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Weight gain among adults with intellectual disabilities receiving atypical antipsychotics

Sherri Lyn Transier

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Weight Gain among Adults with Intellectual Disabilities

Receiving Atypical Antipsychotics

Sherri Lyn Transier

A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

COLLEGE OF EDUCATION
LOUISIANA TECH UNIVERSITY

March 2010

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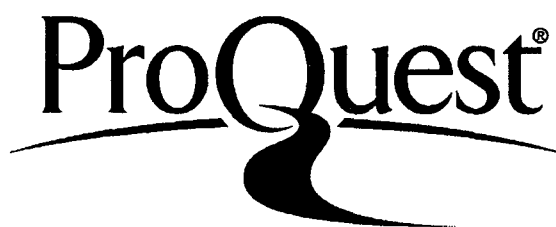
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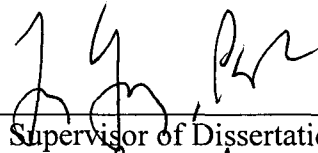
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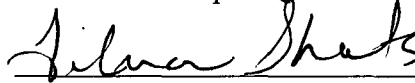
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We hereby recommend that the dissertation prepared under our supervision by Sherri Lyn Transier, M.S. entitled Weight Gain Among Adults with Intellectual Disabilities Receiving Atypical Antipsychotics be accepted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.



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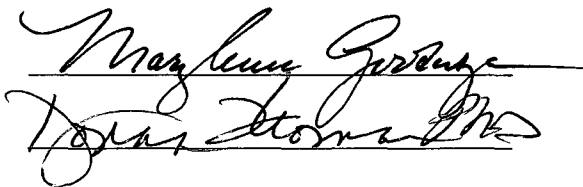


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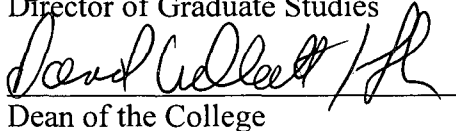


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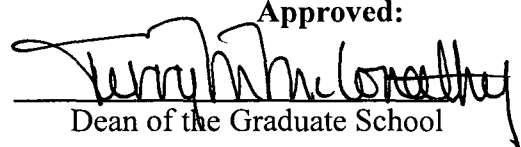


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Abstract

The present study assessed whether the atypical antipsychotic agents olanzapine, risperidone, and quetiapine are associated with significant weight gain among adults with intellectual disabilities after 6 months of drug treatment. The body weights of 79 participants were retrieved 6 months prior to the initiation of drug treatment, at the start of the atypical antipsychotic agent, and after 6 months of drug therapy. Each individual served as his or her own control by utilizing pretreatment baseline trends in weight change to calculate a dependent measure of adjusted posttreatment weight gain. Doing so allowed for a stringent determination of the liability for weight gain during drug treatment. Results indicated that olanzapine, risperidone, and quetiapine are each associated with significant weight gain after 6 months of drug treatment. Individuals with mild to moderate intellectual disabilities evidenced more significant weight gain within that time period than those with severe to profound impairments.

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Author Mimi Janquin
Date 9/10/09

For Dad, Mom, Randy, and Lenny.

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Weight Gain among Adults with Intellectual Disabilities

Receiving Atypical Ant psychotics

For thirty years and as recently as a few years ago, the simple fact of being mentally retarded and residing in an institution meant that one was treated, like it or not, with neuroleptic drugs. The doses were high, the treatment went on for years, and little or no consideration was given to side effects that the drugs would have [emphasis added]. (Gualtieri, 1991, p. 36)

Few issues are more controversial in the field of intellectual disabilities (ID) than the use and potential misuse of psychotropic medication. Landmark epidemiological research published in 1970 found that 51.1% of persons with ID residing in institutional settings were receiving psychotropic medication (Lipman, 1970). More than 39% were being chronically treated with “major tranquilizers”, agents now typically referred to as neuroleptic or antipsychotic drugs. Subsequent investigation revealed that adults with ID comprised the most medicated of all treatment groups in inpatient psychiatric wards (Aman, 1987).

More recent investigations continue to confirm that a substantial percentage of persons with ID are prescribed psychotropic drugs. A 1988 review of the published literature estimated that between 40% to 50% of those in institutional settings and 25% to 35% of those in community settings were being prescribed psychotropic medication (Aman & Singh, 1988). Research from 1997 subsequently revealed that 36.5% of persons with ID enrolled in Oklahoma’s state healthcare system were receiving at least one psychotropic agent (Spreat, Conroy, & Jones, 1997). The majority of individuals, 22.4%,

were being treated with antipsychotic drugs. The remaining 14.1% were receiving antidepressant, anxiolytic, or anticonvulsant agents for mood or behavioral stabilization.

A 2004 extension of this state healthcare research revealed no significant change in psychotropic prevalence rates, with 34.3% of persons with ID continuing to receive at least one psychotropic drug (Spreat, Conroy, & Fullerton, 2004). Antipsychotic agents remained the most widely prescribed psychotropic medication, with an estimated 20.0% of adults receiving this class of drug. The highest prescription rates for antipsychotic drugs occurred among adults with ID living in nursing homes at 31.7%. Prescription rates for antipsychotic drugs were somewhat lower and almost identical for those residing in supported independent living settings and institutional facilities, at 19.6% and 19.5%, respectively.

Antipsychotic drugs generally are separated into two broad categories: the conventional or first-generation agents and the more recently developed atypical or second-generation agents (Baldessarini & Tazari, 2006). Chlorpromazine, also known by the trade name Thorazine, was the first conventional antipsychotic introduced to the U.S. market. The advent of chlorpromazine in 1954 constituted a landmark event for the field of psychopharmacology, and this drug continues to be recognized for revolutionizing the rehabilitation of persons with schizophrenia. Utilization of chlorpromazine from 1954 to 1980 decreased the population of psychiatric inpatients by more than 400,000 in the United States. Furthermore, this drug set the stage and the marker for the development of other agents to treat severe clinical disorders.

Numerous research trials and years of clinical experience have established that antipsychotic drugs are superior to psychological therapies, benzodiazepines,

barbiturates, and electroconvulsive shock in treating the cardinal signs and symptoms of schizophrenia and other disorders marked by psychosis (Baldessarini & Tarazi, 2006). Antipsychotic drugs are recognized to be highly effective in minimizing delusions, hallucinations, combativeness, psychomotor agitation, insomnia, negativism, and anorexia. More variable or delayed responses also are noted with some aspects of cognition, motivation, and self-care. For instance, improvements often are seen in orientation, judgment, insight, and memory during the course of antipsychotic drug treatment.

As a result of their therapeutic efficacy, the Food and Drug Administration (FDA) have approved antipsychotic drugs for a range of disorders (Baldessarini & Tazari, 2006). Common indications include (a) acute and chronic psychotic disorders (e.g., schizophrenia, delusional disorder, brief psychotic disorder, acute idiopathic psychosis, and alcoholic hallucinosis); (b) mood disorders with psychotic features (e.g., bipolar mania and severe depression); (c) cognitive disorders marked by psychomotor agitation or aggression (e.g., delirium and some types of dementia); (d) self-injurious behavior (SIB) associated with ID and pervasive developmental disorders (PDDs) (e.g., autism); (e) Gilles de la Tourette syndrome; (f) Huntington's disease; and (g) nausea and emetism.

Since the introduction of chlorpromazine in 1954, antipsychotic drugs have remained the most frequently prescribed class of psychotropic drug for adults with ID (Aman, 1987; Aman & Singh, 1988; Lipman, 1970; Spreat et al., 1997; Spreat et al., 2004). These agents are used to treat comorbid clinical disorders and, more

controversially, to manage a variety of aberrant behaviors in the absence of an Axis I diagnosis (Ashcroft, Fraser, Kerr, & Ahmed, 2001; Deb, Sohanpal, Soni, Lenotre, & Unwin, 2007; Janowsky, Barnhill, Khalid, & Davis, 2006; Levitas, 2003; McGillivray & McCabe, 2004; Unwin & Deb, 2008). Clinical disorders are believed to be three to four times more prevalent among adults with ID than in the general population (American Psychiatric Association [APA], 2002), with estimates ranging from 9% to 74% across various disorders (American Association on Mental Retardation [AAMR], 2002). However, diagnostic overshadowing, or the tendency for clinicians to attribute sustained disturbances in mood and behavior to ID rather than to a co morbid clinical condition, is believed to contribute to an underdiagnosis of psychotic and mood disorders among adults with ID (Dosen & Day, 2001).

Many persons with ID display behavioral disturbances that are severe and chronic but difficult to classify as a clinical disorder using the criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* (APA, 2002) or the *International Classification of Disease, Tenth Edition* (World Health Organization [WHO], 1992). For instance, many individuals with ID have cognitive and communication deficits that make it challenging for clinicians to reliably identify disturbances of thought and perception (Aman, Crimson, Frances, King, & Rojahn, 2004; Cooper, Melville, & Einfeld, 2003; Dossetor, 2007; Rush, Bowman, Eidman, Toole, & Mortenson, 2004; Rush & Frances, 2000). This diagnostic uncertainty only increases with the severity of ID (Aman et al.; Rush & Frances).

Although the identification of clinical disorders remains ideal in guiding treatment efforts, “Expert Consensus Guidelines” recognize that, other than autism, any diagnosis is

difficult to reliably formulate in persons who function within the severe to profound range of ID (Aman et al., 2004; Rush & Frances, 2000). Thus, observable disturbances in behavior, such as sustained psychomotor agitation, SIB, physical aggression, and property destruction, often become the foci of antipsychotic drug treatment. Because such behavioral signs are not primary diagnostic features of specific clinical disorders, and instead may reflect the current effects of multiple psychosocial and biomedical conditions, they typically are considered nonspecific in nature. Some research supports the use of antipsychotic drugs to treat behavioral disturbances commonly associated with ID, autism, and other PDDs (Aman & Gharabawi, 2004; Cohen, Ihrig, Lott, & Kerrick, 1999; Kahn, 1999; McAdam, Zarcone, Hellings, Napolitano, & Schroeder, 2002; Zarcone, Hellings, Crandall, Reese, Marquis, Fleming, et al., 2000). This practice remains controversial, however, and is viewed by many as a failure to appropriately formulate and treat the underlying etiology of the behavioral disorder (Ashcroft et al., 2001; Deb et al., 2007; Janowsky et al., 2006; La Malfa, Lassi, Bertelli, & Castellani, 2006; Levitas, 2003; Luchins, Dojka, & Hanrahan, 1998; Matson, Bamburg, Mayville, Pinkston, Bielecki, Logan, et al., 2000; Matson, Bielecki, Mayville, & Matson, 2003; McGillivray & McCabe, 2004).

The effectiveness of antipsychotic drug treatment for adults with ID and comorbid clinical disorders is similar to the morbid psychiatric population, although the amount of research published is smaller by comparison (Aman et al., 2004; Duggan & Brylewski, 1999; La Malfa et al., 2006; Shedlack, Hennen, Magee, & Cheron, 2005). Consistent with clinical practice, much of the available research has investigated the effectiveness of antipsychotic drugs in managing behavioral disturbances among persons

with ID (Aman et al.; Aman & Gharabawi, 2004; Ashcroft et al., 2001; Deb et al., 2007; Dinca, Paul, & Spencer, 2005; Hammock, Levine, & Schroeder, 2001; Horrigan & Barnhill, 1999; Janowsky et al., 2006; Kahn, 1999; McAdam et al., 2002; McGillivray & McCabe, 2004; Williams, Clarke, Bouras, Martin, & Hault, 2000; Zarcone et al., 2000). *The International Consensus Handbook* presents a comprehensive research review of the efficacy and effectiveness of different antipsychotic drugs in treating behavioral disturbances commonly evidenced by persons with ID (Baumeister, Sevin, & King 1998). Other than aggression, for which results were mixed, clinical improvements were noted with all aberrant behaviors for the majority of individuals.

The conventional or first-generation antipsychotic drugs, however, do not always effectively treat severe behavioral disturbances evidenced by persons with ID, particularly among those also diagnosed with autism (Baumeister et al., 1998). Furthermore, concerns abound that the low-potency or high-dose conventional antipsychotics largely achieve clinical results by exerting nonspecific effects on a broad range of behaviors. These agents have the potential to cause significant sedation and thereby may suppress aberrant behaviors as well as adaptive performance, cognition, and learning. Consequently, skills training and other habilitative efforts may be made more difficult for persons who are already at pervasive disadvantage. Conversely, the high-potency or low-dose conventional antipsychotics frequently cause neurological damage marked by debilitating and potentially irreversible disturbances in motor activity (Baldessarini & Tazari, 2006).

The life expectancy of persons with ID has dramatically increased over the past 60 years (Chaney & Eyman, 2002; Hogg, Juhlberg, & Lambe, 2007). The frequency and

severity of adverse drug reactions, however, remain significantly higher for the ID population than the general public (Wilson, Lott, & Tsai, 1998). Considering that behavioral and clinical disorders often emerge in childhood and extend throughout adulthood in persons with ID, and that there has been a 50-year trend of antipsychotic drugs being the most widely prescribed psychotropic for these individuals, the issue of antipsychotic drug treatment remains highly charged (Aman & Singh, 1988; Lipman, 1970; Spreat et al., 1997; Spreat et al., 2004).

Pathophysiology of Psychosis: Increased Dopaminergic Activity

To understand the therapeutic and adverse effects of antipsychotic drugs, both the conventional and atypical agents, an overview of their mechanisms of action is necessary. In the brain, dopamine functions as a neurotransmitter and neurohormone that activates five types of receptors--D1, D2, D3, D4, and D5 (Baldessarini & Tazari, 2006). Dopamine is released by naturally reinforcing experiences such as food and sex and is commonly associated with the pleasure system (Berridge & Robinson 2001; Bratcher, Farmer-Dougan, Dougan, Heidenreich, & Garris, 2005). Dopamine has various other functions, however, and also plays an important role in (a) mood (Ruhe, Mason, & Schene, 2007); (b) motor activity (Andersson, Nissbrandt, & Bergquist, 2006; Soiza-Reilly, Fossati, Ibarra, & Azcurra, 2004); (c) wakefulness and sleep (Monti & Jantos, 2008); (d) attention and cognition (Saeedi, Remington, & Christensen, 2006; Savitz, Solms, & Ramesar, 2006; Silkstrom & Soderlund 2007); (e) learning and memory (Cheng & Feenstra, 2006; El-Ghundi, O'Dowd, & George, 2007; Frank & O'Reilly, 2006; Olvera-Cortez, Anquiano-Rodriguez, Lopez-Vazquez, & Alfaro, 2008); and (f) regulation of milk production (Tabak, Toporikova, Freeman, & Bertram, 2007).

Dopaminergic neurons project throughout various structures of the brain (Baldessarini & Tazari, 2006; Kapur, Mizrahi, & Li, 2005; Miyamoto, Duncan, Marx, & Lieberman, 2005). The highest concentrations are found within four major neural tracts that include the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways. The pathophysiology of idiopathic psychoses results from increased dopaminergic activity in the mesolimbic and mesocortical regions of the brain. The mesolimbic pathway is associated with arousal, latent inhibition, goal direction, pleasure, and reward. Overactivity of dopamine in this region is linked with the positive symptoms of psychosis, most notably delusions and hallucinations. The mesocortical pathway is associated with motivated behavior, emotional response, and several neurocognitive functions including memory, attention, and problem solving. Overactivity of dopamine in this region is linked with the negative symptoms of psychosis, such as affective blunting, avolition, and alogia.

To ameliorate the positive and negative symptoms of psychosis, dopaminergic overactivity must be dampened in the mesolimbic and mesocortical brain regions (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). The limbic and cortical systems are connected via parallel circuitry that penetrates the nigrostriatal region of the brain. The nigrostriatal pathway, which forms part of the complex motor loop of the basal ganglia, regulates movement and motor control through the activity of dopaminergic neurons. Degeneration of dopaminergic neurons along the nigrostriatal tract is a major pathological feature of Parkinson's disease and other extrapyramidal disorders.

In addition to the mesocortical, mesolimbic, and nigrostriatal pathways, dopaminergic neurons are also highly concentrated in the tuberoinfundibular region of the

brain (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). This region houses the pituitary gland and assists in regulating the secretion of certain hormones such as prolactin. Dopamine serves to inhibit the release of prolactin in the tuberoinfundibular region, and in its absence milk is continuously secreted (Baldessarini & Tazari; Miyamoto et al.; Tabak et al., 2007).

Although the precise mechanisms of action underlying antipsychotic drugs remain unclear, receptor binding patterns provide clues about their efficacy, tolerability, and safety (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). The affinity of a drug, or the degree to which it binds to a particular receptor site, predicts both drug potency and the likelihood for side effects. Common to all antipsychotic drugs, both the conventional and the atypical agents, is their affinity to antagonize or block the dopamine receptor subtype D₂ in the limbic and prefrontal regions of the cerebral cortex. What differentiates these agents are the method and specificity by which this antagonism occurs.

Conventional Antipsychotic Drugs

A brief history. Conventional antipsychotic drugs are commonly referred to as “neuroleptics”, a term derived from the Greek wherein “neuro” refers to nerves and “lept” means “to seize or take hold” (Baldessarini & Tazari, 2006). Thus, the word neuroleptic literally means “to seize or take hold of nerves”. Conventional antipsychotic drugs originally were called neuroleptics to contrast their effects against barbiturates and other sedative-hypnotics which depress the functioning of the central nervous system (CNS). Although conventional antipsychotic drugs reduce spontaneous motor movements, complex behaviors, and emotional responsiveness, they do not significantly depress other CNS functions respiration, heart rate, spinal reflexes, or unconditioned

avoidance responses. As a result, neuroleptic drugs primarily were regarded as more viable sedative agents, for which they also became known as “tranquilizers” or “major tranquilizers” until their antipsychotic and antimanic properties were well established. Today, the term “tranquilizer” has fallen into general disfavor for conventional antipsychotic drugs because this label falsely implies an association with the benzodiazepines or minor tranquilizers.

The term neuroleptic became increasingly popular after conventional antipsychotic drugs were put to broad use in the chronic treatment of psychosis and their liability to cause movement disorders became apparent (Baldessarini & Tazari, 2006). Historically, the emergence of motor disturbances was considered an important clinical indicator that the drug dose was sufficient to treat psychosis. Such views remained largely intact until the 1980s ushered in significant advances in neurophysiologic research. Conventional antipsychotic drugs were then increasingly recognized as having an impact on many neurotransmitter sites throughout the nervous system, resulting in therapeutic as well as unwanted effects. Disturbances in motor control eventually were understood to be a reliable measure of drug-induced neurological damage rather than a valid index of therapeutic dosing. Today, the term neuroleptic generally is used to reference the neurological disturbances that are strongly associated with the conventional, but not the atypical, antipsychotic drugs.

Pharmacokinetics and pharmacodynamics. Conventional antipsychotics can be divided into eight categories that include 25 different drugs (Baldessarini & Tazari, 2006). Although all are efficacious in treating psychosis, particularly the positive

symptoms, results are achieved at the significant risk for neurological side effects that can be grossly impairing and irreversible (Baldessarini & Tazari; Miyamoto et al., 2005). Knowledge of the mechanisms that underlie both the antipsychotic and neurological effects of conventional antipsychotic drugs remains incomplete. However, their strong affinity to antagonize dopamine in the limbic portions of the forebrain and the basal ganglia are the most prominently discussed.

Conventional antipsychotics are strong antagonists for D₂ receptors in the mesolimbic pathway, and to a lesser extent in the mesocortical pathway, and thereby effectively minimize symptoms of psychosis (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). Because the parallel circuitry of the limbic and cortical systems extends throughout the nigrostriatal brain region, conventional antipsychotics also inactivate the dopaminergic neurons that control involuntary motor movements. Antagonism of D₂ receptors in the nigrostriatal system results in an elevated risk for adverse neurological effects, particularly acute extrapyramidal symptoms upon initiation of the drug and tardive dyskinesia upon the discontinuation of chronic drug treatment or, in more severe cases, while the agent is still being administered.

Extrapyramidal symptoms. Meaningful motor movements, reflexes, balance, and posture are all controlled via the contractions of voluntary and involuntary skeletal muscle (Baldessarini & Tazari, 2006). Two motor tracts in the brain control skeletal muscle, the pyramidal and the extrapyramidal systems. The pyramidal system produces voluntary actions whereas the extrapyramidal system controls involuntary movements.

Voluntary motor movements are initiated in the brain by the primary motor cortex whose neurons have long axons that tighten together as they travel down the spinal cord

(Baldessarini & Tazari, 2006). Motor commands travel down these v-shaped neural tracts, collectively known as the “pyramidal system”, until they synapse with the motor neurons that control skeletal muscle. The pyramidal system thus produces voluntary motor movements through direct innervation of the brain stem and spinal cord.

Neural feedback loops infiltrate the nigrostriatal pathway and basal ganglia to modulate the activity of the motor neurons in the pyramidal system (Baldessarini & Tazari, 2006). These neural feedback loops are housed outside the pyramidal tract and do not directly innervate the motor neurons of the brain stem and spinal cord.

Collectively referred to as the “extrapyramidal system”, these neural loops control involuntary motor movements, posture, and muscle tone. The extrapyramidal system serves as a necessary complement to the pyramidal system by inhibiting involuntary motor movements and thereby promoting the initiation of voluntary actions.

Dysfunction of the extrapyramidal system produces involuntary motor movements and suppresses the ability to initiate voluntary movements (Baldessarini & Tazari, 2006). Any set of conditions in which the quality or quantity of motor movements become abnormal due to dysfunction of this system are referred as extrapyramidal symptoms (EPS). Conventional antipsychotic drugs have prominent extrapyramidal effects due to antagonism of dopaminergic neurons in the nigrostriatal pathway, a major component of the basal ganglia’s complex motor loop (Baldessarini & Tazari; Miyamoto et al., 2005).

Common EPS include (a) akathisia, or restlessness, pacing, and insomnia; (a) dystonia, or repetitive muscular spasms that typically affect the eyes, neck jaw, and tongue; (b) bradykinesia, or decreased voluntary motor movements and abnormalities of

posture and muscle tone (c) akinesia, or an inability to initiate voluntarily movements; (d) drug-induced parkinsonism, or tremors, shuffling gait, muscle stiffness, and rigidity; and (e) tardive dyskinesia, or repetitive, nonrhythmic tics and slow writhing movements of the face, extremities, and trunk (Baldessarini & Tazari, 2006).

An estimated 50% to 75% of individuals treated with conventional antipsychotic drugs develop EPS, with figures exceeding 90% for some high-risk groups (Baldessarini & Tazari, 2006). EPS are recognized as the leading cause of medication noncompliance among persons treated with conventional agents (Linden, Scheel, & Eich, 2006).

Approximately 50% of schizophrenic outpatients and 40% of day hospital patients are thought to be noncompliant with their medication regimen due to EPS. Furthermore, EPS due to conventional antipsychotic drug treatment increases the likelihood for cognitive impairment and neuroleptic dysphoria (Baldessarini & Tazari; Tenback, van Harten, Slooff, van Os, & SOS Study Group, 2006). Anticholinergic drugs such as benztropine (Cogentin) and trixyphenidly (Artane) remain the standard treatments for EPS but carry the potential to further impair learning, cognition, and memory (Chew, Mulsant, & Pollock, 2005).

Tardive dyskinesia. As highlighted by Sadock and Sadock (2005), conventional antipsychotic drugs “have effects that can be distressing even to highly motivated patients, let alone those who are fearful and mistrustful. *An important consideration in drug selection must be the avoidance of the most uncomfortable or dangerous adverse reaction--tardive dyskinesia* [emphasis added]” (p. 242).

The term “tardive dyskinesia” (TD) was coined in 1964 to describe the tics and associated motor disturbances that patients are now recognized to be at high risk for

developing when chronically exposed to or withdrawn from conventional antipsychotic drugs (Baldessarini & Tazari, 2006). “Tardive” refers the delayed onset of the motor abnormalities that arise with chronic or maintenance drug treatment. The literature variably defines chronic drug exposure as 3 to 12 months of medication receipt, not an unusual time course given that antipsychotic agents are a primary treatment for disorders marked by delusions and hallucinations, grossly disorganized and agitated behaviors, and repeated aggressive and self-injurious acts. A potentially irreversible neurological disorder, TD often persists after--and actually can be exacerbated by--the discontinuation of conventional antipsychotic drug treatment.

TD is characterized by a variety of involuntary hyperkinetic movements, choreoathetoid movements, and speech difficulties (Baldessarini & Tazari, 2006). Hyperkinetic movements often affect the orofacial region and include quick, nonrhythmic ticks of tongue, jaw, brow, and facial muscles as well as repetitive lip smacking and oral chewing. Choreoathetoid movements are characterized by slow, writhing movements of the digits, hands, feet, limbs and abdomen and may resemble the squirming of a snake. Speech difficulties typically result from enlargement and protrusion of the tongue due to overdevelopment of the tongue muscles from involuntary motor movements. Severe TD affects the entire body and closely resembles Huntington’s chorea.

The etiology of TD is a neural phenomenon known as “upregulation” (Marchan & Dilda, 2006; Miyamoto et al., 2005). In response to prolonged blockade of dopaminergic receptors, postsynaptic neural membranes in the nigrostriatal region and throughout the basal ganglia develop a compensatory supersensitivity to dopamine by generating additional receptors that are highly responsive to this neurotransmitter. The dopamine-

mediated neural networks that serve motor control consequently have the potential to become easily overstimulated. Upregulation frequently results in TD when a conventional antipsychotic drug is titrated downward or withdrawn. Among chronically treated and high-risk groups, upregulation may become so pronounced that it overcompensate for the drug and causes TD while the agent is still being administered at a maintenance dose.

Approximately 30% of persons treated with conventional antipsychotic drugs develop TD (APA, 2002). Numerous factors are recognized to increase the risk for this adverse drug reaction. For example, within the morbid psychiatric population, the prevalence of neuroleptic-induced TD is approximately 5% for young adults but exceeds 50% for middle-aged and elderly adults (APA).

Factors that have been associated with an increased risk for the development of neuroleptic-induced TD include (a) higher doses of the conventional agent, (b) longer durations of drug treatment, (c) increasing age, (d) psychosis predominantly marked by negative symptoms, and (e) cognitive deficits manifested by learning disabilities and ID (Wszloa, Newell, & Sprague, 2001). A strong positive association has been noted between the degree of neuropsychological impairment and the severity and course of TD (Paulsen, Heaton, & Jeste, 1994; Wonodi, Hong, & Thaker, 2005). Individuals treated with conventional antipsychotic drugs are more likely to develop severe and unremitting TD if they evidence preexisting impairments in (a) attention and information processing, (b) learning and memory, (c) visuoperceptual skills, (d) verbal abstraction, and (e) global cognitive functioning (Paulsen et al.).

Understanding the role of conventional antipsychotic drugs as they relate to motor disturbances in persons with ID remains a complex issue. The prevalence of various neuromuscular disorders, including idiopathic or neuroleptic naïve dyskinesia, is significantly higher in the ID population than both the general public and morbid psychiatric groups (Paulsen et al., 1994; Wonodi et al., 2005). Exposure to conventional antipsychotic drugs dramatically raises the already heightened risk for extrapyramidal disturbances and dyskinesic disorders in persons with ID.

Approximately 75% of persons with ID develop withdrawal TD during the titration or shortly after the discontinuation of conventional antipsychotic drug treatment (Paulsen et al., 1994). Unremitting TD remains in at least 30% these individuals. Reliable identification of neuroleptic-induced movement disorders requires systematic monitoring of persons with ID because self-stimulatory behaviors, stereotypies, tics, muscular dystonias, and degenerative palsies can all mask the presence of TD from even the most observant clinician. As noted by Shedlack et al., (2005), “[t]he presence of any movement disorder or mannerism in these patients makes diagnosis, observation over time, and treatment of the motor condition a puzzle” (p. 57).

Atypical Antipsychotic Drugs

A brief history. In an effort to broaden the therapeutic efficacy and reduce the side effect profile of conventional antipsychotic drugs, the development of new medications began being pursued in the 1980s (Baldessarini & Tazari, 2006). The discovery that specific receptor subtypes are preferentially concentrated in the different brain pathways, and thereby can be selectively or even partially inhibited, allowed for the development of drugs with high antipsychotic efficacy and minimal

liability for extrapyramidal effects. These agents are commonly referred to as the second-generation or atypical antipsychotic drugs, so named due to their substantially reduced risk for adverse neurological effects. Clozapine, also known by the trade name Clozaril, was the first atypical antipsychotic introduced to the U.S. market. The advent of clozapine in 1990 marked the most significant advance in the psychopharmacology of antipsychotic drugs since the introduction of chlorpromazine 46 years earlier.

Clozapine remains the only drug to receive FDA approval for treatment-resistant schizophrenia and reducing the risk of suicidal behaviors in persons with psychotic disorders (Hennen & Baldessarini, 2004). If not for the side effect of agranulocytosis, an acute and potentially lethal suppression of bone marrow for which the FDA restricts clozapine to third-line use and mandates regular blood analyses, this drug would certainly be considered first line of treatment. Nonetheless, clozapine has served as the model for the development of all other atypical antipsychotic drugs.

Since the marketing of clozapine in 1990, five atypical antipsychotic drugs have received approval by the FDA for use in the United States: (a) risperidone (Risperdal) in 1993, (b) olanzapine (Zyprexa) in 1996, (c) quetiapine (Seroquel) in 1997, (d) ziprasidone (Geodon) in 2001, and (e) aripiprazole (Abilify) in 2002 (Baldessarini & Tazari, 2006). All five agents are approved as first lines of treatment for schizophrenia and acute mania associated with bipolar disorder (AstraZeneca Pharmaceuticals, 2007; Bristol-Myers Squibb, 2007; Eli Lilly, 2007; Janssen Pharmaceutica, 2007; Pfizer, 2007). Several atypical drugs also carry approved indications for (a) depressive and mixed episodes of bipolar disorder, (b) prophylaxis of bipolar disorder, (c) major depressive disorder, and (d) irritability associated with autism. Atypical antipsychotic drugs are also

frequently prescribed for several off-label indications that have received support through clinical research, including (a) acute psychosis associated with alcohol intoxication and psychostimulant use; (b) degenerative psychosis associated with Parkinson's disease; (c) tic disorders; (d) trichotillomania; (e) behavioral disturbances associated with personality disorders; and (f) behavioral disorders associated with ID and PDDs (Baldessarini & Tazari, 2006).

Improved clinical outcomes and reduced liability for neurological side effects. Atypical antipsychotic drugs hold several distinct advantages over their conventional predecessors. Placebo-controlled trials, comparative research, and meta-analytic reviews indicate that the atypical antipsychotics have equivalent or improved efficacy and effectiveness in the treatment of positive psychotic symptoms among the morbid psychiatric population (Davis, Chen, & Glick, 2003; Meltzer, Arvanitis, Bauer, & Rein, 2004; Meyer, 2007; Turner & Stewart, 2006; Vohora, 2007; Wang, Savafe, Borisove, Rosenberg, Woolvine, Tucker, et al., 2006) and persons with comorbid ID and PDDs (Aman & Garabawai, 2004; Aman & Madrid, 1999; Hammock et al., 2001; Shedlack et al., 2005). Atypical antipsychotic drugs also are more effective in treating negative psychotic symptoms and cognitive dysfunction and may thereby reduce social withdrawal (Hori, Noguchi, Hashimoto, Nakabayashi, Omori, Takahashi, et al., 2006; Shedlack et al.). Such effects may be particularly significant for the treatment of persons with ID. As noted by Shedlack et al., "social withdrawal is often a constitutional feature of mental retardation and can easily go unrecognized as a treatable complex of negative symptoms. Isolation and introversion may be mistaken for meekness or lacking sophistication rather than preoccupation due to psychosis" (p. 61).

Atypical antipsychotics show markedly improved effectiveness over conventional agents in the treatment of behavioral disorders among persons with ID (Aman & Gharabawi, 2004; Aman & Madrid, 1999; Deb et al., 2007). These drugs more effectively reduce stereotypies, compulsions, SIB, and physical aggression. Furthermore, the atypical antipsychotics demonstrate success with otherwise refractory cases among morbid psychiatric patients (Davis et al., 2003; Dunner, 2005; Meltzer, 2004) and persons with psychiatric or behaviors disorders and comorbid ID, particularly those diagnosed with autism (Aman & Gharabawi; Aman & Madrid; Deb et al.; Hammock et al., 2001; Horrigan & Barnhill, 2001).

The atypical antipsychotic drugs evidence a significantly reduced liability for EPS and TD among the morbid psychiatric population and high risk groups, most notably geriatric adults and persons with ID (Advokat, Mayville, & Matson, 2000; Dunner, 2005; Harpreet & Mendhekar, 2006; Leucht et al., 1999; Meltzer, 2004; Nasrallah, 2006; Tarsy & Baldessarini, 2006). The reduced anticholinergic properties of these drugs also make them less likely to suppress cognition, learning, and adaptive behaviors than the conventional antipsychotic agents (Hori et al., 2006; Shedlack et al., 2005). As a result of their broader therapeutic efficacy and more favorable side-effect profile, medication compliance is approximately 30% higher with the atypical agents than their conventional predecessors (Linden et al., 2006).

Pharmacokinetics and pharmacodynamics. Atypical antipsychotic drugs are able to achieve therapeutic integrity while minimizing many of the adverse effects associated with the conventional antipsychotics by binding more selectively at specific brain regions (Baldessarini & Tazari, 2006). Although the precise mechanisms of action

for this class of drugs remain uncertain and are believed to differ somewhat from agent to agent, the therapeutic efficacy of the atypical antipsychotics is known to derive from more specific modulation of dopamine. All atypical antipsychotics display a reduced affinity for D₂ receptors in the nigrostriatal pathway and basal ganglia and therefore are not significantly associated with extrapyramidal effects (Baldessarini & Tazari; Miyamoto et al., 2005). Nonetheless, these drugs achieve potent antidopaminergic activity in select brain regions though their strong affinity to antagonize one or more serotonin or 5-hydroxytryptamine (5-HT) receptor subtypes--particularly 5-HT_{1A}, 2A, 2C, 3, and 6--as well as the norepinephrine receptor subtypes α_1 and α_2 (Baldessarini & Tazari; Meltzer & Huang, 2008; Miyamoto et al.; Richtand, Welge, Logue, Keck, Strakowski, & McNamara, 2008; Stone, Davis, Leucht, & Pilowsky, 2008).

Antagonism of 5-HT produces regional antagonism of D₂ receptors in the mesolimbic and mesocortical regions of the brain but minimally impacts D₂ receptors in the nigrostriatal region (Baldessarini & Tazari, 2006; Meltzer & Huang, 2008; Miyamoto et al., 2005; Richtand et al., 2008; Stone et al., 2008). Consequently, atypical antipsychotic drugs preferentially impact the D₂ receptors responsible for positive and negative psychotic symptoms over those that control involuntary motor movements, thereby mitigating the probability and severity of EPS and TD. Furthermore, the additional effects on 5-HT receptors, possibly in concert with antagonism of the α_2 -adrenergic receptors located on these neurons, are believed to contribute to the amelioration of negative psychotic symptoms and associated cognitive dysfunction.

Although all atypical antipsychotics selectively impact D₂ receptors in the mesolimbic and mesocortical pathways via antagonism of 5-HT, their affinity for any

particular 5-HT receptor subtype differs by agent (Baldessarini & Tazari, 2006; Miyamoto et al., 2005; Richtand et al., 2008). As a result, each atypical antipsychotic displays relatively unique pharmacologic characteristics in relation to (a) gender (Aichhorn, Gasser, Weiss, Adlassnig, & Marksteiner, 2005; McEvoy, Meyer, Goff, Nasrallah, Davis, Sullivan, et al., 2005); (b) gene expression (Bakker, van Harten, & van Os, 2006; Hill & Reynolds, 2007); (c) mode of action (Meltzer & Huang, 2008; Miyamoto et al.; Richtand et al.; Stone et al., 2008); (d) efficacy (Davis et al., 2003; Meltzer, 2004; Meltzer et al., 2004; Meltzer & Huang; Richtand et al.; Stone et al.); and (e) side effect profile (de Leon & Diaz, 2007; Meltzer; Meltzer et al.; Meltzer & Huang; Meyer, Davis, Goff, McEvoy, Nasrallah, Davis, et al., 2008; Stone et al.; Wilson, D'Souza, Sarkar, Newton, & Hammond, 2003). The atypical antipsychotics are more or less associated with various adverse drug reactions that may include sexual side effects, hypotension, electrocardiographic changes, weight gain, hyperlipidemia, diabetes mellitus (DM) type II, and diabetic ketoacidosis (Baldessarini & Tazari). Weight gain and the associated potential for DM type II with atypical antipsychotic drug treatment has generated the most concern, although the research to date suggests the liability for these side effects substantially differs by agent (de Leon & Diaz; Meltzer et al.; Meyer et al.; Wilson et al.).

The Obesity Epidemic and Associated Health Consequences

The last several decades have witnessed epidemic increases in overweight and obesity among the general population (Baskin, Ard, Franklin, & Allison, 2005; Centers for Disease Control & Prevention [CDC], 2008; Parikh, Pencina, Wang, Lanier, Fox, D'Agostino, et al., 2007). Overweight and obesity, respectively defined as body mass

index (BMI) scores equal to or greater than 25 kg/m² and 30 kg/m², are currently considered the most rapidly increasing and difficult to treat medical conditions worldwide (Caballero, 2007; Potter, 2006; Prentice, 2006; Yach, Stuckler, & Brownell, 2006). As noted by Prentice,

[t]he obesity pandemic originated in the US and crossed to Europe and the world's other rich nations before, remarkably, it penetrated even the world's poorest countries especially in their urban areas [where] projected numbers of new cases of diabetes run into the hundreds of millions within the next 2 decades. (p. 93)

The World Health Organization has used BMI as the standard for recording obesity statistics since the early 1980's (National Institutes of Health, 1998). In 1998, the National Institutes of Health aligned the U.S. definitions of overweight and obesity to correspond with best practice guidelines of the World Health Organization. As a result, approximately 30 million Americans previously considered normal weight came to be defined as clinically overweight or obese. By the year 2000, approximately 35% of men and 33% of women were considered overweight in the United States (Parikh, 2007); an additional 20% of men and 18% of women met criteria for obesity. From 2000 to 2004, trends for overweight remained stable for American adults (Parikh; Ogden, 2006). Obesity, however, increased by 11% for men and 15% for women to total 31% and 33% of the population, respectively (Ogden). Over the past decade, this steady rise in weight has earned the United States first place for obesity statistics among the developed world.

A causal relationship between weight gain and psychological or physical dysfunction is difficult to establish as other factors such as sedentary lifestyle may play a

role in etiology. Nonetheless, an overwhelming amount of research confidently attributes overweight and obesity to a variety of adverse consequences. Individuals who are overweight or obese, for example, have heightened perceptions of discrimination and indeed are more susceptible to social stigmatization than persons who are normal weight (Ashmore, Friedman, Reichmann, & Musante, 2008; Carr & Friedman, 2005). Many of these individuals score significantly lower on measures of self-esteem, psychological well-being, and psychosocial adjustment (Blaine, Rodman, & Newman, 2007; Carr & Friedman; De Hert, Peuskens, Van Winkel, Kalnicka, Hanssens, Van Eyck, et al., 2006; Provencher, Polivy, Wintre, Pratt, Pancer, Birnie-Lefcovitch, et al., 2008). Increased rates of negative affect, depression, anxiety, and binge eating are also noted among persons who are overweight or clinically obese (Ashmore et al.; Carr, Friedman, & Jaffe, 2007; Provencher et al.).

Overweight and obesity also are strongly associated with compromised functioning across multiple body systems including the endocrine, genitourinary, gastrointestinal, musculoskeletal, renal, pulmonary, cardiovascular, and neurological systems (Akinnusi, Pineda, & El Solh, 2008; Bray & Bellanger, 2006; Popkin Kim, Rusev, Du, & Zizza, 2006). In order of direct cost of treatment, overweight and obesity are most strongly associated with the following medical conditions: (a) DM type II; (b) coronary artery disease; (c) osteoarthritis; (d) hypertension; (e) gallbladder disease; and (f) cancer of the colon, breast, endometrium, and prostate (Popkin et al.).

Overweight and obesity are also established risk factors for numerous other medical conditions including hypoventilation, sleep apnea, asthma, gallstones, thromboembolism, atherosclerosis, impaired glucose tolerance, hypertriglyceridemia, hypercholesterolemia,

cardiovascular disease, and stroke (Akinnusi et al.; Bray & Bellanger; Popkin et al.). Furthermore, overweight and obesity are linked to increased mortality from various disease states, with estimates ranging from 20% to 40% for middle-aged adults and 20% to 55% for geriatric adults (Adams, Schatzkin, Harris, Kipnis, Mouw, Ballard-Barbash, et al., 2006; Greenberg, Fontaine, & Allison, 2007; Janssen & Bacon, 2008). Mortality rates may be higher for particular diseases, such as with cardiovascular mortality which increases by approximately 50% for middle-aged adults who are clinically obese (Adams et al.).

Obesity is a well-established risk factor for “metabolic syndrome” or the development of a constellation of diseases that include (a) hypertension or elevated blood pressure, (b) dyslipidemia or high triglycerides and low high-density lipoprotein cholesterol; and (c) impaired fasting glucose (Bray & Bellanger, 2006; Despres, 2006; Lois, Young, & Kumar, 2008). These metabolic disturbances often cluster together and heavily predispose individuals for atherosclerosis, cardiovascular disease, and DM type II. Obesity is additionally recognized to be an independent causative factor for the development of DM type II, the more common form of diabetes that accounts for 95% of all cases in the United States (Bindler, 2007; Gagliari & Wittert, 2007). As summarized by Bindler, “[i]nsulin resistance and metabolic syndrome are direct outcomes of increasing obesity rates, which, in turn, lead to the emergence of type II diabetes” (p. 29).

Obesity is believed to directly contribute to DM type II because adipose or fatty tissue is the primary source of the hormones and cytokines that serve as chemical signals to increase insulin resistance (Aguilera, Gil-Campos, & Gil, 2008; Mobbs, Isoda, Makimura, Mastaitis, Mizumo, Shu, et al., 2005). Individuals who are over 20% their

ideal body weight are at heightened risk of DM type II (CDC, 2005). As of 2002, slightly more than 30% of American adults were diagnosed with DM type II. Over 85% of these individuals weighed significantly more than their recommended weight range.

Approximately 30% met clinical criteria for overweight, and an additional 56% crossed the threshold for obesity (CDC, 2005). Consequently, researchers such as Gagliari and Wittert (2007) have emphasized “management of obesity as *the primary strategy* [italics added] for management of disorders of glucose metabolism” (p. 95)

Overweight and Obesity in Persons with Schizophrenia

An estimated 2.4 million Americans suffer from schizophrenia (Wu, Shi, Birnbaum, Hudson, Kressler, 2006). For nearly a decade, these individuals have been recognized to be at significantly greater risk for overweight and obesity than the general population (Allison, Fontaine, Heo, Mentore, Cappelleri, Changer, et al., 1999; Leas & McCabe, 2007; McEvoy et al., 2005). Indeed, recent estimates suggest that 60% to 63% of adults with schizophrenia meet criteria for obesity (Barnett, Mackin, Chaudhry, Farooqi, Gadsby, Heald, et al., 2007; Kolotkin, Corey-Lisle, Crosby, Swanson, Tuomari, L’italien, et al., 2008).

Overweight and obesity among persons with schizophrenia have been linked to diminished outcomes in several key areas: (a) medication compliance (Perkins, 2002); (b) clinical outcomes (Kurzthaler & Fleischhacker, 2001); (c) self-esteem (De Hert, Peuskens, et al., 2006); (d) quality of life (Kolotkin, Corey-Lisle, et al., 2008; Kolotkin, Crosby, Corey-Lisle, Li, & Swanson, 2006); (e) physical health (Barnett et al., 2007; Kolotkin, Corey-Lisle, et al.; Leas & McCabe, 2007; Miller, Paschall, & Svendsen, 2006); and (f) mortality (Barnett et al.; Miller et al.). Obesity-related medical conditions

such as heart disease and DM type II largely account for the increased mortality rate of persons with schizophrenia which averages 30 years earlier than the general population (Miller et al.). For instance, the increased prevalence of overweight and obesity among persons with schizophrenia increases cardiovascular mortality by 300% over that of the general population.

Various explanations have been proposed to account for the increased prevalence of overweight and obesity among persons with schizophrenia. Low physical activity, inappropriate and excessive food intake, socioeconomic status, antipsychotic drug treatment, and the psychiatric disorder itself have all been discussed as possible contributing factors (Jean-Baptiste, Tek, Liskov, Chakunta, Nicholls, Hassan, et al., 2007; Khazaal, Fresard, Zimmerman, Trombert, Pomini, Grasset, et al., 2006; Leas & McCabe, 2007; Strassnig, Brar, & Ganguli, 2005; Strassnig, Miewald, Keshavan, & Ganguli, 2007; Weber, 2008). In late 2003, the FDA revised the product label requirements for atypical antipsychotic drugs due to media reports and the public's increasing concerns that weight gain may be a class effect of treatment with this class of medication (Burton, 2003; Goode, 2003; Rosack, 2003). Shortly afterward, statements regarding the increased liability for weight gain and DM type II began to be included in the package inserts of all atypical antipsychotics (AstraZeneca, 2008; Bristol-Myers Squibb, 2008; Eli Lilly, 2008; Janssen, 2008; Novartis, 2008; Pfizer, 2008).

The rising concern of weight gain with atypical antipsychotic drug treatment.

The FDA Modernization Act of 1997 streamlined the process for drug approval to three phases which are completed in 10 to 12 months (Oates, 2006). As Oates has detailed, this expedited approval process “can only detect the most profound and overt risks that occur

almost immediately after a drug is given” (p. 133). Although risk assessment is one component of phase three drug trials, the revamped FDA approval process is nonetheless primarily suited to answering questions about drug efficacy. Phase three trials are generally limited to 2,000 to 3,000 carefully selected participants, with only a few hundred receiving drug treatment for more than 3 months, regardless of the anticipated duration of clinical treatment. Consequently, many unanticipated therapeutic and adverse effects are not detected until a drug had come into broad use on the market. As Oates has cautioned:

Because of limitations in the capacity of the premarketing phase of drug development to define delayed or uncommon but significant risks of new drugs, postmarketing surveillance of drug usage is imperative to detect such adverse effects. Some patients, because of unique genetic or environmental factors, are at an extremely high risk, whereas the remainder of the population may be at low or no risk. (p. 133)

In late 2004, concerns about the growing body of postmarket research linking atypical antipsychotic drugs to weight gain and DM type II prompted the American Psychiatric Association, American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and North American Association for the Study of Obesity (NAASO) to convene a consensus development conference to further investigate this issue. This panel concluded that the liability for weight gain varies considerably across atypical antipsychotic drugs and ranges from minimal to significant (APA, ADA, AACE, & NAASO, 2004). Clozapine and olanzapine were judged to have the greatest effects on weight. Risperidone and quetiapine were believed to have intermediate effects,

although the amount of weight gain with these agents was still often significant.

Comparative data for ziprasidone was limited but suggested that this drug has little to no effect on weight. Sufficient data was not available on aripiprazole to make any initial determination of its liability for weight gain. Although studies on aripiprazole remain minimal at this time, limited research suggests that weight gain with this drug is also negligible (De Hert, Hanssens, van Winkel, Wampers, van Eyck, Scheen, et al., 2007; Kim, Ivanova, Abbasi, Lamendola, Reaven, & Glick, 2007).

Weight gain with atypical antipsychotic drug treatment implicated in metabolic syndrome. Atypical antipsychotics continue to be associated with adverse drug reactions unrelated to the neuromuscular system and not typically seen with the conventional agents. Research has increasingly linked atypical antipsychotic drug treatment to the triad of metabolic disturbances collectively known as metabolic syndrome: (a) weight gain and obesity, (b) hyperlipidemia, and (c) glucose dysregulation and DM type II (Baldessarini & Tazari, 2006; Barnes, Paton, Cavanagh, Hancock, & Taylor, 2007; De Hert, Schreurs, Van Eyck, Hanssens, Wampers, Scheen, et al., 2008; de Leon & Diaz, 2007; McKee, Bodfish, Mahorney, Heath, & Ball, 2005; Meltzer, 2004). Indeed, the risk for metabolic syndrome with atypical antipsychotic drug treatment is of such potential significance that it has been called “the tardive dyskinesia” of the second-generation agents (McKee et al., p. 1164). Among the triad of metabolic disturbances associated with the atypical antipsychotics, weight gain represents a particular concern because it is an established causative factor in the dysregulation of both lipid and glucose levels (International Diabetes Federation, 2005).

Although controlled clinical studies remain limited at this time, numerous case reports, retrospective investigations, and epidemiological studies indicate that the risk for weight gain and associated metabolic disturbances is greater with some atypical antipsychotic drugs than others. Moderate to severe metabolic reactions are most frequently implicated with the dibenzodiazepine-derived compounds which include clozapine, olanzapine, and risperidone (Baldessarini & Tazari, 2006; De Hert et al., 2008; McKee et al., 2005; Meltzer, 2004). The majority of research conducted to date focuses on weight gain with olanzapine and risperidone because these two agents are FDA approved as first lines of treatment for schizophrenia and bipolar mania and both demonstrate a strong potential to produce a domino effect of metabolic dysregulation.

Pharmacokinetics and pharmacodynamics. Although the pathophysiology remains obscure, weight gain with atypical antipsychotic drug treatment is believed to be related to changes in histaminergic and monoamine signaling. The atypical antipsychotics most strongly associated with weight gain demonstrate a strong affinity for histamine H₁ and serotonin 5-HT_{2C} receptors and a moderate affinity for adrenergic α_{1A} and α_2 receptors (Baldessarini & Tazari, 2006; De Luca, Mueller, de Bartolmeis, & Kennedy, 2007; Matsui-Sakata, Obtani, & Sawada, 2005; Reynolds, Hill, & Kirk, 2006). Clozapine and olanzapine, which have a high risk for weight gain, show a strong affinity for H₁ and 5-HT_{2C} receptors which affect hunger, satiety, and adipocyte function (Baldessarini & Tazari; Matsui-Sakata et al.). Aripiprazole and ziprasidone, which have a low risk for weight gain, demonstrate minimal affinity for these receptors.

Weight gain due to atypical antipsychotic treatment is believed to be directly responsible for the increased risk of hyperlipidemia among patients receiving these drugs

(Meyer, 2001a; Meyer, 2001b). Hyperlipidemia is a primary culprit for peripheral vascular disease, atherosclerosis, coronary artery disease, and ischemic cerebrovascular disease (Mahley & Bersot, 2006). These conditions account for the majority of morbidity and mortality among middle-aged and older adults. Drug-induced hyperlipidemia and consequent medical diseases represent a particular concern for persons with ID because this population already evidences a significantly higher cardiovascular risk than the general population (Beange, McElduff, & Baker, 1999).

Although most literature on the risk for DM type II with atypical antipsychotic drug treatment involves case reports or open label studies with small sample sizes (for an overview, see de Leon & Diaz, 2007; Miller, Leslie, & Rosenheck, 2005), limited research using larger sample sizes has been published (Basu & Meltzer, 2006; Miller et al.). Preliminary results implicate that both weight gain and elevated serum prolactin occurring with atypical antipsychotic drug treatment increase the risk for glucose dysregulation and new-onset DM type II (de Leon & Diaz; Miller et al.). This increased risk for DM type II translates into additional direct medical costs exceeding \$800 million annually within the US (Basu & Meltzer). Furthermore, diabetes is associated with impairments in processing speed and visual-spatial ability, and the comorbid occurrence of DM type II with mental illness has been related to additional declines in these brain functions as well as to significant deterioration in general cognitive and community functioning (Dickinson, Gold, Dickerson, Medoff, & Dixon, 2008).

New-onset DM type II is generally asymptomatic, and one half of all cases are estimated to remain undiagnosed (Barnes et al., 2007). Consequently, the risk for this disease with atypical antipsychotic drug treatment is likely underappreciated. In an effort

to promote early detection and intervention, diabetes screening programs are being increasingly emphasized as an essential component of treatment monitoring for those receiving atypical antipsychotic drugs (Basu & Meltzer, 2006).

A Closer Look at the Atypical Antipsychotics: Approved Uses, Mechanisms of Action, and Liability for Weight Gain

Clozapine. The first atypical antipsychotic drug to be developed, clozapine, is currently approved by the FDA for treatment-resistant schizophrenia and reducing the risk of recurrent suicidal behavior in schizophrenia and schizoaffective disorder (Hennen & Baldessarini, 2004; Novartis, 2008). Clozapine's profile of binding to dopaminergic and serotonergic receptors classifies it as an atypical antipsychotic (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). Clozapine differs from the conventional agents in that it shows a strong affinity for D₄ and 5HT_{1A} receptors and is preferentially more active in the mesolimbic than the nigrostriatal pathway. Consequently, this drug is highly effective in treating both the positive and negative symptoms of schizophrenia while evidencing a negligible risk for EPS and TD. Clozapine is also a strong antagonist at adrenergic, cholinergic, and histaminergic receptors, with the last two predominantly accounting for its side effect profile.

Clozapine is the most efficacious drug for schizophrenia but is restricted to third line of treatment due to the risk for several potentially fatal side effects:

(a) agranulocytosis, or acute suppression of white blood cells; (b) myocarditis, or acute inflammation of the heart muscle; and (c) cardiomyopathy, or chronic deterioration of the heart muscle (Novartis, 2008). Because of such risks, the FDA requires clozapine to carry five black box warnings, and patients prescribed this drug are required to undergo weekly

blood monitoring through what is commonly known as a “No Blood, No Drug” policy (Baldessarini & Tazari, p. 495; Novartis). In addition to the risk for agranulocytosis and cardiac toxicity, clozapine is also frequently associated with weight gain, hyperglycemia, and new-onset DM type II (Novartis).

Weight gain is a common side effect of clozapine treatment, occurring in more than 30% of persons who received this drug for at least 6 weeks in open-label studies and randomized, placebo-controlled clinical trials (Covell, Weissman, & Essock, 2004; Novartis, 2008). Clozapine also is associated with the greatest weight gain relative to other atypical antipsychotics (ADA et al., 2004; Allison & Casey, 2001). Meta-analysis of 81 studies which utilized 30,000 measures of weight among psychiatric patients without comorbid ID who were treated with atypical antipsychotic drugs identified a mean weight increase of 9.18 lb (4.16 kg) after 10 weeks of clozapine treatment (Allison & Casey). Weight gain has been shown to drastically increase by 6 months of clozapine treatment, with a mean increase of 16.50 lb (7.48 kg) noted in one retrospective analysis (Wirshing, Wirshing, Kysar, Berisford, Goldstein, Pashdag, et al., 1999). Weight gain is believed to contribute to the increased risk of new-onset DM type II among patients receiving clozapine (ADA et al.; Novartis), for which incidence rates range from 12.8% to 43% per recent epidemiological research (Cohen, Stolk, Grobbee, & Gispen-de Wied, 2006; Henderson, Nguyen, Copeland, Hayden, Borba, Louie, et al., 2005; Lamberti, Costea, Olson, Frilly, Maharaj, Tu, et al., 2005).

Olanzapine. Olanzapine is the most frequently prescribed atypical antipsychotic, with an estimated 20 million people receiving treatment worldwide and \$4.2 billion generated annually in drug sales (Berenson, 2007). Olanzapine is currently approved by

the FDA for (a) schizophrenia, (b) acute manic episodes, (c) depressive episodes associated with bipolar disorder, and (d) maintenance treatment of bipolar disorder (Eli Lilly, 2008). Common off-label uses include the treatment of Tourette syndrome and anorexia nervosa and adjunctive treatment of major depressive disorder without psychotic features (Baldessarini & Tazari, 2006). Case reports and open-label study also suggest that olanzapine may be an effective augmentative treatment for refractory generalized anxiety disorder and panic disorders (Hollifield, Thompson, Ruiz, Uhlenhuth, 2005; Pollack, Simon, Salta, Worthington, Hoge, Mick, et al., 2006).

Olanzapine is classified as an atypical antipsychotic due to its high affinity for several 5-HT receptor subtypes which, in concert with regional antagonism of D₂ receptors, accounts for the therapeutic effects of this drug (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). Antagonism of 5-HT_{2C} receptors and H₁ receptors are implicated in olanzapine's frequent and severe liability for weight gain; these receptors are thought to affect hunger and satiety as well as promote fat deposition through direct effects on adipocyte function.

Weight gain is a common side effect of olanzapine treatment, occurring in over 75% of persons who received this drug for 4 to 6 weeks in open-label studies and randomized, placebo-controlled clinical trials (Bobes, Rejas, Garcia-Garcia, Rico-Villadernoros, Garcia-Portilla, Fernandez, et al., 2003; Eli Lilly, 2008).

The magnitude of weight gain with olanzapine is only slightly less than clozapine and the most severe among the atypical antipsychotic drugs approved as first lines of treatment (ADA et al., 2004; Allison & Casey, 2001). Meta-analysis of over 80 studies on weight gain among psychiatric patients treated with atypical antipsychotic drugs identified a

mean increase of 9.15 lb (4.15 kg) after 10 weeks of olanzapine treatment, second to clozapine by a mere 0.03 lb (0.01 kg) (Allison & Casey). Randomized, prospective research investigating longer periods of time found that mean weight gain with olanzapine was 18.51 lb (8.4 kg) after 3 months and 24.02 lb (10.9 kg) after 1 year (Perez-Iglesias, Crespo-Facorro, Martinez-Garcia, Ramirez-Bonilla, Alvarez-Jimenez, Pelayo-Teran, et al., 2008). Weight gain was higher in other prospective research, with a mean increase of 37.10 lb (16.91 kg) identified after 1 year of olanzapine treatment (Strassnig et al., 2007).

The FDA defines clinically significant weight gain as a greater than 7% increase in baseline body weight (Sachs & Guille, 1999), a diagnostic criterion embraced by most current research. Medication package inserts routinely include information on the percent of persons who evidence clinically significant weight gain during placebo-controlled monotherapy drug trials. Results of 13 pooled clinical trials found that 26% of persons who received olanzapine for 6 to 8 weeks gained more than 7% of their baseline body weight, with 4% evidencing a 15% or greater increase in weight (Eli Lilly, 2008). After 6 months of olanzapine treatment, 56% of persons gained more than 7% of their baseline body weight; mean weight gain was 11.9 lb (5.4 kg) at that time. Of the 1,500 individuals who participated in clinical trials by Eli Lilly, (a) 55% gained between 1.0 to 11.9 lb (0.5 to 5.4 kg), (b) 26% gained between 12.0 to 22.9 lb (5.5 to 10.4 kg), (c) 12% gained between 23.0 to 33.9 lb (10.5 to 15.4 kg), and (d) 6% gained 34.0 lb (15.5 kg) or more. Results of recent prospective research found that, by 1 year of olanzapine treatment, 91% of persons gained more than 7% of their baseline body weight (Strassnig et al., 2007).

Weight gain is believed to contribute to the increased incidence of new-onset DM type II among psychiatric patients treated with olanzapine (ADA et al., 2004; Eli Lilly, 2008; Lambert, Cunningham, Miller, Dalack, & Hur, 2006). A recent study identified a significant acute decrease in insulin sensitivity among 14 healthy males who received olanzapine 10 mg/day for 10 days (Sacher, Mossaheb, Spindelegger, Klein, Geiss-Granadia, Sauermann, et al., 2008). Administration of higher dosages of olanzapine has been shown to cause acute hyperglycemia by increasing plasma glucose by 100% to 140% of basal values without significantly impacting insulin levels (Savory, Ashton, Miller, Nedza, Spracklin, Hawthorn, et al., 2008).

Pooled results from five placebo-controlled monotherapy drug trials extending 6 to 12 weeks found that fasting glucose levels rose to levels diagnostic of DM type II (<126 mg/dL) among 2.2% of persons who baseline values were normal (<100 mg/dL) and 17.4% of persons who baseline values were borderline (\geq 100 mg/dL and <126 mg/dL) (Eli Lilly). Recent epidemiological research identified a comparable 18.2% incidence for new-onset DM type II among psychiatric outpatients treated with olanzapine for 3 months (Cohen et al., 2006). Retrospective research of over 1,200 patients in the Department of Veterans Affairs (VA) system found that, after 3 months of olanzapine treatment, the incidence of new-onset DM type II was 29.9% (Leslie & Rosenheck, 2005).

Such results underscore the findings of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study conducted by the National Institute of Mental Health on olanzapine, risperidone, quetiapine, and ziprasidone (Lieberman, Stroup, McEvoy, Swartz, Rosenheck, Perkins, et al., 2005). The randomized, double-blind

CATIE trial, which cost an estimated \$42.6 million, extended 18 months and included 1,400 participants across 57 U.S. cities. Results indicated that olanzapine is superior among the first-line atypical antipsychotic drugs for the treatment of schizophrenia but that this increased efficacy is mitigated by severe metabolic effects. Mean weight gain was 2.0 lb (0.91 kg) per month across the course of drug treatment. Approximately 30% of persons treated with olanzapine gained 24 lb (10.89 kg) or more after 1 year of treatment, with this figure rising to 42 lbs (19.05 kg) or greater by 18 months. Several conclusions were reached regarding olanzapine.

Its apparent superior efficacy is indicated by the lower rate of discontinuation, greater reduction in psychopathology, longer duration of successful treatment, and lower rate of hospitalizations for an exacerbation of schizophrenia [benefits that must be weighted against the risk for] greater increases in weight and indexes of glucose and lipid metabolism. (Lieberman et al., p. 1223)

Shortly after the National Institute of Mental Health published the risks of olanzapine treatment that were identified in the CATIE study (Lieberman et al., 2005), public and legal controversy ensued. On December 17, 2006, a *New York Times* article reported that the newspaper had acquired internal documents and e-mail messages passed among top executives of Eli Lilly (Berenson). According to the *New York Times* article, these documents revealed a decade-long effort by Eli Lilly to minimize knowledge about the adverse risks of olanzapine, including obesity, hyperglycemia, and diabetes.

Within weeks, the *London Times* printed excerpts of these documents in which Eli Lilly identified the risk of drug-induced obesity as a "top threat to sales" since 1998 (Pagnamenta, 2007). Excerpts included an October 2000 report by senior Eli Lilly

research physician Robert Baker who allegedly wrote a top advisory board about being “quite impressed by the magnitude of weight gain on olanzapine and implications for glucose”. By January 4, 2007, Judge Weinstein of the U.S. District Court had issued a restraining order to suppress all further printing, posting, and dissemination of Eli Lilly documents via media, print, and internet (“Legal Battle”, 2007). By that time, Eli Lilly had agreed to pay \$1.2 billion to settle 28,000 lawsuits from litigants who claimed they had gained significant weight and developed new-onset DM type II while being treated with olanzapine (Berenson, 2007).

Risperidone. Risperidone is currently approved by the FDA for (a) schizophrenia; (b) mixed and manic states associated with bipolar disorder; and (c) irritability in children, adolescents, and adults with autistic disorder (Janssen, 2008). Off-label uses commonly include the treatment of (a) refractory depression without psychotic features, (b) anxiety disorders, (c) eating disorders, (d) Tourette syndrome, and (e) disruptive behavior disorders in children (Baldessarini & Tazari; 2006).

Risperidone is classified as an atypical antipsychotic due to its high affinity for several 5-HT receptor subtypes, including 5-HT_{1A}, 2A, and 2C, and regional antagonism of D₂ receptors (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). Antagonism of 5-HT_{2A} and D₂ receptors largely accounts for the therapeutic effects of risperidone, while antagonism of 5-HT_{2C} receptors is implicated in the liability for weight gain with this drug. Risperidone also has some potential to induce motor disturbances. However, this drug evidences a relatively low affinity for D₂ receptors in the nigrostriatal region at daily doses of 6 mg or less, the amount recommended by the FDA, which effectively limits the risk for EPS (Janssen, 2008).

Weight gain is a common side effect of risperidone treatment. Large sample, cross-sectional research found that approximately 53% of outpatients with schizophrenia who received this drug for 4 weeks evidenced some degree of weight gain (Bobes et al., 2003). The magnitude of weight gain with risperidone is considered intermediate among the atypical antipsychotics (ADA et al., 2004). Meta-analysis of over 80 studies about weight gain among psychiatric patients treated with atypical antipsychotic drugs identified a mean increase of 4.63 lb (2.10 kg) after 10 weeks of risperidone treatment (Allison & Casey, 2001). Randomized, prospective research investigating longer periods of time found that mean weight gain with risperidone was 13.00 lb (5.9 kg) after 3 months and 19.62 lb (8.9 kg) after 1 year (Perez-Iglesias et al., 2008). Results are comparable to the findings from another prospective study that identified a mean increase of 16.60 lb (7.53 kg) after 1 year of risperidone treatment (Strassnig et al., 2007).

Results of pooled, placebo-controlled clinical trials indicate that 18% of persons who received risperidone for 6 to 8 weeks gained more than 7% of their baseline body weight (Janssen, 2008). These figures are comparable to the percent of persons in the CATIE trials who evidenced clinically significant weight gain after 1 year of risperidone treatment; approximately 14% of the 300 participants receiving risperidone gained more than 7% of their baseline body weight after 1 year, with a mean increase of 14.4 lbs (6.53 kg) noted at that time (Lieberman et al., 2005). Recent prospective research found much higher weight gains, however, with a staggering 51% of individuals having gained more than 7% of their baseline body weight after 1 year of risperidone treatment (Strassnig et al., 2007).

Weight gain is believed to increase the risk for new-onset DM type II among persons who are treated with risperidone (ADA, 2004; Janssen; Lambert et al., 2006). Recent epidemiological research identified incidence rates of 11.6% for hyperglycemic events and 16.3% for new-onset DM type II among psychiatric outpatients treated with olanzapine for 3 months (Cohen et al., 2006). Retrospective research involving almost 1,000 patients from the VA system who were treated with risperidone for 3 months found a higher incidence rate of 23.3% for new-onset DM type II (Leslie & Rosenheck, 2005).

Quetiapine. Quetiapine is currently approved by the FDA for the treatment of (a) schizophrenia, (b) acute manic episodes associated with bipolar disorder, (c) depressive episodes associated with bipolar disorder, and (d) bipolar maintenance (AstraZeneca, 2008). Off-label uses commonly include the treatment of (a) refractory depression marked by insomnia, (b) post-traumatic stress disorder, (c) alcoholism, (d) obsessive-compulsive disorder, (e) Tourette syndrome, and (f) irritability associated with autism (Baldessarini & Tazari, 2006). Retrospective research also suggests quetiapine may be an effective treatment for opioid withdrawal by reducing somatic pain, cravings, anxiety, and insomnia (Pinkofsky, Hahn, Campbell, Rueda, Daley, & Douaihy, 2005).

Quetiapine is classified as an atypical antipsychotic due to its high affinity for 5-HT_{1A} and several 5-HT₂ receptor subtypes as well as regional antagonism of D₂ receptors (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). Quetiapine is recognized as the only antipsychotic drug with a placebo-level incidence for EPS (AstraZeneca, 2008; Kopala, Good, Milliken, Buiteman, Woodley, Rui, et al., 2006; Nasrallah, Brecher, & Paulsson, 2006; Timdahl, Carlsson, & Stening, 2007). The negligible risk for

neuromuscular disorders with this agent is attributable to both the reduced occupancy of and rapid disassociation from D₂ receptors in the nigrostriatal region of the brain (Baldessarini & Tazari; Miyamoto et al.). Quetiapine evidences a strong affinity for H₁ receptors, however, which is thought to account for the notable sedative effects of this drug. Furthermore, antagonism of H₁ and α_2 receptors is believed to impede satiety and contribute to an increased risk for weight gain with this agent.

Somnolence and sedation, rather than weight gain, are the most common side effects of quetiapine treatment (AstraZeneca, 2008; Timdahl et al., 2007) and likely account for recent reports of abuse of this drug (Pierre, Shnyder, Wirshing, & Wirshing, 2004; Pinta & Taylor, 2007; Waters & Joshi, 2007). Anecdotal accounts suggest that as many as 30% of inmates in correctional settings malingering psychotic symptoms to obtain and potentially sell quetiapine (Pierre et al.) which has become popularly known as “quell” (Pierre et al., p. 1718), “Susie Q” (Pinta & Taylor, p. 174), or “baby heroin” (Waters & Joshi, p. 173). Prisoners reportedly inhale or intravenously inject quetiapine for optimal anxiolytic and sedative effects. Several clinicians have called for research to examine the addiction potential of quetiapine, noting that they “have not seen similar drug-seeking behavior with other second-generation antipsychotics” (Pinta & Taylor, p. 174) which is “reminiscent of the era before the widespread use of atypical antipsychotic compounds, when a select group of patients would inappropriately seek . . . low-potency [conventional] antipsychotics” (Pierre et al., p. 1718).

Weight gain is a notable side effect of quetiapine treatment although the prevalence, magnitude, and course are less severe with this drug than clozapine, olanzapine, and risperidone (ADA et al., 2004). Randomized, double-blind research of

134 patients with psychosis who received quetiapine for 3 months found a mean weight increase of 8.12 lb (3.68 kg) (McEvoy, Lieberman, Perkins, Hamer, Hongbin, Lazarus, et al., 2007). The larger CATIE trial identified a mean weight gain of 6.0 lb (2.72 kg) after 1 year of quetiapine treatment, with this figure rising to just 6.3 lb (2.86 kg) at 18 months (Lieberman et al., 2005). Results of pooled, placebo-controlled clinical trials are similar, with a mean increase of 7.02 lb (3.18 kg) identified after 1 year of quetiapine treatment (Brecher, Leong, Stening, Osterling-Koskinen, & Jones, 2007). Longitudinal analysis of weight change indicated that the majority of weight gain, more than 60%, occurred during the first 12 weeks of drug treatment. No clear relationship was identified between drug dose and weight change, although the magnitude of weight gain was inversely related to baseline body mass index.

Results of pooled, placebo-controlled clinical trials indicate that 23% of schizophrenic outpatients who received quetiapine for 3 to 6 weeks gained more than 7% of their baseline body weight (AstraZeneca, 2008). Randomized, double-blind research found that 29% evidenced clinically significant weight gain after 3 months of quetiapine treatment (McEvoy et al., 2007). The CATIE trial furthermore found that 23% of persons gained more than 7% of their baseline body weight after 18 months of quetiapine treatment (Lieberman et al., 2005), again suggesting that weight typically stabilizes within the first few months of drug treatment.

Weight gain is believed to increase the risk for new-onset DM type II among persons treated with quetiapine (ADA, 2004; AstraZeneca, 2008; Lambert et al., 2006). In placebo-controlled monotherapy drug trials, fasting glucose levels rose to levels diagnostic of DM type II (<126 mg/dL) among 3.5% and 4.3% of persons treated with

quetiapine for 12 and 24 weeks, respectively (AstraZeneca). Results are similar to retrospective research that identified an incidence rate of 3.0% for new-onset DM type II among 120 patients in the VA system treated with quetiapine for 3 months (Leslie & Rosenheck, 2005). Longer-term, placebo-controlled drug trials found that fasting glucose levels <126 mg/dL occurred in 10.7% of persons treated with quetiapine for 30 weeks (AstraZeneca, 2008). Despite the risk for quetiapine to precipitate diabetes, published reports remains contradictory about whether or not this drug is associated with a significantly greater risk for new-onset DM type II relative to conventional antipsychotic drugs (Lambert et al.; Leslie & Rosenheck).

Ziprasidone. The brand name for ziprasidone, Geodon, has been suggested to denote the phrase “down to earth” in reference to the goal of this drug (Baldessarini & Tazari, 2006). Ziprasidone currently is approved by the FDA for the treatment of (a) schizophrenia, (b) manic and mixed states associated with bipolar disorder, and (c) acute agitation in persons with schizophrenia (Pfizer, 2008). Limited research also suggests that ziprasidone may be an effective treatment for aggressive behaviors in adolescents (Bastiaens, 2008) and behavioral and psychological symptoms of dementia (Rocha, Hara, Ramos, Kascher, Santos, de Oliveira Lanca, et al., 2006).

Ziprasidone is classified as an atypical antipsychotic due to its high affinity for 5-HT_{1D}, 2A, and 2C receptors and regional antagonism of D₂ receptors (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). This drug differs from other atypical antipsychotics in that it also agonizes some serotonin neurotransmitters, most notably 5-HT_{1A}, and it also inhibits norepinephrine reuptake with moderate potency (Miyamoto et al., 2005). Antagonism of 5-HT_{1D}, agonism of 5-HT_{1A}, and inhibition of norepinephrine reuptake are

believed to be responsible for the anxiolytic and antidepressant effects of ziprasidone. This drug also evidences a moderate affinity for H_1 and α_2 receptors, however, which may contribute to sedation and weight gain.

Somnolence is the most common side effect of ziprasidone treatment (Pfizer, 2008). The existing research on weight gain with ziprasidone remains limited, but it strongly suggests that this drug has a low risk relative to other atypical antipsychotics (APA et al., 2004; Pfizer). Results of four pooled, placebo-controlled clinical trials identified a median weight increase of 1.10 lb (0.5 kg) after 4 to 6 weeks of ziprasidone treatment (Pfizer). Meta-analysis of more than 80 studies on weight gain among psychiatric patients treated with atypical antipsychotics identified a mean gain of just 0.09 lb (0.04 kg) after 10 weeks of ziprasidone treatment (Allison & Casey, 2001).

The frequently cited CATIE trial identified a mean weight gain of 3.6 lb (1.63 kg) after 1 year of ziprasidone treatment, with this figure rising to 5.4 lbs (2.24 kg) at 18 months (Lieberman et al., 2005). It should be noted, however, that placebo-controlled clinical trials extending 52 weeks found that weight change with ziprasidone varied as a function of baseline BMI category (Pfizer, 2008). These long-term studies identified (a) a 2.87 lb (1.4 kg) mean weight gain among patients with low baseline BMI scores ($<23 \text{ kg/m}^2$), (b) no mean weight change among those with normal baseline BMI scores ($23\text{-}27 \text{ kg/m}^2$), and (c) a mean weight loss of 2.87 lb (1.3 kg) among patients with high baseline BMI scores ($>27 \text{ kg/m}^2$). A recent open-label investigation of weight change among 114 outpatients diagnosed with schizophrenia or schizoaffective disorder who were switched from olanzapine or risperidone to ziprasidone found significant, sustained improvements in weight across the course of 52 weeks (Weiden, Newcomer, Loebel, Yang, & Lebovitz,

2008). From baseline to endpoint, mean weight reductions were 21.60 lb (9.8 kg) and 15.21 lb (6.9 kg) for patients who were previously treated with olanzapine and risperidone, respectively.

Results of pooled, placebo-controlled clinical trials indicate that 6% percent of persons who received ziprasidone for 6 to 8 weeks gained more than 7% of their baseline body weight (Pfizer, 2008). The CATIE trial found that just 7% of persons gained more than 7% of their baseline body weight after 18 months of ziprasidone treatment (Lieberman et al., 2005) which suggests that weight may stabilize shortly after the initiation of this drug. Laboratory research on female rats treated with ziprasidone for 28 days indicated clinically significant weight gain on day 28 but failed to identify any significant change in eating behavior or intra-abdominal fat (Fell, Gibson, McDermott, Sisodia, Marshall, & Neill, 2005).

The low liability for significant weight gain with ziprasidone is believed to equate to a negligible risk for new-onset DM type II among persons receiving this drug (ADA et al., 2004). Although ziprasidone has been associated with new-onset DM type II in at least one case report (Sanchez-Barranco, 2005), a recent study failed to identify any significant change in insulin sensitivity among 15 healthy males who received this drug for 10 days (Sacher et al., 2008). Other research identified significant reductions in mean weight (-11.24 lb or -5.1 kg), BMI (-1.6 kg/m²), and serum glucose (-14.0 mg/dL) among 84 outpatients with schizophrenia or schizoaffective disorder who were switched to ziprasidone for 6 months due to evidencing weight gain, glucose intolerance, diabetes, or dyslipidemia with other atypical antipsychotic drugs (Montes, Rodriguez, Balbo, Sopolana, Martin, Soto, et al., 2007). Despite the current lack of research on incidence

rates for new-onset DM type II with ziprasidone treatment, Pfizer (2008) has noted “few reports of hyperglycemia or diabetes. . . . Although fewer patients have been treated with GEODON [ziprasidone], it is not known if this more limited experience is the sole reason for the paucity of such reports” (p. 12).

Aripiprazole. The sixth atypical antipsychotic drug to be developed, aripiprazole currently is approved by the FDA for the treatment of (a) schizophrenia in adults and adolescents aged 13 to 17 years; (b) acute manic and mixed states associated with bipolar disorder in adults and pediatric patients aged 10 to 17 years; (c) agitation associated with schizophrenia and bipolar mania in adults; and (d) major depressive disorder in adults, as an adjunct (Bristol-Meyers Squibb, 2008). Off-label use frequently includes the treatment of psychosis associated with abuse of 3,4-methylenedioxymethylamphetamine, more commonly known ecstasy (Baldessarini & Tazari, 2006). Limited research also suggests that aripiprazole may be effective in the treatment of (a) delirium (Straker, Shapiro, & Muskin, 2006); (b) bipolar depression (McElroy, Suppes, Frye, Altshuler, Stanford, Martens, et al., 2007; Dunn, Stann, Chriki, Filkowski, Ghaemi, 2008); (c) anxiety (Adson, Kushner, & Fahnhorst, 2005); and (d) aggressive behaviors (Bastiaens, 2008).

Aripiprazole is classified as an atypical antipsychotic due to its high affinity for 5-HT_{2A} receptors and regional antagonism of D₂ receptors (Baldessarini & Tazari, 2006; Miyamoto et al., 2005). Aripiprazole evidences a novel mechanism of action in that its antipsychotic effects are primarily mediated by functional or ligand-dependent selectivity for D₂ receptors in the mesolimbic and mesocortical brain regions rather than antagonism or partial agonism at these sites (Urban, Vargas, Zastrow, & Mailman, 2007).

Because aripiprazole is the only ligand-dependent antipsychotic agent approved by the FDA, it also is known as “the atypical atypical drug” (p. 72). Partial agonism at 5-HT_{1A} receptors is believed to be responsible for the anxiolytic and antidepressant effects of aripiprazole (Baldessarini & Tazari; Miyamoto et al.). This drug also evidences a moderate affinity for H₁ and α_A receptors which may contribute to sedation and weight gain.

Although research on weight gain with aripiprazole remains limited, this agent is generally regarded as having the most favorable side-effect profile of all atypical antipsychotic drugs (Baldessarini & Tazari, 2006). Placebo-controlled clinical trials investigating weight gain after 4 to 6 weeks of aripiprazole treatment identified a mean increase of (a) 1.32 lb (0.60 kg) among persons with mania (Bristol-Myers Squibb, 2008); (b) 1.54 lb (0.71 kg) among those with schizophrenia (Marder, McQuade, Stock, Kaplita, Marcus, Safferman, et al., 2003); and (c) 2.87 lb (1.30 kg) among those with major depression (Bristol-Myers Squibb). Small, open-label research identified a similar increase of 1.76 lb (0.80 kg) among 31 persons with acute bipolar depression treated with aripiprazole for 8 weeks (McElroy et al., 2007).

Placebo-controlled clinical trials investigating longer periods of time identified mean weight decreases across all BMI categories after 26 weeks of aripiprazole treatment; specifically, mean weight loss was (a) -1.10 lb (-0.5 kg) among persons with low baseline BMI scores (<23 kg/m²) (b) -2.87 lb (-1.3 kg) among those with normal baseline BMI scores (23-27 kg/m²), and (c) -4.63 lb (-2.1 kg) among those with high baseline BMI scores (>27 kg/m²) (Bristol-Myers Squibb, 2008). Clinical drug trials extending 52 weeks found mean weight increases of 5.73 lb (2.6 kg) among persons with

low baseline BMI scores and 3.09 lb (1.4 kg) among those with normal baseline BMI scores; a mean decrease of -2.65 lb (-1.2 kg) was noted among persons with high baseline BMI scores. Results of pooled, placebo-controlled clinical trials found that 4% of persons with depression and 5% of persons with schizophrenia who were treated with aripiprazole for 6 to 8 weeks gained more than 7% of their baseline body weight (Bristol-Myers Squibb). No individuals with acute bipolar mania who received drug treatment during short-term clinical trials evidenced clinically significant weight gain.

Little research has been conducted on the liability new-onset DM type II with aripiprazole treatment. However, aripiprazole is associated with a more favorable plasma lipid profile than olanzapine, potentially indicative of a lower metabolic risk with this drug (McQuade, Stock, Marcus, Jody, Gharbia, Vanveggel, et al., 2004). Furthermore, a recent open-label pilot study found that patients who evidenced side effects or an inadequate response with other atypical antipsychotics experienced significant reductions in fasting glucose and insulin resistance and no longer met criteria for new-onset DM type II after 3 months of aripiprazole treatment (De Hert et al., 2007). At this time, initial pharmaceutical investigations suggest more than 100 but less than 1,000 persons are diagnosed with DM type II after starting aripiprazole (Bristol-Myers Squibb, 2008).

Genetic Variation in Pharmacokinetics and Pharmacodynamics

Little is known about interindividual differences with adverse drug reactions, particularly with regard to genetic variation in pharmacokinetics and pharmacodynamics (Buxton, 2006). Pharmacokinetics involves the processes by which the body absorbs, distributes, metabolizes, and eliminates a drug. Conversely, pharmacodynamics relates to how a drug affects the biochemistry and physiology of the body. Gender and age are

known to impact pharmacokinetics and sometimes demonstrate interactive effects on pharmacodynamics (Buxton; Hilmer, McLachlan, & Le Couteur, 2007; Kaasinen, Kemppainen, Nagren, Helenius, Kurki, & Rinne, 2002; Schwartz, 2007). For instance, although the frequency of drug side effects is typically equivalent between genders, the severity is often greater among females (Buxton; Miller, 2001). Both the frequency and severity of side effects increase among geriatric adults, as does the likelihood for serious drug interactions (Buxton; Hilmer et al.; Schwartz, 2007). Furthermore, age-related changes in neurotransmitters occur at different rates by gender (Schwartz), including the organic loss of extrastriatal D₂ receptors (Kaasinen et al.).

As adults age, gradual changes in pharmacokinetics and pharmacodynamics increase the interindividual variability of drug dosages necessary to produce a given effect (Buxton, 2006; Hilmer et al., 2007; Schwartz, 2007). Geriatric adults have a reduced capacity to metabolize and eliminate many drugs. Such pharmacokinetic deterioration results from changes in body composition and decreased efficiency of the organs responsible for drug elimination. For instance, renal functioning among elderly individuals declines to approximately 50% of that for young adults (Hilmer et al.). Drug metabolism and hepatic blood flow also decline with age, although the variability in these changes is great.

The elimination half-lives of drugs frequently increase among geriatric adults due to larger volume distributions of lipid soluble drugs and reductions in renal and metabolic clearance (Buxton, 2006; Hilmer et al., 2007; Schwartz, 2007). As a result, elderly individuals typically require one half to one fourth the drug doses necessary to effectively treat young adults (Hilmer et al., 2007). However, even if drug dosages are appropriately

titrated to account for age-related pharmacokinetic changes, increased sensitivity to drugs may remain due to physiological changes and loss of homeostatic resilience.

Genetic factors such as gender and age have been hypothesized to impact clinical outcomes and side effects to antipsychotic drug treatment for some time (Murray, 2006; Nnadi & Malhotra, 2007; Reynolds, Templeman, & Zang, 2005; Usall, Suarez, Haro & SOHO Study Group, 2007). Some research suggests that females show greater clinical response and improvement in quality of life with antipsychotic drug treatment (Usall et al.) but also an increased susceptibility to weight gain, diabetes, and cardiovascular events (Seeman, 2008). Females also are believed to require lower maintenance doses of atypical antipsychotics, and doses may need to be titrated among aging women (Seeman, 2006). Both gender and age are recognized to impact the liability for weight gain among outpatient groups treated with olanzapine (Basson, Kinon, Taylor, Szymanski, Gilmore, & Tollefson, 2001; Bobes et al., 2003; Hormel, Casey, & Allison, 2002), and some research suggests that gender may also increase the risk for weight gain with risperidone (Bobes et al.; Hormel et al.).

Females and geriatric patients treated with olanzapine appear to be more likely to experience a variety of adverse drug reactions, including increased body weight, regardless of drug dose (Basson et al., 2001; Bobes et al., 2003; Hormel et al., 2002). Steady-state plasma concentrations of olanzapine differ by gender and age and may be one reason that females and elderly adults have a higher prevalence of side effects (Weiss, Marksteiner, Kemmler, Saria, & Aichhorn, 2006). Weight-corrected olanzapine plasma concentration/dose ratios average 33.5% higher in females than males,

irrespective of age. Furthermore, weight-corrected concentration/dose ratios increase an average of 9.4% per decade of life.

Research regarding whether or not gender impacts weight gain with risperidone remains contradictory. Several studies found that females are at increased risk for weight gain with risperidone (Bobes et al., 2003; Hormel et al., 2002), although other research indicates that gender does not significantly affect weight with this agent (Basson et al., 2002). Initial study of quetiapine suggests that neither gender nor age significantly impact weight change with this drug (Emsley et al., 2005). No research is yet available on the susceptibility for weight change by gender and age with aripiprazole and ziprasidone.

Although the prevalence of schizophrenia is approximately equal between the genders and higher among persons with ID, the majority of clinical trials on atypical antipsychotic drugs have been conducted with male participants without comorbid ID (Chaves & Seeman, 2006). Review of 67 randomized, controlled trials of atypical antipsychotic drug treatment among persons with psychotic disorders found the median percentage of women in the total sample was 33.3% with some trials including less than 7% (Chaves & Seeman). Chaves and Seeman (2008) noted that “sex differences in antipsychotic pharmacokinetics and pharmacodynamics that may result in differential effectiveness and susceptibility to adverse effects cannot be ascertained when the percentage of women in clinical trials is as low as it is” (p. 19). Furthermore, only one placebo-controlled study has been conducted to date on atypical antipsychotic drug treatment among adults with comorbid ID (Hellings et al. 2002). This trial was limited to an analysis of risperidone and included a sample size of 8 adult participants.

Genetic polymorphisms, or allelic variations independent of gender, have been linked to interindividual differences in the efficacy and toxicity of many drugs due to differences in drug-metabolizing enzymes and receptors. In this vein, Santosh and Baird (1999) noted “an urgent need to understand and establish the pharmacokinetics, pharmacodynamics, and side-effect profiles of psychotropic medication in this [the ID] population” (p. 233). A recent analysis of empirical studies, literature reviews, and policies over the past 25 years furthermore found that, although clinical disorders are higher among women who have comorbid ID than those who do not, minimal research has been conducted with this unique treatment group (Taggart, McMillan, & Lawson, 2008). Clearly, additional research designed to be sensitive to how basic pharmacogenetic factors such as gender, age, and ID may interact with one another and impact adverse drug reactions is needed at this time.

Weight Gain in Adults with ID Receiving Atypical Antipsychotics

The majority of research on weight gain with atypical antipsychotic drug treatment has been conducted on outpatient psychiatric groups without comorbid ID. Review of the literature reveals that five studies have been published to date that investigate or include an analysis of weight change among adults with ID treated with atypical antipsychotic drugs. One study has been conducted with olanzapine (Janowsky, Barnhill, & Davis, 2003), two with risperidone (Cohen, Glazewski, Kahn, & Kahn, 2001; Hellings, Zarcone, Crandall, Wallace, & Schroeder, 2002), and two with ziprasidone (Cohen, Fitzgerald, Kahn, & Kahn, 2004; Cohen, Fitzgerald, Okos, Khan, & Khan, 2003). Although one of these studies assessed weight change across children,

adolescents, and adults (Hellings et al.), none included analyses according to gender, race, level of ID, or increasing age of adults.

Olanzapine. The effectiveness of olanzapine in managing behavioral disorders among 20 institutionalized adults with ID was evaluated using a retrospective, open-label, naturalistic design (Janowsky et al., 2003). All participants were receiving multiple psychotropic drugs at baseline, including conventional antipsychotics, and were prescribed olanzapine as adjunctive treatment for destructive behaviors, physical aggression, or SIB. Maladaptive behaviors significantly decreased with add-on olanzapine treatment, although significant weight gain also was noted. Mean weight increase was 7.50 lb (3.40 kg) after 6 months of adjunctive olanzapine treatment.

Risperidone. Weight gain with risperidone was investigated in 39 adults with ID using a retrospective, open-label, naturalistic design (Cohen et al., 2002). Risperidone was prescribed to manage both clinical and behavioral disorders among participants, and some also were receiving other psychotropic drugs. Over 2 years, 37 of the 39 participants evidenced clinically significant weight gain on risperidone. Mean weight increase was 18.80 lb (8.53 kg) with no association noted between drug dosage and magnitude of weight gain. The diets of 20 of the 37 participants were calorie restricted, suggesting that nutritional interventions may be of limited effectiveness in preventing or ameliorating weight gain among adults with ID treated with risperidone.

In the only placebo-controlled, double-blind, crossover study conducted to date, weight gain attributable to risperidone was evaluated for five children, six adolescents, and eight adults diagnosed with ID and autism (Hellings et al., 2002). Significant weight

gain was noted across all age groups. After 1 year of risperidone treatment, mean weight increase was 11.88 lb (5.39 kg) for adults, 18.48 lb (8.38 kg) for adolescents, and 18.04 lb (8.18 kg) for children. Rate of weight gain markedly diminished upon tapering and discontinuation of risperidone treatment.

Ziprasidone. Weight change among 40 adults with ID and maladaptive behaviors who were switched to ziprasidone after showing a poor clinical response or significant weight gain with other atypical antipsychotic drugs was investigated in a retrospective, open-label, naturalistic study (Cohen et al., 2003). Several variables were assessed at baseline and after 6 months of drug treatment, including weight, triglycerides, cholesterol, and the frequency of maladaptive behaviors. Ziprasidone was associated with significant weight loss as well as significant reductions in triglycerides and total cholesterol, suggesting that this drug carries a reduced risk for metabolic disturbances relative to other atypical antipsychotic drugs. Participants evidenced a mean weight loss of 8.10 lb (3.6 kg) after been switched from other atypical agents to ziprasidone. The frequency of maladaptive behaviors was unchanged or improved for 18 of the 25 participants (72%) for whom data was available.

A replication of this study was conducted with 10 adults diagnosed with both ID and autism who were switched from other atypical antipsychotic drugs to ziprasidone due to poor clinical response or significant weight gain with the previous agent (Cohen et al., 2004). Mean weight loss was slightly greater for this sample than participants only diagnosed with ID. Eight of the 10 participants lost weight after 6 months of ziprasidone treatment, with a mean decrease of 13.10 lb (5.94 kg) noted for these individuals. Four of the five participants for whom data was available evidenced a decrease in total

cholesterol and triglycerides values. The frequency of maladaptive behaviors was unchanged or improved for seven of the 10 participants.

Goals of the Present Research

Weight gain is a common and potentially severe adverse reaction to atypical antipsychotic drug treatment and an area worthy of further investigation. The majority of research conducted to date has involved relatively small sample sizes or included disproportionately large percentages of males so that the opportunity to investigate subgroups with adequate statistical power has generally been limited to main medication groups (for reviews see Chaves & Seeman, 2006; Miller et al., 2005). Furthermore, most studies assessing the liability for weight gain with atypical antipsychotic drugs have been restricted to samples with clinical disorders but without comorbid ID (e.g., ADA et al., 2004; Allison & Casey, 2001; Bobes et al., 2003).

Knowledge of the liability for weight gain among persons with ID clearly remains tentative due to a paucity of published research. Any attempt to generalize research findings from clinical samples of persons who function within the average range of intellectual functioning to persons who have ID carries the risk for error due to variability in environmental, genetic, pharmacokinetic, and pharmacodynamic factors.

The prevalence and controversy of antipsychotic drug treatment with the ID population calls for further research be conducted with this unique treatment group. In 2004, the Consensus Panel called for research that examines adverse metabolic reactions with atypical antipsychotic drug treatment for specific demographic groups (APA et al., 2004). An adequate reply has yet to be heard from researchers specializing in the field of ID.

Small sample size represents a particular concern with the few existing studies that investigated weight gain among adults with ID treated with atypical antipsychotic drugs. For the five studies published to date, sample sizes ranged from eight to 40 persons per study (Cohen et al., 2002; Cohen et al., 2003; Cohen et al., 2004; Hellings et al., 2002; Janowsky et al., 2003). As a result, analysis of the potential interaction between atypical antipsychotic drug treatment and gender, age, race, or level of ID has not yet been possible (Aichhorn et al., 2005). Furthermore, direct comparative data are not available on the liability for weight gain across atypical antipsychotic drugs because each study was limited to the investigation of one agent. Because antipsychotic drugs continue to be the most frequently prescribed class of psychotropic medication for persons with ID, and as there remains a dearth of research on weight gain as an adverse reaction within this unique and vulnerable treatment group, additional investigation clearly is warranted.

The atypical antipsychotic drugs olanzapine (Eli Lilly, 2008), risperidone (Janssen, 2008), and quetiapine (AstrasZeneca, 2008) have been approved by the FDA as first-lines of treatment for schizophrenia and have been determined by the Consensus Panel to carry either a high or intermediate risk for weight gain (APA et al., 2004). The goals of the present research are as follows for these drugs: (a) determine if olanzapine, risperidone, and quetiapine are associated with significant weight gain among adults with ID after 6 months of drug treatment; (b) determine the average amount of weight that adults with ID gain after 6 months of drug treatment; (c) determine the proportion of adults with ID who evidence clinically significant weight gain, defined as a greater than 7% increase in bodyweight, after 6 months of drug treatment; and

(d) identify basic demographic and clinical characteristics of adults with ID who evidence significant weight gain during drug treatment, including analyses of chlorpromazine equivalent dose, gender, and level of ID.

Method

Participants

All participants who were involved in this study reside at the largest Intermediate Care Facility for Individuals with Mental Retardation (ICFMR) in the state of Louisiana. Criteria for inclusion in the current research included (a) age 18 years or older; (b) diagnosis of ID; and (c) at least 6 months of continuous treatment with olanzapine, risperidone, or quetiapine for a comorbid psychiatric or behavioral disorder. A sample of 79 participants met inclusion criteria from a population of 487 individuals. Demographic characteristics of participants were (a) adults ranging in age from 23 years to 79 years; (b) 47 males and 32 females; (c) 59 Caucasians and 20 African Americans; and (d) 14 persons with a diagnosis of mild ID (IQ 50-55 to 70), 21 persons with a diagnosis of moderate ID (IQ 35-40 to 50-55), 11 persons with a diagnosis of severe ID (IQ 20-25 to 35-40), and 33 persons with a diagnosis of profound ID (IQ < 20-25).

The participants included in this study receive habilitative treatment for adaptive skills deficits and behavioral treatment for comorbid psychiatric or behavioral disorders as mandated by state and federal regulatory guidelines. Licensed, doctoral-level psychologists complete psychological evaluations and behavior treatment plans on participants on a yearly or more frequent basis. All evaluations include the administration of standardized scales to assess (a) level of ID; (b) level of adaptive behavior functioning; (c) positive and negative social behaviors; (d) nutritional concerns, feeding problems, and mealtime behaviors; (e) signs of psychopathology; and (f) establishing operations and maintaining variables for maladaptive behaviors and psychiatric signs. This information is used to assist in the development of behavior treatment plans that outline positive skills

training and prevention and management techniques to minimize the frequency, duration, and intensity of the behavioral or psychiatric disorder.

All participants undergo routine psychiatric evaluations on a quarterly basis or more frequently when indicated by a change in clinical status. To ensure that drug treatment is warranted, efficacious, and prescribed at the minimally effective dose, the following persons attend psychiatric consultations: (a) the individual being treated; (b) psychiatrist; (c) primary care physician; (c) pharmacist; (d) psychiatric nurse; (e) licensed, doctoral-level psychologist; (f) master's level associate to a psychologist; (g) bachelor's level team coordinator; (h) behavior shaping specialist; and (i) residential support staff.

All participants are weighed monthly by registered nurses who use calibrated scales and document results. Participants have dietary orders that are individualized according to caloric and consistency needs, per the recommendations of registered dietitians and primary care physicians. Dietary orders and weight status are reviewed for nutritional appropriateness on a monthly basis or more frequently as needed to promote participants achieving and maintaining optimal health status.

The behavioral, psychiatric, nutritional, and medical status of participants are monitored and formally reviewed by interdisciplinary teams (IDTs) on a monthly or more frequent basis to ensure ongoing clinical integrity. IDTs are composed of the following members: (a) the individual being treated; (b) psychiatrist; (c) primary care physician; (c) pharmacist; (d) psychiatric nurse; (e) licensed, doctoral-level psychologist; (f) master's level associate to a psychologist; (g) registered dietitian; (h) medical

occupational therapist; (i) physical therapist; (j) speech pathologist; (k) bachelor's level team coordinator; (l) behavior shaping specialist; and (m) home manager.

Additional habilitative and clinical personnel who may also serve as IDT members include neurologists, recreation therapists, and employment service representatives.

Multiple review boards are in place to ensure quality control, monitor clinical progress, and provide treatment recommendations. Review boards include the (a) Clinical Review Committee, (b) Behavioral Intervention Committee, (c) Human Rights Committee, (d) Nutritional and Physical Supports Committee, (e) Medical Risks Review Committee, and (f) Pharmacy and Therapeutics Committee.

Measures

Demographic characteristics. Age, gender, race, and level of ID were gathered for all participants. Participants were divided into two race groups: (a) Caucasian and (b) African American. After ascertaining level of ID, participants were also assigned to one of two ID groups: (a) mild to moderate ID and (b) severe to profound ID.

This grouping was undertaken to further consolidate the sample according to general level of sensorimotor, communicative, social, and vocational functioning.

Individuals with mild to moderate ID constitute 95% of those with the disorder (APA, 2002). As a group, they generally acquire social and communication skills during the preschool to early childhood years and academic skills that range from the second to sixth grade level. Individuals who function within the mild to moderate range of ID typically benefit from training in social and vocational skills. They can perform occupational tasks in the community or at sheltered workshops, which is oftentimes adequate for minimum self-support.

By contrast, individuals with severe to profound ID constitute 5% of those with the disorder (APA, 2002). As a group, they evidence a greater likelihood for neurological, neuromuscular, cardiovascular, and other medical conditions, and many have an identified neurological disorder that accounts for their ID. These individuals acquire little to no communicative speech during the early childhood years and profit only to a limited extent from instruction in pre-academic subjects such as counting.

Chlorpromazine equivalent dose. Mean 6 month drug dosages of olanzapine, risperidone, or quetiapine were calculated for all participants. Mean drug doses were then transformed to chlorpromazine equivalent doses using standard equivalency data in order to allow for direct dosage comparisons across drugs (Crismon & Dorson, 2006). Standardization of drug dosages allowed for an absolute comparison of risk for weight gain during drug treatment.

Body Weight. Body weights were retrieved on all participants for the following time intervals: (a) 6 months prior to the initiation of atypical antipsychotic drug treatment (W1), (b) upon starting the atypical antipsychotic drug (W2), and (c) after 6 consecutive months of drug treatment (W3). Two weight change scores were calculated for all participants. The first score (WC1) provided a baseline measure of weight change during the 6 months prior to the initiation of atypical antipsychotic drug treatment. That is, WC1 served as the pretreatment measure of weight change. WC1 was calculated by subtracting weight 6 months prior to the initiation of the atypical antipsychotic drug from weight at the initiation of drug treatment. For example, if a participant weighted 175 lbs (79.38 kg) 6 months prior to the initiation of olanzapine and 180 lb (82.65 kg) upon starting this

drug, a calculation of $180 - 175$ was completed to arrive at a WC1 score of 5 lb (2.27 kg). The second score (WC2) provided an initial measure of weight change during the first 6 months of atypical antipsychotic drug treatment. That is, WC2 served as an unadjusted posttreatment measure of weight change. WC2 was calculated by subtracting weight at the initiation of drug treatment from weight after 6 months of drug receipt. For example, if the same participant weighed 200 lbs (90.72 kg) after 6 consecutive months of olanzapine treatment, a calculation of $200 - 180$ was completed to arrive at a WC2 score of 20 lb (9.07 kg).

A third weight change score (WC3) was then calculated for all participants. This score provided an additional measure of weight change during the first 6 months of atypical antipsychotic drug treatment, after accounting for individual changes in weight during the 6 months prior to the initiation of the drug. Thus, WC3 served as an adjusted posttreatment measure of weight change. WC3 was calculated by subtracting weight change during the 6 months prior to the initiation of the drug from weight change after 6 months of drug receipt. Continuing the above example, a participant gained 20 lb (9.07 kg) during the first 6 months of olanzapine treatment but already was evidencing an upward weight change trend of 5 lb (2.27 kg) during the 6 months prior to the receipt of the drug. Thus, a calculation of $20 \text{ lb (9.07 kg)} - 5 \text{ lb (2.27 kg)}$ was completed to arrive at a WC3 score of 15 lb (6.80 kg). As noted above, WC3 scores were calculated to provide an adjusted post-treatment measure for weight change after accounting for individual changes in weight prior to drug receipt.

The unique value of utilizing the WC1 score is its utility in providing a pretreatment baseline trend versus a discrete baseline point as the standard for

comparison in assessing weight gain after the initiation of drug treatment. Utilization of two weight change scores, WC1 and WC2, allowed for a more stringent determination of the liability for weight gain during atypical antipsychotic drug treatment. That is, WC3 provided for an adjusted dependent measure of weight gain that used each individual as his or her own control.

Weight increases of more than 7% of body weight also were calculated to determine the proportion of individuals who evidenced clinically significant weight gain (a) during the 6 months prior to atypical antipsychotic drug treatment, (b) after 6 months of drug treatment, and (c) after 6 months of drug treatment with adjustments made for pretreatment weight change. These calculations were performed because much of the drug research published to date includes an analysis of the proportion of individuals who evidenced a greater than 7% increase in baseline body weight during drug treatment. The FDA also mandates that such proportions be reported in medication package insets of atypical antipsychotic drugs.

Procedure

All data was accessed from pharmacy databases and medical archival records that are routinely maintained on participants. Licensed, doctoral-level psychologists had diagnosed all participants with ID and reviewed the appropriateness of these diagnoses within the past year. Severity of ID had been determined according to *DSM-IV-TR* (APA, 2002) diagnostic criteria for mental retardation using standardized intellectual assessments and informant-based adaptive behavior skills assessments.

Psychiatric and behavioral disorders targeted for atypical antipsychotic drug treatment had been dually established by licensed, doctoral-level psychologists and

prescribing psychiatrists. Diagnostic formulations and antipsychotic drug treatments were evaluated and approved by the Behavior Intervention Committee and Human Rights Committee of the ICFMR. Informed consent for antipsychotic drug treatment had been obtained from the curators of participants whose legal status is interdicted adult and from both the individuals and primary correspondents of persons whose legal status is competent major. Informed consent grants that all data routinely gathered on the resident of the ICFMR can be utilized for the advancement of professional research.

The treatment of participant records was in accordance with the “Ethical Principles of Psychologists and Code of Conduct” (American Psychological Association [APA], 1992). The ICFMR where the current project was conducted judged the research procedures to be minimally disruptive to clinical and facility operations. Furthermore, the project was identified as falling within the minimal to no risk category of the 2005 Department of Health and Human Services’ “Code of Federal Regulations”, Title 45 – Public Welfare, Part 461 – Protection of Human Rights. The research design and procedures were reviewed and approved by the Institutional Review Boards of the ICFMR where the research was conducted (see Appendix A), Louisiana Tech University (see Appendix B), and the Department of Health and Hospitals for the state of Louisiana (see Appendix C).

Data Analysis

A retrospective longitudinal design was used to assess changes in body weight associated with olanzapine, risperidone, and quetiapine treatment. Parameters analyzed were (a) mean lb (kg) change in body weight after 6 consecutive months of drug

treatment, (b) percentage change in body weight after 6 consecutive months of drug treatment, (c) chlorpromazine equivalent dose, (d) gender, and (e) severity of ID.

As noted previously, calculations of change in body weight after 6 months of drug treatment included adjustments that corrected for baseline body weight trends during the 6 months prior to drug receipt.

Several descriptive analyses were conducted across drug categories and for each atypical antipsychotic drug. First, descriptive analyses were performed to determine mean age and the distribution of gender, race, and level of ID. Descriptive analyses were then performed to determine mean weights and standard deviations (a) 6 months prior to atypical antipsychotic drug treatment, (b) at the start of drug treatment, and (c) after 6 consecutive months of drug receipt. Descriptive analyses also were performed to determine means and standard deviations for (a) pretreatment weight change, (b) posttreatment weight change, and (c) adjusted posttreatment weight change. Last, the proportion of individuals who evidenced clinically significant weight gain, as defined by a greater than 7% increase in body weight, was calculated in relation to (a) pretreatment weight change, (b) posttreatment weight change, and (c) adjusted posttreatment weight change.

Several statistical tests were conducted. Paired sample *t*-tests were performed to determine if there was a significant difference between pretreatment and posttreatment weight change across drug categories as well as for each atypical antipsychotic drug. Univariate analysis of variance (ANOVA) was performed to determine if there were significant differences in adjusted posttreatment weight gain between atypical antipsychotic drugs. Pearson's product-moment correlation was performed to determine

if there was a significant relationship between adjusted posttreatment weight gain and chlorpromazine equivalent dose. Last, independent samples *t*-tests were performed to determine if there was a significant difference in adjusted posttreatment weight gain between (a) males and females and (b) persons diagnosed with mild to moderate ID versus severe to profound ID.

Results

Detailed descriptive data on the demographic and clinical features of participants are provided in Table 1. The mean age of participants across the sample was 50 years (range 23 - 79 years) and closely matched the ages for those receiving olanzapine ($M = 51$, range 33 – 78), quetiapine ($M = 49$, range 33 – 66), and risperidone ($M = 50$, range 23 – 79). The sample was composed of 47 males (59%) and 32 females (41%). Males were slightly overrepresented within each of the three drug categories:

(a) Twenty-two males (59%) and 15 females (41%) received olanzapine, (b) 16 males (62%) and 10 females (38%) received risperidone, and (c) 9 males (56%) and 7 females (44%) received quetiapine.

The sample largely defined was by Caucasian membership. Fifty-nine Caucasians (75%) and 20 African Americans (25%) composed the overall sample. Caucasians were overrepresented within each of the three drug categories: (a) Twenty-eight Caucasians (76%) and 9 African Americans (24%) received olanzapine; (b) 18 Caucasians (69%) and 8 African Americans (31%) received risperidone, and (c) 13 Caucasians (81%) and 3 African Americans (19%) received quetiapine.

The distribution for level of ID, categorized as either mild to moderate or severe to profound, was well balanced across the overall sample. Thirty-five persons (44%) functioned in the mild to moderate range of ID, and 44 persons (56%) functioned in the severe to profound range.

Table 1

Demographic and Clinical Characteristics of Participants

Variable	All (<i>N</i> = 79)	Olanzapine (<i>n</i> = 37)	Quetiapine (<i>n</i> = 16)	Risperidone (<i>n</i> = 26)
Age, <i>M</i> (Range)	50 (23–79)	51 (33–78)	49 (33–66)	50 (23–79)
Sex, <i>n</i> (%)				
Male	47 (59%)	22 (59%)	9 (56%)	16 (62%)
Female	32 (41%)	15 (41%)	7 (44%)	10 (38%)
Race, <i>n</i> (%)				
Caucasian	59 (75%)	28 (76%)	13 (81%)	18 (69%)
African American	20 (25%)	9 (24%)	3 (19%)	8 (31%)
Level of ID, <i>n</i> (%)				
Mild	14 (18%)	7 (19%)	1 (6%)	6 (23%)
Moderate	21 (26%)	8 (21%)	6 (38%)	7 (27%)
Severe	11 (14%)	4 (11%)	3 (18%)	4 (15%)
Profound	33 (42%)	18 (49%)	6 (38%)	9 (35%)

Level of ID within each of drug category was as follows: (a) For olanzapine, 15 participants (40%) functioned in the mild to moderate range, and 22 (60%) functioned in the severe to profound range; (b) for risperidone, 13 (50%) functioned in the mild to moderate range, and 13 (50%) functioned in the severe to profound range; and (c) for quetiapine, 7 participants (44%) functioned in the mild to moderate range, and 9 (56%) functioned in the severe to profound range.

Detailed descriptive data on the weight trends of participants are presented in Tables 2, 3, and 4. At the initiation of drug treatment, mean participant weight was 149.92 lb (67.99 kg). Participants gained a mean of 1.67 lb (0.78 kg) during the 6 months prior to the initiation of drug treatment, with 3.80% of the sample evidencing a greater than 7% increase on body weight over that time. After 6 consecutive months of atypical antipsychotic drug treatment, mean participant weight increased from 149.92 lb (67.99 kg) to 162.04 lb (73.49 kg). Participants gained a mean of 12.11 lb (5.49 kg) over that time, with 41.77% evidencing a greater than 7% increase in body weight and an additional 12.66% evidencing a greater than 15% increase.

Mean weight increase over the first 6 months of drug treatment was 14.11 lb (6.40 kg) for olanzapine, 11.31 lb (5.13 kg) for risperidone, and 8.81 lb (4.00 kg) for quetiapine. A greater than 7% increase in body weight was evidenced by 51.35% of those receiving olanzapine, 42.31% of those receiving risperidone, and 18.75% of those receiving quetiapine. An additional 16.22% of those receiving olanzapine, 11.54% of those receiving risperidone, and 6.25% of those receiving quetiapine evidenced a greater than 15% increase in body weight.

Table 2

Weights of Participants

Variable	W1 ^a	W2 ^b	W3 ^c
Olanzapine, lb (kg)			
<i>M</i>	147.62 (66.96)	148.76 (67.46)	162.86 (73.86)
<i>SD</i>	32.71 (14.83)	33.34 (15.12)	34.51 (15.65)
Quetiapine, lb (kg)			
<i>M</i>	155.25 (70.41)	157.19 (71.29)	166.00 (75.28)
<i>SD</i>	35.89 (16.28)	35.22 (15.97)	35.65 (16.17)
Risperidone, lb (kg)			
<i>M</i>	144.85 (65.69)	147.12 (66.72)	158.42 (71.84)
<i>SD</i>	24.82 (11.26)	23.74 (10.77)	25.00 (11.34)
All, lb (kg)			
<i>M</i>	148.25 (67.23)	149.92 (67.99)	162.04 (73.49)
<i>SD</i>	30.88 (14.00)	30.77 (13.95)	31.66 (14.36)

^aWeight 6 months prior to the initiation of atypical antipsychotic drug treatment is reported under column W1. ^bWeight upon starting atypical antipsychotic drug treatment is reported under column W2. ^cWeight after 6 consecutive months of atypical antipsychotic drug treatment is reported under column W3.

Table 3

Weight Difference Scores of Participants

Variable	WC1 ^a	WC2 ^b	WC3 ^c
Olanzapine, lb (kg)			
<i>M</i>	1.14 (0.52)	14.11 (6.40)	12.97 (5.88)
<i>SD</i>	3.74 (1.70)	6.77 (3.07)	7.78 (3.53)
Quetiapine, lb (kg)			
<i>M</i>	1.94 (0.89)	8.81 (4.00)	6.87 (3.11)
<i>SD</i>	2.46 (1.12)	5.21 (2.36)	6.37 (2.89)
Risperidone, lb (kg)			
<i>M</i>	2.27 (1.03)	11.31 (5.13)	9.04 (4.10)
<i>SD</i>	3.31 (1.50)	6.34 (2.88)	6.89 (3.12)
All, lb (kg)			
<i>M</i>	1.67 (0.78)	12.11 (5.49)	10.44 (4.71)
<i>SD</i>	3.38 (1.53)	6.60 (2.99)	7.46 (3.38)

^aWeight change during the 6 months prior to the initiation of atypical antipsychotic drug treatment is reported under column WC1. ^bWeight change during the first 6 months of atypical antipsychotic drug treatment is reported under column WC2. ^cWeight change during the first 6 months of atypical antipsychotic drug treatment, after adjusting for individual changes in weight during the 6 months prior to drug treatment, is reported in column WC3.

Table 4

Percent of Participants Who Evidenced a Clinically Significant Increase in Body Weight

Variable	WC1 ^a	WC2 ^b	WC3 ^c
Olanzapine			
>7% weight increase	0.00%	51.35%	43.24%
>15% weight increase	0.00%	16.22%	12.66%
Quetiapine			
>7% weight increase	6.25%	18.75%	12.50%
>15% weight increase	0.00%	6.25%	6.25%
Risperidone			
>7% weight increase	7.69%	42.31%	38.46%
> 15% weight increase	0.00%	11.54%	3.85%
All			
>7% weight increase	3.80%	41.77%	35.44%
>15% weight increase	0.00%	12.66%	10.13%

^aWeight change during the 6 months prior to the initiation of atypical antipsychotic drug treatment is reported under column WC1. ^bWeight change during the first 6 months of atypical antipsychotic drug treatment is reported under column WC2. ^cWeight change during the first 6 months of atypical antipsychotic drug treatment, after adjusting for individual changes in weight during the 6 months prior to drug treatment, is reported in column WC3.

Paired sample *t*-tests comparing pretreatment and adjusted posttreatment weight change were performed across drug categories as well as for each atypical antipsychotic agent (see Table 5). An adjusted mean weight gain of 8.44 lb (3.82 kg) ($SD = 9.09$ lb, 4.12 kg) was noted across atypical antipsychotic drugs and found to be significant, $t(78) = 8.26, p = .000$ (two-tailed). For olanzapine, a mean weight gain of 11.14 lb (5.05 kg) ($SD = 9.13$ lb, 4.14 kg) was noted and found to be significant $t(36) = 7.42, p = .000$ (two-tailed). For risperidone, a mean gain of 6.77 lb (3.07 kg) ($SD = 8.75$ lb, 3.97 kg) was noted and found to be significant $t(25) = 3.94, p = .001$ (two-tailed). Lastly, for quetiapine, a mean gain of 4.94 lb (2.24 kg) ($SD = 8.13$ lb, 3.69 kg) was noted and also found to be significant $t(15) = 2.43, p = .028$ (two-tailed). Findings indicate that significant weight was associated with 6 months of atypical antipsychotic drug treatment and with each of the individual agents investigated.

Univariate ANOVA was completed to test for differences in the magnitude of adjusted posttreatment weight gain across the three atypical antipsychotic drugs investigated in the study (see Table 6). Analysis yielded a significant difference between groups, $F(2, 76) = 4.68, p = .012$. Tukey multiple comparisons indicated that olanzapine ($M = 12.97$ lb, 5.88 kg) and quetiapine ($M = 6.87$ lb, 3.12 kg) was the only pairwise comparison to reach significance, with a mean weight difference of 6.10 lb (2.77 kg) ($SE = 2.17$ lb, 0.98 kg), $p = .017$. A mean difference of 3.93 lb (1.78 kg) for adjusted posttreatment weight gain was noted between olanzapine ($M = 12.97$ lb, 5.88 kg) and risperidone ($M = 9.04$ lb, 4.10 kg) but failed to reach significance, $p = .092$.

Table 5

*Paired Sample t-Tests Comparing Pretreatment and Adjusted Posttreatment**Weight Change*

Pair	<i>M</i>	<i>SD</i>	<i>t</i>	<i>df</i>	<i>p</i>
(WC3 ^a – WC1 ^b)					
Total, lb (kg)	8.44 (3.82)	9.09 (4.12)	8.26*	78	.000
Olanzapine, lb (kg)	11.14 (5.05)	9.13 (4.14)	7.42*	36	.000
Quetiapine, lb (kg)	4.94 (2.24)	8.13 (3.69)	2.43***	15	.028
Risperidone, lb (kg)	6.77 (3.07)	8.75 (3.97)	3.94**	25	.001

^aWC3 represents weight change during the first 6 months of atypical antipsychotic drug treatment, after adjusting for individual changes in weight during the 6 months prior to drug treatment. ^bWC1 represents weight change during the 6 months prior to the initiation of atypical antipsychotic drug treatment.

* $p < .001$, two-tailed. ** $p < .01$, two-tailed. *** $p < .05$, two-tailed.

Table 6

Analysis of Variance for Adjusted Posttreatment Weight Change by Atypical Antipsychotic Drug

Source	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>
Between Groups	2	245.91	4.68	.012
Within Groups	76	52.55		
Total	78			

Tukey Multiple Comparisons

Comparison	<i>M difference</i>	<i>SE</i>	<i>p</i>
olanzapine v. quetiapine, lb (kg)	6.10 (2.77)*	2.17 (0.98)	.017
olanzapine v. risperidone, lb (kg)	3.93 (1.78)	1.86 (0.84)	.092
risperidone v. quetiapine, lb (kg)	2.16 (0.98)	2.30 (1.04)	.617

* $p < .05$.

A mean difference of 2.16 lb (0.98 kg) for adjusted posttreatment weight gain was noted between risperidone ($M = 9.04$ lb, 4.10 kg) and quetiapine ($M = 6.87$ lb, 312 kg) also failed to achieve significance, $p = .617$.

Finally, a series of analyses were completed to test the relationship between adjusted posttreatment weight gain and chlorpromazine equivalent dose, gender, and level of ID. The relationship between adjusted posttreatment weight gain and chlorpromazine equivalent dosage was assessed by completing a Pearson's correlation coefficient. Results did not indicate any significant relationship between weight gain and drug dosage, $r = .160$, $p = .158$. An independent samples t -test was performed to determine if there was a significant difference in adjusted posttreatment weight gain between males and females (see Table 7). The 1.13 lb (0.51 kg) mean difference in weight gain noted between males ($M = 10.57$ lb, 4.79 kg) and females ($M = 9.44$ lb, 4.28 kg) did not reach significance, $t(77) = .66$, $p = .51$ (two-tailed). Last, an independent samples t -test was performed to determine if there was a significant difference in weight gain between persons who functioned in the mild to moderate range of ID versus the severe to profound range of ID (see Table 8). A mean difference of 3.75 lb (1.70 kg) was noted between persons functioned in the mild to moderate range of ID ($M = 14.20$ lb, 6.44 kg) versus severe to profound range ($M = 10.45$ lb, 4.74 kg). Results were found to be significant, $t(77) = 2.59$, $p = .011$ (two-tailed), and indicate that individuals with lesser degrees of intellectual impairment have a greater liability for weight gain than those with greater degrees of impairment.

Table 7

Independent Samples T-Test Comparing Adjusted Posttreatment Weight Change by Gender

	<i>M</i>	<i>SD</i>	<i>SE</i>
Males, lb (kg) (<i>n</i> = 47)	10.57 (4.79)	7.89 (3.58)	1.15 (0.52)
Females, lb (kg) (<i>n</i> = 32)	9.44 (4.28)	6.86 (3.11)	1.21 (0.55)
	<i>t</i>	<i>df</i>	<i>M difference</i>
	.66	77	1.13 (0.51)
			<i>p</i>
			.51

Table 8

Independent Samples T-test Comparing Adjusted Posttreatment Weight Change by

Level of Intellectual Disability

	<i>M</i>	<i>SD</i>	<i>SE</i>
Mild to Moderate ID, lb (kg) (<i>n</i> = 35)	14.20 (6.44)	6.04 (2.74)	1.02 (0.46)
Severe to Profound ID, lb (kg) (<i>n</i> = 44)	10.45 (4.74)	6.62 (3.00)	1.00 (0.45)
	<i>t</i>	<i>df</i>	<i>M difference</i>
	2.59*	77	3.75 (1.70)
			<i>p</i>
			.011

**p* < .05, two-tailed.

Discussion

The current study approached the assessment of weight gain with atypical antipsychotic drug treatment in a unique manner, even among studies conducted with typically developed participants. This unique approach to assessing the significance of weight gain involved comparing weight differences associated with drug treatment to weight differences observed prior to treatment. In other words, the significance of weight gain associated with atypical antipsychotic drug treatment was based on comparison with a baseline weight trend versus a discrete baseline point. Such an approach has clear methodological implications in that it provides a dependent measure of weight gain that uses the individual as his or her own control. Such an approach also has potential clinical implications in that it encourages clinicians and researchers to consider the issue of weight gain within a broader temporal context.

Even with this more stringent standard for assessing weight gain, results of the current study demonstrate that significant weight gain is associated with the use of atypical antipsychotic drugs among persons with ID. Although there have been a small number of studies demonstrating weight gain with atypical antipsychotic drug treatment among persons with ID (Cohen et al. 2002; Cohen et al. 2003; Cohen et al. 2004; Hellings et al. 2002; Janowsky et al. 2003), this was the first study to approach the issue with any significant methodological complexity. The few previous studies conducted to date have been limited to assessing weight gain associated with singular atypical antipsychotic agents, and no research had previously been conducted on the liability for weight gain with quetiapine among persons with ID. The current study, by contrast, systematically assessed weight gain across a variety of specific atypical antipsychotic

drugs, specifically the three most frequently prescribed atypical agents—olanzapine, risperidone, and quetiapine.

Results of the current study indicate that a substantial proportion of individuals with ID evidence a significant increase in body weight during treatment with olanzapine, risperidone, and quetiapine, even after adjusting for individual trends in weight change prior to drug treatment. Consistent with studies conducted among typically developed participants, the current research also supports olanzapine as carrying a heightened liability for weight gain compared to risperidone and quetiapine. Within the typically developed population, the magnitude of weight gain with olanzapine is recognized to be the most severe among the atypical antipsychotics considered first line of treatment, followed by risperidone and then quetiapine (ADA et al. 2004; Allison & Casey, 2001). By assessing weight change across multiple atypical antipsychotic agents, the current research is the first of its kind to replicate this finding within the ID population.

The current study also assessed potential risk factors for weight gain among persons with ID. Analyses of chlorpromazine equivalent drug dosages, gender, and level of ID were undertaken to evaluate the impact of these variables on liability for weight gain. Consistent with the literature on atypical antipsychotic drug treatment and weight gain among typically developed individuals (e.g., see Brecher et al. 2007), the current study failed to find a significant relationship between drug dosage and magnitude of weight gain among persons with ID.

Over the past several years, genetic factors such as gender have been hypothesized to have the potential to impact side effects with antipsychotic drug treatment (Murray, 2006; Nnadi & Malhotra, 2007; Reynolds et al. 2005; Usall et al.

2007). However, results of empirical research remain mixed. Preliminary research with typically developed individuals suggests that female gender may increase the liability for weight gain with olanzapine (Basson et al. 2001; Bobes et al. 2003; Hormel et al. 2002). Research remains contradictory as to whether gender increases the risk for weight gain with risperidone (Basson et al. 2002; Bobes et al.; Hormel et al.). Furthermore, initial study of quetiapine suggests that gender does not significantly impact weight gain with this drug (Emsley et al. 2005). Results of the current study found that gender did not significantly impact the liability for weight gain among adults with ID who received olanzapine, risperidone, and quetiapine.

The current research does, however, implicate the severity of ID as an important risk factor in the liability for weight gain with atypical antipsychotic drug treatment. Results of the current study found persons with mild to moderate ID were more likely to sustain significant weight gain than individuals with severe to profound ID. Given that individuals with more severe intellectual impairments carry a greater likelihood of medical challenges, this finding is surprising. Whether severity of ID represents a pharmacokinetic risk that it impacts the processes by which the body absorbs and metabolizes drugs or a differential risk in relation to the daily choices of individuals with ID, such as exercise and dietary habits, remains an area open for further investigation. All individuals involved in the current research had been prescribed diets that were individualized according to caloric and medical needs, per the recommendations of registered dietitians and primary care physicians. However, it may be that individuals with lesser degrees of intellectual impairment are more able to make choices resulting in greater caloric intake. That is, these individuals may have more intake options due to

increased independence with mobility, daily routine, and finances. Replicating this finding and exploring the possible determinants could prove revealing, not just for persons with ID but also for the individuals who are typically developed.

A number of limitations with the current research must be acknowledged. The most obvious limitations are those associated with characteristics of the sample. The current study was limited to the three most frequently prescribed atypical antipsychotic drugs. Furthermore, sample size for each of the three atypical agents was relatively small thus calling into question findings related to specific drugs due to questions of sufficient cell size and power.

The univariate nature of the current study is also a potential concern. Weight gain as a complication of atypical antipsychotic drug receipt is only a small part of a larger concern within the scope of health issues such as lipid metabolism, diabetes, and metabolic syndrome. Future studies would be of greater benefit if they included a broader range of dependent measures. Future studies could also include a broader consideration of possible risk factors for the development of problematic weight gain, in addition to gender and severity of ID. As already noted in the discussion of degree of intellectual impairment as a risk factor, the detection and exploration of risk factors in those with ID may prove fruitful not only for persons with ID but also for the general population.

Appendices

Appendix A

Human Rights Committee Approval from Pinecrest Supports & Services Center

MEMORANDUM

TO: John Newsom, DHH Institutional Review Board

FROM: Amanda Pittman, Chair, Human Rights Committee, Pinecrest Supports & Services Center

DATE: April 17, 2009

Weight Gain among Adults with Intellectual Disabilities Receiving Atypical Antipsychotics

I have reviewed the above-entitled research proposal. The research procedures appear to be minimally disruptive to clinical and facility operations. I agree to provide the necessary support requested in the application and hereby designate myself as the staff member responsible for monitoring these research activities.

I understand that any modifications to the research proposal must be approved by the DHH IRB prior to implementation. I agree to suspend research activities and to report to the DHH IRB any unauthorized research modifications or instances in which client rights appear to be violated.

I understand that the researcher is not authorized to begin research activities at this facility until written authorization from the Secretary or designee is received.

Appendix B

Institutional Review Board Approval from Louisiana Tech University

MEMORANDUM

TO: Dr. Tony Young
FROM: Barbara Talbot, University Research
SUBJECT: HUMAN USE COMMITTEE REVIEW
DATE: June 24, 2009

In order to facilitate your project, an EXPEDITED REVIEW has been done for your proposed study entitled:

**“Weight Gain among Adults with Intellectual Disabilities
Receiving Atypical Antipsychotics”**

HUC 654*

The proposed study’s revised procedures were found to provide reasonable and adequate safeguards against possible risks involving human subjects. The information to be collected may be personal in nature or implication. Therefore, diligent care needs to be taken to protect the privacy of the participants and to assure that the data are kept confidential. Informed consent is a critical part of the research process. The subjects must be informed that their participation is voluntary. It is important that consent materials be presented in a language understandable to every participant. If you have participants in your study whose first language is not English, be sure that informed consent materials are adequately explained or translated. Since your reviewed project appears to do no damage to the participants, the Human Use Committee grants approval of the involvement of human subjects as outlined.

Projects should be renewed annually. *This approval was finalized on June 24, 2009 and this project will need to receive a continuation review by the IRB if the project, including data analysis, continues beyond June 24, 2010.* Any discrepancies in procedure or changes that have been made including approved changes should be noted in the review application. Projects involving NIH funds require annual education training to be documented. For more information regarding this, contact the Office of University Research.

You are requested to maintain written records of your procedures, data collected, and subjects involved. These records will need to be available upon request during the conduct of the study and retained by the university for three years after the conclusion of the study. If changes occur in recruiting of subjects, informed consent process or in your research protocol, or if unanticipated problems should arise it is the Researchers responsibility to notify the Office of Research or IRB in writing. The project should be discontinued until modifications can be reviewed and approved.

If you have any questions, please contact Dr. Mary Livingston at 257-4315.

***NOTE: Approval contingent on DHH IRB final written approval in our file before data collection can begin.**

Appendix C

Institutional Review Board Approval from the Department of Health and Hospitals



State of Louisiana

Department of Health and Hospitals

July 21, 2009

Sherri Transier, M.S.
1927 White street
Alexandria, LA 71301

Re: Weight Disturbances in Adults with Intellectual Disabilities Receiving Atypical Antipsychotics

Dear Ms Transier:

Thank you for submitting the above protocol for DHH IRB review. Your protocol has been reviewed under Expedited Review procedures and is approved for start-up at your convenience. It is noted that the study has received approval of the Louisiana Tech Institutional Review Board.

I am requesting that any emergent problems, serious adverse reactions, or changes to protocol that may affect the status of the investigation be reported to this office and that no such changes be instituted prior to DHH IRB review, except where necessary in order to eliminate immediate hazards. The investigator also agrees to periodic review of this project by the DHH IRB at intervals appropriate to the degree of risk to assure that it is being conducted in compliance with the DHH IRB's understanding and recommendations.

If we can be of any further assistance please feel free to call.

Sincerely,
John D. Newsom, II, M.A., CPM
Chair, DHH IRB

IRB #: 00003451
FWA #: 00004713

c: Julia Kenny
Kathy Kliebert
Amanda Pittman.

References

- Aalto, S., Bruck, A., Lain, M., Nagren, K., & Rinne, J.O. (2005). Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: A positron emission tomography study using the high-affinity dopamine D₂ receptor Ligand [¹¹C]FLB 457. *Journal of Neuroscience*, *25*, 2471-2477.
- Adams, K.F., Schatzkin, A., Harris, T.B., Kipnis, V., Mouw, T., Ballard-Barbash, R., Hollenbeck, A., & Leitzmann, M.F. (2006). Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *New England Journal of Medicine*, *355*, 763-788.
- Adson, D.E., Kushner, M.G., & Fahnhorst, T.A. (2005). Treatment of residual anxiety symptoms with adjunctive aripiprazole in depressed patients taking selective serotonin reuptake inhibitors. *Journal of Affective Disorders*, *86*, 99-104.
- Advokat, Mayville, & Matson (2000). Side effect profile of atypical antipsychotics, typical antipsychotics, or no psychotropic medications in persons with mental retardation. *Research in Developmental Disabilities*, *21*, 75-84.
- Aguilera, C.M. Gil-Campos, M., & Gil, A. (2008). Alterations in plasma and tissue lipids associated with obesity and metabolic syndrome. *Clinical Science*, *114*, 183-193.
- Aichhorn, W., Gasser, M., Weiss, E.M., Adlassnig, C., & Marksteiner, J. (2005). Gender differences in pharmacokinetics and side effects of second generation antipsychotic drugs. *Current Neuropharmacology*, *3*, 73-85.
- Akinnusi, M.E., Pineda, L.A., & El Solh, A.A. (2008). Effect of obesity on intensive care morbidity and mortality: A meta-analysis. *Critical Care Medicine*, *36*, 151-158.
- Allison, D.B., & Casey, D.E. (2001). Antipsychotic-induced weight gain: A review of the literature. *Journal of Clinical Psychiatry*, *62* (suppl 7), 22-31.
- Allison, D.B., Fontaine, K.R., Heo, M., Mentore, J.L., Cappelleri, J.C., Chandler, L.P., Weiden, P.J., Cheskin, L.J. (1999). The distribution of body mass index among individuals with and without schizophrenia. *Journal of Clinical Psychiatry*, *60*, 215-220.
- Aman, M.G. (1987). Overview of pharmacotherapy: Current status and future directions. *Journal of Mental Deficiency Research*, *31*, 121-130.
- Aman, M.G., Crimson, Frances, King, & Rojahn, R. (Eds.), (2004). *Treatment of psychiatric and behavioral problems in mental retardation: An update of the Expert Consensus Guidelines for mental retardation/ developmental disability populations*. Englewood, CO: Postgraduate Institute for Medicine.

- Aman, M.G., & Gharabawi, G.M. (2004). Treatment of behavior disorders in mental retardation: Report on transitioning to atypical antipsychotics, with an emphasis on risperidone. *Journal of Clinical Psychiatry* 65, 1197-1210.
- Aman, M.G., & Madrid, A. (1999). Atypical antipsychotics in persons with developmental disabilities. *Mental Retardation and Developmental Disabilities Research Reviews*, 5, 253-263.
- Aman, M.G., & Singh, N. (1988). Patterns of drug use, methodological considerations, measurement techniques, and future trends. In M.G. Aman & N.N. Singh (Eds.), *Psychopharmacology of the developmental disabilities* (pp. 1 – 28). New York: Springer-Verlag.
- American Association on Mental Retardation (2002). Physical and mental health. In *Mental retardation: Definition, classification, and systems of supports* (pp. 169 – 182). Washington, DC: Author.
- American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, & North American Association for the Study of Obesity (2004). Consensus development conference on antipsychotic drugs and obesity and diabetes. *Journal of Clinical Psychiatry*, 65, 267-272.
- American Psychiatric Association (2002). *Diagnostic and statistical manual of mental disorders* (4th revised). Washington, D.C.: Author.
- Andersson, D.R., Nissbrandt, H., & Bergquist, F. (2006). Partial depletion of dopamine in substantia nigra impairs motor performance without altering striatal dopamine neurotransmission. *European Journal of Neuroscience*, 24, 617-624.
- Ashcroft, R., Fraser, B., Kerr, M., & Ahmed, Z. (2001). Are antipsychotic drugs the right treatment for challenging behaviour in learning disability?: The place of a randomized trial. *Journal of Medical Ethics*, 27, 338-343.
- Ashmore, J.A., Friedman, K.E., Reichmann, S.K., & Musante, G.J. (2008). Weight-based stigmatization, psychological distress, & binge eating behavior among obese treatment-seeking adults. *Eating Behaviors*, 9, 203-209.
- AstraZeneca. (2008). *Seroquel (quetiapine) prescribing information*. Wilmington, DE: Author.
- Bakker, P.R., van Harten, P.N., & van Os. (2006). Antipsychotic-induced tardive dyskinesia and the Ser9Gly polymorphism in the DRD3 gene: A meta analysis. *Schizophrenia Research*, 83, 185-192.

- Baldessarini, R.J., & Tazari, F.I. (2006). Pharmacotherapy of psychosis and mania. In L.L. Brunton, J.S. Lazo, & K.L. Parkers (Eds.). *The pharmacological basis of therapeutics* (11th ed., pp. 461-500). New York: McGraw-Hill.
- Barnes, T.R.E., Paton, C., Cavanagh, M., Hancock, E., & Taylor, D.M. (2007). A UK audit of screening for the metabolic side effects of antipsychotics in community patients. *Schizophrenia Bulletin*, *33*, 1397-1403.
- Barnett, A.H., Mackin, P., Chaudhry, I., Farooqi, A., Gadsby, R., Heald, A., Hill, J., Milar, H., Peveler, R., Rees, A., Singh, D., Taylore, D., Vora, J., & Jones, P.B. (2007). Minimizing metabolic and cardiovascular risk in schizophrenia: Diabetes, obesity and dyslipidaemia. *Journal of Psychopharmacology*, *21*, 357-373.
- Baskin, M.L., Ard, J., Franklin, F., & Allison, D.B. (2005). Prevalence of obesity in the United States. *Obesity Reviews*, *6*, 5-7.
- Basson, B.R., Kinon, B.J., Taylor, C.C., Szymanski, K.A., Gilmore, J.A., & Tollefson, G.D. (2001). Factors influencing weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. *Journal of Clinical Psychiatry*, *62*, 231, 238.
- Bastiaens, L. (2008). A non-randomized, open study with aripiprazole and ziprasidone for the treatment of aggressive behavior in youth in a community clinic. *Community Mental Health Journal*, *8*, 154-157.
- Basu, A., & Meltzer, H.Y. (2006). Differential trends in prevalence of diabetes and unrelated general medical illness for schizophrenia patients before and after the atypical antipsychotic era. *Schizophrenia Research*, *86*, 99-109.
- Baumeister, A.A., Sevin, J.A., & King, B.H. (1998). Neuroleptics. In S. Reiss & M.G. Aman (Eds.), *Psychotropic medications and developmental disabilities: The international consensus handbook* (pp. 133-150). Columbus: Ohio State University Nisonger Center.
- Beange, H., McElduff, A., & Baker, W. (1999). Medical disorders of adults with mental retardation: A population study. *American Journal of Mental Retardation*, *99*, 595-604.
- Berenson, A. (2006, December 17). Eli Lilly said to play down risk of top pill. *New York Times*, p. B1-B2.
- Berenson, A. (2007, January 4). Lilly to pay up to \$500 million to settle claims. *New York Times*, p. B1.

- Berridge, K., & Robinson, T. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research and Review*, 28, 309-69.
- Bindler, R.C. (2007). A cascade of events--obesity, metabolic syndrome, and type 2 diabetes mellitus in youth. *Nursing Clinics of North America*, 42, 29-42.
- Blaine, B.E., Rodman, J., & Newman, J.M. (2007). Weight loss treatment and psychological well-being: A review and meta-analysis. *Journal of Health Psychology*, 12, 66-82.
- Bobes, J., Rejas, J., Garcia-Garcia, M., Rico-Villadernoros, F., Garcia-Portilla, M.P., Fernandez, I. & Hernandez, G. (2003). Weight gain in patients with schizophrenia treated with risperidone, olanzapine, quetiapine, or haloperidol: Results of the EIRE study. *Schizophrenia Research*, 62, 77-86.
- Bratcher, N.A., Farmer-Dougan, V., Dougan, J.D., Heidenreich, B.A., & Garris, P.A. (2005). The role of dopamine in reinforcement: Changes in reinforcement sensitivity induced by D₁-type, D₂-type, and nonselective dopamine receptor agonists. *Journal of the Experimental Analysis of Behavior*, 84, 371-399.
- Bray, G.A., & Bellanger, T. (2006). Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. *Endocrine*, 29, 109-117.
- Brecher, M., Leong, R.W., Stening, G., Osterling-Koskinen, L., & Jones, A.M. (2007). Quetiapine and long-term weight change: A comprehensive data review of patients with schizophrenia. *Journal of Clinical Psychiatry*, 68, 597-603.
- Bristol-Myers Squibb. (2008). *Abilify (aripiprazole) prescribing information*. Tokyo: Author.
- Burton, T.M. (2003). New antipsychotic-drug class is tied to increase in diabetes. *Wall Street Journal*. August 22, 2003.
- Buxton, I.L.O. (2006). Pharmacokinetics and pharmacodynamics: The dynamics of drug absorption, distribution, action, and elimination. In L.L. Brunton, J.S. Lazo, & K.L. Parkers (Eds.). *The pharmacological basis of therapeutics* (11th ed., pp. 461-500). New York: McGraw-Hill.
- Caballero, B. (2007). The global epidemic of obesity: An overview. *Epidemiologic Reviews*, 29, 1-5.
- Carr, D., & Friedman, M.A., (2005). Is obesity stigmatizing? Body weight, perceived discrimination, and psychological well-being in the United States. *Journal of Health and Social Behavior*, 46, 244-259.

- Carr, D., Friedman, M.A., & Jaffe, K. (2007). Understanding the relationship between obesity and positive and negative affect: the role of psychosocial mechanisms. *Body Image, 4*, 165-177.
- Centers for Disease Control & Prevention. (2005). Prevalence of overweight and obesity among adults with diagnosed diabetes: United States, 1988-1994 and 1999-2002. *Journal of the American Medical Association, 293*, 546-547.
- Centers for Disease Control & Prevention. (2008). State-specific prevalence of obesity among adults--United States, 2007. *Journal of the American Medical Association, 57*, 765-768.
- Chaney, R.H., & Eyman, R.K. (2000). Patterns in mortality over 60 years among persons with mental retardation in a residential facility. *Mental Retardation, 38*, 289-293.
- Chaves, A.C., & Seeman, M.V. (2006). Sex selection bias in schizophrenia antipsychotic trials. *Journal of Clinical Psychopharmacology, 26*, 489-494.
- Cheng, J., & Feenstra, M.G. (2006). Individual differences in dopamine efflux in nucleus accumbens shell and core during instrumental learning. *Learning and Memory, 12*, 168-177.
- Chew, M.L., Mulsant, B.H., & Pollock, B.G. (2005). Serum anticholinergic activity and cognition in patients with moderate to severe dementia. *American Journal of Geriatric Psychiatry, 13*, 535-538.
- Cohen, S.A., Fitzgerald, B., Kahn, S.R., & Kahn, A. (2004). The effect of a switch to ziprasidone in an adult population with autistic disorder: chart review of naturalistic open-label treatment. *Journal of Clinical Psychiatry, 65*, 110-113.
- Cohen, S.A., Fitzgerald, B., Okos, A., Khan, S. & Khan, A. (2003). Weight, lipids, glucose, and behavioral measures with ziprasidone treatment in a population with mental retardation. *Journal of Clinical Psychiatry, 64*, 60-62.
- Cohen, S.A., Glazewski, R., Khan, S., & Kahn, A. (2001). Weight gain with risperidone among patients with mental retardation: Effects of calorie restriction. *Journal of Clinical Psychiatry, 62*, 114 – 116.
- Cohen, S.A., Ihrig, K., Lott, R.S., & Kerrick, J.M. (1999). Risperidone for aggression and self-injurious behavior in adults with mental retardation. *Journal of Autism and Developmental Disorders, 28*, 229-233.
- Cohen, D., Stolk, R.P., Grobbee, D.E. & Gispen-de Wied, C. (2006). Hyperglycemia and diabetes in patients with schizophrenia or schizoaffective disorders. *Diabetes Care, 29*, 786-791.

- Cooper, S., Melville, C.A., & Einfeld, S. L. (2003). Psychiatric diagnosis, intellectual disabilities, and the Diagnostic Criteria for Psychiatric Disorder for Use with Adults with Learning Disabilities/Mental Retardation (DC-LD). *Journal of Intellectual Disability Research*, *13*, 3-15.
- Covell, N.H., Weissman, E.M., & Essock, S.M. (2004). Weight gain with clozapine compared to first generation antipsychotic medications. *Schizophrenia Bulletin*, *30*, 229-240.
- Crismon, M.L., & Dorson, P.G. (2006). Schizophrenia. In J.T. Dipiro, R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Well, & L.M. Posey (Eds.). *Pharmacotherapy: A pathophysiologic approach* (6th ed., pp. 1219-1242). McGraw-Hill: New York, NY.
- Davis, J.M., Chen, N., & Glick, I.D. (2003). A meta-analysis of the efficacy of second-generation antipsychotics. *Archives of General Psychiatry*, *60*, 553-564.
- Deb, S. Sohanpal, S.K., Soni, R., Lenotre, L., & Unwin, G. (2007). The effectiveness of antipsychotic medication in the management of behaviour problems in adults with intellectual disabilities. *Journal of Intellectual Disability Research*, *51*, 766-777.
- De Hert, M., Hanssens, L., van Winkel, R., Wampers, M., Van Eyck, D., Scheen, A., & Peuskens, J. (2007). A case series: Evaluation of the metabolic safety of aripiprazole. *Schizophrenia Bulletin*, *33*, 823-830.
- De Hert, M., Schreurs, V., Van Eyck, D., Hanssens, L., Sinko, S., Wampers, M., Scheen, A., Peuskens, J., & van Winkel, R. (2008). Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: A retrospective chart review. *Schizophrenia Research*, *101*, 295-303.
- De Hert, M., Peuskens, B., van Winkel, R., Kalnicka, D., Hanssens, L., Van Eyck, D., Wyckaert, S., & Peuskens, J. (2006). Body weight and self-esteem in patients with schizophrenia evaluated with B-WISE. *Schizophrenia Research*, *88*, 222-226.
- de Leon, J., & Diaz, F.J. (2007). Planning for the optimal design of studies to personalize antipsychotic prescriptions in the post-CATIE era: The clinical and pharmacoepidemiological data suggest that pursuing the pharmacogenetics of metabolic syndrome complications (hypertension, diabetes mellitus and hyperlipidemia) may be a reasonable strategy. *Schizophrenia Research*, *96*, 185-197.
- De Luca, V., Mueller, D.J., de Bartolomeis, A., & Kenndey, J.L. (2007). Association of the HTR2C gene and antipsychotic induced weight gain: A meta-analysis. *International Journal of Neuropsychopharmacology*, *10*, 697-704.

- Deb, S., Sohanpal, S.K., Soni, R., Lenotre, L., & Unwin, G. (2007). The effectiveness of antipsychotic medication in the management of behaviour problems in adults with intellectual disabilities. *Journal of Intellectual Disability Research, 51*, 766-777.
- Department of Health and Human Services. (2005). Protection of human subjects. In *Code of federal regulations* (pp. 1 – 12). Washington, D.C.: Author.
- Despres, J.P. (2006). Is visceral obesity the cause of the metabolic syndrome? *Annals of Medicine, 38*, 52-63.
- Dickinson, D., Gold, J., Dickerson, F.B., Medoff, D., & Dixon, L.B. (2008). Evidence of exacerbated cognitive deficits in schizophrenia patients with comorbid diabetes. *Psychosomatics, 49*, 123-131.
- Dinca, O., Paul, M., & Spencer, N.J., (2005). Systematic review of randomized controlled trials of atypical antipsychotics and selective serotonin reuptake inhibitors for behavioural problems associated with pervasive developmental disorders. *Journal of Psychopharmacology, 19*, 521-532.
- Dosen, A. & Day, K. (2001). Epidemiology, etiology, and presentation of mental illness and behavior disorders in persons with mental retardation. In A. Dosen & K. Day (Eds.). *Treating mental illness and behavior disorders in children and adults with mental retardation* (pp. 3-24). Washington, DC: American Psychiatric Press.
- Dossetor, D.R. (2007). All that glitters is not gold: Misdiagnosis of psychosis in pervasive developmental disorders – a case series. *Clinical Psychology and Psychiatry, 12*, 537-548.
- Duggan, L. & Brylewski, J. (1999). Effectiveness of antipsychotic medication in people with intellectual disability and schizophrenia: A systematic review. *Journal of Intellectual Disability Research, 43*, 94-104.
- Dunn, R.T., Stan, V.A., Chriki, L.S., Filkowski, M.M., & Ghaemi, S.N. (2008). A prospective, open-label study of Aripiprazole mono- and adjunctive treatment in acute bipolar depression. *Journal of Affective Disorders, 110*, 70-74.
- Dunner, D.L. (2005). Atypical antipsychotics: Efficacy across bipolar disorder subpopulations. *Journal of Clinical Psychiatry, 66*, 20-27.
- El-Ghundi, M., O’Dowd, B.F., & George, S.R., (2007). Insights into the role of dopamine receptor systems in learning and memory. *Review of Neuroscience, 18*, 37-66.
- Eli Lilly. (2008). *Zyprexa (olanzapine) prescribing information*. Indianapolis, IN: Author.

- Emsley, R., Turner, H.J., Schronen, J., Botha, K., & Smit, R. (2005). Effects of quetiapine and haloperidol on body mass index and glycaemic control: A long-term, randomized, controlled trial. *International Journal of Neuropsychopharmacology*, 8, 175-182.
- Fell, M.J., McDermott, E., Sisodia, G., Marshall, K.M., & Neill, J.C. (2005). Investigation into the effects of the novel antipsychotic ziprasidone on weight gain and reproductive function in female rats. *Behavioural Brain Research*, 160, 338-343.
- Frank, M.J., & O'Reilly, R.C. (2006). A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. *Behavioral Neuroscience*, 120, 497-517.
- Gagliari, L., & Wittert, G. (2007). Management of obesity in patients with type 2 diabetes mellitus. *Current Diabetes Review*, 3, 95-101.
- Goode, E. (2003, August 25). Three schizophrenia drugs may raise diabetes risk, study says. *New York Times*, p. A8.
- Greenberg, J.A., Fontaine, K., & Allison, D.B. (2007). Putative biases in estimating mortality attributable to obesity in the US population. *International Journal of Obesity*, 31, 1449-1455.
- Gualtieri, T.C. (1991). NMS: A system for prevention and control. In J. Ratey (Ed.), *Mental retardation: Developing pharmacotherapies* (pp. 35-49). Washington, DC: American Psychiatric Press.
- Hammock, R.G., Levine, W.R., & Schroeder, S.R. (2001). The effect of clozapine on self-injurious behavior. *Journal of Autism and Developmental Disorders*, 31, 109-113.
- Harpreet, S.D. & Mendhekar, D.N. (2006). Atypical antipsychotics, tardive dyskinesia, and D₂ receptors. *American Journal of Psychiatry*, 163, 1449-1450.
- Hellings, J.A., Zarcone, J.R., Crandall, K., Wallace, D., & Schroeder, S.R. (2002). Weight gain in a controlled study of risperidone in children, adolescents, and adults with mental retardation and autism. *Journal of Child and Adolescent Psychopharmacology*, 11, 229-238.
- Henderson, D.C., Nguyen, D.D., Copeland, P.M., Hayden, D.L., Borba, C.P., Louie, P.M., Freudenreich, O., Evins, A.E., Cather, C., & Goff, D.C. (2005). Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: Results of a 10-year naturalistic study. *Journal of Clinical Psychiatry*, 66, 1116-1121.
- Hennen, J. & Baldessarini, R.J. (2004). Reduced suicidal risk with clozapine: A meta-analysis. *Schizophrenia Research*, 60, 82-91.

- Hill, M.J., & Reynolds, G.P. (2007). 5-HT_{2C} receptor gene polymorphisms associated with antipsychotic drug action alter promoter activity. *Brain Research*, *1149*, 14-17.
- Hilmer, S.N., McLachlan, A.J., & Le Couteur, D.G. (2007). Clinical pharmacology in the geriatric patient. *Fundamentals of Clinical Pharmacology*, *21*, 217-230.
- Hogg, J., Juhlberg, K., & Lambe, L. (2007). Policy, service pathways and mortality: A 10-year longitudinal study of people with profound intellectual and multiple disabilities. *Journal of Intellectual Disability Research*, *51*, 366-376.
- Hollifield, M., Thompson, P.M., Ruiz, J.E., & Uhlenhuth, E.H. (2005). Potential effectiveness and safety of olanzapine in refractory panic disorder. *Depression and Anxiety*, *21*, 33-40.
- Hori, H., Noguchi, H., Hashimoto, R., Nakabayashi, T., Omori, M., Takahashi, S., Tsukue, R., Anami, K., Hirabayashi, N., Harado, S., Saitaoh, O., Iwase, M., Kajimoto, O., Takeda, M., Okabe, S., & Kunugi, H. (2006). Antipsychotic medication and cognitive function in schizophrenia. *Schizophrenia Research*, *86*, 138-146.
- Hormel, P., Casey, D., & Allsion, D.B. (2002). Changes in body mass index for individuals with and without schizophrenia, 1987-1996. *Schizophrenia Research*, *55*, 277-284.
- Horrigan, J.P., & Barnhill, L.J. (1999). Risperidone and explosive aggressive autism. *Journal of Autism and Developmental Disorders*, *27*, 213-217.
- International Diabetes Federation (2005, April). *The IDF consensus worldwide definition of the metabolic syndrome*. Retrieved July 31, 2008, from http://www.idf.org/webdata/docs/Meta_syndrome_def.pdf
- Janowsky, D.S., Barnhill, L.J., & Davis, J.M. (2003). Olanzapine for self-injurious, aggressive, and disruptive behaviors in intellectually disabled adults: A retrospective, open-label, naturalistic trial. *Journal of Clinical Psychiatry*, *64*, 1258-1265.
- Janowsky, D.S., Barnhill, L.J., Khalid, A.S., & Davis, J.M. (2006). Relapse of aggressive and disruptive behavior in mentally retarded adults following antipsychotic drug withdrawal predicts psychotropic drug use a decade later. *Journal of Clinical Psychiatry*, *67*, 1272-1277.
- Janssen. (2008) *Risperdal (risperidone) prescribing information*. Titusville, NJ: Author.

- Janssen, I., & Bacon, E. (2008). Effect of current and midlife obesity status on mortality risk in the elderly. *Obesity, 4*, 1038-1048.
- Jean-Baptiste, M., Tek, C., Liskov, E., Chakunta, U.R., Nicholls, S., Hassan, A.Q. Brownell, K.D., & Wexler, B.E. (2007). A pilot study of a weight management program with food provision in schizophrenia. *Schizophrenia Research, 96*, 198-205.
- Kaasinen, V., Kemppainen, N., Nagren, K., Helenius, H., Kurki, T., & Rinne, J.O. (2002). Age-related loss of extrastriatal dopamine D(2) receptors in women. *Journal of Neurochemistry, 81*, 1005-1010.
- Kahn, B.U. (1999). Risperidone for severely disturbed behavior and tardive dyskinesia in developmentally disabled adults. *Journal of Autism and Developmental Disorders, 27*, 479-489.
- Kapur, S., Mizrahi, R., & Li, M. (2005). From dopamine to salience to psychosis--linking biology, pharmacology and phenomenology of psychosis. *Schizophrenia Research, 79*, 59-68.
- Khazaal, Y., Fresard, W., Zimmerman, G., Trombert, N.M., Pomini, V., Grasset, F., Borgeat, F., & Zullino, D. (2006). Eating and weight related cognitions in people with schizophrenia : A case control study. *Clinical Practice and Epidemiology in Mental Health, 2*, 29.
- Kim, S.H., Ivanova, O., Abbasi, F.A., Lamendola, C.A., Reaven, G.M., & Glick, I.D. (2007). Metabolic impact of switching antipsychotic therapy to aripiprazole after weight gain: A pilot study. *Journal of Clinical Psychopharmacology, 27*, 365-368.
- Kloiber, S., Ising, M., Reppermund, S., Horstmann, S., Dose, T., Majer, M., Zihl, J., Pfister, H., Unschuld, P.G., Holsboer, F., & Lucae, S. (2007). Overweight and obesity affect treatment response in major depression. *Biological Psychiatry, 62*, 321-326.
- Kolotkin, R.L., Corey-Lisle, P.K., Crosby, R.D., Swanson, J.M., Tuomari, A.V., L'italien, G.J., & Mitchell, J.E. (2008). Impact of obesity on health-related quality of life in schizophrenia and bipolar disorder. *Obesity, 16*, 749-754.
- Kolotkin, R.L., Crosby, R.D., Corey-Lisle, P.K., Li, H., & Swanson, J.M. (2006). Performance of a weight-related measure of Quality of Life in a psychiatric sample. *Quality of Life Research, 15*, 587-596.
- Kopala, L.C., Good, K.P., Milliken, H., Buiteman, C., Woodley, H., Rui, Q., Whitehorn, D., Love, L., Balshaw, R., Kiss, I., & Honer, W.G. (2006). Treatment of a first episode of psychotic illness with quetiapine: An analysis of 2 year outcomes. *Schizophrenia Research, 81*, 29-39.

- Kurzthaler, I., & Fleischhacker, W.W. (2001). The clinical implications of weight gain in schizophrenia. *Journal of Clinical Psychiatry*, 62(Suppl. 7), 32-37.
- La Malfa, G., Lassi, S., Bertelli, M., & Castellani, A. (2006). Reviewing the use of antipsychotic drugs in people with intellectual disability. *Human Psychopharmacology*, 21, 73-89.
- Lamberti, J.S., Costea, G.O., Olson, D., Frilly, J.F., Maharaj, K., Tu, X., Froman, A., Dietz, M.B., Bushey, M.P., Olivares, T., & Weiner, K. (2005). Diabetes mellitus among outpatients receiving clozapine: Prevalence and clinical-demographic correlates. *Journal of Clinical Psychiatry*, 66, 900-906.
- Lambert, B.L., Cunningham, F.E., Miller, D.R., Dalack, G.W., & Hur, K. (2006). Diabetes risk associated with use of olanzapine, risperidone, and quetiapine in Veteran's Health Administration patients with schizophrenia. *American Journal of Epidemiology*, 164, 672-681.
- Leas, L., & McCabe, M. (2007). Health behaviors among individuals with schizophrenia and depression. *Journal of Health Psychology*, 12, 563-579.
- Legal battle over controversial prescription drug zyprexa. (2007, January 8). *Electronic Frontier Foundation*, p. 4.
- Leslie, D.L., & Rosenheck, R.A. (2005). Pharmacotherapy and health care costs among patients with schizophrenia and newly diagnosed diabetes. *Psychiatric Services*, 56, 803-809.
- Leucht, S., Pitschel-Walz, G., Abraham, D., & Kissling, W. (1999). Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: A meta-analysis of randomized controlled trials. *Schizophrenia Research*, 35, 51-68.
- Levitas, A. (2003). Reader response to "Effects of risperidone on aberrant behavior of persons with developmental disabilities: A double-blind crossover study using multiple measures". *American Journal of Mental Retardation*, 108, 212-214.
- Lieberman, J., Stroup, T.S., McEvoy, J.P., Marvin, S.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J.S., Hsiao, J.K., & the Clinical Antipsychotics Trials of Intervention Effectiveness (CATIE) Investigators (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine*, 353, 1209-1223.
- Linden, M., Scheel, T., & Eich, F. (2006). Improvement of patient compliance after switching from conventional neuroleptics to the atypical neuroleptics. *Journal of Psychopharmacology*, 20, 815-823.

- Lipman, R.S. (1970). The use of psychopharmacological agents in residential facilities for the retarded. In F.J. Menolascino, (Ed.), *Psychiatric approaches to mental retardation* (pp. 387-398), New York: Basic Books.
- Lois, K., Young, J., & Kumar, S. (2008). Obesity: Epiphenomenon or cause of metabolic syndrome? *International Journal of Clinical Practice*, *62*, 932-938.
- Luchins, D.J., Dojka, D.M., & Hanrahan, P. (1998). Factors associated with reduction in antipsychotic medication dosage in adults with mental retardation. *American Journal of Mental Retardation*, *98*, 165-172.
- Mahley, R.W. & Bersot, T.P. (2006). Drug therapy for hypercholesterolemia and dyslipidemia. In L.L. Brunton, J.S. Lazo, & K.L. Parkers (Eds.). *The pharmacological basis of therapeutics* (11th ed., pp. 461-500). New York: McGraw-Hill.
- Marder, S.R., McQuade, R.D., Stock, E., Kaplita, S., Marcus, R., Safferman, A.Z., Saha, A., Ali, M., & Iwamoto, T. (2003). Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophrenia Research*, *61*, 123-126.
- Matson, J.L., Bamburg, J.W., Mayville, E.A., Pinkston, J., Bielecki, J., Logan, J.R., & Kuhn, D. (2000). Psychopharmacology and mental retardation: A 10 year review (1990-1999). *Research in Developmental Disabilities*, *21*, 263-296.
- Matson, J.L., Bielecki, J., Mayville, S.B., & Matson, M.L. (2003). Psychopharmacology research for individuals with mental retardation: Methodological issues and suggestions. *Research in Developmental Disabilities*, *24*, 149-157.
- Matsui-Sakata, A., Obtani, H., & Sawada, Y. (2008). Receptor occupancy-based analysis of the contributions of various receptors to antipsychotics-induced weight gain and diabetes mellitus. *Drug Metabolism and Pharmacokinetics*, *20*, 368-378.
- McAdam, D.B., Zarcone, J.R., Hellings, J., Napolitano, D.A., & Schroeder, S.R. (2002). Effects of risperidone on aberrant behavior in persons with developmental disabilities. *American Journal on Mental Retardation*, *107*, 261-269.
- McElroy, S.L., Suppes, T., Frye, M.A., Altshuler, L.L., Stanford, K., Martens, B., Leverich, G.S., Post, R.M., & Keck, P.E. (2007). Open-label aripiprazole in the treatment of acute bipolar depression: A prospective pilot trial. *Journal of Affective Disorders*, *101*, 275-281.
- McEvoy, J.P., Lieberman, J.A., Perkins, D.O., Hamer, R.M., Hongbin, G., Lazarus, A., Sweitzer, D., Olexy, C., Weiden, P., & Strakowski, S.D. (2007). Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis. *American Journal of Psychiatry*, *164*, 1050-1060.

- McEvoy, J.P., Meyer, J.M., Goff, D.C., Nasrallah, H.A., Davis, S.M., Sullivan, L., Meltzer, H.Y., Hsiao, J., Stroup, T.S., & Leiberman, J.A. (2005). Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophrenia Research*, *80*, 19-32.
- McGillivray, J.A., & McCabe, M.P. (2004). Pharmacological management of challenging behavior of individuals with intellectual disability. *Research in Developmental Disabilities*, *25*, 523-537.
- McKee, J.R., Bodfish, J.W., Mahorney, S.L., Heath, W.L., & Ball, M. P. (2005). Metabolic effects associated with atypical antipsychotic treatment in the developmentally disabled. *Journal of Clinical Psychiatry*, *66*, 1161-1168.
- McQuade, R.D., Stock, E., Marcus, R., Jody, D., Gharbia, N.A., Vanveggel, S., Archibald, D., & Carson, W. (2004). A comparison of weight change during treatment with olanzapine or aripiprazole: Results from a randomized, double-blind study. *Journal of Clinical Psychiatry*, *65*(Suppl. 18), 47-55.
- Meltzer, H.Y. (2004). Putting metabolic side effects into perspective: Risk versus benefits of atypical antipsychotics. *Journal of Clinical Psychiatry*, *62*(Suppl. 27), 35-39.
- Meltzer, H.Y., Arvanitis, L., Bauer, D., & Rein, W. (2004). Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. *American Journal of Psychiatry*, *161*, 975-984.
- Meltzer, H.Y., & Huang, M. (2008). In vivo actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. *Progress in Brain Research*, *172*, 177-197.
- Meyer, J.M. (2001a). Effects of atypical antipsychotics on weight and serum lipid levels. *Journal of Clinical Psychiatry*, *62*, 27-34.
- Meyer, J.M. (2001b). Novel antipsychotics and severe hyperlipidemia. *Journal of Clinical Psychopharmacology*, *21*, 369-374.
- Meyer, J.M. (2007). Antipsychotic safety and efficacy concerns. *Journal of Clinical Psychiatry*, *68*, (Suppl 14), 20-26.
- Meyer, J.M., Davis, V.G., Goff, D.C., McEvoy, J.P., Nasrallah, H.A., Davis, S.M., Rosenheck, R.A., Daumit, G.L., Hsiao, J., Swartz, M.S., Stroup, T.S., & Leiberman, J.A. (2008). Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: Prospective data from phase 1. *Schizophrenia Research*, *101*, 273-286.

- Miller, B.J., Paschall, C.B., & Svendsen, D.P. (2006). Mortality and medical comorbidity among patients with serious mental illness. *Psychiatric Services, 57*, 1482-1487.
- Miller, M.A. (2001). Gender-based differences in the toxicity of pharmaceuticals: The Food and Drug Administration's perspective. *International Journal of Toxicology, 20*, 149-152.
- Miller, M.A., Leslie, D.L., & Rosenheck, R.A. (2005). Incidence of new-onset diabetes mellitus among patients receiving atypical neuroleptics in the treatment of mental illness: Evidence from a privately insured population. *Journal of Nervous and Mental Disease, 193*, 387-395.
- Miyamoto S., Duncan G.E., Marx C.E., & Lieberman J.A. (2005). Treatments for schizophrenia: A critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Molecular Psychiatry, 10*, 79-104.
- Mobbs, CV., Isoda, F., Makimura, H., Mastaitis, J., Mizuno, T., Shu, I.W., Yen, K., & Zang, X.J. (2005). Impaired glucose signaling as a cause of obesity and the metabolic syndrome: The glucoadipostatic hypothesis. *Physiology & Behavior, 85*, 3-32.
- Montes, J.M., Rodriguez, J.L., Balbo, E., Sopelana, P., Martin, E., Soto, J.A., Delgado, J.F., Diez, T., & Villardaga, I. (2007). Improvement in antipsychotic-related metabolic disturbances in patients with schizophrenia switched to ziprasidone. *Progress in Neuropsychopharmacology and Biological Psychiatry, 31*, 383-388.
- Monti, J.M., & Jantos, H. (2008). The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking. *Progress in Brain Research, 172*, 625-646.
- Murray, M. (2006). Role of CYP pharmacogenetics and drug-drug interactions in the efficacy and safety of atypical and other antipsychotic agents. *Journal of Pharmacy and Pharmacology, 58*, 871-875.
- Nasrallah, H.A. (2006). Focus on lower risk of tardive dyskinesia with atypical antipsychotics. *Annals of Clinical Psychiatry, 18*, 57-62.
- Nasrallah, H.A., Brecher, M., & Paulsson, B. (2006). Placebo-level incidence of extrapyramidal symptoms (EPS) with quetiapine in controlled studies of patients with bipolar mania. *Bipolar Disorder, 8*, 467-474.
- National Institutes of Health. (1998). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The evidence report. *Obesity Research, 6*(Suppl. 2), 51-209.
- Nnadi, C.U., & Malhotra, A.K. (2007). Individualizing antipsychotic drug therapy in schizophrenia: The promise of pharmacogenetics. *Current Psychiatry Reports, 9*, 313-318.

- Novartis. (2008). *Clozaril (clozapine) prescribing information*. East Hanover, NJ: Author.
- Oates, J.A. (2006). The science of drug therapy. In L. Brunton, J. Lazo, & K. Parker (Eds.), *Goodman and Gilman's the pharmacological basis of therapeutics* (11th.ed., pp. 117-136). New York: McGraw-Hill.
- Ogden, C.L. (2006). Prevalence of overweight and obesity in the United States, 1999-2004. *Journal of the American Medical Association*, 295, 1549-1555.
- Olvera-Cortez, M.E., Anquiano-Rodriguez, P., Lopez-Vazquez, M.A., & Alfaro, J.M. (2008). Serotonin/dopamine interaction in learning. *Progress in Brain Research*, 172, 567-602.
- Pagnamenta, R. (2007, January 23). Eli Lilly was concerned by zyprexa side-effects since 1998: Concerns revealed in internal papers \$4bn treatment linked to diabetes. *London Times*, p. H1.
- Parikh, N.I., Pencina, M.J., Wang, T.J., Lanier, K.J., Fox, C.S., D'Agostino, R.B. & Vasan, R.S. (2007). Increasing trends in incidence of overweight and obesity over 5 decades. *American Journal of Medicine*, 120, 242-250.
- Paulsen, J.S., Heaton, R.K., & Jeste, D.V. (1994). Neuropsychological impairment in tardive dyskinesia. *Neuropsychology*, 8, 227-241.
- Perez-Iglesias, R., Crespo-Facorro, B., Martinez-Garcia, O., Ramirez-Bonilla, M.L., Alvarez-Jimenez, M., Pelayo-Teran, J.M., Garcia-Unzueta, M.T., Amado, J.A., & Vazquez-Barquero, J.L. (2008). Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: Findings of a randomized clinical trial in a drug-naïve population. *Schizophrenia Research*, 99, 12 -22.
- Perkins, D.O. (2002). Predictors of noncompliance in patients with schizophrenia. *Journal of Clinical Psychiatry*, 62, 1121-1128.
- Pfizer. (2008). *Geodon (ziprasidone) prescribing information*. NY: Author.
- Pierre, J.M., Shnayder, I., Wirshing, D.A., & Wirshing, W.C. (2004). Intranasal quetiapine abuse. *American Journal of Psychiatry*, 161, 1718.
- Pinkofsky, H.B., Hahn, A.M., Campbell, F.A., Rueda, J., Daley, D.C., & Douaihy, A.B. (2005), Reduction of opioid-withdrawal symptoms with quetiapine. *Journal of Clinical Psychiatry*, 66, 1285–1288.
- Pinta, E.R., & Taylor, R.E. (2007). Quetiapine addiction? *American Journal of Psychiatry*, 164, 174.

- Pollack MH, Simon NM, Zalta AK, Worthington JJ, Hoge EA, Mick E, Kinrys G, Oppenheimer J. (2006). Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: A placebo controlled study. *Biological Psychiatry*, 59, 211-215.
- Popkin, B.M., Kim, S., Rusev, E.R., Du, S., & Zizza. C. (2006). Measuring the full economic costs of diet, physical activity and obesity-related chronic diseases. *Obesity Reviews*, 7, 271-293.
- Potter, J.D.. (2006). Epidemiologic research in the face of an obesity epidemic. *Epidemiology*, 12, 124-127.
- Prentice, A.M. (2006). The emerging epidemic of obesity in developing countries. *International Journal of Epidemiology*, 35, 93-99.
- Provencher, V., Polivy, J., Wintre, M.G., Pratt, M.W., Pancer, S.M., Birnie-Lefcovitch, S., & Adams, G.R. (2008). Who gains or who loses weight? Psychosocial factors among first-year university students. *Physiology and Behavior*, 16, 1930-1939.
- Reynolds, G.P., Hill, M.J., & Kirk, S.L. (2006). The 5-HT_{2C} receptor and antipsychotic induced weight gain – mechanisms and genetics. *Journal of Psychopharmacology*, 20, 15-18.
- Reynolds, G.P., Templeman, L.A., & Zhang, Z.J. (2005). The role of 5-HT_{2C} receptor polymorphisms in the pharmacogenetics of antipsychotic drug treatment. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 29, 1021-1028.
- Richtand, N.M., Welge, J.A., Logue, A.D., Keck, P.E., Strakowski, S.M., & McNamara, R.K. (2008). Role of serotonin and dopamine receptor binding in antipsychotic efficacy. *Progress in Brain Research*, 172, 155-175.
- Rocha, F.L., Hara, C., Ramos, M.G., Kascher, G.G., Santos, M.A., de Oliveira Lanca, G., & Magalhaes-Scoralick, F. (2006). An exploratory open-label trial of ziprasidone for the treatment of behavioral and psychological symptoms of dementia. *Dementia and Geriatric Cognitive Disorders*, 22, 445-448.
- Rosack, J. (2003). FDA to require diabetes warning on antipsychotics. *Psychiatric News*, 38, 1.
- Ruhe, H.G., Mason, N.S., & Schene, A.H. (2007). Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Molecular Psychiatry*, 12, 331-359.

- Rush, K.S., Bowman L.G., Eidman, S.L., Toole, L.M., & Mortenson, B.P. (2004). Assessing psychopathology in individuals with developmental disabilities. *Behavior Modification, 28*, 621-637.
- Rush, A.J., & Frances, A. (2000). The expert consensus guideline series: Treatment of psychiatric and behavioral problems in mental retardation. *American Journal of Mental Retardation, 105*, 159-226.
- Sacher, J., Mossaheb, N., Spindelegger, C., Klein, N., Geiss-Granadia, T., Sauermann, R., Lackner, E., Joukhadar, C., Muller, M., & Kasper, S. (2008). Effects of olanzapine and ziprasidone on glucose tolerance in healthy volunteers. *Neuropsychopharmacology, 33*, 1633-1641.
- Sachs, G.S. & Guille, C. (1999). Weight gain associated with use of psychotropic medications. *Journal of Clinical Psychiatry, 60*, 16-19.
- Sadock, B.J., & Sadock, V.A. (2005). Kaplan & Sadock's pocket handbook of clinical psychiatry (4th ed.) Philadelphia: Lippincott Williams & Wilkins.
- Saeedi, H., Remington, G., & Christensen, B.K. (2006). Impact of haloperidol, a dopamine D2 antagonist, on cognition and mood. *Schizophrenia Research, 85*, 222-231.
- Sanchez-Barranco, P. (2005). New onset of diabetes mellitus with ziprasidone: A case report. *Journal of Clinical Psychiatry, 66*, 268-269.
- Santosh, P.J., & Baird, G. (1999). Psychopharmacotherapy in children and adults with intellectual disability. *Lancet, 354*, 233-242.
- Savitz, J., Solms, M., & Ramesar, R. (2006). The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes, Brain, Behavior, 5*, 311-328.
- Savoy, Y.E., Ashton, M.A., Miller, M.W., Nedza, F.M., Spracklin, D.K., Hawthorn, H.R., Matos, F.F., & Hajos-Korcsok. (2008). Differential effects of various typical and atypical antipsychotics on plasma glucose and insulin levels in the mouse: Evidence for the involvement of sympathetic regulation. *Schizophrenia Bulletin, 10*, 103-109.
- Schwartz, J.B. (2007). The current state of knowledge on age, sex, and their interactions on clinical pharmacology. *Clinical Pharmacology & Therapeutics, 82*, 87-96.
- Seeman, M.V.S. (2006). Gender differences in the prescribing of antipsychotic drugs. *Focus, 4*, 115-124.
- Seeman, M.V. (2008). Secondary effects of antipsychotics: Women at greater risk than men. *Schizophrenia Bulletin, 10*, 1093-1103.

- Shedlack, K.J., Hennen, J., Magee, C., & Cheron, D. (2005). Assessing the utility of atypical antipsychotic medications in adults with mild mental retardation and comorbid psychiatric disorders. *Journal of Clinical Psychiatry, 66*, 52-62.
- Silkstrom, S., & Soderlund, G. (2007). Stimulus-dependent dopamine release in attention-deficit/hyperactivity disorder. *Psychological Review, 114*, 1047-1075.
- Soiza-Reilly, M., Fossati, M., Ibarra, G.R., & Azcurra, J.M. (2004). Different dopamine D1 and D2 receptors expression after motor activity in the striatal critical period. *Brain Research, 2*, 217-221.
- Spreat, S., Conroy, J.W., & Fullerton, A. (2004). Statewide longitudinal survey of psychotropic medication use for persons with mental retardation: 1994 to 2000. *American Journal of Mental Retardation, 109*, 322-331.
- Spreat, S., Conroy, J.W., & Jones, J.C. (1997). Use of psychotropic medication in Oklahoma: A statewide survey. *American Journal of Mental Retardation, 102*, 80-85.
- Stone, J.M., Davis, J.M., Leucht, S., & Pilowsky, L.S. (2008). Cortical dopamine D₂/D₃ receptors are a common site of action for antipsychotic drugs: An original patient data meta-analysis of the SPECT and PET in vivo receptor imaging literature. *Schizophrenia Bulletin, 10*, 1093-1099.
- Straker, D.A., Shapiro, P.A., & Muskin, P.R. (2006). Aripiprazole in the treatment of delirium. *Psychosomatics, 47*, 385 - 391.
- Strassnig, M., Brar, J.S., & Ganguli, R. (2005). Self-reported body weight perception and dieting practices in community-dwelling patients with schizophrenia. *Schizophrenia Research, 75*, 425-432.
- Strassnig, M., Miewald, J., Keshavan, M., & Ganguli, R., (2007). Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: One-year analysis. *Schizophrenia Research, 93*, 98-98.
- Urban, J.D., Vargas, G.A., von Zastrow, M., Mailman, R.B. (2007). Aripiprazole has functionally selective actions at dopamine D2 receptor-mediated signaling pathways. *Neuropsychopharmacology, 32*, 67-77.
- Usall, J., Suarez, D., Haro, J.M., & SOHO Study Group. (2007). Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. *Psychiatry Research, 153*, 225-231.
- Tabak, J., Toporikova, N., Freeman, M.E., & Bertram, R. (2007). Low dose of dopamine may stimulate prolactin secretion by increasing fast potassium currents. *Journal of Neuroscience, 22*, 211-222.

- Taggart, L., McMillan, R., & Lawson, A. (2008). Women with and without intellectual disability and psychiatric disorders. *Journal of Intellectual Disabilities Research, 12*, 191-211.
- Tarsy, D., & Baldessarini, R.J. (2006). Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? *Movement Disorders, 21*, 589-598.
- Tenback, D.E., van Harten, P.N., Slooff, C.J., van Os, J., & SOS Study Group (2006). Evidence that early extrapyramidal symptoms predict later tardive dyskinesia: A prospective analysis of 10,000 patients in the European schizophrenia outpatient health outcomes (SOHO) study. *American Journal of Psychiatry, 163*, 1438-1440.
- Timdahl, K., Carlsson, A., & Stening, G. (2007). An analysis of safety and tolerability data from controlled, comparative studies of quetiapine in patients with schizophrenia, focusing on extrapyramidal symptoms. *Human Psychopharmacology, 22*, 315-325.
- Turner, M.S., & Stewart, D.W. (2006). Review of the evidence for the long-term efficacy of atypical antipsychotic agents in the treatment of patients with schizophrenia and related psychoses. *Journal of Psychopharmacology, 20*, 20-37.
- Vohora, D. (2007). Atypical antipsychotic drugs: Current issues of safety and efficacy in the management of schizophrenia. *Current Opinions in Investigational Drugs, 8*, 531-538.
- Unwin, G.L., & Deb, S. (2008). Use of medication for the management of behavior problems among adults with intellectual disabilities: A clinicians' consensus survey. *American Journal of Mental Retardation, 113*, 19-31.
- Urban, J.D., Vargas, G.A., von Zastrow, M., & Mailman, R.B. (2007). Aripiprazole has functionally selective actions at dopamine D2 receptor-mediated signaling pathways. *Neuropsychopharmacology, 32*, 66-77.
- Usall, J., Suarez, D., Haro, J.M., & SOHO Study Group. (2007). Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. *Psychiatry Research, 153*, 225-231.
- Wang, X., Savafe, R., Borisove, A., Rosenberg, J., Woolvine, B., Tucker, M., May, R., Feldman, J., Nemeroff, C.B., & Miller, A.H. (2006). Efficacy of risperidone versus olanzapine in patients with schizophrenia previously on chronic conventional antipsychotic therapy: A switch study. *Journal of Psychiatric Research, 40*, 669-676.
- Waters, B.M., & Joshi, K.G. (2007). Intravenous quetiapine-cocaine use ("q-ball"). *American Journal of Psychiatry, 164*, 173.

- Weber, M. (2008). Metformin and lifestyle changes reduce antipsychotic-related weight gain in adults with schizophrenia. *Evidence Based Mental Health, 11*, 82.
- Weiden, P.J., Newcomer, J.W., Loebel, A.D., Yang, R., & Lebovitz, H.E. (2008). Long-term changes in weight and plasma lipids during maintenance treatment with ziprasidone. *Neuropsychopharmacology, 33*, 985-994.
- Weiss, Marksteiner, Kemmler, Saria, & Aichhorn (2006). Effects of age and sex on olanzapine plasma concentrations. *Journal of Clinical Psychopharmacology, 25*, 570-574.
- Williams, H., Clarke, R., Bouras, N., Martin, J., & Holt, G. (2000). Use of the atypical antipsychotics olanzapine and risperidone in adults with intellectual disability. *Journal of Intellectual Disability Research, 44*, 164-169.
- Wilson, D.R., D'Souza, L., Sarkar, N., Newton, M., & Hammond, C. (2003). New-onset diabetes and ketoacidosis with atypical antipsychotics. *Schizophrenia Research, 59*, 1-6.
- Wilson, J.G., Lott, R.S., & Tsai, L. (1998). Side-effect recognition and management. In A. Reiss & M.G. Aman (Eds.), *Psychotropic medication and developmental disabilities: The international consensus handbook* (pp. 95-114). The Ohio State University Press, Columbus, OH.
- Wirshing, D.A., Wirshing, W.C., Kysar, L., Berisford, M.A., Goldstein, D., Pashdag, J., Mintz, J., & Marder, S.R. (1999). Novel antipsychotic drugs: Comparison of weight gain liabilities. *Journal of Clinical Psychiatry, 60*, 358-363.
- Wonodi, I., Hong, L.E., & Thaker, G.K. (2005). Psychopathological and cognitive correlates of tardive dyskinesia in patients treated with neuroleptics. *Advances in Neurology, 96*, 336-349.
- World Health Organization (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. Geneva, Switzerland: Author.
- Wszloa, B.A., Newell, K.M., & Sprague, R.L. (2001). Risk factors for tardive dyskinesia in a large population of youths and adults. *Experimental and Clinical Psychopharmacology, 9*, 285-296.
- Wu, E.Q., Shi, L., Birnbaum, H., Hudson, T., & Kessler, R. (2006). Annual prevalence of diagnosed schizophrenia in the USA: A claims data analysis approach. *Psychological Medicine, 36*, 1535-40.

Yach, D., Stuckler, D., & Brownell, K.D., (2006). Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. *Nature Medicine*, *12*, 62-66.

Zarcone, J.R., Hellings, J.A., Crandall, K., Reese, R.M., Marquis, J., Fleming, K., Shores, R., Williams, D., & Schroeder, S.R. (2001). Effects of risperidone on aberrant behavior of persons with developmental disabilities: A double-blind crossover study using multiple measures. *American Journal of Mental Retardation*, *106*, 525-538.

Vita

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