychotic medication is stopped. Other EPS's include dystonia; sudden spasms of the muscles in the head, neck, lips, and tongue; pseudoparkinsonism, which consists of muscular rigidity, mask-like face, and a stiff walk; akathisia, characterized by constant pacing, moving of hands and feet, and a feeling of nervousness; and akinesia, manifested by a loss of spontaneity in facial expression or gesturing, decreased social spontaneity, diminished conversation, apathy, and disinclination to initiate normal activity.

Common, non-muscle related effects are a second broad category of side effects seen in antipsychotic medications. This category includes effects such as, depression, depersonalization, akinesia, confusion, somatic delusion, and dysphoria. These side effects are seen more in the typical antidepressants (Diamond, 2002). Anticholinergic side effects such as dry mouth, blurred vision, and constipation are also included in this category. As anticholinergic medications block the sweating response, temperature regulation problems are another common set of side effects. Most of the anticholinergic side effects seen actually come from the medications used to treat the muscle related side effects of the antipsychotic medications, such as cogentin, donepezil, galantamine, and rivastigmine (Tammenmaa, McGrath, Sailas, & Soares-Weiser, 2004). Another set of non-muscle related side effects are alpha-adrenergic. These include orthostatic hypotension, a sudden drop in blood pressure when an individual stands up and transient dizziness. Again, these side effects are seen more in typical antipsychotics. However, in atypical medications the effects are worse with clozapine and risperidone. As antipsychotic medications block the D_2 receptor they cause an increase in prolactin, again seen more with typical antipsychotic medications. This can result in breast enlargement, secretion of breast liquid from men and women, interference with menstrual

periods in women, and a decreased sex drive. Photosensitivity is another side effect caused by antipsychotic medications.

Antidepressant Medications

The discovery of the antipsychotic properties of chlorpromazine began the revolution in the pharmacological treatment of psychosis. Similarly, the accidental discovery of the antidepressant properties of the antituberculosis drug iproniazid revolutionized the treatment of depression in the 1950's (Mendelowitz, Dawkins, & Lieberman, 2000). Until this time no effective antidepressants existed. In the early 1950's it was noted that a side effect of iproniazid was euphoria. This observation led to clinical trials during which it was discovered that iproniazid was useful for tuberculosis patients with depression (Crane, 1957). Another accidentally discovered antidepressant was imipramine, which was originally developed as a potential antipsychotic. However, during clinical trials it was noted that imipramine elevated mood in individuals with schizophrenia. This discovery led to effective trials with individuals with depression (Kuhn, 1958). Both of these medications have different mechanisms of action. Iproniazid's therapeutic efficacy involves the inhibition of the enzymes that degraded monoamines, which in turn increase norepinephrine, serotonin and dopamine activity. However, Imipramine's mechanism of action involves blocking the reuptake of serotonin and norepinephrine. Thus, there are at least two neurotransmitters responsible for depression: serotonin and norepinephrine. However, it is not fully understood how antidepressant medications work. What is known is that all effective antidepressants interact with one or more neurotransmitter receptors or enzymes (Stahl, 1996).

Mechanism

The theoretical mechanism of action of antidepressant medications involves the serotonergic and catecholaminergic systems in the central nervous system (Mendelowitz et al., 2000). There are four classes of antidepressant medications: (1) the monoamine oxidase inhibitors (MAOIs), (2)

tricyclic antidepressants (TCAs), (3) selective serotonin reuptake inhibitors (SSRIs) and (4) serotonin-norepinephrine reuptake inhibitors (SNRIs).

The first clinically effective antidepressants were drugs that inhibited the monoamine oxidase enzyme and were accidentally discovered while researchers were searching for an antituberculosis drug. When the antituberculosis drug was given to tuberculosis patients the drug was observed to help their depressive symptoms. As is had already been discovered that the antituberculosis drug inhibited the monoamine oxidase (MAO) enzyme, it was hypothesized that this biological event accounted for the drugs antidepressant effects. The MAO enzyme is responsible for breaking down monoamine neurotransmitters such as dopamine, serotonin, and norepinephrine thereby functionally decreasing the levels of these neurotransmitters (Janicak et al., 1993). All of the original MAOIs are irreversible enzyme inhibitors that bind to, and destroy, the monoamines in the cytoplasm. The effects of the MAOIs continue for 10 to 14 days after their used has been discontinued, until new MAO enzymes can be synthesized. MAOIs are beneficial in the treatment and management of atypical depression, mixed anxiety and depressive disorders.

MAO has two subtypes, A and B. Subtype A metabolizes serotonin and norepinephrine, the monoamine neurotransmitters most closely linked to depression (Stahl, 1996). The subtype B enzyme is believed to metabolize dopamine and phenylethlamine into toxins that may damage neurons. Inhibiting the B form of MAO is linked to the prevention of some neurodegenerative processes such as those found in Parkinson's. All of the original MAOIs inhibited both of these subtypes and were therefore nonselective. However, in recent years, new MAOIs have been produced that selectively inhibit MAO A or MAO B. Further, for MAO A's, the new drugs are reversible and are therefore called reversible inhibitors of MAO A (RIMAs). A new RIMA, Moclobemide, is now available in Canada and the United Kingdom. However, is not yet in the United States (Mendelowitz et al., 2000).

Tricyclic antidepressant (TCAs) medications are so named because of their organic three-ring molecular structure. The results of clinical trials were disappointing and TCAs were almost discarded. However, researchers noted that TCAs helped relieve some of the depressive symptoms in patients with schizophrenia who had comorbid depression. It was not until later that researchers discovered TCAs worked by blocking the presynaptic reuptake of norepinephrine and serotonin, and, to some degree, dopamine. In addition to these effects, to some degree all TCAs block muscarinic cholinergic, H1 histamine, and alpha 1 adrenergic receptors (Stahl, 1996). The therapeutic antidepressant effects of TCAs are thought to be due to the blockage of serotonin and norepinephrine reuptake, while the blockade of these other three-receptor systems are responsible for the TCAs side effects.

TCAs modulate the reuptake of neurotransmitters to various degrees. Older TCAs, such as imipramine and amitriptyline, the tertiary amines, are metabolized into secondary amines by hepatic enzymes. The tertiary amine TCAs have a greater effect at blocking the reuptake of serotonin than do the secondary amines which are more effective at blocking the reuptake of norepinephrine. More importantly, these TCAs have differing clinical effects. Secondary amine TCAs are less likely to interact with other receptors, as such, the side effect profiles of the secondary amines are improved over the tertiary amines. All TCAs are considered to be nonselective in that each blocks the reuptake of monoamines. However, they also interact with a wide variety of other neurotransmitter receptor systems (Mendelowitz et al., 2000).

The second generation of antidepressant medications selectively blocks the reuptake of one neurotransmitter receptor system, usually serotonin. This new generation of antidepressants is known as selective serotonin reuptake inhibitors (SSRIs) as they effectively block the reuptake of serotonin while having little effect on adrenergic, histaminergic, or cholinergic receptor systems. Functionally, all SSRIs increase the amount of serotonin available in the synapse. Increased

serotonin at receptor sites has, for some individuals, the therapeutic effect of relieving some of the symptoms of depression.

One of the newest second-generation antidepressant medications being developed are serotonin-norepinephrine reuptake inhibitors (SNRIs). SNRI drugs, such as venlafaxine, share the inhibitory reuptake properties of the classical TCAs. However, they do not effect the adrenergic, histaminergic, or cholinergic receptor systems and thus have different therapeutic and side effect profiles. The blocking properties of venlafaxine are dose dependant; it is most effective in blocking serotonin and at low doses, norepinephrine at higher doses, and dopamine at the highest doses. Although SNRIs are clinically effective as antidepressants, it remains unclear whether or not they have advantages over SSRIs in terms of efficacy or side effect profile (Stahl, 1996).

Side Effects

The use of MAOIs in the United States has begun to decline in recent years. This is primarily due to the need for dietary restrictions and the potential for serious side effects (Mendelowitz et al., 2000). The most common long-term side effects of MAOIs are weight gain, edema, muscle twitching, and decreased sexual functioning. Other side effects of MAOIs include anticholinergic effects such as blurred vision, dry mouth, urinary hesitancy, constipation, behavioral problems, and memory impairment. A less common but more serious side effect of MAOIs is a hypertensive crisis caused by the interaction of the MAOI with tyramine found in food or a medication that contains a sympathomimetic amine, amines that have an effect on the sympathetic nervous system. MAOIs work by interfering with the enzymes that break down neurotransmitters. However, some of these enzymes also break down tyramine. Therefore, tyramine levels can increase to high levels and cause an increase in blood pressure. The hypertensive crisis is usually preceded by a sudden increase in blood pressure, headache, stiff neck, and vomiting (Maxmen & Ward, 2002). While rare, the hypertensive crisis may be fatal and requires immediate treatment. Besides a wide

range of foods, MAOIs also interact with a large number of medications, including many over-the-counter medications and other antidepressants. Further, MAOIs have an activating effect that may result in manic episodes, psychosis, behavioral outbursts, loss of sleep, and decreased attention.

NDRIs are effective antidepressants and are reported to have fewer side effects than the older antidepressant medications, because they do not affect serotonin systems. One of the major advantages of NDRIs is that they do not cause any sexual side effects; in fact, it can actually reverse the sexual side effects of other antidepressant medications (Diamond, 2002). As with MAOIs, NDRIs are also activating and thus cause side effects such as restlessness and sleep problems. However, the occurrence of these side effects is less than with MAOIs. Rare side effects of NDRIs include nausea and slight tremors. Unfortunately, NDRIs have an increased risk of grand mal seizure than most other antidepressants (Stahl, 1996). This risk is dose related and increases as the dosage of the NDRI increases.

Tricyclic antidepressant medications, although older, are just as clinically effective as the new antidepressant medications. However, the major problem is that TCAs are much more dangerous especially when taken as an overdose; a month's worth of any TCA is lethal if taken all at once. Individuals taking TCAs typically feel drugged and sedated more than with the newer antidepressants. As TCAs block the muscarinic cholinergic, H1 histamine, and alpha 1 adrenergic receptors, they have many more side effects that most of the newer, selective antidepressant medications (Mendelowitz et al., 2000). The anticholinergic properties of TCAs cause side effects such as dry mouth, blurred vision, heart palpitations, urinary retention, confusion, and delirium while blockage of the histamine receptors causes sedation and weight gain. Blocking the adrenergic receptors creates one of the TCAs most frequent and limiting side effects, orthostatic hypotension, the sudden loss of blood pressure, and cardiac arrhythmias due to the inability of electrical impulses in the heart to spread normally (Diamond, 2002). While rare, these cardiac complications have been

reported to cause death. TCAs also potentiate the effects of alcohol and individuals who drink while on TCAs may become more intoxicated than usual. Further, TCAs increase the lethality of alcohol and put the individual at risk for overdose. Other side effects of TCAs are loss of sexual function, manic episodes, allergies, nightmares and seizures.

The advantage of the SSRIs is that they are much safer and better tolerated than the older antidepressant medications. This is because the SSRIs only selectively inhibit the reuptake of serotonin and have little, if any, interaction with histaminergic, muscarinic, or alpha-adrenergic receptors. Thus, the side effect profiles seen in the SSRIs are caused by the blockage of serotonin reuptake. As such, while not significantly more effective than older and other antidepressants, SSRIs are becoming more widely used because of the fewer side effects they cause. Some of the common side effects caused by SSRIs are nausea, vomiting, anorexia, tremors, initial weight gain, and diarrhea. However, most of these are dose dependent and can be lessened by titrating the medication more slowly and having the individual take the medication with food (Mendelowitz et al., 2000). Like some of the other antidepressants discussed earlier, SSRIs tend to be activating, thus some individuals feel agitation, restlessness, and some sleep disturbance. Further, some SSRIs such as fluoxetine (Prozac) cause akathisia, a type of motor restlessness. Also, some individuals feel an emotional blunting. Although most antidepressants cause some degree of sexual dysfunction, the incidence of sexual dysfunction in SSRIs is more common (Janicak et al., 1993). These side effects include decreased libido, anorgasmia in women and delayed ejaculation in men.

SSRIs also interact with other medications in dangerous ways by blocking their metabolism in the liver (Diamond, 2002). By blocking the break down of other drugs, SSRIs can cause the levels of other medications to rise to toxic levels. Specifically, SSRIs interfere with a set of enzymes in the liver called the P450 system. To complicate matters, different SSRIs interfere with different enzymes in the P450 system, thus different SSRIs interact with different medications to cause

different problems. SSRIs also interact with many medications used to treat HIV. Research shows that individuals taking HIV medication should only be prescribed ¼ to ½ of the normal dose (Diamond, 2002). The most dangerous and common interaction between SSRIs and other medications occur when the individuals is also taking an MAOI antidepressant. This combination, the SSRI and an MAOI, can result in serotonin syndrome whose symptoms include agitation, confusion, sweating, increased reflexes, sudden jerking movements, shivering, tremors, coordination problems, and fever.

Mood-Stabilizing Medications

The discovery of medications that could stabilize an individual's mood dates back to the late 1940's. The first drug used as an anti-manic was lithium that had been used in medicine since the mid-19th century to treat a variety of disorders such as diabetes, gout, rheumatism, and urinary calculi. During the early 1940's it was used as a salt substitute for cardiac patients. However, lithium caused a number of toxic reactions and deaths (Janicak et al., 1993). Then in late 1949, John Cade, an Australian physician injected lithium urate into guinea pigs. Cade mistakenly took the toxic effects of lithium as sedating and, based on this, ran a successful open trial of lithium with manic patients. In 1954, Mogens Schou used lithium in a series of methodologically rigorous studies that demonstrated its efficacy in stabilizing both phases of bipolar disorder and preventing recurrences of unipolar depressive disorder in patients (Schou, Juel-Neilson, Stromgren, & Voldby, 1954). After lithium's anti-manic properties were discovered, a series of studies were conducted that replicated Cade's initial findings. While these studies demonstrated lithium's usefulness, they also revealed that lithium was still toxic and lethal when used as an anti-manic. It was not until the 1960's when Samuel Gershon reintroduced lithium as a viable treatment for mania that it became the standard therapy for bipolar disorder and was approved for use in the United States in 1970 (Hopkins & Gelenberg, 2000).

However, recent research has begun to acknowledge that a significant proportion of patients cannot tolerate or do not benefit from lithium therapy (Janicak et al., 1993). Individuals who do not seem to respond to lithium include those that present with dysphoric and mixed episodes of mania, rapid cycling, a history of neurological disease, and comorbid substance abuse (Hopkins & Gelenberg, 2000). This has led to investigations into alternative treatments such as electroconvulsive therapy (ECT) and antiepileptics. The most common antiepileptics used to treat mania in patients that are unresponsive to lithium are valproate (VPA) and carbamazepine (CBZ). As with most of the other psychotropics, the anti-manic properties of antiepileptic medications, specifically CBZ, were discovered by accident. In the 1960s, researchers were studying the effects of CBZ in epileptic patients and noted that it also had anti-aggressive properties (Dehing, 1968). While VPA is approved for the acute care of mania, this section will focus on the mechanism and side effects of lithium as used as a mood stabilizer. VPA and CBZ will be discussed further in the antiepileptic section along with other antiepileptic medications that are currently being researched for their anti-manic properties.

Mechanism

While many of lithium's effects on the body are known, the exact mechanism that is responsible for its mood stabilizing properties are not fully understood, although several theories have been postulated (Viesselman, 1999). One theory is that it affects those neurotransmitter systems implicated in affective disorders, norepinephrine, acetylcholine, serotonin, and dopamine. Lithium has a variable effect on norepinephrine by inhibiting its release and seems to enhance acetylcholine function. Its antidepressant effects may be due to its enhancement of serotonin activity and its anti-manic properties are thought to be due to its prevention of dopamine receptor super sensitivity and inhibition of its release (Hopkins & Gelenberg, 2000).

Another theory is that lithium affects cellular processes, specifically affecting second-messenger G-protein systems and signal-transduction systems. A third theory is that lithium alters neuron functioning by substituting or competing with other ions, as it shares properties with potassium, sodium, magnesium, and calcium, and altering their distribution throughout the body. A fourth theory is that lithium may modulate the interaction between several neurotransmitters and act as a neuromodulator and balance various neurotransmitter systems. Research continues to determine the exact nature of lithium's therapeutic effects as a mood stabilizer.

Side Effects

Lithium produces a wide variety of side effects, some of which the individual may become tolerant of and others that may warrant the use of adjunctive or alternative therapies. The most common side effect of lithium is fine tremor of the hands during the first few days of treatment (Stahl, 1996). Other initial side effects of lithium are nausea, vomiting, abdominal pain, thirst, and fatigue. However, most of these disappear after the first few weeks of treatment. Other reported side effects include mild weight gain, a metallic taste in the mouth, headache, memory and concentration difficulties, dermatitis, and polyuria (Maxmen & Ward, 2002). Lithium is also known to affect thyroid function by inhibiting several steps of thyroid hormone synthesis and degradation resulting in hypothyroidism. As the kidney excretes lithium, it also has a direct effect on renal functioning and may cause a syndrome called nephrogenic diabetes insipides characterized by increased fluid intake and urination. However, very few individuals who receive long-term lithium therapy suffer permanent, life-threatening kidney damage. Lithium has a low therapeutic index, and increased blood concentrations can cause eventual coma or death (Stahl, 1996). The initial symptoms of lithium toxicity look like more severe presentations of common lithium side effects such as thirst, decreased appetite, diarrhea, and vomiting. These symptoms can progress to tremors, confusion, slurred speech, and muscle twitching. If left untreated, the toxic lithium blood levels can

cause permanent central nervous system damage, increased reflexes, renal shutdown, seizures, permanent brain damage, coma, and possible death.

Antianxiety Medications

The discovery of antianxiety medications, also known as anxiolytics, did not have an accidental beginning like most other psychotropics. The use of anxiolytics can be traced back centuries to alcohol and its progression can be followed from there to the use of opiates to the synthesis of bromides and barbiturates to the formulation of benzodiazepines in the 1960s (Janicak et al., 1993). All of these medications have similar affects; they all have antianxiety and sedative properties caused by depression of the central nervous system. The earliest treatment for general anxiety was barbiturates, which were highly sedating. In fact, the antianxiety effect of barbiturates was directly proportional to its sedating affect, thus its effects were not anxiety specific. That is, these drugs reduced anxiety by inducing sedation. Also, this class of antianxiety medication had some serious problems such as dependency and withdrawal effects, and safety concerns when combined with other medications or in overdose. Barbiturates were supplanted when benzodiazepines, a new class of antianxiety medication, were discovered. These new drugs had fewer problems, were effective in a wider range or disorders, safe with most other medications, and caused less sedative effects than barbiturates (Diamond, 2002). For the first time, selective antianxiety effects were observed. Benzodiazepines were hailed as a breakthrough and remain among the most widely prescribed drugs in the world. Recently, a new class of anxiolytic drug has been formulated called azapirones that are not chemically related to barbiturates or benzodiazepines and affects different neurotransmitter systems. Currently, buspirone is the only azapirone indicated for the treatment of anxiety. This section will focus on benzodiazepines and the newer anti-anxiety medication, buspirone.

Mechanism

All benzodiazepines are comprised of a 6-member benzene ring fused to a 7-member diazepine ring, and thus get their name from their chemical structure. The different pharmacokinetic properties seen within benzodiazepines results from different substitutions on the diazepine ring in different positions; therefore, each structure differs in potency, duration of action, and the type and frequency of side effects (Janicak et al., 1993). The wide diversity in therapeutic and side effect profiles of the different benzodiazepines is due to the speed of onset of action, potency, and the half-life of the specific medication. These factors allow for the selection of specific medications to fit the needs of the individual. However, as all benzodiazepines have the same basic chemical structure, they all share four principal therapeutic actions to some extent: anxiolytic, myorelaxant (muscle relaxant), anticonvulsive, and sedative-hypnotic (Fogelman & Greenblatt, 2000).

Benzodiazepines produce their antianxiety effect by potentiating the neurotransmitter gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system that acts in the cortex, substantia nigra, and in the cerebellum. GABA receptor complexes can be divided into two physiologically and pharmacologically distinct subtypes that regulate GABA neurotransmission, $GABA_A$ and $GABA_B$. The $GABA_B$ receptor subtype is not modulated by benzodiazepines and its physiological role is not well known. However, it appears that $GABA_B$ may not be linked to anxiety disorders or the effects of anxiolytic medications (Janicak et al., 1993). $GABA_A$ receptors are, on the other hand, indicated in anxiety disorders and the therapeutic effects of benzodiazepines.

Three subtypes of benzodiazepine receptors exist. Type 1 receptors, also known as omega-1 receptors, are located preferentially in the cerebellum and amygdala and seem to be responsible for the anxiolytic and sedative responses to benzodiazepines. Type 2 benzodiazepine receptors, also

known as omega-2, are located primarily in the spinal cord and striatum. As such, these receptors may be responsible for mediating the muscle relaxant effects of benzodiazepines. The last type of benzodiazepine receptor, type 3 or omega-3, is located primarily in the peripheral nervous system and its role concerning the mediation of the anxiolytic effect of benzodiazepines is unclear (Stahl, 1996).

In effect, benzodiazepines facilitate GABA-mediated transmission and thus act as an indirect $GABA_A$ agonist by enhancing the receptor site affinity of GABA and potentiating its inhibitory action. When benzodiazepines bind to the receptor site, a conformational change takes place and the subunit's affinity for GABA increases. This increases the probability of GABA binding to its receptor site and a net increase in the frequency chloride channel opening, movement of chloride into the neuron, and hyperpolarization of the cell. If GABA is not present in the synapse, benzodiazepines have no pharmacological action. Only when GABA and the benzodiazepine are present does the interaction between the medication and the GABA receptor complex promote the anxiolytic therapeutic effects of benzodiazepines.

A new class of anxiolytics not chemically related to benzodiazepines recently developed is azapirone. Buspirone is the first medication from this class that has been approved for the treatment of anxiety. The therapeutic profile of buspirone, or buspar, is quite different from the benzodiazepines in that it has no effect on the GABA receptors. Instead, buspar seems to act primarily at serotonin and dopamine receptor sites. As such, it does not have the sedative, myorelaxant, or anticonvulsive properties seen in benzodiazepines. While the exact anxiolytic mechanism of buspar remains unknown, it appears that buspar act as a partial serotonin agonist at postsynaptic receptors and a full agonist at presynaptic receptors (Werry & Aman, 1999). Thus, buspar seems to regulate serotonin systems and return their functioning to normal levels (Fogelman & Greenblatt, 2000). For example, in conditions of serotonin deficiency, buspar's overall effect is to

increase serotonergic activity. Currently there are several other azapirones that are being tested for their anxiolytic properties; these include drugs such as gepirone, tandospirone, and ipsapirone. While promising, some question has arisen as to their efficacy in treating certain anxiety related disorders and their overall effectiveness when compared to benzodiazepines.

Side Effects

While the side effects of benzodiazepines are broad, they are generally well tolerated and dose dependant. The most common side effects are drowsiness, sedation, anterograde amnesia, impaired psychomotor performance, and ataxia. The degree of these side effects is, again, related to dose and also the particular subgroup of benzodiazepine being used (Maxmen & Ward, 2002). A major concern with this class of medication is its addictive properties. Those benzodiazepines with rapid onset, such as Valium, are much more likely to cause dependence than those with slow onset, such as Librium. However, all benzodiazepines have addictive properties and may also cause sweating, nausea, disinhibition, hyperactivity, irritability, and aggressiveness along with a rebound of the initial symptoms after discontinuation. Another concern with the use of benzodiazepines is memory impairment and impairment of other cognitive functions. These effects are particularly applicable to the elderly, and individuals with memory impairment, mental retardation or developmental disabilities.

A major advantage of buspar is its lack of abuse potential. Also, buspar is non-sedating, does not increase an individual's sensitivity to alcohol, and is not a myorelaxant. Some common side effects include nervousness, dizziness, headache, and some gastrointestinal upsetting. It appears that buspar's side effect profile is significantly less than those of the benzodiazepines. However, there are some factors that may limit buspar use with some individuals. One factor is its delayed onset of action. While some benzodiazepines work almost immediately, buspar may take several weeks to exert its full therapeutic effect and it must be used regularly during this time. Another

factor is its effectiveness across a range of anxiety disorders. As a wide array of benzodiazepines exists, a specific medication can be selected to fit the individual and their symptom presentation; the same is not true for buspar. Individuals who have not previously used a benzodiazepine report that buspar is very effective in controlling their anxiety while individuals who previously used a benzodiazepine reported that buspar was not as effective as their previous medication (Diamond, 2002). Research suggests that buspar may be particularly useful for individuals who may be drug users and cannot tolerate the various cognitive side effects of the benzodiazepines.

Antiepileptic Medications

Although carbamazepine (CBZ) was developed in the late 1950's, its antiepileptic properties were not reported until 1963. In the early 1960's CBZs antiepileptic and psychotropic effects began to appear in the research literature (McElroy & Keck, 1995). In 1974 the U.S. Food and Drug Administration (FDA) approved its use as an antiepileptic for adults; in 1978 the FDA approved CBZ for use with children, and in 1987 CBZ was approved without an age limitation. Currently, CBZ is a major antiepileptic medication whose use is increasing due to its relatively few psychological and neurological toxic side effects. Since the introduction of CBZ, several other antiepileptic medications have been developed or discovered. However, many of these, such as phenobarbital and phenytoin are no longer widely used as they have many behavioral and cognitive side effects, some of which are often irreversible (Iivanainen, 1998; Ingram, 1986).

An alternative antiepileptic being widely used today is valproate, or valproic acid (VPA). First discovered in 1882 and used as an organic solvent, the discovery of its antiepileptic properties was serendipitous. VPAs antiepileptic properties were discovered in 1963 in France where VPA was originally used to deliver other drugs being tested for their antiepileptic properties. Researchers noted that some compounds, when administered alone, did not have antiepileptic properties. However, when these compounds were dissolved in VPA they inhibited seizure activity. It was soon

concluded that VPA was responsible for this observed result. Initial clinical trials concerning VPAs efficacy as an antiepileptic were conducted in the mid 1960's and the drug became available in the United States in 1978. As discussed previously, VPA is also currently approved as a mood stabilizing medication.

In addition to CBZ and VPA, benzodiazepines are also used as antiepileptic medications, especially clonazepam and clorazepate. However, while benzodiazepines are considered to be one of the safest having fewer severe side effects, it does have significant sedative properties (Mycek, Harvey, & Champe, 1997). Further, its efficacy as an antiepileptic is not well documented and its role is typically as a therapeutic adjunct. There are a number of newer antiepileptic medications such as gabapentin, lamotrigine, and vigabatrin that have fewer and less severe side effect profiles (Bhaumik, Branford, Duggirala, & Ismail, 1997). However, few studies can be found on their efficacy and use on individuals with mental retardation. As such, this section will be limited to CBZ and VPA, two of the more current and widely used antiepileptic medications. Although significant in the development of antiepileptics, phenobarbital and phenytoin will not be discussed in this section.

Mechanism

Carbamazepine is typically used for the control of both partial and generalized tonic-clonic seizures and its chemical structure is similar to that of the TCA imipramine. Its actions can be divided into two mechanisms (MacDonald, 1989). One mechanism involves CBZs effects on synaptic and postsynaptic neurotransmitter transmission. CBZ has been reported to alter neurotransmitter concentrations, metabolism, receptors, and second messenger systems (McElroy & Keck, 1995). It is this mechanism that is believed to be responsible for the mood stabilizing effects of CBZ. The second mechanism of CBZ involves its effects on neuronal ion channels that reduce high-frequency repetitive firing of action potentials. Research suggests that this latter mechanism is

responsible for the antiepileptic properties of CBZ (McElroy & Keck, 1995). Recently, research has suggested that CBZ also acts on potassium channels to increase potassium conductance (Post, Weiss, & Chuang, 1992). This may be another possible mechanism explaining the antiepileptic properties of CBZ.

VPA is useful in controlling a wider variety of seizure types than CBZ including absence, myoclonic, tonic-clonic, and complex partial seizures (Vining, Carpenter, & Aman, 1999). The exact mechanism that is responsible for valproate's antiepileptic properties remains unknown. One theory is that VPA exerts its therapeutic effects by changing how the neurotransmitter GABA is metabolized (McElroy & Keck, 1995). VPA seems to inhibit the catabolism of GABA causing an increase in GABA release, a decrease in GABA turnover, and increases $GABA_B$ receptor density. Another theory is that VPA produces its antiepileptic properties by regulating the intake and excretion of sodium and potassium (Post, Weiss, & Chuang, 1992). Further research is needed to determine the exact mechanism responsible for VPA's antiepileptic properties.

Side Effects

CBZ's side effect profile is somewhat more favorable than those of lithium, antipsychotics, and other antiepileptic medications (Smith & Bleck, 1991). Importantly, CBZ rarely causes EPS or renal side effects, and is associated with fewer cognitive and neurological side effects than previous antiepileptic medications. Further, CBZ produces less weight gain, hair loss, and tremor than VPA (Diamond, 2002). However, CBZ does cause increased sedation, has a higher incidence of serious side effects, and has the potential to be fatal in an overdose. Common neurological side effects blurred vision, fatigue, nausea, vertigo, and ataxia. These side effects are dose dependent and most disappear after a few weeks. Some medically dangerous side effects associated with CBZ are leukopenia, a drop in the number of available white blood cells; temporary increases in liver

enzymes, and hyponatremia. Rare side effects are liver problems, hepatic failure, exfoliative dermatitis, pancreatitis, and psychological disturbances such as psychosis and mania.

Generally, the side effects of VPA are well tolerated and provide a viable alternative for many individuals who cannot take other medications a viable alternative (Diamond, 2002). Research indicates that there is a low incidence of adverse effects when compared to lithium, antipsychotics, and other antiepileptics including CBZ (Smith & Bleck, 1991). Further, VPA is less likely to cause cognitive impairments as compared to other antiepileptic medications (Vining, 1987). Like CBZ, VPA also has a low incidence of EPS and renal side effects. However, VPA rarely causes thyroid, cardiac, dermatologic, or allergy effects unlike CBZ. Most side effects of VPA are dose related and include gastrointestinal disturbance, sedation, tremor, and weight fluctuations. Weight gain is the most common side effect and seen in approximately half of individuals taking VPA (Diamond, 2002). Other common side effects that tend to disappear after a few weeks are nausea, vomiting, and indigestion. Although sedation is a side effect of VPA, it is less common than with CBZ (McElroy & Keck, 1995). More serious side effects are liver toxicity in children and pancreatitis.

It is evident that each class of medication and each medication within each class have varying therapeutic effects and side effects associated with them that need to be considered when deciding if and which medication may be right for an individual. As mentioned previously, there are several guidelines and medication algorithms available to aide clinicians in their choice of medication. However, often other factors also play a part in the decision to use psychotropic medications. For example, individuals in large institutions have been shown to receive more antipsychotic medications than the general population, especially individuals with mental retardation. The variance in prescribing practices across populations is due to a number of reasons ranging from physicians personal preference to the presence of a drug company representative to the type of symptomology being treated. Given the number of medications available and the uses for each, it is important to

look at the reasons behind the use of respective psychotropic medications and the appropriateness of their usage in each population.

USE OF PSYCHOTROPIC MEDICATION

Given the prevalence and specificity of psychotropic medications, the question of appropriate usage arises. The most common reason for psychotropic medication use is for the management of behavioral problems (Clarke, Kelly, Thinn, & Corbett, 1990; Coughlan, 2000; Molyneaux, Emerson, & Caine, 1999; Stolker, Heerdink, Leufkens, Clerkx, & Nolen, 2001). However, authors such as Aman and Singh (1988), Baumeister, Sevin, and King (1998) and Gadow and Poling (1988) have described such practices as controversial for the following reasons: (1) there is limited evidence suggesting that such drugs are actually effective in reducing behavior problems, and (2) the adverse effects of antipsychotic medications that produce changes in central and autonomic nervous system functioning, including tardive dyskinesia, akathisia, and other disorders. Further, several studies have reported that the withdrawal or reduction of antipsychotic medication had either beneficial or, at least, neutral effects on behavior and increased skill acquisition (Davis et al., 1998; La Mendola, Zaharia, & Carver, 1980; Luchins, Dojka, & Hanrahan, 1993).

When using psychotropic medications to treat behavioral symptoms, clinicians should follow specific treatment guidelines or test a specific behavioral-pharmacological hypothesis. The former involves the use of specific guidelines or an algorithm to determine the best course of medication for an individual given certain measurable factors such as age, race, diagnosis, and response to treatment. In the latter case, the clinician may suspect that an individual's behavioral presentation is a manifestation of an underlying physiological disorder. For example, a dysfunction of the endogenous opioid system has been implicated in the etiology of self-injury. Thus, an imbalance in a neurotransmitter system is manifested behaviorally as self-injury. The hypothesis is that an individual will engage in self-injury to elevate his level of endogenous opioids, thereby receiving a pleasurable response. This suggests that the primary treatment would be psychopharmacological rather than behavioral. However, a behavioral training program consisting of vigorous, regular

exercise may be used as an adjunctive therapy because it too assists in the elevation of endogenous opioids—the so-called "runner's high" or "being in the zone" effect. Nonetheless, most individuals with mental retardation will not engage in exercise at a consistent level that will produce an increase in their endogenous opioids, so a pharmacological intervention would be the treatment of choice, with adjunctive behavior therapy.

In addition to the presence of behavioral and physiological problems, several other predictive variables that contribute to the use of such drugs among individuals with mental retardation have been identified. Demographic variables that have not been associated with an increase in psychotropic medication use in this population are race/ethnicity (Cullinan, Gadow, & Epstein, 1987) and gender (Singh et al., 1997). However, variables such as age, severity of mental retardation, and the restrictiveness and size of facility have all been associated with the use of psychotropic medications (Singh et al., 1997). In some studies, age has been positively correlated in older populations, specifically middle-aged adults (Jacobson, 1988), while in others age has been found to have no effect (Stolker et al., 2001). In addition, the severity of an individual's mental retardation has been shown to have an effect on the use of psychotropic medications. Generally, the more severe the individuals' disability, the greater number and higher the dosage of medications prescribed (Aman, Sarphare, & Burrow, 1995; Jacobson, 1988). Finally, the size and restrictiveness of the facility is highly correlated with medication use with the highest effect being in larger and more restrictive facilities; these findings hold across both community and institutional settings (Aman, Field, & Bridgman, 1985; Singh et al., 1997; Singh & Winton, 1989).

Not surprisingly, psychiatric diagnosis is highly correlated with the use of psychotropic medications in both individuals with and without mental retardation. While the efficacy of medication to treat specific psychiatric disorders has been well established in the literature with individuals without mental retardation, there is a paucity of such literature regarding individuals with

mental retardation and developmental disabilities. Of the literature available, most studies tend to focus on the use of antipsychotic medications to treat behavioral problems rather than on psychiatric symptomology and their use tends to be based on weak scientific evidence (Singh et al., 1997). When comparing the use of psychotropic medications among individuals with and without mental retardation, there is a higher prevalence of drug use in the former population (Jacobson, 1988; Intagliata & Rinck, 1985; Stolker et al., 2001). However, the appropriateness of these prescriptions remains questionable given the difficulty in diagnosing psychiatric disorders in most individuals with mental retardation.

Given that several factors have been identified that predict the use of psychotropic medications, the question remains as to the appropriateness of drug usage. Indeed, if these variables predict drug use, are there specific guidelines being followed or a behavioral-pharmacological hypothesis being tested? If the answer is "No," then the use of psychotropic medications to treat psychiatric disorders and behavior problems among individuals with mental retardation becomes one of trial and error. If a drug is to be used, there must be a hypothesized mechanism as to why a particular drug would produce beneficial effects, or there is evidence that the specific psychiatric disorder being targeted is medication responsive.

Bates et al., (1986) reported the first study that examined the appropriateness of psychotropic medication usage among this population. They evaluated the appropriateness of psychotherapeutic medications regimens of 242 individuals with mental retardation residing in institutionalized settings in Ohio. The sample consisted of 108 women and 134 men who ranged in age from 16 to 78 and in level of retardation from mild to profound. Specifically, Bates et al. examined the relationship between medication regimens and psychiatric diagnosis according to standards for the treatment of specific psychiatric diagnoses for individuals without mental retardation. The standards used in this study were based on the Manual for Psychiatric Peer Review

(APA, 1981), as well as textbooks in psychiatry (Kaplan & Sadock, 1984) and psychopharmacology (Klein, Gittelman, Quitkin, & Rafkin, 1980). According to the standards used, 45.4% to 60.9% of the medication regimens evaluated were rated as appropriate while 39.1% to 54.6% were rated as inappropriate across settings.

Young and Hawkins (2002) reported the only other study to examine the reasons individuals with mental retardation are prescribed psychotropic medication. They examined the psychotropic medication regimens of 71 individuals with mental retardation receiving services from a community based mental health/mental retardation center in Texas. The individuals in this survey ranged in age from 18 to 80 and included 42 males and 29 females, whose level of mental retardation ranged from mild to profound. To determine the appropriateness of each medication regimen as it related to the individual's psychiatric diagnosis, the authors used prescribing guidelines set forth in the Clinical Handbook of Psychotropic Drugs (Bezchlibnyk-Butler, & Jeffries, 1996) for individuals without mental retardation. Based on the standards used, 59% of the medication regimens examined were considered appropriate for the targeted diagnosis while 20% were considered inappropriate. These results compared fairly well to those of Bates et al. (1986), especially in terms of the appropriateness of drug prescriptions. Although the inappropriate use of medications was lower in this study, it still suggested that many individuals with developmental disabilities were receiving psychotropic medications not based on rational pharmacotherapy.

These two studies advanced our understanding of drug therapy for people with mental retardation beyond looking at the prevalence and patterns of drug therapy. They forged a new direction in our research by focusing at the appropriateness of the drug prescription. While the prevalence and patterns of drug prescriptions gives us an overall view of the field, it does little to tell us whether rational pharmacotherapy is taking place. We need to know how drug prescription decisions are made.

PURPOSE

The purpose of this study was to examine the approaches taken in prescribing psychotropic drugs to individuals with mental retardation in one state facility. As stated previously, there are three ways of conceptualizing psychopharmacotherapy in people with mental retardation that can be documented. Currently, there is no literature on this subject and it remains unclear how physicians are conceptualizing the use of psychopharmacological regimens in individuals with mental retardation. The hypothesis of this study is that the three approaches (primary illness, target symptom, and behavioral-pharmacologic) are used equally. In addition to the primary hypothesis, additional analyses will be conducted to examine the presence of any patterns or predictors of psychopharmacology in this sample of individuals with mental retardation.

It behooves us to assess how psychotropic medications are prescribed in people with mental retardation and developmental disabilities. Researchers have shown that the prevalence of psychotropic medication use among individuals with mental retardation is relatively high when compared to people with other disabilities and that the reasons for these drug prescriptions may not be based on rational pharmacotherapy (Bates et al., 1985; Young & Hawkins, 2002). We need data on the prescribing physician/psychiatrist's adherence to consensus guidelines or algorithms developed to enhance rational psychopharmacotherapy. However, in order to do this we must first examine the rationales being used by physicians when they decide to prescribe a medication. From this line of research, instruments and algorithms could be developed that are based on scientific evidence and current best practice to aid clinicians in their treatment selection and provide a bridge between the research literature and clinical practice in the area of psychopharmacology of developmental disabilities.

METHOD

Sample

The sample consisted of individuals residing at Pinecrest Developmental Center (PDC) in central Louisiana. PDC is the largest state-supported residential developmental and training facility in Louisiana. The center provides services to approximately 584 individuals with varying degrees of mental retardation and types of developmental disabilities. Individuals range in age from 8 to 92 years, and each individual is provided active treatment through a 'Learning-Based Supports' Plan developed by the individual's interdisciplinary team. The subset of individuals that are the focus of this study are residents on psychotropic medication for behavior problems or psychiatric disorders (n = 87).

Procedure

Data on the 87 study participants were collected through the PDC client database and a chart review of the individuals on psychotropic medications. Medications were those prescribed for their psychotropic effects with the aim of controlling problem behaviors or specific mental health disorders. Antiepileptic drugs (AEDs) prescribed specifically for seizure disorders were not counted as psychotropic drugs. AEDs prescribed for their psychotropic effects for controlling behavior problems (e.g., aggression) or psychiatric symptoms (e.g., mood) were counted as psychotropic drugs.

Data Collection

In the first step of data collection, the primary researcher collected all sociodemographic data from the PDC client database for each of the 87 individuals who were prescribed psychotropic medications. Data were comprised of the following elements: name, age, age group, gender, race, primary Axis I diagnosis, disorder type, level of mental retardation, medication, medication type, approach type, number of target symptoms and specific target symptoms. The demographic

variables of interest in this study have shown to be correlated with psychotropic medication use (Aman et al., 1995; Aman & Singh, 1988; Bisconer et al., 1996; Singh et al., 1997; Young & Hawkins, 2002).

In the second step of data collection, the clinical decision-making of the prescribing physician was determined in terms of approaches outlined previously, namely: (a) a target symptom approach, (b) a primary illness approach, and (c) a behavioral-pharmacologic hypothesis approach. A fourth category (i.e., no apparent approach) was also included for cases where there was no clear or documented evidence of a specific approach being taken by the physician. The approach chosen by the prescribing physician for each drug prescription was obtained from each individual's "Learning-Based Supports" Plan - specifically from the Medication Plan section.

The following algorithm was used as a guide by both the primary and secondary researchers to determine which of the three approaches was used by the prescribing physician:

a. Is the target symptom approach used? Yes, if:
    I. Specific behaviors, such as aggression or self-injury, are listed as the target of medication treatment
b. Is a primary illness approach used? Yes, if:
    I. A psychiatric disorder, or specific signs and symptoms of a psychiatric disorder, is the listed focus of medication intervention
c. Is a behavioral-pharmacological hypothesis approach used? Yes, if:
    I. A specific biological dysregulation is listed as the cause of the behavior being treated with medication
d. If none of the above approaches is used, then:
    I. The prescription was counted as "no apparent approach" for analysis purposes.

Data Analysis/Research Design

In the first part of this analysis, demographic data were summarized to determine the characteristics of the sample population. In the second part of this analysis, the approaches taken by the prescribing physicians were examined. A Chi Square procedure was used to test the primary hypothesis and determine if there were any significant differences between the observed and expected frequencies of each approach type. The expected value for each approach type was set at 29 (33.3%) because it was predicted each of the approaches (i.e., target symptom, primary illness, and behavioral-psychopharmacological hypothesis) would be used equally. In addition, cross-tabulations were conducted to examine any patterns in the data regarding approach type by gender, race, diagnosis, level of mental retardation, medication type, and age group.

Inter-rater Reliability

A second rater was trained by the primary researcher on how to collect the data. The primary investigator devised ten sample datasets representative of data that would be found in an individual's chart and in the PDC database. One of these sample datasets was used for training where both researchers collected data at the same time. The remaining datasets were used as independent reliability checks. When 100% agreement was achieved on three of the sample data sets the additional rater was considered trained.

The primary researcher collected all the socio-demographic data on each of the 87 individuals receiving psychotropic medications. The primary researcher and the secondary rater collected the same data on 20% (n = 17) of randomly selected individuals from the total sample (N = 87) to determine interrater reliability. Inter-rater reliability was calculated using Cohen's Kappa because this method was specifically developed to measure inter-rater reliability of categorical data (Cohen, 1960, 1968; Hartmann, 1977). The reliability coefficient (Kappa) between the primary researcher and the second rater was .92.

RESULTS

There were 87 participants with mental retardation who were prescribed at least one psychotropic medication for the treatment of an Axis I psychiatric diagnosis or a target behavior problem. Table 1 presents the demographic characteristics of the sample population.

To examine differences between the observed frequency of the approach types and the expected frequencies of the approach types a chi square analysis was conducted. As shown in Table 2, the chi square indicated a significant difference between the observed and expected frequencies of the approach types $x^2(2, N = 87) = 115.76, p = .05$. Thus, the hypothesis that each approach type would be used equally does not hold. In prescribing medication for the psychiatric disorders, physicians used the primary illness approach with 75 (86%) of the 87 individuals. They used the target symptom approach with 9 (10%) individuals and no apparent rationale with another 3 (4%). They did not use the behavioral-pharmacological approach at all.

Table 1. Demographic characteristics

Characteristic	**Frequency**	**Percentage**
Age		
18-41	14	16.1
42-65	58	66.7
66-87	15	17.2
Gender		
Female	38	43.7
Male	49	56.3

(table continued)

Race		
African-American	16	18.4
Caucasian	71	81.6
Level of MR		
Mild	4	4.6
Moderate	11	12.6
Severe	13	14.9
Profound	54	62.1
Unspecified	5	5.8
Diagnosis Type		
Anxiety Disorder	13	14.9
Childhood Disorder	10	11.5
Mood Disorder	52	59.8
Psychotic Disorder	12	13.8
Medication Classes		
Anti-Anxiety	6	6.9
Antidepressant	27	31.0
Antipsychotic	37	42.5
Mood Stabilizer	17	19.5

Table 3 presents the Axis I diagnosis, signs and symptoms targeted by the medication, and the class of medication prescribed for the disorder or target behavior. In 30 cases (35%), no signs and symptoms of the disorder were specified and it was unclear as to what behavioral end-points of the psychiatric disorder were being targeted by the psychopharmacology treatment plan. On the

other hand, multiple symptoms (i.e., up to 8) were listed for a single psychiatric disorder and it was unclear which symptoms were being targeted. While an assumption can be made that all listed symptoms of the disorder were evident in the individual, there was often no supporting data in the individual's chart to verify this assumption.

Table 2. Chi Square for observed and expected frequencies of approach type.

	Frequency	
Approach Type	**Observed**	**Expected**
Primary Illness	75	29
Target Symptom	9	29
Behavioral-Pharmacological	0	29

Table 3. Primary Axis I diagnosis and symptoms targeted in psychopharmacology treatment plan.

Subject Number	Primary Axis I Diagnosis	Associated Symptoms	Medication Type	Number of Symptoms
1	Stereotypic Movement Disorder	no diagnosis-specific symptoms listed	antidepressant	0
2	Bipolar I Disorder	decreased social contact, distractibility, psychomotor agitation, restlessness, constant movement	antipsychotic	5
3	Bipolar Disorder, NOS	irritability, social isolation, psychomotor agitation, weight loss, impulsivity	mood stabilizer	5
4	Generalized Anxiety Disorder	pacing, difficulty sitting still, fidgeting, yelling, screaming, worrying, irritability	antianxiety	7

(table continued)

5	Bipolar I Disorder	crying, psychomotor agitation, increase in goal-directed activity	antipsychotic	3
6	Mood Disorder, NOS	no diagnosis-specific symptoms listed	antidepressant	0
7	Depressive Disorder, NOS	crying, irritability, social withdrawal	antidepressant	3
8	Anxiety Disorder, NOS	no diagnosis-specific symptoms listed	mood stabilizer	0
9	Bipolar I Disorder	agitation, driven motor activity, irritability, poor sleep	antipsychotic	4
10	Schizoaffective Disorder	delusions, hallucinations, emotional lability, crying, depression	antipsychotic	5
11	Anxiety Disorder, NOS	fidgeting	antidepressant	1
12	Major Depressive Disorder	crying, irritability, psychomotor agitation	antidepressant	3
13	Dysthymic Disorder	sad affect, crying, increased sleep, fatigue, irritability, decreased interest	antidepressant	6
14	Bipolar I Disorder	no diagnosis-specific symptoms listed	mood stabilizer	0
15	Psychotic Disorder, NOS	no diagnosis-specific symptoms listed	antipsychotic	0
16	Bipolar I Disorder	increased activity, decreased judgment, poor sleep	antipsychotic	3
17	Schizophrenia	no diagnosis-specific symptoms listed	antipsychotic	0
18	Schizophrenia	no diagnosis-specific symptoms listed	antipsychotic	0
19	Bipolar I Disorder	decreased sleep, increased activity, excessive vocalizations	mood stabilizer	3
20	Psychotic Disorder, NOS	no diagnosis-specific symptoms listed	antipsychotic	0
21	Bipolar Disorder, NOS	psychomotor agitation, decreased sleep, impulsivity, increased activity, crying, excessive vocalizations	mood stabilizer	6
22	Tourette's Disorder	rapid eye blinking, lip popping, head twitching	antipsychotic	3

(table continued)

23	Bipolar I Disorder	increased activity, decreased sleep, elevated mood, irritability	mood stabilizer	4
24	Disruptive Behavior Disorder, NOS	irritability, aggression, impulsivity	antipsychotic	3
25	Mood Disorder, Depressed	irritability, sleep disturbance, psychomotor agitation, depressed mood	antidepressant	4
26	Bipolar Disorder, NOS	no diagnosis-specific symptoms listed	antipsychotic	0
27	Bipolar I Disorder	irritability, psychomotor agitation, sleep disturbance	antipsychotic	3
28	Bipolar I Disorder	no diagnosis-specific symptoms listed	antipsychotic	0
29	Bipolar I Disorder	irritability, psychomotor agitation, pressured speech, poor concentration	mood stabilizer	4
30	Bipolar I Disorder	lethargy, decreased appetite, decreased interactions, irritability, sleep disturbance, increased speech	antipsychotic	6
31	Bipolar I Disorder	psychomotor agitation, irritability, decreased sleep	mood stabilizer	3
32	Dysthymic Disorder	depressed mood, decreased energy, crying, psychomotor agitation	antidepressant	4
33	Bipolar I Disorder	psychomotor acceleration, sleep disturbance, impulsivity	mood stabilizer	3
34	Disruptive Behavior Disorder, NOS	no diagnosis-specific symptoms listed	antipsychotic	0
35	Psychotic Disorder, NOS	no diagnosis-specific symptoms listed	antipsychotic	0
36	Bipolar I Disorder	no diagnosis-specific symptoms listed	mood stabilizer	0
37	Psychotic Disorder, NOS	no diagnosis-specific symptoms listed	antipsychotic	0

(table continued)

38	Bipolar I Disorder	psychomotor agitation, decreased sleep, crying	antidepressant	3
39	Bipolar I Disorder	increased activity, psychomotor agitation, flat affect, sleep disturbance	mood stabilizer	4
40	Bipolar Disorder, NOS	psychomotor agitation	antipsychotic	1
41	Bipolar I Disorder	psychomotor agitation, impulsivity, reduced sleep, increased vocalizations	antipsychotic	4
42	Schizophrenia	no diagnosis-specific symptoms listed	antipsychotic	0
43	Schizoaffective Disorder	no diagnosis-specific symptoms listed	antipsychotic	0
44	Bipolar I Disorder	psychomotor agitation, sleep disturbance, crying	antipsychotic	4
45	Generalized Anxiety Disorder	worrying	antidepressant	1
46	Stereotypic Movement Disorder	skin picking, hand shaking	antipsychotic	2
47	Generalized Anxiety Disorder	worrying, restlessness, decreased sleep, irritability	antianxiety	4
48	Mood Disorder, NOS	no diagnosis-specific symptoms listed	antidepressant	0
49	Schizophrenia	attending to internal stimuli, bizarre motor posturing, paranoia, flat affect	antipsychotic	4
50	Depressive Disorder, NOS	crying, irritability, poor sleep	antidepressant	3
51	Anxiety Disorder, NOS	worrying, nervousness	antianxiety	2
52	Major Depressive Disorder	no diagnosis-specific symptoms listed	antidepressant	0
53	Bipolar I Disorder	agitation, decreased sleep, increased motor activity	mood stabilizer	3
54	Bipolar Disorder, NOS	no diagnosis-specific symptoms listed	antipsychotic	0
55	Bipolar Disorder, NOS	hypersomnia, weight loss, irritability, decreased engagement, social withdrawal	antidepressant	5

(table continued)

56	Bipolar Disorder, NOS	irritability, psychomotor agitation, sleep disturbance	mood stabilizer	3
57	Post Traumatic Stress Disorder	no diagnosis-specific symptoms listed	antidepressant	0
58	Psychotic Disorder, NOS	no diagnosis-specific symptoms listed	antipsychotic	0
59	Pica	no diagnosis-specific symptoms listed	antidepressant	0
60	Intermittent Explosive Disorder	no diagnosis-specific symptoms listed	antidepressant	0
61	Bipolar I Disorder	decreased sleep, psychomotor agitation, crying, weight loss	antipsychotic	3
62	Bipolar Disorder, NOS	psychomotor agitation, elevated mood, decreased sleep, irritability	antipsychotic	4
63	Stereotypic Movement Disorder	no diagnosis-specific symptoms listed	antipsychotic	0
64	Obsessive-Compulsive Disorder	hoarding, repetitive cleaning	antidepressant	2
65	Post Traumatic Stress Disorder	repeatedly discussing past abuse, nightmares, avoidance, exaggerated startle response, trembling	antidepressant	6
66	Anxiety Disorder, NOS	sleep disturbance, irritability, restlessness, muscle tension	antianxiety	4
67	Bipolar I Disorder	no diagnosis-specific symptoms listed	antipsychotic	0
68	Depressive Disorder, NOS	depressed mood, crying, irritability, insomnia, fatigue, psychomotor retardation	antidepressant	6
69	Bipolar I Disorder	decreased sleep, psychomotor agitation, social withdrawal	antipsychotic	3
70	Psychotic Disorder, NOS	hallucinations, paranoia	antipsychotic	2
71	Bipolar Disorder, NOS	easily distracted, extremely talkative, irritability, psychomotor agitation	antipsychotic	4
72	Anxiety Disorder, NOS	no diagnosis-specific symptoms listed	antianxiety	0

(table continued)

73	Bipolar I Disorder	decreased sleep, crying, psychomotor agitation	mood stabilizer	3
74	Anxiety Disorder, NOS	restlessness	antidepressant	1
75	Bipolar II Disorder	sleep disturbance, distractibility, psychomotor agitation	antipsychotic	3
76	Major Depressive Disorder	social isolation	antidepressant	1
77	Bipolar Disorder, NOS	decreased sleep, irritability, increased activity, pressured speech	mood stabilizer	4
78	Major Depressive Disorder	irritability, anhedonia, sleep disturbance, lethargy, depressed mood, decreased appetite, distractibility, social withdrawal	antidepressant	8
79	Major Depressive Disorder	psychomotor agitation, depressed mood, crying, sleep disturbance, lack of interest	antidepressant	5
80	Mood Disorder, NOS	no diagnosis-specific symptoms listed	antipsychotic	0
81	Major Depressive Disorder	irritability, restlessness, social isolation, weight loss, psychomotor retardation	antidepressant	5
82	Depressive Disorder, NOS	social isolation, irritability, decreased appetite, decreased interest, lethargy	antidepressant	5
83	Pica	no diagnosis-specific symptoms listed	antianxiety	0
84	Bipolar I Disorder	no diagnosis-specific symptoms listed	mood stabilizer	0
85	Stereotypic Movement Disorder	no diagnosis-specific symptoms listed	antipsychotic	0
86	Bipolar II Disorder	sleep disruption, agitation, decreased appetite	mood stabilizer	3
87	Anxiety Disorder, NOS	restlessness, poor attention, low concentration	antidepressant	3

Table 4 presents the Axis I psychiatric diagnosis and the specific medications prescribed for each of them by the number of individuals with each of the disorders. Especially for those more

frequently occurring disorders, there was no clear information in each individual's medical chart why one drug was chosen over another.

Cross tabulation analyses were conducted to explore any relationships among the data collected. These analyses showed that of the 75 cases following a primary illness approach, 47 (62.7%) had a diagnosis of a mood disorder, 11 (14.7%) had a diagnosis of an anxiety disorder, 9 (12%) had a diagnosis of a psychotic disorder and 8 (10.7%) had a diagnosis of a childhood disorder. Of these 75 cases, 47 (62.7%) were individuals with profound mental retardation, 12 (16%) with severe mental retardation, 8 (10.7%) with moderate mental retardation, 4 (5.3%) with mild mental retardation and 4 (5.3%) with unspecified level of mental retardation. In 31 (41.3%) cases, the individuals were prescribed an antipsychotic medication, 24 (32%) were prescribed an anti-depressant, 14 (18.7%) a mood stabilizer and 6 (8%) were prescribed an anxiolytic. Further, 11 of the 75 individuals (14.7%) were between the ages of 18 and 41, 49 (65.3%) were between the ages of 42 and 65, and 15 (20%) were between the ages of 66 and 87. Of the 75, 60 (80%) individuals were Caucasian and 15 (20%) were African Americans; 35 (46.7%) were females.

Table 4. Diagnosis and medications prescribed by approach taken.

Primary Illness Approach		
Primary Diagnosis	**Medication Prescribed**	**Total**
Anxiety Disorder, NOS	Buspar (3)	6
	Luvox (1)	
	Remeron (1)	
	Zoloft (1)	

(table continued)

Bipolar Disorder, NOS	Depakote (2)	9
	Lithium (1)	
	Olanzapine (2)	
	Paxil (1)	
	Risperidone (2)	
	Tegretol (1)	
Bipolar I Disorder	Abilify (2)	22
	Depakote (4)	
	Lithium (1)	
	Neurontin (1)	
	Olanzapine (8)	
	Prozac (1)	
	Risperidone (1)	
	Seroquel (1)	
	Tegretol (3)	
Bipolar II Disorder	Depakote (1)	2
	Olanzapine (1)	
Depressive Disorder, NOS	Paxil (1)	3
	Remeron (1)	
	Wellbutrin (1)	
Disruptive Behavior Disorder, NOS	Depakote (1)	2
	Risperidone (1)	

(table continued)

Dysthymic Disorder	Paxil (2)	2
Generalized Anxiety Disorder	Clonazepam (2)	3
	Paxil (1)	
Intermittent Explosive Disorder	Depakote (1)	1
Major Depressive Disorder	Celexa (1)	6
	Pamelor (1)	
	Paxil (3)	
	Serzone (1)	
Mood Disorder, Depressed	Paxil (1)	1
Mood Disorder, NOS	Prozac (2)	2
Obsessive-Compulsive Disorder	Luvox (1)	1
Pica	Clonazepam (1)	2
	Luvox (1)	
Post Traumatic Stress Disorder	Zoloft (1)	1
Psychotic Disorder	Olanzapine (4)	5
	Seroquel (1)	
Schizoaffective Disorder	Olanzapine (1)	1
Schizophrenia	Olanzapine (2)	3
	Seroquel (1)	
Stereotypic Movement Disorder	Risperidone (2)	2
Tourette's Disorder	Risperidone (1)	1
Total		**75**

(table continued)

Target Symptom Approach		
Target Symptom	**Medication Prescribed**	**Total**
Aggression	Neurontin	1
Aggression	Lithium	1
Aggression	Olanzapine	1
Aggression	Abilify	1
Aggression	Risperidone	1
Hallucinations	Risperidone	1
Weight Loss	Mellaril	1
Sleep Disturbance	Zoloft	1
Involuntary Movement	Olanzapine	1
Total		**9**

No Apparent Approach		
Primary Diagnosis	**Medication Prescribed**	**Total**
Stereotypic Movement Disorder	Luvox	1
Major Depressive Disorder, NOS	Zoloft	1
Bipolar I Disorder	Depakote	1
Total		**3**

Of the nine individuals whose psychopharmacology plan followed a target symptom approach, 3 (33.3%) had a diagnosis of a mood disorder, 3 (33.3%) had a diagnosis of a psychotic disorder, 2 (22.2%) had a diagnosis of an anxiety disorder, and 1 (11.1%) had a diagnosis of a childhood disorder. Six (66.7%) individuals were diagnosed with profound mental retardation, 2 (22.2%) with moderate mental retardation, and 1 (11.1%) with severe mental retardation. An

antipsychotic was prescribed to 6 (66.7%) of these 9 individuals. In 2 (22.2%) cases, the individual was prescribed a mood stabilizer and in 1 (11.1%) case an antidepressant. Anxiolytic medications were not prescribed in this group. Further, 3 (33.3%) individuals were between the ages of 18 and 41 and 6 (66.7%) were between the ages of 42 and 65. and. Eight (88.9%) of the 9 individuals were Caucasian and 1 (11.1%) was an African American; 8 (88.9%) were males.

Of those three individuals whose psychopharmacology plan followed an apparent approach, 2 (66.7%) had a diagnosis of a mood disorder and the other had a diagnosis of a childhood disorder. One of these individuals was diagnosed with profound mental retardation, another was diagnosed with moderate mental retardation and the third had an unspecified level of mental retardation. Two individuals (66.7%) of were prescribed an antidepressant and the other individual was prescribed a mood stabilizer. All three of these individuals were from the 42 to 65 age group, all three were Caucasian, and 2 (66.7%) were female.

DISCUSSION

The results showed that physicians at one facility for individuals with developmental disabilities typically used a primary illness approach in prescribing psychotropic medication for Axis I psychiatric disorders. Of the 87 individuals prescribed psychotropic medications for Axis I psychiatric disorders, 75 of them had a psychopharmacology treatment plan derived from a primary illness approach. This approach assumes that the behavioral end-points of the psychiatric disorder can be managed, controlled or eliminated by treating the disorder itself. For example, aggression arising from command hallucinations can be reduced or eliminated by treating hallucinations without specifically targeting the aggression itself.

The primary illness approach provides clinicians with a method of conceptualizing an individual's treatment plan before they begin actual treatment. It enables an interdisciplinary treatment team to determine how different symptoms and behaviors will be treated, and how to integrate psychopharmacological, behavioral and other treatments. For example, when presented with an individual who has an Axis I diagnosis of schizophrenia and an Axis II diagnosis of mild mental retardation, the treatment team typically determines the nature and manifestations of the schizophrenia in the individual prior to developing a treatment plan. The individual may present as having command hallucinations that tell him to hurt himself and others, and is uncommunicative, withdrawn, does not engage in activities of daily living skills (ADL skills), and is not motivated to initiate or engage in assigned tasks.

In this case, the treatment team must decide if taking a primary illness approach will control and manage his positive symptoms of schizophrenia (i.e., command hallucinations, aggression), as well as his negative symptoms (i.e., uncommunicative, withdrawn, does not engage in activities of daily living skills, and is not motivated to initiate or engage in assigned tasks). The physician may determine that a drug prescription would be appropriate for the positive symptoms but that it may

not greatly affect this individual's negative symptoms. Thus, the team may use a primary illness approach to treat the command hallucinations, thereby taking care of the aggression resulting from command hallucinations. Thus, no behavioral intervention may be necessary specifically for aggression. Further, the team may decide that while some benefits may accrue in the negative symptoms due to the drug treatment for hallucinations, the negative symptoms are compounded with the individual's Axis II diagnosis of mental retardation and that there is an associated skills deficit in communication, social skills and ADL skills. Thus, a target symptom approach would be taken and the treatment plan includes skills training programs.

The primary illness approach works best in an integrated treatment planning system where all disciplines provide input into the treatment plan. It also enhances the treatment team's ability to integrate different treatment modalities within a single treatment plan (Singh et al., 2002), particularly behavioral and psychopharmacological. However, it does require the treatment team to have a good understanding of the psychopharmacology of developmental disabilities in terms of Axis I psychiatric disorders. For example, they need to know which drugs are effective with positive symptoms, negative symptoms, or both. Current research suggests that the typical antipsychotic medications target the positive symptoms of schizophrenia while the atypical antipsychotic medications target both positive and negative symptoms, and, within the atypical group, Olanzapine appears to be most effective with negative symptoms (Emsley & Oosthuizen, 2003). The typical antipsychotics tend have more cognitive side effects such as memory and concentration problems, trouble with executive functioning, and attention. Thus, physicians will need to have a good working knowledge of the various effects and side effects of psychotropic medications so that they can assist the treatment team to develop the best combination of treatments for specific disorders in a given individual.

The target symptom approach was used far less often, only 10% in this sample of 87 individuals. This approach assumes that there is a specific problem that needs treatment, and that there is a specific treatment for the problem. This approach does not assume that the specific treatment will also ameliorate the underlying psychopathology that is the cause of the problem although it may. For example, in general medicine, an individual may present with fever that is high enough to warrant immediate treatment regardless of the underlying medical condition that gave rise to it. The fever is treated as a target symptom and brought under control while tests are undertaken to find the cause of the fever. Sometimes, the cause of the fever may be apparent (e.g., recurrence of cancer) but it cannot be treated and palliative medical treatment is provided for the cancer.

Similarly, in developmental disabilities, an individual may exhibit aggressive behavior that is of high frequency and intensity and present a danger to self or others. The origin of the aggressive behavior may be faulty learning and therefore treated via behavioral methods. This would be a good example of a target symptom approach. An alternative would be that the aggressive behavior is a manifestation of psychosis that is a part of the schizophrenia symptomatology of the individual. In this case, because the aggressive behavior is dangerous to self or others and the psychosis is not well controlled with current medication, a target symptom approach may be taken to control the aggression while further tests and analyses are completed and a new psychopharmacology plan is developed. A further alternative would be that the aggression is sometimes an outcome of the psychosis and is an instrumental response at other times. In this case, a combined primary illness and target symptom approach would be appropriate, as in combined pharmacological-behavioral treatments.

In this facility, only 10% (n = 9) of the drug prescriptions were based on a target symptom approach. However, it was unclear from the medical records of the nine individuals if the behaviors targeted were only instrumental in nature or had any psychiatric symptoms. There was one specific

case in which a target symptom approach was used with a behavior (i.e., hallucinations) that is typically a symptom of psychosis. In this case, the hallucinations were unrelated to an Axis I disorder and the symptom was treated pharmacologically as a target behavior. There were five cases in which aggression was treated with psychotropic medication, but in each of these cases there was an associated behavioral plan for the reduction of the instrumental component of the aggression. What was not clear from the medical records was the underlying psychopathology of the aggression that made the behavior responsive to medication. In one case, involuntary movement was apparently treated with Olanzapine. It was not clear from the medical records why this drug was deemed appropriate for this behavior.

The behavioral-pharmacological hypothesis approach provides clinicians a useful way of conceptualizing treatment when there is clear empirical evidence that a certain drug may be effective for a given behavior because there is a hypothesized mechanism of action that may account for the effectiveness of the drug. For example, individuals with developmental disabilities engage in self-injury for a variety of reasons, including biological, maladaptive learning, and environmental reasons (Schroeder, Oster-Granite, & Thompson, 2002). There are two opiate hypotheses regarding self-injury in some individuals and their treatment. In the first hypothesis, it is assumed that self-injury results from general sensory depression and an insensitivity to pain that may be related to chronic elevations of endogenous opiates (Sandman & Hetrick, 1995). In the second hypothesis, it is assumed that self-injury functions to release β-endorphins and enables the individual to achieve an opiate "high" (Sandman & Hetrick, 1995). In either case, the self-injury can be treated successfully with opiate blockers, such as naloxone and naltrexone (Sandman et al., 2000). The behavioral-pharmacological hypothesis was not used in this facility.

There were three cases where it was totally unclear as to the rationale used by the physician to prescribe the psychotropic medication. The data in the individuals' medical charts did not

contain any psychopharmacology plan or an explanation of the reasons why the drugs were prescribed.

In general, the documentation in the charts regarding assessments, diagnostic formulation, differential diagnosis, and rationale of pharmacotherapy was not very clear or missing. Often, the signs and symptoms of the disorders were listed but it was not made clear if the individual manifested some or all of them. In many cases, the symptoms listed were generic and not individualized. For example, for an individual with schizophrenia, the symptoms were listed as auditory hallucinations, delusions, and thought disorder without any specifications as to the form and content. In other cases, the listed symptoms did not comport to the given diagnosis. For example, in one case, the single symptom listed for Major Depressive Disorder was social isolation. It could be that all other symptoms were well controlled by medication and psychosocial interventions or that the given diagnosis is open to question. Further, there were 30 (34.5%) individuals with a "not otherwise specified" diagnosis. While this is a legitimate diagnosis, if it is arrived at by eliminating all other possibilities that would account for the observed signs and symptoms, there was very limited documentation of differential diagnosis leading to a "not otherwise specified" diagnosis.

One of the limitations of this study is that there was no accounting for appropriate assessment and diagnosis. It was assumed that appropriate assessments informed the diagnosis and that the diagnosis informed further assessments for differential diagnosis. This was not assessed and it is possible, at least for some individuals, that their diagnosis was incorrect, as reported in previous studies (e.g., Bates et al., 1985), and that they were inappropriately medicated. Future studies should investigate the accuracy of the diagnostic formulation and differential diagnosis.

Future studies should also investigate the appropriateness of the medications prescribed for the purported diagnosis. In this study, it was noted that several medications were prescribed for

given disorders and there was no clear rationale for choosing one drug over another. In one of the few studies that investigated this issue in a small sample of individuals, it was found that there were mismatches between the disorder and the drug prescribed (Young & Hawkins, 2002). Further studies are needed to corroborate this finding. In addition, given that the field of psychopharmacology in developmental disabilities now has a psychopharmacology consensus handbook (Reiss & Aman, 1998) as well as expert consensus guidelines (Rush & Frances, 2002), it is an opportune time to use these as the basis for determining the quality of the match between the diagnosis and the prescribed medication.

In summary, the results of this study showed that physicians at one developmental center rely mainly on a primary illness approach to prescribe psychotropic medication to individuals with developmental disabilities who have an Axis I psychiatric disorder. To a much lesser extent, they use a target symptom approach. No variables were apparent that predicted the use of a specific approach with any specific individual.

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