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Sex Differences in Response to Treatment with Risperidone

by

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ABSTRACT

This is a retrospective cohort study involving 81 female and 149 male patients diagnosed with schizophrenia and related disorders. The objectives were to determine if there were sex differences in the discontinuation rates of risperidone, a novel antipsychotic used to treat these illnesses. Rates of sexual side effects experienced were also investigated for sex differences.

Females were found to discontinue risperidone at significantly higher rates than did male patients at two of the three sites involved over one year of treatment. The third site utilized demonstrated no sex differences; this site may demonstrate a different subset of patients with the illness. Females at all sites demonstrated higher rates of sexual side effects during treatment with risperidone compared to males.

These findings suggest that at least some females may have a lower tolerance to risperidone treatment. Possible reasons for these significant findings are explored further in the subsequent discussion.

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DEDICATION

To all those living with schizophrenia

I am humbled by your strength and courage

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LIST OF ABBREVIATIONS

FDA	-	Food and Drug Administration
CBP	-	Child bearing potential
IRB	-	Investigational review board
GAO	-	General Accounting Office
ORWH	-	Office of Research on Women's Health
NIH	-	National Institute of Health
HPB	-	Health Protection Branch
DSM-IV	-	Diagnostic and Statistical Manual of Mental Disorders, Version IV
D	-	dopamine
$\mathbf{D_n}$	-	dopamine receptor, classified by number denoted by 'n' (eg. D_1, D_2)
5HT	-	serotonin (or 5-hydroxytryptamine)
$\mathbf{5HT_n}$	-	serotonin receptor, classified by number denoted by 'n' (eg. 5-HT_2)
α_n	-	alpha noradrenaline receptor (eg. α_1, α_2)
$\mathbf{H_n}$	-	histamine receptor (eg. H_1)
$\mathbf{M_n}$	-	muscarinic acetylcholine receptor
EPS	-	extrapyramidal syndrome
TD	-	tardive dyskinesia

CHAPTER ONE: INTRODUCTION

1.1 OVERVIEW

Despite research efforts, the etiology of mental disorders are for the most part unknown; current therapies enable clinicians to treat only the resultant symptoms. The cause of schizophrenia, one of the most debilitating disorders, continues to evade both researchers and clinicians. Much of what is known today regarding psychopathology and treatment has been learned through the serendipitous discovery of new medications. It is increasingly evident in the literature that in the population, this illness appears to be heterogeneous, yet the lack of treatment options does not reflect this observation. Many patients are prescribed several different medications before one is found that treats the symptoms, often with only limited success and at the cost of significant side effects. Furthermore, a number of patients do not appear to respond to any medications and are so called treatment resistant.

Recent clinical trials of new antipsychotic drugs have expanded knowledge of drug therapies but there are inherent problems in the data collected given the selected and small populations the drugs are tested on, and the short period of testing involved. One aspect of drug testing and treatment in schizophrenia which has consistently been underinvestigated is the problem of sex differences. Investigators and pharmaceutical companies have seldom acknowledged possible differences in the way male and female patients respond to medications. This has resulted in medications being released on the market with limited information on their effects

in female patients, particularly women of childbearing potential. Clinical trials are not the endpoint of investigation, but the beginning; only with widespread use of new drug treatments in different population subgroups can sufficient data be obtained to truly assess the treatments in the population. For this reason, investigations into sex differences in efficacy and safety profiles of drugs are imperative.

This is a post-release study comparing drug discontinuation rates of male and female patients prescribed risperidone, a novel antipsychotic used to treat schizophrenia. Possible reasons for discontinuing risperidone and side effect profiles were also investigated as these may produce valuable information on differential benefits and risks of the medication for each sex. Both male and female patients can benefit from accurate information on treatments for their illnesses.

1.2 REVIEW OF THE LITERATURE

1.2.1 History of Clinical Trial Policies

To gain insight into the paucity of the literature on treatment response data in women, the history of clinical investigations must be considered. Although the design and conduct of clinical trials have evolved parallel to the advance of modern medicine, there are strong influences from the past with regards to inclusion of women, the problems of which affect the present and future.

The investigation of novel medical interventions demonstrates a history of problems, both ethically and scientifically. In the early nineteenth century, the inclusion of vulnerable populations giving no regard to consent was seen as an opportunity rather than a breach of ethical principles. One of the earlier examples of such practices was the use of American slave women to test new surgical interventions in repairing vesicovaginal fistulas. Anesthetics were not used, and it was regarded as 'resourceful' of these pioneer surgeons to utilize the slave women as participants in research *"to which no free white woman would have subjected herself"*.[1]

In the twentieth century, slaves were replaced by incarcerated individuals, both from prisons and insane asylums, comprising the majority of research subjects. Many prisoners volunteered during World War II for opportunities to test new treatments for tropical diseases

affecting American soldiers overseas. Government sponsored programs had no shortage of volunteers from this population hoping to impress a parole board or earn extra money and privileges. It has been estimated that until 1972, more than 90% of all investigational drugs were first tested on prisoners.[1]

Following World War II and the controversial Nuremberg trials convicting Nazi scientists for 'crimes against humanity', an international standard for human research, the Nuremberg Code of Ethics was established in the late 1940's, recognizing the fundamental and sacred dignity of human subjects.[2] During this period, the public regarded research as dangerous and of little value to individual subjects. A significant lack of trust by the public and hesitancy to participate in clinical trials were the result of exposure of past research scandals. These societal attitudes combined with researcher's fear of exploiting 'vulnerable' populations caused a dramatic increase in using white males in medical investigations.[2] Using this population was viewed as convenient and safer with regard to possible accusations of prejudicial practices.

Several tragic events resulted in the view that female subjects were a particular hazard in medical research, both scientifically and legally. Perhaps the most noted of these was the use of thalidomide, a new hypnotic released in the 1960's which resulted in an epidemic of malformed infants due to the lack of well-conducted research on the drug before release.[3] The appearance in the 1970s of vaginal adenocarcinoma in daughters of women who, decades earlier, had been prescribed diethylstilbestrol during pregnancy to avoid miscarriage

served to demonstrate the timeline which must be considered when assessing long term safety of new medications.[3]

These experiences caused women of child bearing potential to rapidly become regarded as 'undesirable' subjects by both industry and the research community. At this time, the male body was considered the 'normal' physiological state, while women were regarded as a variation of the 'male model', and therefore there was no compelling reason to subject them to the potential risks of early clinical trials.[1]

In 1977 the Food and Drug Administration (FDA) issued a policy banning women of child bearing potential (CBP) from participating in Phase I and early Phase II clinical trials of new medications due to growing concerns of risks to potential unborn fetuses. Exceptions were made to this rule for compassionate use of drugs to treat life-threatening illnesses.[4] Although the policy only applied to smaller early stage trials, many investigators and Investigational Review Boards (IRBs) extended the policy to all phases of clinical trials. The fear of liability grew to proportions exceeding actual liabilities posed in practice.[2] Little thought was given to the fact that as a result of this legislation, exposing women of CBP to drugs untested on female subjects could result in greater harm to far more patients.

The 1977 policy raised many issues regarding the autonomous right of women to make decisions about their bodies. The FDA defined women of child bearing potential as *"all premenopausal women with a uterus who could physiologically be capable of becoming*

pregnant" [5], which did not give credit to the ability of women to control their own fertility and lifestyles. Women with little or no risk of pregnancy, including lesbians, women with vasectomized spouses and nuns were not eligible to participate in trials under these terms.[6] The complete exclusion of female subjects assumed the paternalistic view that all females are alike, are sexually active and are unreliable in their contraceptive practices.[7]

Some have argued that the same exclusionary practices should apply to fertile sexually active men; if society deems the health of potential future children enough to justify blanket exclusion of fertile females, then all fertile subjects should be excluded, male and female.[7] There is growing evidence that many substances are damaging to sperm and can result in birth defects in offspring [8], and since men's reproductive period is longer, they could be excluded for more years than women.[7]

Subsequent studies showed that in fact women were very different from men in their responses to various medications.[9] This data reinforced the argument proposed by women's groups advocating the reform of societal attitudes towards the autonomy of female subjects. Researchers began advocating for women's participation in clinical trials of medications which would ultimately be used by women, as this information was essential to evaluate the safety and efficacy profiles in this demographic group. Because inclusion of women was not occurring, the results of medical research were in effect, being extrapolated to women without sufficient evidence that the conclusions applied to women.[10]

Examples of trials being conducted on men and erroneous conclusions being drawn are numerous. Cardiovascular medicine has perhaps gained the most attention in this matter. Heart disease has frequently been described as a 'male disease' as it is frequent in young men. Most studies on risk factors for heart disease were carried out on middle aged, middle class white males, yet it is the leading cause of death in older women.[11] Due to these studies in men, the American Heart Association recommended a diet for their patients that could actually exacerbate risk of the illness in women.[7]

The first twenty years of a major federal study on health and aging included only men, yet two thirds of the elderly are women.[7] In another study, findings that aspirin could help prevent migraine headaches were based on studies using only males, yet women suffer from migraines three times as often as men.[7] Perhaps the most absurd of these studies was the pilot project on the importance of obesity on breast and uterine cancer which was conducted solely on male subjects.[7]

Many researchers have tried to defend their exclusionary practices, stating that clinical research requires 'clean simple data' from a homogeneous population. The more alike the subjects are, the more any variation can be attributed to the experimental intervention being tested.[7] This theory fails to recognize a more important issue: the data from such homogenous subjects is useless if it is not generalizable to the population affected with the illness, which in most cases includes females. Representative samples are required for results to have applicability to the society they serve to describe.

Reports published by the US General Accounting Office (GAO) in 1990 stated that women were routinely being excluded from all phases of clinical trials and sex-specific analyses on results were not being performed.[12] These findings lead to the formation of the Office of Research on Women's Health (ORWH) at the National Institute of Health (NIH). Part of their mandate was to encourage research in diseases more frequent in women or in which there were different risks for women, as well as to ensure women were appropriately represented in all research studies supported by the NIH.[13] In 1992, the ORWH released a report recommending research initiatives in diseases affecting women and analyses which must be performed to gain insight into sex differences which may be present.

The FDA's Centre for Drug Evaluation and Research initially examined their databases in 1982, then again in 1988 and 1992 to investigate whether women and other subpopulations were included in representative numbers in clinical trials. Results from this and other investigations indicated that the numbers of women included did not increase from 1977 to 1992 and even when data stratified on sex is available, such data generally is not analyzed.[1,14] In a survey conducted in 1991, researchers examined all drug trials published in *Clinical Pharmacology and Therapeutics* between 1981 and 1991. They also found no significant change in the number of studies including women during that time period.[15]

Subsequent to these reports, pressures from the health care community resulted in the reversal of the FDA policy in 1993 to allow inclusion of women of CBP in all stages of clinical trials.[16] This new policy also included the statement that pharmaceutical companies

were required to conduct thorough analyses of their data in order to discern any sex differences during drug development.[17] At this time, the FDA adopted the view that IRBs, investigators and patients should have a greater role in determining whether women should participate in studies and how fetal exposure to toxic drugs can best be prevented. In addition, it was stated that the inclusion of women in early pharmacokinetic studies will yield sex-related differences that will enable the design of better phase III studies.[1]

Following the changes at the FDA, the NIH also revised their guidelines, a process in which the ORWH was instrumental. These new guidelines resulted in much tighter control on studies funded by the NIH, stipulating that the research had to conform to criteria producing gender sensitive results, including appropriate sample selection and data analysis by sex.[18]

Although similar searches for literature on policy in Canada were carried out, such legislation does not appear to exist within the policies of the Canadian government and the Health Protection Branch (HPB), the government body responsible for regulating the development of new drugs. One reason for this omission may be the fact that the vast majority of pharmaceutical companies are based outside of Canada. The HPB can withhold investigational drugs from being released in Canada as a result of the methodology by which they were developed. But they do not have the same control over the design of trials as the FDA if the clinical trials are for the most part conducted in the US. The views and policies of the FDA may also be more pertinent to the process as the American population is much greater, representing a larger market after the drug's release. Whatever the reason may be for

the lack of appropriate policy work, the Canadian Health Protection Branch does not appear to have taken the initiative in enforcing policies to ensure sufficient data on gender differences in treatment response.

1.2.2 Changes in Clinical Trial Policies and Consequences

The impact of the FDA's policy changes on pharmacological research, and the recognition of the importance of including female subjects, is not yet clear. While females are now included in clinical trials, their numbers may be too small to draw useful conclusions. The data presented is often not stratified by sex so differences in response between males and females is unavailable, and often not even investigated.

Reasons for the poor representation of women in clinical trials are not clearly understood. Some researchers have stated that it is difficult to recruit female subjects. One NIH official questioned on recruitment for a cardiology trial was noted in saying that it is *"doubtful that a sufficient number of females would be interested in participating and be content to go through the hassle of taking a placebo."* [19] The reason for this assumption is unclear as women who are adequately informed of their risk of heart disease would have as much incentive as men to participate.[7] Some cardiac illnesses are known to be misdiagnosed in women and be associated with a lack of recognition and validation by clinicians.[7] Underdiagnosis of these diseases would lower the number of available female patients for potential inclusion in clinical trials.

The Pharmaceutical Manufacturers Association has conducted its own studies showing that the industry actively recruited women for drug trials, citing that over 90% of the largest companies recruited representative numbers of women for clinical trials.[20] Interestingly, the GAO produced different results with respect to this issue. In their review of pharmaceutical companies whose products received FDA approval between 1988 and 1991, 25% of manufacturers did not actively recruit women for clinical trials. Furthermore, in 60% of trials women were underrepresented based on the gender distribution of the corresponding disease, and in at least 30% of trials fewer than the minimum number of women participants recommended by the FDA were included.[21]

Studies have also demonstrated that the percentage of drug trials in which only men were enrolled increased between 1969 and 1991. This result is not accounted for simply by the fact that total numbers of drug trials increased. Although this is true, the percentage of trials including both men and women did not change and the percentage of trials including only women decreased in this same time period.[22]

Ironically, recent data from the FDA demonstrates that females of childbearing potential (20-39 years of age) exhibited nearly twice as many adverse drug reactions as age matched males; this statistic held true for all age groups except those 19 and under.[23] These results strengthen the case for including females in clinical trials, supporting the hypothesis that medications act differently in men and women, therefore these differences must be investigated.

Clinical trials of psychotropic medications have suffered from similar problems as in other drug investigations. Several reviews have been performed recently demonstrating that insufficient research has been conducted to determine whether there are clinically meaningful differences related to sex for most drugs used in psychiatric treatment.[24,25] Given that women represent approximately 60% of the consumers of psychotherapeutic drugs [26], it is particularly important to conduct appropriate studies to detect sex differences in these medications. It has been reported that women taking these medications also experience a disproportionate number of adverse events [26], which may have in part arisen due to a lack of information from clinical trials.

One of the results of testing drugs primarily in male subjects arises due to the fact that men normally require higher doses than do women. An example of this was the introduction of the antidepressant buproprion. Dosages concluded to be appropriate from clinical trial data resulted in seizures in bulimic women after buproprion was released on the market, causing the pharmaceutical company to conduct further study and eventually revise their dosage recommendations for female patients.[27]

While the development of the next generation of new drugs will be positively affected by the new FDA legislations, the medications already available on the market require further investigation *post hoc* to determine differences in safety and efficacy. The relatively long time frame from initial clinical trials to the marketing of medications indicates that many newly released drugs were studied under the old rules which prevented women from fully

participating in testing. Long term data on safety and efficacy of all new drugs can only be gained by longer studies than are currently seen in premarket investigations. Due to the lack of women in these earlier trials, the need for rigorous postmarketing investigations on the effects of medications in women may be particularly important.

1.2.3 Schizophrenia

Schizophrenia is a brain disease characterized by a heterogeneous group of symptoms associated with impaired social functioning. The primary classification system used by North American psychiatric health care workers is the Diagnostic and Statistical Manual of Mental Disorders, the most recent version being the DSM-IV, or the fourth edition.[28] The DSM-IV specifies various criteria for the diagnosis of schizophrenia (DSM-IV code 295). Key to the diagnosis is the presence of characteristic symptoms, commonly separated into two broad categories - positive and negative. Positive symptoms are named for the additions or excesses beyond the usual pre-morbid behaviour of the patient, whereas negative symptoms represent a diminution or loss of normal function.[29] The illness can be manifested as different groups of symptoms in different patients. Common symptoms classified into these two groups are shown in Table 1.

Table 1. Positive and negative symptoms of schizophrenia. Adapted from references 28 and 30.

Positive Symptoms	***Negative Symptoms***
Delusions Hallucinations Formal thought disorder Disorganized behaviour	Flattened affect Alogia Avolition/apathy Emotional/social withdrawal Dysphoric mood Psychomotor retardation Poor attention

While the use of the positive-negative symptoms method of classification of schizophrenia is an oversimplification of the illness, it is widely used and therefore will be adopted for the purposes of this study. However, it is important to note that the course and symptomatology of schizophrenia extend beyond these categories and affect multiple facets of health including both cognitive and behavioural impairment.

Positive symptoms are most commonly associated with schizophrenia as they are more apparent to the untrained observer and are the indications of frank psychosis. They are also more acute and often transient in nature. However many have suggested that it is the negative symptoms which are more chronic and often produce more long-term damage to the patient's ability to relate to others and sense of self-worth.[31] In this regard, negative symptoms can be particularly disabling, as not only do they exert their effects directly, but symptoms like amotivation and anhedonia can also contribute to the patient's inability to work towards improving his or her own well-being.

Positive and/or negative symptoms are accompanied by social or occupational dysfunction and must have persisted for longer than six months to qualify for a diagnosis of schizophrenia. Also, the possibility of symptoms occurring as a result of a medical condition or organic cause must have been ruled out.[28]

Symptomatology in schizophreniform disorder (DSM-IV code 295.40) is identical to that of schizophrenia with the exceptions that duration of illness is shorter (between one and six months), and social dysfunction may or may not be present. Patients diagnosed with schizoaffective disorder (DSM-IV code 295.70) share the same core symptoms as those with schizophrenia. However, in these patients the disorder is accompanied by prominent symptoms of mood disorder, including depressive or manic symptoms or a mix of the two.[28]

Although the etiology of schizophrenia is as yet unknown, the most widely used model to account for all the contributing factors is that of the stress-diathesis model. It postulates that a person may have a pre-existing vulnerability (diathesis) that when under stressful influences, results in the appearance of symptoms of the illness.[29] Since schizophrenia has been demonstrated to have a genetic component, it has been suggested that genetic predisposition may form the diathesis upon which environmental stress can act. These factors of stress and diathesis are not both required for onset of the illness, as the lifetime prevalence rate of schizophrenia is approximately 1% in the general population, including those with no family history of the disorder, and is consistent across all cultures of the world.[32]

The symptoms seen in schizophrenia were historically thought to be caused by an excess of the neurotransmitter dopamine in certain areas of the brain. Most of the information leading to this theory came from the first medications used to treat the illness, drugs which acted as antagonists at dopamine receptors and resulted in relief of positive symptoms in some patients.

While the hyperdopaminergic theory has gained credibility, it appears that it may only be applicable to the mesolimbic tract, one of several dopamine pathways in the brain. There is evidence to suggest that this pathway may become overactivated in patients with schizophrenia. Positive symptoms are thought to be due to the increase in dopamine in this tract, hence the demonstrated efficacy of dopaminergic antagonists for these symptoms.[33]

Other dopaminergic pathways, namely the nigrostriatial and mesocortical tracts, are postulated to be involved in negative symptomatology and cognitive impairment, although the involvement of the nigrostriatial tract has been disputed.[34] It appears that there is a lack of dopamine in these pathways in contrast with the hyperdopaminergic state of the mesolimbic tract.[33] There is convincing evidence that addition of a dopamine precursor such as L-dopa as adjunctive therapy to a typical antipsychotic may alleviate negative symptoms for some patients.[35]

The fourth major dopamine tract affected by the treatment of schizophrenia is the tuberoinfundibular system, which controls neuroendocrine secretion. Altered dopamine

levels in this tract have not been found in schizophrenic patients.[33]

Complicating the issue has been the isolation of several different subtypes of dopamine receptors, including five classes labelled D_1-D_5.[36] These subtypes each vary in number and distribution among different structures in the brain. D_2 receptors are by far the best characterized, and are the targets of all antipsychotics to some degree. The alleviation of positive symptoms has been proven to be closely correlated with occupancy of the D_2 receptors.[37] D_1, D_3 and D_4 receptors are also attracting attention in the search for new sites of activity for novel antipsychotics.[38] It is hypothesized that developing compounds more selective for certain receptor subtypes and tracts of neurotransmission will decrease the negative effects on the brain caused by non-selective antidopaminergic compounds.[39]

In the last decade, more medications acting at various receptors in the brain have been produced and found to be efficacious in treating some symptoms for some patients. These findings are providing evidence to researchers that many different receptor systems and pathways may be involved in the manifestations of schizophrenia.[32]

Aside from dopamine, the neurotransmitter attracting the most attention in the field of research in schizophrenia is serotonin or 5-hydroxytryptamine (5-HT). The involvement of serotonin is based on the hypothesis that 5HT hyperactivity may be related to dopamine hypoactivity in the nigrostriatial and mesocortical tracts of the schizophrenic brain.[40] Many newer antipsychotics are being developed which have potent 5HT antagonism. Preliminary

investigations indicate that these medications may be successful in treating the negative symptoms of the illness, supporting the hypothesis that 5HT may be involved.[41] One existing theory is that it may be the ratio of $5HT_2/D_2$ antagonism which is important in treating the illness and not absolute quantities of antagonism at either receptor.[42]

Other neurotransmitters currently being investigated for involvement in psychopathology include norepinephrine, gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA).[43] Although extensive discussion of neurotransmitter research is beyond the scope of this review, it does provide insight into the complexity involved in the presentation of schizophrenia.

1.2.4 Treatment of Schizophrenia

Current treatment of schizophrenia utilizes biological, psychological and social interventions. Longitudinal research has demonstrated that psychotherapy alone is ineffective in treating these patients. The large majority of patients are treated with medications at least periodically, often in combination with psychotherapeutic techniques and/or rehabilitation strategies.[31] This allows the clinician to treat both the proposed underlying biochemical imbalance as well as the behavioural and cognitive dysfunctions which often arise due to the symptomatology of the disorder. Virtually all patients are treated pharmacologically for the acute first break of symptoms. Although 25-30% of patients may succeed in discontinuing medication and not relapsing following the initial break, the majority of patients can

unfortunately expect to require ongoing treatment with medications, whether intermittently or continuously.[44]

Various chemical classes of antipsychotics have been developed since the 1950's. The majority of these fall into a group termed the 'typical' neuroleptics, characterized by their potent action on dopamine (D_2) receptors in the brain. These drugs have been found to be effective in ameliorating the positive symptoms of schizophrenia, but have very little effect on negative symptoms for most patients.[45] The theory of negative symptoms correlating with hypodopaminergic activity in the nigrostriatial and mesocortical areas is supported by the inefficacy of typical neuroleptics in treating this spectrum of the illness; most of these drugs are non-selective D_2 antagonists throughout the brain and these patients may already have an insufficient level of dopamine in the pertinent areas.[33]

Other receptors are affected by some typical neuroleptics, including the histamine (H_1) receptor and the alpha (α_1) adrenoreceptor. Antagonism at both of these sites causes sedation, a side effect affecting an estimated 35% of treated patients.[29,46] Orthostatic hypotension is also a result of H_1 and α_1 antagonism, another common problem seen more frequently in elderly patients.[47] The frequency of orthostatic hypotension has been estimated to be 22% across all age groups.[46] Weight gain has been estimated to affect one third of treated patients and is suspected to be due to antagonism of hypothalamic 5HT receptors.[47] Many antipsychotics have antagonist action at acetylcholine muscarinic (M) receptors, causing such autonomic effects as blurry vision, decreased salivation and constipation.[47]

Perhaps the most serious of the common side effects are the extrapyramidal symptoms (EPS) associated with these medications. EPS is a term given to a group of movement disorders characterized by muscle rigidity, involuntary movements and restlessness.[48] Acute EPS is hypothesized to be due to hypodopaminergic activity in the nigrostriatial tract of the brain, also termed the extrapyramidal pathway.[33] Antipsychotic medications due to their dopamine antagonist properties, reduce the levels of dopamine in this pathway, causing EPS to emerge. A therapeutic window for antipsychotic medications is thought to exist between a minimum D_2 receptor occupancy required for antipsychotic efficacy (70%), and a maximum receptor occupancy above which EPS will occur (80%).[49]

EPS has been estimated to occur in up to 90% of patients taking standard neuroleptics; this high rate may be due to including symptoms such as akinesia, which is often indistinguishable from negative symptoms that are features of the illness itself.[50] One of the more common extrapyramidal symptoms, pseudoparkinsonism, is estimated to occur in 15-50% of patients treated with conventional antipsychotics.[51] Another common symptom in this spectrum is akathisia, or restlessness, which has been thought to be the most distressing for patients, and the primary reason they become non-compliant with their medications.[52,53]

Tardive dyskinesia (TD) is a chronic form of EPS due to long-term neuroleptic use.[54] The symptom is characterized by involuntary movements, usually of the jaw, tongue or face, but occasionally the trunk and limbs are affected. TD may be due to compensatory development of supersensitive dopamine receptors following chronic blockade by antipsychotics.[29] It is

estimated that after one year of exposure to conventional antipsychotic treatment, 5% of patients will develop TD, and continued exposure will elevate the frequency of TD by about 5% a year.[55]

Other side effects common with neuroleptics are associated with elevation of prolactin, a hormone involved in lactation post-partum.[56] Prolactin normally exists at low levels in the blood; basal levels are in the range of 5 - 25 ng/mL in men and nonpregnant, nonlactating women.[57] Prolactin levels in drug-free schizophrenic patients have not been found to differ from healthy controls.[58,59] Dopamine is known to be a prolactin inhibiting factor (PIF), blocking release of the hormone from lactotrophs, specialized cells in the anterior pituitary gland. Antipsychotics may therefore cause elevation of prolactin by blocking dopamine release in the tuberoinfundibular tract leading to the pituitary and removing the inhibition on prolactin release from the lactotrophs.[60]

The magnitude of prolactin increase due to D_2 antagonism by typical antipsychotics has been shown to be directly related to the dosage given.[61] Levels appear to plateau after approximately one week of treatment, and normalization of levels has also been found in some patients treated with antipsychotics.[62,63] Prolactin levels have been reported to return to baseline for most patients within days of discontinuation of therapy, although some patients continue to experience hyperprolactinemia for three weeks or longer.[64]

Prolactin elevation causes a host of side effects in both men and women. Included in this

group are sexual side effects, which include both those effects involving sexual function (impotence, orgasmic dysfunction) and those involving reproductive function (menstrual disorders, galactorrhea).[9] Sexual side effects have been shown to occur at prolactin levels above 40 ng/mL [9] (levels in pregnant women at term generally reach between 200-300 ng/mL).[65] Antipsychotics are known to elevate prolactin to levels well above 40 ng/mL, some approaching the levels of pregnant women.[58,66]

The actions and effects of prolactin have not all been elucidated, however it is known to interact with other hormones and neurotransmitters directly involved in sexual function. Galactorrhea, gynecomastia and amenorrhea are direct results of hyperprolactinemia, effects normally seen in breastfeeding women postpartum. High levels of prolactin can cause decreased testosterone levels, which results in decreased desire or libido, as well as impotence in men.[9]

Hyposexuality or decreased desire, has been demonstrated to affect untreated schizophrenics at higher rates than medicated patients, indicating that perhaps there may be several etiological factors involved. It has been postulated that antipsychotic treatment may improve some of the more cognitive dimensions of sexual function such as sexual thoughts and desire for sex, but impairs the more physiological dimensions such as arousal, orgasm and sexual satisfaction.[67]

While prolactin has not been proven to cause all identified sexual side effects, it may be

involved in many facets of sexual and reproductive function, whether directly or indirectly. It has been estimated that up to 50% of patients taking antipsychotic medications have some level of sexual dysfunction which in a third of cases can be directly attributed to the medication. These effects have been shown to increase non-compliance significantly, particularly in young men.[45]

Such side effects and treatment resistance to traditional neuroleptics accelerated the search for new antipsychotics. Researchers began to focus their attention on other receptors, in particular the $5HT_2$ receptor. Clozapine was the first such 'atypical' drug re-released in 1990 after being withdrawn from the market for many years due to the discovery of dangerous hematological side effects. This medication has activity at multiple receptors in the brain, including both $5HT_2$ and D_2 receptors, and has proven to be efficacious for many hitherto treatment resistant patients, treating both positive and negative symptoms.[68] Risperidone followed in 1993 with potent affinity for $5HT_2$ receptors and a relatively lower affinity for D_2 receptors.[69]

A list of sexual side effects resulting from antipsychotic treatment is shown in Table 2.

Table 2. Sexual side effects resulting from antipsychotic treatment. Adapted from reference 9.

Sexual Side Effects	
Both males and females	
Desire disorders Hyposexuality Hypersexuality (rare) **Breast Disorders** Gynecomastia Galactorrhea Pain/tenderness	**Orgasm irregularities** Anorgasmia Diminished frequency of orgasms Orgasmic inhibition Dyspareunia **Infertility** Hypogonadism
Males	
Erection difficulties Inability/difficulty obtaining/maintaining Decreased quality of erection Priapism **Infertility** Decreased or malformed spermatogenesis	**Ejaculation difficulties** Retarded ejaculation Ejaculatory inhibition Orgasm without ejaculation Decreased ejaculatory volume Anesthetic ejaculation
Females	
Menstrual Disorders Amenorrhea Dysmenorrhea/menorrhagia	

Various definitions have been proposed to separate 'typical' antipsychotics from the novel 'atypical' medications. Most involve the observed tendency for atypicals to induce lower levels of EPS than is seen with the typical drugs.[70] In 1989 it was noted that all medications termed atypical had proportionately higher affinity for $5HT_2$ receptors than D_2 receptors, and

a definition incorporating the effects on EPS was formed.[71] Seeman [42] has suggested that a $5HT_2/D_2$ ratio of ten is necessary to avoid EPS, therefore this ratio has been accepted by some as a 'recipe for atypicality' in antipsychotic development.

As this definition of an atypical neuroleptic involves a lower affinity for D_2 receptors, it is plausible to speculate that the prolactin response to such a medication would be lower relative to standard antipsychotics which have higher affinities for D_2 receptors. This is due to the observation that prolactin elevation with these medications is dose dependent, or more specifically receptor binding affinity dependent. This result is seen with the novel antipsychotic clozapine, which has a relatively low affinity for D_2 receptors and shows no significant prolactin elevation from baseline.[72,73] Olanzapine, a new atypical antipsychotic released in 1997, shows proportionately higher binding affinity for $5HT_2$ receptors than for D_2 receptors and also appears to have a minimal effect on prolactin levels, although these are preliminary reports.[74] Such observations have caused some researchers to include the lack of prolactin elevation in the definition of an atypical antipsychotic.

1.2.5 Sex Differences in the Presentation of Schizophrenia

Research into sex-specific differences in the course and symptomatology of schizophrenia is imperative, for if there are differences in the way the illness manifests itself in males and females, the treatment should be modified to fit the illness. Sex differences in schizophrenia have been of interest to researchers for many years. The demographics of various disorders

have been well documented, leading researchers to try to understand the factors underlying differences between males and females.

Although the majority of surveys report the lifetime prevalence of schizophrenia to be approximately equal in males and females [75], there are sex differences in the course and outcome of the illness. Women tend to have a later onset than do men [76], and also demonstrate a second 'peak' of illness onset much later in life [77,78], a phenomenon which is not seen in men. Male patients were also reported to demonstrate a longer duration of illness prior to seeking treatment (77 weeks) than did female patients (33 weeks) [79], which may be important as a longer treatment lag time has been associated with poorer outcome.[80]

In the literature, male patients have demonstrated a higher frequency of negative symptoms associated with their illness than females, while females are hypothesized to demonstrate more affective symptoms [81,82], although this result has not been replicated in other studies.[83,84]

Sex differences have also been elucidated in the familial transmission of schizophrenia. Several studies have shown that relatives of female schizophrenic probands have a greater risk of developing schizophrenia than do relatives of male probands with schizophrenia.[85,86] It has been suggested from these findings that environmental factors may play a larger role in the appearance of the illness in males to account for the equal prevalence between the sexes.

In an extensive meta-analysis performed on treatment outcome data from several studies, males were shown to spend more days in hospital and were at higher risk for rehospitalization than females, although actual numbers of hospitalizations was not found to differ.[87] The authors concluded that the sex differences were not accounted for by age at first hospitalization or other demographic factors, and therefore must be considered in the context of sex related factors.

One theory which exists concerning sex differences involves the presence of the sex hormone estrogen, which is hypothesized to have a dopamine blocking effect. This effect would theoretically result in the more benign form of schizophrenia commonly seen in female patients.[88] Dopamine receptors have been demonstrated to increase in response to chronic estrogen treatment [89], and similar effects have been found in noradrenergic [90] and serotonergic [91] systems, although the effects of each of these on clinical presentation has not been elucidated.

Additional support for the estrogen hypothesis is found in the fact that in pre-menopausal women exacerbations of the illness occur most frequently premenstrually and post-partum when estrogen levels drop off.[92] The second peak of onset of schizophrenia in women coincides with, and has been attributed to the occurrence of menopause, again when estrogen levels decrease.[93] It has been found that as women age and reach menopause, gender differences in the course of illness may disappear over time.[94]

Other theories exist concerning the cause of sex differences in the course of illness including better psychosocial adaptation in females at the time of illness onset.[95] This may be due to the later average age of onset; women may have more social supports in place at this time.

Structural brain differences have also been found between male and female children, indicating possible neurodevelopmental differences.[96] Brains of male patients have consistently been found to have more deviance in morphology than the brains of female patients.[97] It is hypothesized that the genes responsible for the disorder are expressed early in life and act to impair neuronal migration. The pace of brain maturation is different in male and female fetuses, and variations of hormone levels affect neurodevelopment. Greater exposure to ovarian hormones may protect females against perinatal hypoxia and/or trauma.[92] These factors may cause gender differences in both age of onset and course of illness.[98]

Prenatal infection is also theorized to be a predisposing factor to later development of schizophrenia; this effect has been found to be more frequent in female offspring than male [99], although there have been contradicting reports on these results.

Sex differences in the course of schizophrenia are important to consider in the context of treatment response. The same factors causing variation in the presentation of the illness may be producing similar deviations in treatment response and tolerance of medications. Differences in the symptomatology of the illness in men and women also provide valuable

insight into the possible reasons for treatment failure in each sex.

1.2.6 Sex Differences in the Treatment of Schizophrenia

While sex differences in the onset and course of schizophrenia exist and warrant further research, clinical research having a more immediate impact on treatment of these patients is also urgently required. An understanding of sex specific differences in treatment response and adverse events to available antipsychotic medications leads to better treatment management for both male and female patients. The differences seen in both the course of illness and treatment response between men and women also strengthen the argument for the inclusion of females in all stages of psychopharmacologic investigations. As biological therapies have been determined to be the mainstay of treatment for this population, this discussion will be limited to these modalities. However it is important to note that the psychosocial aspects of treatment of schizophrenia are pertinent, and likely involve various gender related differences as well.

Although the basic mechanism of action of neuroleptics is the same in either sex, differences between men and women do exist in the pharmacokinetics (bioavailability, absorption and metabolism) and pharmacodynamics (therapeutic action) of these drugs. Proposed reasons include differences in gastric emptying times, proportions of lean body mass and adipose tissue composition which can affect clearance times. Also, fluctuating levels of endogenous or exogenous hormones can affect hepatic enzyme systems and protein binding of

pharmacological compounds.[24,100]

Women and men have different profiles of efficacy on antipsychotic medication; women generally respond better, require shorter trials of medication to respond and lower dosages, both in the initial response and long term maintenance phases of pharmacotherapy.[101] Likewise, female schizophrenics were found to have greater plasma neuroleptic levels than their male counterparts on similar medication dosages, even after correction for differences in weight.[61] Females have also been found to have higher utilization rates of medication. One study reported a rate of psychotropic drug consumption of 142.3 females /1000 inhabitants vs. 50 males/1000 inhabitants.[102] This evidence, combined with the pharmacokinetic properties in women, suggests that females may not be optimally served by current prescribing practices.

Neuroleptics used in the treatment of schizophrenia, with the exception of clozapine [72,103] and possibly some of the newer atypical neuroleptics, are all known to increase prolactin levels in both men and women.[104] Higher levels of prolactin have been reported in women, [58,61] perhaps due to sensitization of the pituitary by estrogen.[58] This elevation of prolactin along with other sex hormones can cause a range of side effects including amenorrhea and galactorrhea in women and impotence and ejaculatory dysfunction in men.[104] These side effects are documented in the literature from clinical trials, but there is rarely any breakdown in the analysis of discontinuation rates resulting from such events between men and women, or between pre-menopausal and post-menopausal women. In one review of side effects of

antipsychotic medications, the authors concluded that this class of drugs causes sexual side effects in 30-60% of patients. However, fewer than 10 of the studies reviewed included more than 20 subjects, and only one study included any female subjects.[105]

Despite the severity of psychotic symptomatology, patients in a subjective response study conducted by Finn [106] indicated that they were more 'bothered' by genital/sexual side effects than by any of their symptoms of schizophrenia, with the exception of paranoid delusions. Sexual side effects in these patients are often not recognized or detected in many patients. When these side effects are discovered, they are often poorly managed by clinicians. The mistake is often made by clinicians of presuming that sexual function or perhaps more importantly, sexual dysfunction, is not important to those without sexual partners and the information is therefore not asked of the patient.[100] Sexual side effects are also seen by many patients to be a difficult topic for discussion in the clinical environment. In a study of 28 galactorrheic women, only 8 patients volunteered the information regarding their galactorrhea; the remainder found it a personal and embarrassing issue.[107] Due to these communication problems on the parts of both the clinician and patient, it is likely that these side effects are vastly underreported in the literature and underrecognized in the clinic.

A related problem with many clinical trials is the actual length of the trial. The majority of pre-market investigations of new neuroleptics last less than three months [100], which may be too short-term to be able to accurately assess the emergence of many side effects. Some of these, including some sexual side effects such as amenorrhea, can take months to arise.[100]

It has been estimated that a clinical trial of a neuroleptic should be at least six months long for an accurate evaluation of sexual side effects.[9]

Sample size is also a key issue in investigations of sexual side effects. Many of these effects occur at rates under 10%. At these rates, the number of patients required in a study to produce meaningful results can be relatively high. While males are generally included in sufficient numbers, this may not be true of female subjects. Sexual side effects due to antipsychotic medications are reported more often in males; part of the reason for this may be the fact that the sample size of female patients did not result in sufficient statistical power to detect a difference in sexual side effects relative to other treatment groups.

The most comprehensive study on side effects of antipsychotics was conducted by Lingjaerde et al (1987) [46] involving 2391 patients (1132 females, 1259 males). This study was also one of the only ones using sex-stratified analysis. Sexual side effects were found to occur most frequently between three and six months into treatment. The most common side effect in both men and women was hyposexuality or reduced desire, occurring in 36.9% of women and 36.6% of men. This data is contrary to prominent statements in the literature suggesting that hyposexuality is more common in male patients.[65] Orgasmic dysfunction was more common in women (19.3%) than men (15.9%), as was galactorrhea (5.3% in women, 2.7% in men). Gynecomastia was reported to be more common in men (6.0%) than women (3.0%), however it has been stated that gynecomastia is very difficult to detect in women, particularly in the absence of breast pain and/or tenderness.[9] Erectile dysfunction and ejaculatory

dysfunction occurred in men at rates of 21.5% and 18.7%, respectively. In this study it is noteworthy that the sexual side effects did not change with duration of treatment, indicating that tolerance of the medications did not occur. As long as patients remained on the neuroleptic, most continued to experience sexual side effects.[46]

Teusch et al [108] conducted a study in 1995 on mentally ill patients with various diagnoses and compared their rates of sexual dysfunction to normal controls. Sexual dysfunction categories included interest/desire, emotional arousal and orgasm in both sexes, erectile and ejaculatory dysfunction in males and vaginal lubrication, vaginism and menstrual disorders in females. In almost all categories, schizophrenic patients were found to have higher frequencies of dysfunction. In the female group, 93% of schizophrenic patients displayed at least one sexual dysfunction (including menstrual disorders) compared to 63% of controls. Female patients also exhibited higher rates of hyposexuality (60% vs. 26% of controls) and menstrual disorders (67% vs. 11% of controls). Male schizophrenics also demonstrated higher values than normal controls: 87% of these patients showed at least one sexual dysfunction compared to 27% of controls. Also elevated in the male group was the frequency of orgasmic dysfunction (53% vs. 9% of controls) and ejaculatory dysfunction (43% vs. 0% of controls). In all categories the values demonstrated statistical significance with the exception of emotional arousal, vaginal lubrication and vaginism in the female group.

The prevalence of tardive dyskinesia, postulated to be due to chronic conventional neuroleptic treatment, is also known to show sex differences, particularly later in life.

Postmenopausal women are known to have higher rates of TD associated with neuroleptic use than either men or young women.[109] This effect is also hypothesized to be related to the lower level of estrogen protection of dopamine receptors in these women.

Some of the older 'typical' (principally dopamine antagonist) neuroleptics have been investigated after release by independent investigators to determine the differences in response between the genders [110], but the same has not been carried out for the 'atypical' neuroleptics, with the exception of clozapine in a recent publication.[111] This study was carried out in order to examine whether sex differences occur in the group of patients non-responsive to the majority of neuroleptics, more commonly referred to as treatment-refractory schizophrenics for whom clozapine is normally prescribed. Contrary to existing literature on treatment response, the female group showed a poorer response in psychopathologic indices and dropped out at a higher rate. The authors concluded that this group of patients may represent a unique subgroup of schizophrenic patients due to their treatment resistance and may not be comparable to the entire population with this illness.[111]

Risperidone is also an atypical antipsychotic currently being prescribed for many patients; unlike clozapine, risperidone has not been studied for any sex differences in treatment response. This medication may also be dissimilar from other medications in ways particularly important to women's health, which will be discussed in the next section.

1.2.7 Risperidone

Risperidone is a novel antipsychotic released in 1993, termed 'atypical' due to its higher antagonistic affinity for serotonin ($5HT_2$) receptors than for dopamine (D_2) receptors and its propensity to cause less EPS at effective antipsychotic doses. It was the first atypical antipsychotic post-clozapine to be released, and as such caused much excitement in the field in the anticipation that an efficacious medication was finally available which did not cause either the same levels of EPS as the typical antipsychotics, nor the hematological problems associated with clozapine.

Data from various clinical trials conducted before and after the drug was released on the market indicate that risperidone has not demonstrated a significant advantage in treating positive symptoms over standard antipsychotics, except perhaps in a subgroup of patients non-responsive to conventional medications.[112] However, negative symptoms have been shown to be ameliorated in patients taking risperidone [113], compared to typical antipsychotics which as a group are relatively ineffective in treating the negative syndrome of schizophrenia.[45] Preliminary results also suggest that cognitive deficits [114] and affective symptoms [115,116] seen in the illness may be improved with risperidone.

Risperidone's high $5HT_2/D_2$ ratio is hypothesized to be the reason for the lower incidence of EPS seen with risperidone relative to the standard neuroleptics, which act primarily on D_2 receptors and often have high rates of EPS associated with their use. In 1993, a variety of

neuroleptics were tested in Cebus monkeys for 'atypicality' using the definition of high (typical) vs. low (atypical) propensity to cause EPS.[117] According to these criteria, risperidone was classified as atypical at low doses and typical at higher doses. This would indicate that the drug causes EPS, but only at doses higher than is normally required for antipsychotic efficacy.

The various receptors involved in the chemical profile of risperidone and potential resultant side effects is shown in Table 3.

Table 3. Receptor binding affinities and possible actions of risperidone. Adapted from reference 70.

Receptor	***Affinity***	***Potential effects***
$5HT_2$	++++	↓negative symptoms, sexual dysfunction?, weight gain?
D_2	++	↓positive symptoms, EPS, ↑prolactin
α_1	+++	orthostatic hypotension, heart palpitations, ↓symptoms?
H_1	+	sedation, orthostatic hypotension

The efficacy profile of risperidone is curvilinear or bell-shaped, unlike most other antipsychotics which have a direct dose-response relationship. This indicates that the efficacy of risperidone in treating symptoms of schizophrenia increases with dose until a critical point (approximately 6 mg/day) after which it starts to decrease; at doses above 12 mg/day risperidone was found to be no more effective in the treatment of psychosis than haloperidol,

a traditional neuroleptic. At 16 mg/day, risperidone also produced as much EPS as haloperidol.[1992]

Postural hypotension is a common side effect of risperidone, particularly during the first week of treatment. However, adaptation was found to occur, so a gradual titration scheme was recommended by the pharmaceutical company to avoid appearance of this effect.[118] Similarly, insomnia was found to be a common side effect with risperidone due to the fact that it is not as sedating as other neuroleptics, although patients also adapted to this effect after the initial period.[119]

Risperidone appears to elevate prolactin to higher levels than other neuroleptics.[70] Experiments revealed that risperidone was 3-5 times more potent than haloperidol (a potent D_2 antagonist) in elevating prolactin levels in rats [120], while 4-week trials in humans showed an initial 7-fold increase in prolactin levels which did not decline until the drug was discontinued.[121] The mechanism for this effect on prolactin is unclear as its binding affinity for dopamine receptors is almost 20 times weaker than its affinity for serotonin receptors and is half that of haloperidol's affinity for D_2 receptors.[113] Regardless of the cause, this effect on prolactin is a concern for clinicians treating premenopausal women with risperidone as the possible higher incidence of side effects due to the elevation may make the drug intolerable for some patients.[66] This is particularly pertinent given the finding that females may be more sensitive to dopamine blockade, causing proportionally higher prolactin levels than seen in men.[58,61] In fact, some authors subscribing to the importance of prolactin in the

definition of atypicality will not classify risperidone as atypical due to its ability to increase prolactin to significant levels.

Much clinically relevant data is lacking from clinical trials on risperidone. While information on symptom reduction and some side effects is extensive in treatment groups, there is rarely any stratification according to sex, nor is there documentation of many side effects perhaps considered less important to clinical outcome. In a review of 21 clinical evaluations on risperidone prior to its release [118,121-140], it was shown that only 3 were found to have any sex-specific analysis (although minimal, simply including numbers of each sex in each treatment group), one trial was composed of all males and 2 trials didn't publish numbers of males and females enrolled. Only 4 trials were more than three months in length; most lasted between four and eight weeks. As stated earlier, this is clearly not long enough to be able to evaluate many side effects in some subjects.[100]

A further problem with deriving side effect data from clinical trials is the high discontinuation rates common to these investigations. In five of the trials completed with risperidone, the dropout rate in the risperidone groups ranged from 38-56%, relative to an average of 59% dropout on haloperidol and 69% on placebo.[122,127,131,135,140] These comparison rates are misleading, as the standard dose of haloperidol in these studies is 20 mg/day. This dose is considered to be in the high range for this medication, and is very likely intolerable for many patients, particularly females. In the only trial publishing sex differences in dropout rates, 4 out of 5 patients discontinuing treatment were female, although this sample size was

small (N = 13).[131] Compliance with clinical trial procedures may also be a problem in generalizing treatment response data as it may result in more or less discontinuation of treatment than would be seen in the clinical population.

Although most clinical trial data publish reasons for discontinuation, ie: side effects or otherwise, it is often difficult to determine all the factors entering into the equation of discontinuation. Adverse events in many clinical trials are only the 'spontaneously reported' events, which may miss side effects of a more sensitive nature; patients may be more hesitant to report such adverse events on their own initiative. In particular this may affect the reporting of sexual side effects. In one clinical trial of risperidone, sexual dysfunction and menstrual disturbances were reported in greater than 5% of patients when the information was elicited using a checklist, but less than 5% when patients were relied upon to report spontaneously.[141]

Risperidone was chosen for investigation in this study for important reasons. This medication has been viewed favourably for its low effect on extrapyramidal symptoms. However, higher prolactin levels seen with the drug may cause other side effects, some of which may be just as distressing to the patient, and may ultimately result in discontinuation of treatment. As the medication was released in 1993, this provided a favourable opportunity to observe the first sample of patients being prescribed risperidone in a clinical setting, the results of which should more closely describe the treatment situation than is seen with clinical trial methodology.

1.3 STUDY DESIGN AND OBJECTIVES:

This study is a retrospective cohort study examining discontinuation of a specific novel antipsychotic, risperidone, in patients with clinical diagnoses in the schizophrenia spectrum, including schizophrenia, schizoaffective disorder and schizophreniform disorder. The two cohorts being compared are male patients and female patients. Patient charts from three psychiatric outpatient clinics were reviewed to collect data on discontinuation of risperidone treatment during the one year period of time following initiation of risperidone. All patients, both male and female, identified as having discontinued risperidone prior to completing one year of treatment were invited for an interview on their attitudes towards both medications in general and specifically risperidone, and their reasons for discontinuation of risperidone, ie: side effects or otherwise.

Primary Objective

To determine the sex differences in discontinuation rates of a sample of patients who started risperidone treatment during the first two years of its release on the market.

Hypothesis

H_0: There is no difference in discontinuation rates between male and female patients.

H_a: Female patients who have been treated with risperidone will show a higher rate of discontinuation in comparison with male patients.

Secondary Objective/Research Question

To examine the frequencies of sexual side effects in the two sexes and any differences existing between them.

CHAPTER TWO: METHODOLOGY

2.1 SUBJECTS

2.1.1 Source of Sample

All participants in the study were receiving psychiatric treatment at one of the three outpatient clinics involved in sample generation. Two of the clinics involved (Sites 1 and 3) are general hospital outpatient programs, while the third clinic (Site 2) is a non-hospital based clinic. Site 1 is a structured day hospital program incorporating rehabilitation strategies, while Site 3 is a clinic offering patients medication and support for such, but no other rehabilitation services, similar to Site 2. The patients were initially identified from the Mental Health Clinical Integrated Database (MHCID), a case tracking system set up in 1992 in Calgary, Alberta. The objective of MHCID is to improve continuity of care in the chronically mentally ill population in this area by providing caregivers at various sites rapid access to basic patient information.[142] This database includes all patients with diagnoses in the schizophrenia spectrum as well as other psychotic disorders, who received treatment at one of the sites participating in record collection. The list of 1441 patients for the current study was initially generated by clinical staff from the three sites involved. Permission to access this list was obtained from MHCID Committee Advisory Board members representing the three sites. Expanded patient lists, considered to be more current, were provided by the clinical directors at each of the three clinics to supplement the MHCID list.

2.1.2 Inclusion Criteria:

a) diagnosis of schizophrenia (DSM-IV code 295.**, excluding 295.40 and 295.70), schizoaffective disorder (295.70) or schizophreniform disorder (295.40) at the time of risperidone initiation based on the attending psychiatrist's charted diagnosis

b) risperidone treatment initiated between May 1, 1993 and October 31, 1995 (30 months total)

2.1.3 Exclusion Criteria:

a) participation in a clinical trial of risperidone at the time of drug initiation

2.2 PROCEDURES:

2.2.1 Phase I - Chart Review:

Clinic charts were reviewed by the investigator in this study. The following data were extracted: demographics (date of birth, sex, race), attending psychiatrist's charted diagnosis, age of onset of illness, date of risperidone initiation, dosage range of risperidone throughout treatment, date of and documented reason(s) for risperidone discontinuation and the dosage at time of discontinuation. Chart data were collected for one year following initiation of risperidone treatment (or until discontinuation, whichever came first) for each patient. All side effects charted at the time of discontinuation, and concurrent medications prescribed, psychiatric and non-psychiatric, were recorded. Wherever possible, menopausal status (ie: pre or post) of female patients was recorded, as well as hormone treatments and hysterectomies.

2.2.2 Phase II - Interview:

From the chart review, all patients identified as discontinuers of risperidone who were currently receiving psychiatric treatment at any of the three sites, were invited to participate in a short interview. The process of consent involved the attending psychiatrist or primary therapist initially approaching the patient and asking for their permission to be contacted by the investigator. If the patient agreed, the investigator contacted the patient by phone or in

person and discussed the study and the interview with the patient and asked them to sign the consent form. Patients deemed to be incompetent by the attending psychiatrist or primary therapist were not approached for an interview.

The interview was conducted by the investigator and involved asking the patient about their reasons for discontinuation of risperidone using the Side Effect Checklist (SEC), an investigator generated checklist. This checklist included an open-ended question inquiring into the occurrence of side effects and reasons for discontinuation to obtain spontaneous information from the patient, as well as a checklist of recognized side effects of risperidone treatment. The Drug Attitude Inventory (DAI)[143] was administered to obtain information regarding the patient's attitude towards antipsychotic medications and to predict compliance. When menopausal status of female patients was not ascertainable from the chart, the patient was asked for this information during the interview, as well as information regarding hormone replacement therapy and hysterectomies. The interviewer was blinded to information previously obtained from the chart regarding side effects and compliance.

2.3 RESEARCH INSTRUMENTS:

2.3.1 Drug Attitude Inventory:

The Drug Attitude Inventory (Appendix 3) was designed by T. Hogan and Dr. A.G. Awad at The Clarke Institute of Psychiatry, Toronto in 1983 and is well validated in international trials.[143] The scale is designed to measure subjective responses to neuroleptics with the intention of detecting possible non-compliance in a clinical setting. It is a self-report questionnaire consisting of 10 true/false items on the attitudes of patients towards medications and the different components which make up these attitudes.

The scale items are derived from clinical practice and are comprised of patient statements which are not expressions of side effects. These statements reflect both subjective feelings and attitudes of the patients. Items are short and written at an elementary level, and in most cases can be completed by the patient without assistance. The ten items included in the DAI-10 are comprised of six factors organized on their factoral identity.

Factor 1 - positive subjective feelings attributed to neuroleptics (items 1,4,7,9),

Factor 2 - involves negative subjective feelings (items 2,5),

Factor 3 - describes the patient's model of health (items 6,8),

Factor 5 - describes the patient's attitude towards the locus of control in taking medications (item 3),

Factor 6 - describes the patient's belief in the effect of neuroleptics in forestalling relapse (item 10).

(The components of Factor 4 overlap with those of Factor 5 and therefore none of these items were included in the condensed DAI-10)

Reliability of the scale was found to be 0.93 ($P<0.001$) reflecting a high average correlation among items or questions. This indicates that in general, the items are all measuring the same entity, that of the patient's perception of drug treatment. Retest reliability was found to be 0.82.

In this study, the DAI was intended as an additional measure to gain insight into the event of discontinuation and the patient's subjective response to it. A patient who has negative attitudes towards one medication in particular (i.e. risperidone) and not towards other medications should be seen as different from the patient who holds negative attitudes towards medications in general. The DAI is such a tool to detect these patients classically referred to as having 'neuroleptic dysphoria'. While the hospital or clinic chart may have this information documented, it is often not reliable as a sole measure of treatment compliance. For this reason the DAI has been added to this design as a supplemental measure. (Appendix 3)

2.3.2 Side Effect Checklist:

The Side Effect Checklist (Appendix 3) was formulated by the investigator and is intended to examine possible reasons for discontinuing risperidone treatment. The checklist includes any side effects previously identified from published clinical trial data as being associated (generally at rates > 1%) with risperidone use including both sexual side effects and other known side effects. Sexual side effects include those which are involved with sexual function or reproductive function. Reported side effects were investigated further to determine if they played a role in the patient's discontinuation of risperidone. Also included in this list are other reasons for discontinuation including lack of efficacy, non-compliance with dosage regimens, "don't remember" and "no recorded reason". The new scale was included with the goal of obtaining information which may not be documented in the charts, including menopausal status of the female patients. The list was not given directly to the patient but was used by the interviewer to elicit patient recall of side effects while on risperidone. As this scale was designed for this study, it has not been previously tested, and no statements can be made concerning reliability or validity. (Appendix 3)

2.4 DEFINITION OF VARIABLES:

Age of Onset

Age of onset was defined as the age at which the patient first received psychiatric treatment for a schizophrenia spectrum diagnosis. Psychiatric treatment is defined as pharmacologic and/or non-pharmacologic interventions.

Race

Patients were grouped into one of six classifications based on race. These included: a) Caucasian, b) African Descent, c) East Asian (Chinese, Japanese, Korean), d) West Asian (Indian Sub-continent, Pakistani), e) Hispanic and f) Other (Mixed Parentage, Native Indian, Inuit)

Diagnosis

Patients were coded as having either a) schizophrenia, b) schizoaffective disorder or c) schizophreniform disorder. Diagnosis was based on the attending psychiatrist's diagnosis at the time of risperidone initiation.

Dates of Risperidone Start and Stop

Start and stop dates of risperidone treatment were taken as the dates of first and last doses, respectively. Where the date of last dose is not known to the exact day, ie. when a patient discontinued on their own initiative, a best estimate from the chart notes was made.

Dosages of Risperidone - High, Low and Stop Dosage

High and low doses of risperidone indicate the highest and lowest total daily doses recorded on the chart throughout treatment, regardless of whether it was prescribed or self-administered. These doses exclude the initial titration period required for risperidone; this was considered to last one week. Stop dose is the total daily dose the patient was on when his/her treatment was discontinued.

Concomitant Medication Usage

All concomitant medications patients received while on risperidone were noted. Concomitant medications, both drug name and dosage, were recorded and subsequently classified for analysis as: a) another antipsychotic, b) antidepressant, c) antiparkinsonian, d) anxiolytic, e) anticonvulsant, f) antimanic, g) hypnotic, h) other. Medications taken during the titration period at the start of risperidone treatment (one week unless otherwise noted in the chart notes) were not included. The antipsychotic the patient was switched to at the end of

risperidone treatment was also not included if a titration scheme was followed.

Side Effects - Chart

All side effects noted on the chart during risperidone treatment were recorded. These included all adverse events whether or not they have been clinically proven to be due to risperidone use. For the purposes of this research, the patients were coded as having: a) sexual side effects only, b) non-sexual side effects only, c) sexual side-effects and non-sexual side effects, or d) no side effects. Positive and negative symptoms of schizophrenia exhibited were also recorded during risperidone treatment; the DSM-IV was used as a guide for classifying these symptoms. (See Appendix 3 for a list of symptoms and definitions)

Treatment Compliance

Patients were classified into one of three groups based on clinician's perceived compliance as charted. Non-compliers included patients whose charts had documented indications of non-compliance in the progress notes by the clinic staff; those coded as compliers had no indications of non-compliance in the progress notes of their charts. A third group termed "possible non-compliers" included patients with indications of "possible non-compliance" on their chart, or who may have intermittently discontinued their medication on their own initiative for a short period of time (up to two weeks) but then restarted and did not stop their medication in this manner again.

Side Effects - Side Effect Checklist

All side effects noted by the patient in the interview were recorded on the Side Effect Checklist (see Appendix 3). For each side effect, the patient was asked if it contributed to the reasons for discontinuing the medication. As with the charted side effects, the patient was coded as having: a) sexual side effects only, b) non-sexual side effects only, c) sexual side effects and non-sexual side effects, or d) no side effects.

Drug Attitude Inventory Score

The scores for the Drug Attitude Inventory (see Appendix 3) have a possible range of values from -10 to +10, where a negative value corresponds to a negative subjective response predicting non-compliance and a positive value corresponds to a positive subjective response predicting compliance.[143]

Menopausal Status

All female patients were coded as either being premenopausal, perimenopausal or postmenopausal according to chart progress notes written by clinic staff. In cases where *no information on menopausal status was charted:*

a) Patients *under 42 years* were assumed to be premenopausal and patients *over 58 years* were assumed to be postmenopausal. These cut-offs were used due to the fact that statistically, 95% of natural menopause should occur between these age limits, equally distributed around the average age of 50.[100]

b) Psychiatrists or primary therapists of patients *between the ages of 42 and 58 years* old were contacted. If staff could not provide further information on menopausal status, the patient, with proper consent, was contacted to obtain the necessary information.

2.5 ETHICAL CONSIDERATIONS:

All data was recorded using anonymous numeric codes only; no indicators of identification were used. The original list of patient names and hospital numbers was available only to the investigator for the purpose of obtaining charts and to the research assistant verifying the data.

Informed consent forms were produced for both the chart review and interview phases of the study. The first form was designed for use when a patient had moved to the care of a psychiatrist or other physician outside the practice of the clinicians at the sites involved. In this case, the attending physician was contacted and asked to discuss chart access with the patient, and if the patient was in agreement, he/she was asked to sign the study consent form as well as the CGH Release of Information form. The attending physician then forwarded the appropriate data from the current chart to the investigator.

The second consent form was for the interview of patients identified as discontinuers of risperidone therapy. The patient's attending psychiatrist or primary therapist asked the patient for consent to be contacted by the investigator. The investigator then contacted the patient either by telephone or in person on the hospital unit. All patients agreeing to be interviewed were required to sign the consent form before the interview was conducted. All information obtained was documented on forms identifying the patient only by their study number; no traceable identifiers were used. If a patient was deemed to be incompetent by their

psychiatrist or primary therapist, they were not contacted for an interview.

This protocol was reviewed and accepted by both the Centre for Advancement of Health Research and Development Committee of the Calgary Regional Health Authority and the Conjoint Medical Research Ethics Board of the University of Calgary.

2.6 STATISTICAL ANALYSES:

2.6.1 Data Verification

The data for this study was collected by the primary investigator, and was therefore subject to possible misinterpretation due to the fact that objectives and hypotheses were known by the individual collecting data. Therefore data verification was carried out after data collection. A research nurse qualified to conduct chart reviews, blinded to the study objectives and hypotheses generated a random sample of 20 numbers representing 9% of the patients used in this study. All variables previously collected by the investigator were separately collected (without the aid of the original data) by the research nurse and results were compared.

2.6.2 Descriptive Analyses

All demographic variables including race, DSM-IV diagnosis, age of onset and age at risperidone initiation were compared between males and females and displayed using boxplots or bar graphs where appropriate. All dosage variables and concomitant medications were displayed in this manner, as were frequencies (with 95% confidence intervals) of various side effects. Measures of central tendency and dispersion are represented in the boxplots such that the middle horizontal line in the box represents the median (or 50th percentile) and the upper and lower borders of the box represent the upper and lower

quartiles (or 75th and 25th percentiles) of the data, respectively. 95% confidence intervals represent the fact that 95% of intervals constructed in this manner will contain the true value in the population.

Chi-squared tests (and t-tests for continuous variables) were utilized to test for site and gender differences where warranted. Analysis of variance was used to test for differences between three or more groups of a continuous variable. Where multiple comparisons were made, t-tests were accompanied by the Bonferroni correction to control the overall Type I error rate involved in such comparisons.

Where differences were seen between continuers and discontinuers, stratified analyses were displayed. Premenopausal women were compared with postmenopausal women on all parameters of interest.

2.6.3 Primary Analysis - Discontinuation of risperidone

Survival analysis using Kaplan-Meier methodology was used to compare the two groups (male vs. female) in terms of their overall discontinuation rates as well as the discontinuation patterns over the year of treatment to examine any differences in the length of treatment and time trends surrounding termination of risperidone therapy.

Two curves plotting the survival function (the probability of remaining on risperidone

treatment over the twelve months of follow-up) were constructed, one for each sex. The difference between these functions was tested statistically using a log rank statistic, testing at a conventional value of $\alpha = 0.05$. Potential confounding or interaction between independent variables was investigated by inspection of the functions and logrank statistics.

2.6.4 Secondary Analysis - Sexual side effects on risperidone

All sexual side effects experienced were tabulated for frequency in the two groups stratified by sex. The proportions of sexual side effects occurring in each sex were compared using odds ratios. The data was checked for suspected confounding variables by stratification and tested for homogeneity of stratum-specific odds ratios if necessary. If stratum specific odds ratios were considered to be homogeneous, a summary odds ratio was calculated using the Mantel-Hanszael statistic, and compared with the crude odds ratio. A 95% confidence interval was constructed for the summary odds ratio and hypothesis testing was performed using $\alpha = 0.05$. Logistic regression was performed to further assess the effect of potential confounding or interacting variables, and to confirm values of odds ratios obtained.

CHAPTER THREE: RESULTS

3.1 DATA VERIFICATION

All data for a random sample of 20 cases (representing 9% of total sample) for this study was checked by a research nurse qualified to conduct chart reviews. The research nurse was blinded to the study objectives and did not have the original data present during data collection. Upon comparison of the two datasets, 0 errors (0%) in data collection were found to exist.

3.2 DESCRIPTIVE ANALYSES

3.2.1 Demographics

Approximately 1200 charts were reviewed for this study; an exact number is not known as some patients had charts at more than one site and many patients were represented on both the original MCHID lists and the current clinic lists. The final sample of patients meeting inclusion criteria for this study was comprised of 230 patients total, 81 (35.2%) women and 149 (64.8%) men from three sites. As the two comparison groups are divided on the basis of sex, all further comparisons were made according to these groupings. The distribution of patients from each site is presented in Table 4. When compared using a chi-squared test, there were significant differences found in the distribution of males and females between the sites ($\chi^2 = 7.21$, $p = 0.027$).

Table 4. Distribution of male and female patients at each of the three sites.

Site	*Total (% of total)*	*N Females (% of site)*	*N Males (% of site)*
1	82 (35.7%)	20 (24.4%)	62 (75.6%)
2	48 (20.9%)	22 (45.8%)	26 (54.2%)
3	100 (43.5%)	39 (39.0%)	61 (61.0%)
Total	**230 (100 %)**	**81 (35.2% of total)**	**149 (64.8% of total)**

The two groups were found to be very similar in both race and diagnostic categories, as can be seen in Figures 1 and 2. The majority of female patients were considered to be

premenopausal (Figure 3).

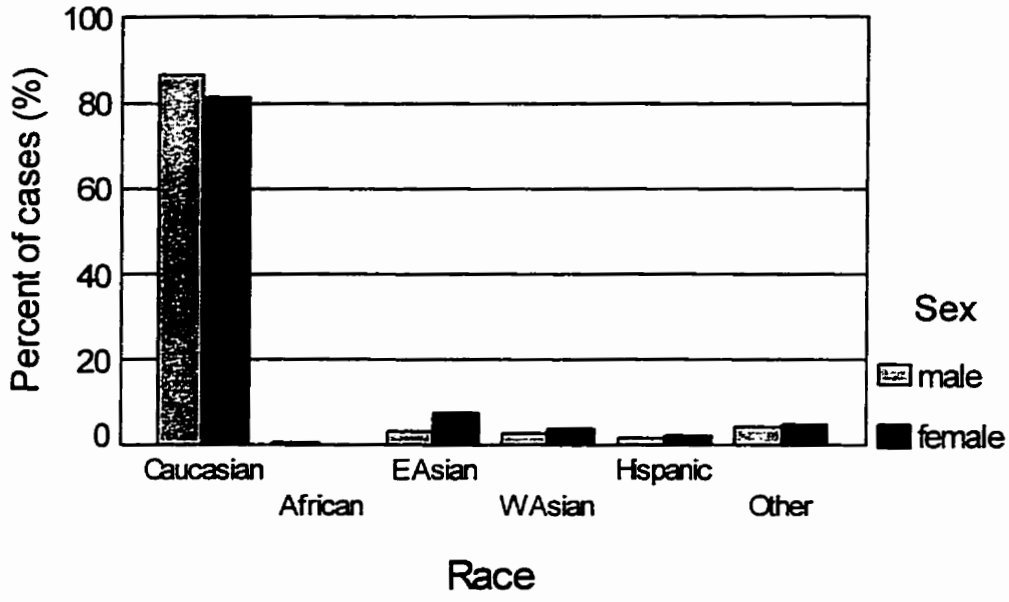


Figure 1 - Distribution of sample among categories of race.

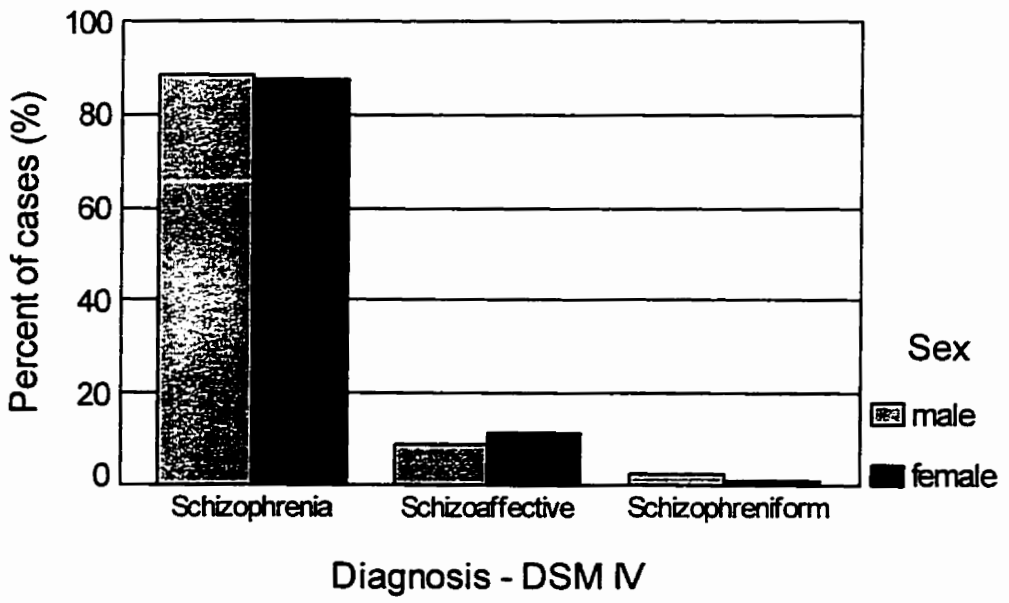


Figure 2 - Distribution of sample in diagnostic categories.

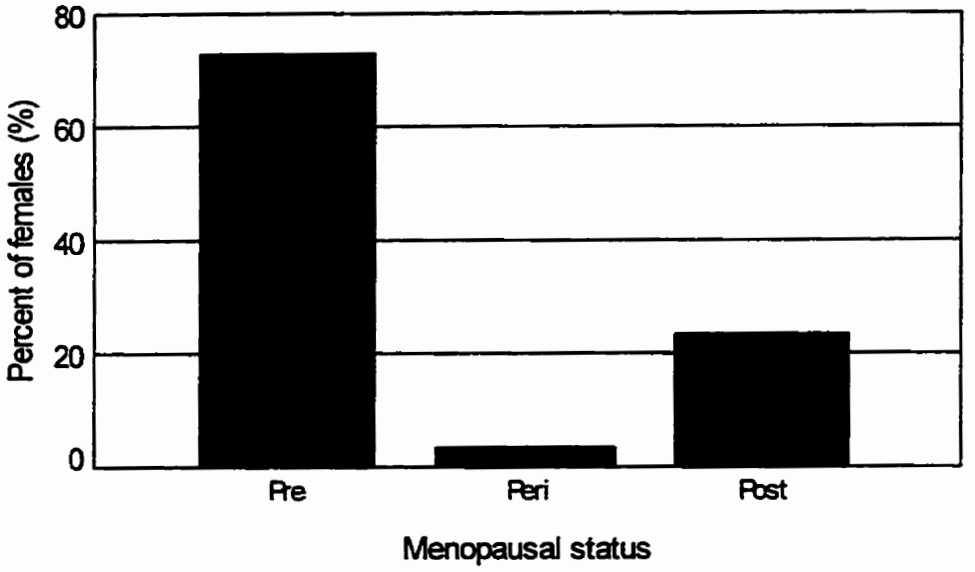


Figure 3 - Menopausal status of the female patients.

Demographic variables were further analyzed to investigate possible differences between sites, and there were no site differences found in age at illness onset ($F = 1.71$, $p = 0.183$), menopausal status ($\chi^2 = 0.775$, $p = 0.679$) or diagnosis ($\chi^2 = 3.14$, $p = 0.208$). Age at risperidone initiation was found to show site differences using analysis of variance ($F = 5.37$, $p = 0.005$). Sites 1 and 3 were found to be significantly different using t-tests and the Bonferroni correction.

Males and females did not appear to differ greatly with regards to either age at onset of illness (Figure 4) or age at risperidone initiation (Figure 5), although women did show higher median values and wider ranges of both variables. Age ranges of women in different groups based on menopausal status are shown in Table 5. Menopausal status for all patients was

determined from the charts and clinic staff; no patients needed to be contacted to obtain this information.

Table 5. Age ranges of each menopausal status group.

Menopausal Status Group	*N (%)*	*Age range (yrs)*
Premenopausal	59 (72.8%)	17 - 52
Perimenopausal	3 (3.7%)	46 - 49
Postmenopausal	19 (23.5%)	42 - 72

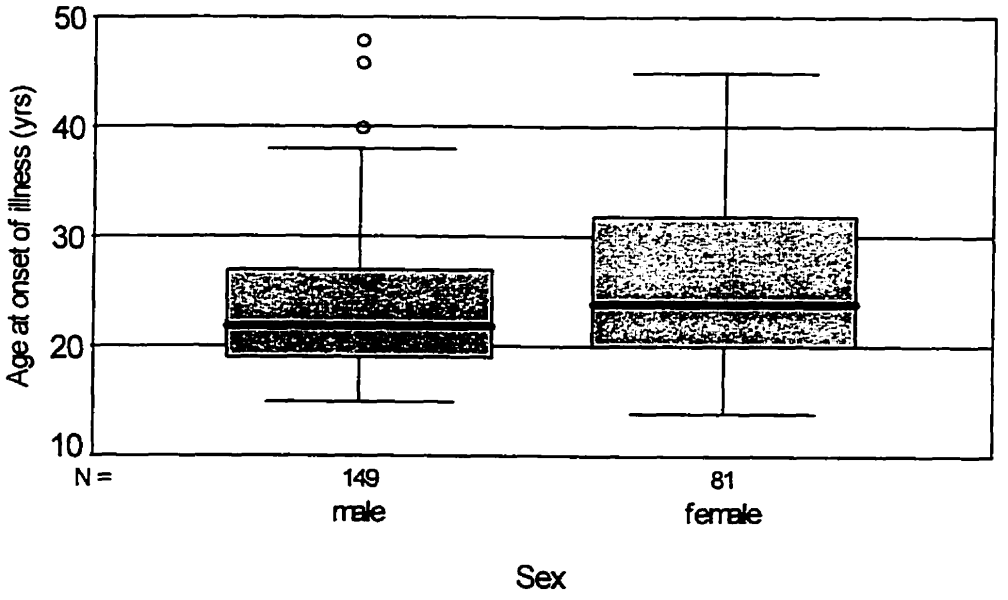


Figure 4 - Age at onset of illness in males and females.

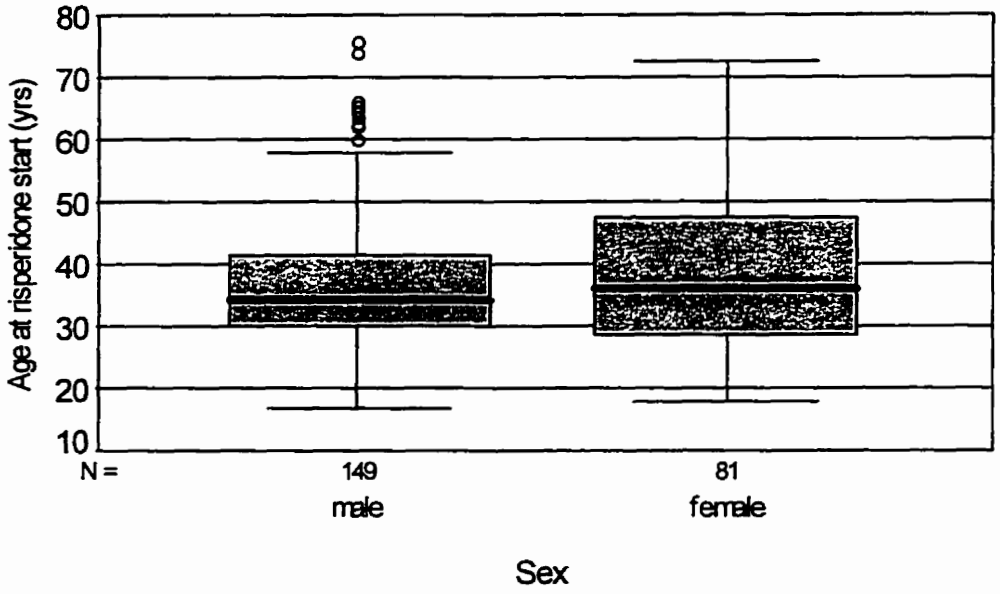


Figure 5 - Age at risperidone initiation in males and females.

3.2.2 Risperidone dosages

Dose ranges during risperidone treatment were recorded for all patients, including lowest and highest dose taken, as well as the dose upon discontinuation for those stopping risperidone. (Tables 6 - 8). Risperidone dosages between the sites were compared using one way analysis of variance, which demonstrated that there were no differences between the sites in the variables of highest dose ($F = 2.06$, $p = 0.129$) or dose at discontinuation ($F = 0.031$, $p = 0.970$). The variable of lowest dose did produce a significant result using one way analysis of variance ($F = 3.77$, $p = 0.025$). However, when each pair of sites were compared using t-

tests and the Bonferroni correction for multiple comparisons, no sites were found to differ from one another at the 0.05 level of significance.

Examination of highest doses taken by each patient reveal that males and females were distributed similarly between low, medium and high dose ranges (Table 6), further reflected in the statistical results for these distributions ($\chi^2 = 5.29$, $p = 0.071$). The median highest dose of risperidone was the same for both sexes (6 mg/day).

Table 6. Frequency of patients at various highest doses of risperidone.
Low = 0.1 - 3.9 mg/day, Medium = 4.0 - 7.9 mg/day, High = 8.0+ mg/day.
Percentages indicate percent within each sex.

	Low	*Medium*	*High*	*Total*
Females	14 (17.3%)	56 (69.1%)	11 (13.6%)	81
Males	14 (9.4%)	100 (67.1%)	35 (23.5%)	149
Total	28 (12.2%)	156 (67.8%)	46 (20.0%)	230

Lowest doses of risperidone were found to differ between the sexes (Table 7), with proportionately more males distributed among the higher values ($\chi^2 = 3.96$, $p = 0.047$). Due to the minimum cell content requirement for the chi-squared test, the medium (3.9 - 7.9 mg/day) and high (8.0+ mg/day) categories were combined for this analysis. Males also displayed a higher median lowest dose (4 mg/day) than did females (3 mg/day).

Table 7. Frequency of patients at various lowest doses of risperidone.
Low = 0.1 - 3.9 mg/day, Medium/High = 4.0+ mg/day.
Percentages indicate percent within each sex.

	Low	*Medium/High*	*Total*
Females	47 (58.0%)	34 (42.0%)	81
Males	66 (44.3%)	83 (55.7%)	149
Total	113 (49.1%)	117 (50.9%)	230

In the subgroup of patients discontinuing risperidone, females were found to discontinue at lower doses of risperidone (Table 8). Statistical testing revealed that proportionately more females were distributed in the lower dose ranges ($\chi^2 = 6.94$, $p = 0.031$). Females also showed a lower median value of dose at discontinuation (4 mg/day vs. 6 mg/day in males).

Table 8. Frequency of patients at various discontinuation doses of risperidone.
Low = 0.1 - 3.9 mg/day, Medium = 4.0 - 7.9 mg/day, High = 8.0+ mg/day.
Percentages indicate percent within each sex.

	Low	*Medium*	*High*	*Total*
Females	20 (40.8%)	24 (49.0%)	5 (10.2%)	49
Males	13 (18.8%)	45 (65.2%)	11 (15.9%)	69
Total	33 (28.0%)	69 (58.5%)	16 (13.6%)	118

Compliance with risperidone in the whole sample was 74%. Females showed an 81% compliance rate while 70% of males were found to be compliant, a difference found to be significant ($\chi^2 = 7.81$, $p = 0.020$). Site differences were also found to exist upon analysis of compliance ($\chi^2 = 12.56$, $p = 0.002$), therefore a table demonstrating compliance by site is

shown in Table 9.

Table 9. Distribution of patients demonstrating compliance between the sites.
Percentages indicate percent at each site.

	Site 1	*Site 2*	*Site 3*	*Total*
Compliant	51 (62.2%)	43 (89.6%)	77 (77.0%)	171 (74.3%)
Non-compliant	31 (37.8%)	5 (10.4%)	23 (23.0%)	59 (25.7%)
Total	82	48	100	230

3.2.3 Adverse Events/Side Effects

Adverse events experienced by all patients on risperidone were recorded from the clinic chart for the duration of their treatment (Table 10). All events were directly recorded as they appeared in the chart; there was no subjective interpretation or diagnosis by the investigator. For the purposes of these analyses, non-sexual side effects are referred to as "adverse events" as the cause of such effects cannot be undoubtedly attributed to risperidone in all cases. As sexual side effects are more directly attributable to risperidone, they are clearly denoted as side effects. Sexual side effects were documented separately and were not included in this analysis. Positive and negative symptoms were tabulated and are presented with the side effects, however they were not included in the overall tabulation of adverse events.

Slightly more females experienced adverse events overall (93.8%) than did males (87.2%), although the sexes fared similarly within most separate adverse events. Females did display twice as much headache, weight gain and tardive dyskinesia. Although tardive dyskinesia is considered an extrapyramidal syndrome, it was separated from EPS in the tabulation for the purpose of investigating sex differences. Nausea and/or vomiting was experienced in three times as many women as men. Men appeared to show more signs of irritability, reduced concentration and orthostatic hypotension, although the numbers in these categories are too small to be generalizable. Patients may have experienced more than one side effect; total side effects represent the number of patients experiencing at least one side effect. All confidence intervals are wide as a result of the relatively low numbers experiencing these events.

Table 10. All adverse events (sexual side effects excluded) experienced at frequencies ≥ 5% (in either group) by males and females. Includes 95% confidence intervals.

Adverse Event	*Females N=81*		*Males N=149*	
Psychiatric	***%***	***(95% CI)***	***%***	***(95% CI)***
positive symptoms	**66.7**	(55.3 - 76.8)	**62.4**	(54.1 - 70.2)
negative symptoms	**44.4**	(33.4 - 55.9)	**44.3**	(36.2 - 52.6)
insomnia	**40.7**	(30.0 - 52.2)	**43.0**	(34.9 - 51.3)
somnolence	**33.3**	(23.2 - 44.7)	**29.5**	(22.3 - 37.5)
depression	**28.4**	(18.9 - 39.5)	**28.9**	(21.7 - 36.8)
anxiety	**16.0**	(8.8 - 25.9)	**15.4**	(10.0 - 22.2)
agitation	**14.8**	(7.9 - 24.4)	**12.1**	(7.3 - 18.4)
labile mood	**7.4**	(2.8 - 15.4)	**4.7**	(1.9 - 9.4)
reduced concentration	**2.5**	(0.3 - 8.6)	**6.0**	(2.8 - 11.2)
irritability	**2.5**	(0.3 - 8.6)	**6.0**	(2.8 - 11.2)
Neurological				
extrapyramidal syndrome	**58.0**	(46.5 - 68.9)	**59.1**	(50.7 - 67.0)
dizziness	**13.6**	(7.0 - 23.0)	**12.1**	(7.3 - 18.4)
tardive dyskinesia	**12.3**	(6.1 - 21.5)	**6.0**	(2.8 - 11.2)
headache	**12.3**	(6.1 - 21.5)	**6.0**	(2.8 - 11.2)
Other systems				
weight gain	**21.0**	(12.7 - 31.5)	**12.1**	(7.3 - 18.4)
nausea/vomiting	**17.3**	(9.8 - 27.3)	**6.0**	(2.8 - 11.2)
fatigue	**9.9**	(4.4 - 18.5)	**10.7**	(6.3 - 16.9)
orthostatic hypotension	**2.5**	(0.3 - 8.6)	**6.0**	(2.8 - 11.2)
Any Adverse Event:	**93.8**	(86.2 - 98.0)	**87.2**	(80.8 - 92.1)

The frequency of adverse events were investigated for site differences, and no significant difference was found to exist ($\chi^2 = 3.98$, $p = 0.137$).

Other adverse events occurring in <5% of patients involved various systems and are included in Appendix 1.

Sexual side effects were also documented for each group (Table 11). Overall, females experienced twice as many sexual side effects as did males (37.0% vs 18.1% in males, statistical analysis shown in section 3.4). The most common side effect in males was erectile dysfunction (9.4%), while amenorrhea was most common in females (23.7%) followed by galactorrhea (13.6%).

Site differences were found to exist in the frequency of sexual side effects ($\chi^2 = 8.27$, $p = 0.016$), which are explored in further detail in section 3.4.

The female group was stratified by menopausal status to determine if there were differences in the frequencies of sexual side effects reported on the charts. As there were only 3 patients classified as perimenopausal, these patients were not included in the analysis. The percentage of premenopausal women experiencing sexual side effects was 42%, while postmenopausal women demonstrated sexual side effects at a frequency of 11% (2 patients out of 19). One of the two postmenopausal women experienced anorgasmia, while the other experienced hyposexuality.

Table 11. Frequencies of all sexual side effects experienced by males and females.
Includes 95% confidence intervals.

Sexual Side Effect	*Females % (95% CI) N = 81*	*Males % (95% CI) N = 149*
galactorrhea	13.6 (7.0 - 23.0)	0.7 (0.02 - 3.7)
hyposexuality	6.2 (2.0 - 13.8)	5.4 (2.3 - 10.3)
anorgasmia	1.2 (0.3 - 6.7)	0.7 (0.02 - 3.7)
gynecomastia	0.0 (0.0 - 4.4)*	0.7 (0.02 - 3.7)
breast tenderness	1.2 (0.3 - 6.7)	0.0 (0.0 - 2.4)*
painful intercourse	1.2 (0.3 - 6.7)	0.0 (0.0 - 2.4)*
hypersexuality	0.0 (0.0 - 4.4)*	0.7 (0.02 - 3.7)
preoccupied with sex	0.0 (0.0 - 4.4)*	0.7 (0.02 - 3.7)
amenorrhea	23.7 (13.6 - 36.6)†	
dysmenorrhea	6.8 (1.9 - 16.5)†	
irregular menses/flow	3.4 (0.4 - 11.7)†	
erectile dysfunction		9.4 (5.2 - 15.3)
retrograde ejaculation		6.0 (2.8 - 11.2)
delayed ejaculation		1.3 (0.2 - 4.8)
anejaculation		0.7 (0.02 - 3.7)
Any Sexual Side Effect:	37.0 (26.5 - 48.5)	18.1 (12.3 - 25.3)

* - 97.5% confidence interval (one-tailed) † - premenopausal women only

3.2.4 Concomitant Medications

Concomitant medications were recorded for all patients and were classified into one of six commonly prescribed categories in this patient population. Overall, there was minimal difference in the proportion of males and females taking concomitant medications: 78.5% of males and 86.4% of females were taking other drugs with risperidone ($\chi^2 = 2.15$, $p = 0.142$). However, males and females varied within different classes: females took more antiparkinsonian, antipsychotic, anxiolytic, antimanic and other unclassified medications than did male patients. Males took more anticonvulsant medications, while the rest of the classes were essentially prescribed at the same frequency in either sex. Figure 6 shows the percentage of patients in each sex taking each class of drug. Female patients were shown to take a higher number of different classes of medications than did male patients ($\chi^2 = 6.09$, $p = 0.048$) (Figure 7). Concomitant medications overall were not prescribed at significantly different rates between the sites ($\chi^2 = 4.16$, $p = 0.125$), nor did the number of classes prescribed vary between the sites ($\chi^2 = 2.21$, $p = 0.696$).

All medications were classified based on categories published in the Compendium of Pharmaceuticals and Specialties (1996). [144]

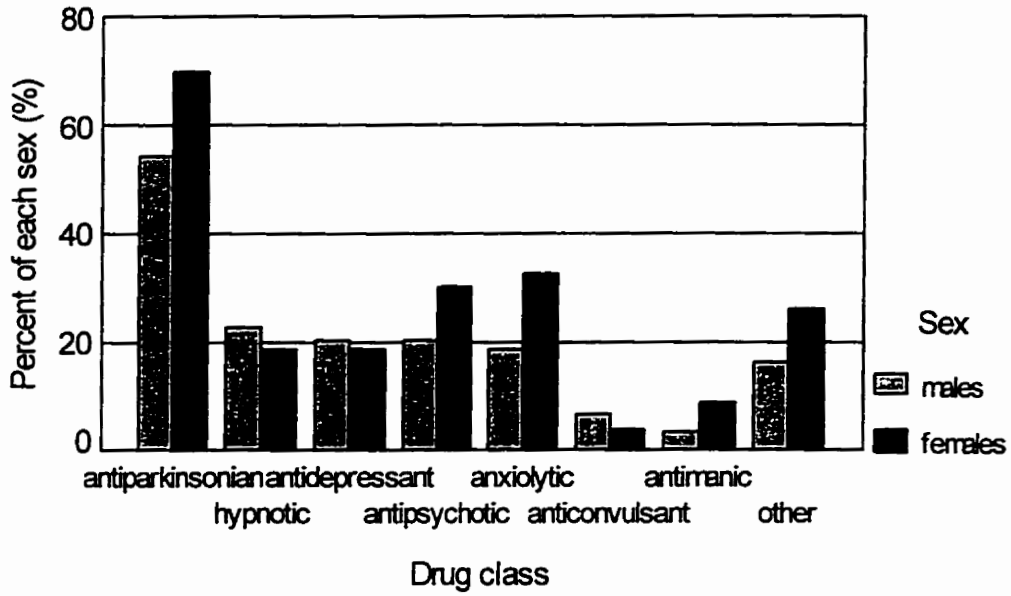


Figure 6. Percentages of males and females taking various classes of concomitant medications.

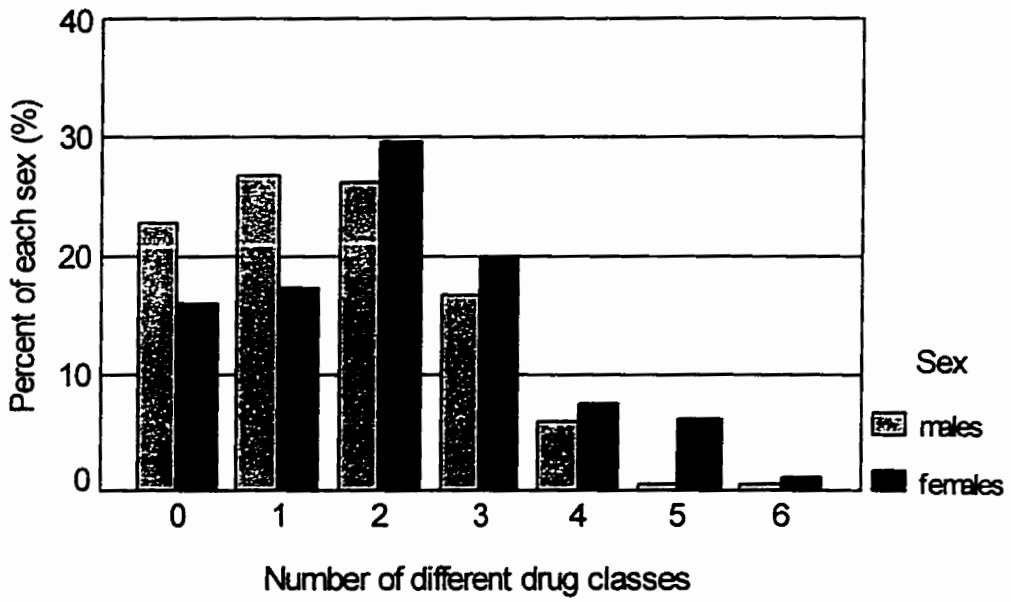


Figure 7. Numbers of different classes of concomitant medications taken by males and females.

3.2.5 Subgroup Analyses - Continuers vs. Discontinuers

Male and female patients were further stratified into continuers and discontinuers, based on whether or not they had remained on risperidone for a full year of observation. Comparing all variables between these groups, demographics including race, diagnosis and ages at illness onset and risperidone start were found to be very comparable (within each sex) and are therefore not displayed here (see Appendix 1). Any differences present between males and females remained after stratification on discontinuation status.

The proportion of female patients in each menopausal status group discontinuing risperidone is illustrated in Table 12. More premenopausal women were found to discontinue risperidone relative to their numbers in the sample than either perimenopausal or postmenopausal women, although these numbers did not reach statistical significance ($\chi^2 = 1.74$, $p = 0.187$). In total, 64% of premenopausal women discontinued, while 47% of postmenopausal women discontinued risperidone.

Table 12. Distribution of continuing and discontinuing female patients between each menopausal status group. Percentages indicate percent of menopausal status group.

	Premenopausal	***Perimenopausal***	***Postmenopausal***	***Total***
Discontinuers	38 (64.4%)	2 (66.7%)	9 (47.4%)	49 (60.5%)
Continuers	21 (35.6%)	1 (33.3%)	10 (52.6%)	32 (39.5%)
Total	59	3	19	81

Risperidone dosages were all found to be similar between continuers and discontinuers within each sex. However a difference between subgroups was found in the prescription of concomitant medications. In both sexes, continuers appeared to take more concomitant therapy than did their discontinuing counterparts (Table 13), although this was only significant in the males. In the male group, 87.5% of continuers were taking concurrent therapy, in comparison to 68.1% of patients discontinuing risperidone ($\chi^2 = 8.25$, $p = 0.004$). Similarly, 93.8% of female continuers took concomitant therapy compared to 81.6% of females discontinuing risperidone ($\chi^2 = 2.42$, $p = 0.120$).

When actual number of classes of concomitant medication were compared, male continuers appeared to take the same number of classes as male discontinuers ($\chi^2 = 2.00$, $p = 0.367$). However in the female group, continuers took significantly more different classes of concomitant medication than did discontinuing patients ($\chi^2 = 7.86$, $p = 0.020$).

Within separate drug classes, two of these appear to be different between continuers and discontinuers (shown in bold). In males, 30% of the continuing group were taking antidepressants compared to 9% of discontinuers. Similarly in females, 47% of continuers were taking anxiolytics, while only 22% of discontinuers were receiving anxiolytic medication.

Discontinuers and continuers were found to differ in terms of compliance with medication. Overall, 69% of discontinuing patients were considered to be compliant, while 80% of

patients remaining on risperidone for the full year of follow-up were found to be compliant ($\chi^2 = 4.13$, $p = 0.042$).

Table 13. Frequency of concomitant medication use by males and females, stratified by discontinuation status. Includes 95% confidence intervals.

Drug Class	*Female Disc. % (95% CI) N = 49*	*Female Cont. % (95% CI) N = 32*	*Male Disc. % (95% CI) N = 69*	*Male Cont. % (95% CI) N = 80*
anti convulsant	2.0 (0.05-10.8)	6.3 (0.8-20.8)	7.2 (2.4-16.1)	6.3 (2.1-14.0)
anti depressant	16.3 (7.3-29.6)	21.9 (9.3-40.0)	**8.7** (3.3-18.0)	**30.0** (20.2-41.3)
anti parkinson	63.3 (48.3-76.6)	75.0 (56.6-88.5)	52.2 (39.8-64.4)	56.3 (44.7-67.3)
anti manic	8.2 (2.3-19.6)	9.4 (2.0-25.0)	4.3 (0.9-12.2)	2.5 (0.3-8.7)
anti psychotic	30.6 (18.2-45.4)	28.1 (13.7-46.7)	18.8 (10.4-30.1)	21.3 (12.9-31.8)
anxiolytic	**22.4** (11.8-36.6)	**46.9** (29.1-65.2)	15.9 (8.2-26.7)	21.3 (12.9-31.8)
hypnotic	14.3 (5.9-27.3)	25.0 (11.5-43.4)	26.1 (16.3-38.1)	20.0 (11.9-30.4)
other	16.3 (7.3-29.6)	40.6 (23.7-59.4)	8.7 (3.3-18.0)	22.5 (13.9-33.2)
Any Conc. Meds	**81.6** (68.0-91.2)	**93.8** (79.2-99.2)	**68.1** (55.8-78.8)	**87.5** (78.2-93.8)

Frequencies of some side effects experienced, including both sexual and non-sexual, appeared to differ between discontinuers and continuers. Side effects appearing to be different upon stratification are presented in Tables 14 and 15. 'Any side effects' represents the frequency of patients reporting at least one adverse event/sexual side effect in each category.

Table 14. Non-sexual adverse events experienced at differing rates by continuers and discontinuers of risperidone therapy, stratified on gender. Includes 95% confidence intervals.

Adverse Event	*Female disc. % (95% CI) N = 49*	*Female cont. % (95% CI) N = 32*	*Male disc. % (95% CI) N = 69*	*Male cont. % (95% CI) N = 80*
Psychiatric				
anxiety	**18.4** (8.8 - 32.0)	**12.5** (3.5 -29.0)	**8.7** (3.3-18.0)	**21.3** (12.9-31.8)
agitation	**18.4** (8.8 - 32.0)	**9.4** (2.0 -25.0)	13.0 (6.1-23.3)	11.3 (5.3 - 20.3)
labile mood	**10.2** (3.4 - 22.2)	**3.1** (0.08-16.2)	5.8 (1.6-14.2)	3.8 (0.8 - 10.6)
reduced concentration	4.1 (0.5 - 14.0)	0.0 (0.0-10.9)	**10.1** (4.2-19.8)	**2.5** (0.3 - 8.7)
Neurological				
EPS	53.1 (38.3 -67.5)	65.6 (46.8-81.4)	**40.6** (28.9-53.1)	**75.0** (64.1-84.0)
Other systems				
weight gain	**14.3** (5.9 - 27.3)	**31.3** (16.1-50.0)	**8.7** (3.3-18.0)	**15.0** (8.0-24.8)
nausea/ vomiting	**26.5** (14.9-41.1)	**3.1** (0.08-16.2)	**10.1** (4.2-19.8)	**2.5** (0.3 - 8.7)
fatigue	**12.2** (4.6 - 24.8)	**6.3** (0.8-20.8)	10.1 (4.2-19.8)	11.3 (5.3-20.3)
Any Adverse Events	**93.9** (83.2 -98.7)	**93.8** (79.2-99.2)	**85.5** (74.9-92.8)	**88.8** (79.7-94.7)

Table 15. Sexual side effects experienced at differing rates by continuers and discontinuers of risperidone therapy, stratified on gender.
Includes 95% confidence intervals.

Sexual Side Effect	*Female disc. % (95% CI) N = 49*	*Female cont. % (95% CI) N = 32*	*Male disc. % (95% CI) N = 69*	*Male cont. % (95% CI) N = 80*
galactorrhea	**16.3** (7.3 -29.6)	**9.4** (2.0-25.0)	0.0 (0.0-5.2)*	1.3 (0.03-6.8)
hyposexuality	**0.0** (0.0-7.3)*	**15.6** (5.3-32.8)	5.8 (1.6-14.2)	5.0 (1.4-12.3)
dysmenorrhea	**2.6** (0.07-13.8)†	**14.3** (3.0-36.3)†		
retrograde ejaculation			**1.4** (0.04-7.8)	**10.0** (4.4-18.7)
Any Sexual Side Effect	**42.9** (28.8-57.8)	**56.3** (37.7-73.6)	**20.3** (11.6-31.7)	**31.3** (21.4-42.6)

* - 97.5% confidence interval (one-tailed) † - premenopausal women only

3.2.6 Interviews of Discontinuers

Subsequent to chart review, the group of patients identified as discontinuers of risperidone were invited to be interviewed, with the following exceptions. Of the 118 discontinuers, 20 were no longer receiving treatment at one of the three sites therefore they were not contacted. 23 patients were deemed by their attending psychiatrist to be incompetent for interview at the time, and 32 had not come into the clinic for treatment and therefore were not notified of the interviews. Therefore, 43 patients responded to the interview request, of which 20 accepted the offer and were interviewed, representing a 47% acceptance rate and a 19% response rate overall. 12 men and 8 women were interviewed. The numbers of patients

interviewed from each site were representative of the sample numbers at the sites. Due to the small numbers interviewed, all data reported in this study is from chart review only, unless otherwise stated explicitly.

This data was explored for frequency of side effects and responses to the Drug Attitude Inventory, upon which chart information was compared.

Scores on the DAI ranged from 0 to +10; the average score was 6.2. Males had scores ranging from 2 to +10 (average 6.2) while females ranged from 0 to +10 (average 6.3). These scores, due to the fact that they are greater than zero, are predictive of compliance, and when compared with chart data on compliance, matched very closely. All but one patient were considered to be compliant from information on the chart; the one exception was coded as 'possibly non-compliant'.

Comparison of side effects from the chart and interview demonstrates only a moderate level of correlation. 11 of the 20 patients (55%) reported the same side effects in the interview as were recorded on the chart. Of the remaining 9 patients, 6 stated they had sexual side effects which were not recorded on the chart, while 3 reported no sexual side effects despite the fact that such effects were found on the chart. In total, 12 out of 20 patients reported they experienced sexual side effects and 2 patients (one male, one female) stated that these effects were the primary reason for discontinuing the medication. The most common reason for discontinuation was lack of efficacy for symptoms of schizophrenia, while other reasons

included EPS, insomnia, palpitations, weight gain and nausea/vomiting. The average length of time between risperidone discontinuation and the interviews was 29.5 months. A summary of interview data for each patient is included in Appendix 1.

3.3 PRIMARY ANALYSIS - DISCONTINUATION OF RISPERIDONE

The total proportions of patients discontinuing risperidone in the one year period were found to be 61% among female patients and 46% among male patients. 64% of premenopausal women discontinued compared to 47% of postmenopausal women. 2 out of the 3 perimenopausal women also stopped risperidone therapy. Survival analysis was utilized to examine male and female discontinuation rates and patterns over the year of follow-up. The full year of information was obtained for all 230 patients; there was no loss to follow-up for any patients.

Survival functions were constructed for each site to determine if site was influencing discontinuation. These functions are shown in Figure 8.

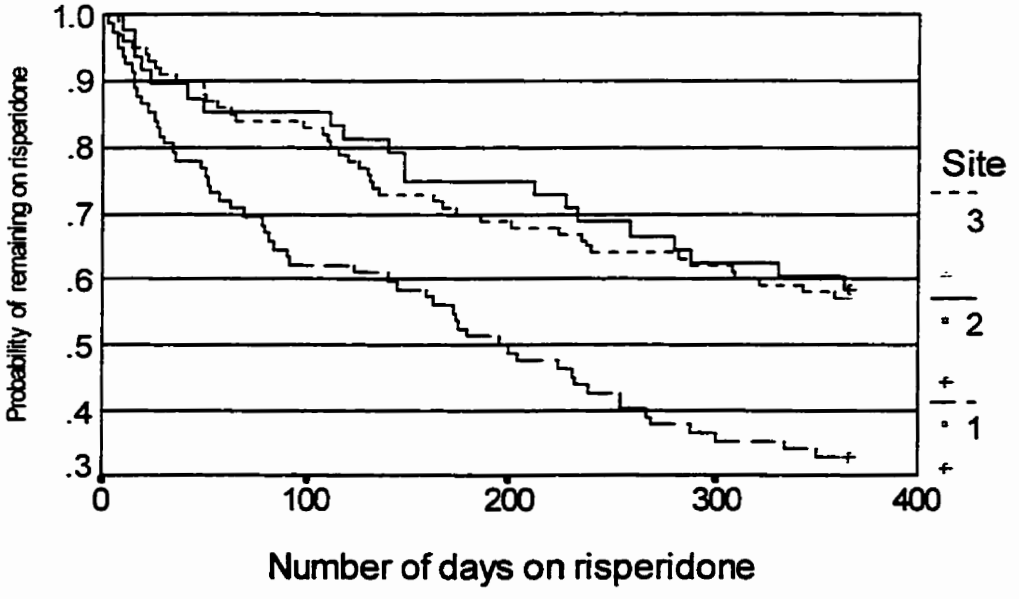
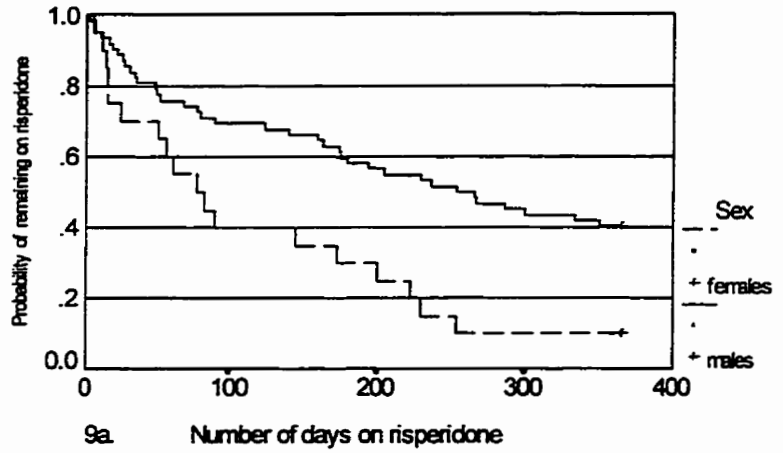


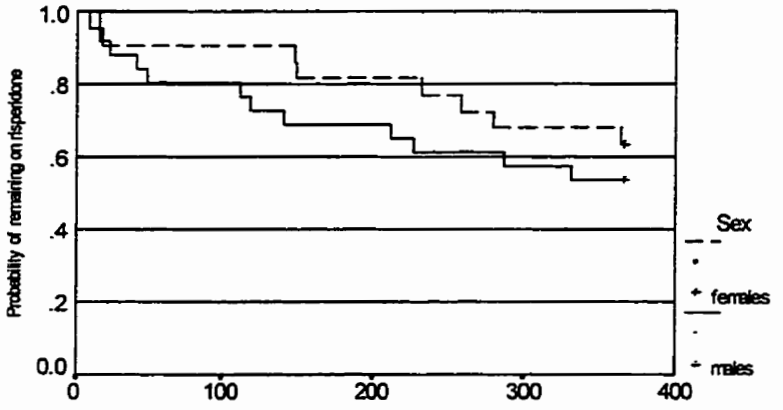
Figure 8. Survival functions of discontinuation stratified by site.

Site 1 demonstrates the highest rate of discontinuation with patients at one year having a 33% probability of remaining on risperidone compared with a 58% and 57% probability of remaining on risperidone at Sites 2 and 3, respectively. Site 2 differed from Sites 1 and 3 in that males at this site discontinued at a higher rate than did female patients, whereas the other sites demonstrated proportionately more females discontinuing risperidone during the year of treatment.

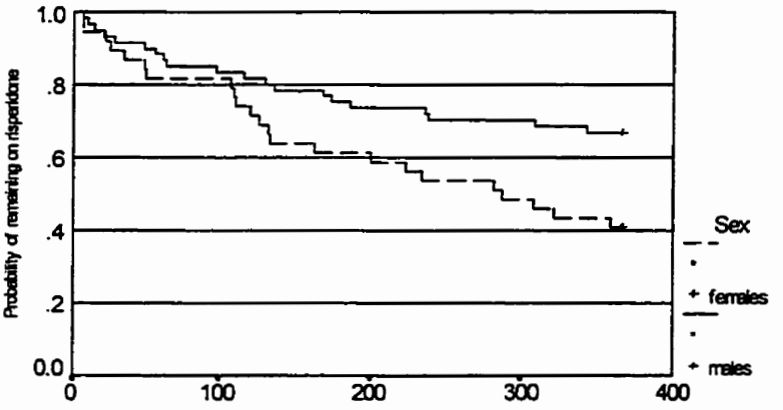
The logrank statistic performed on these functions demonstrated a significant difference between sites ($\chi^2 = 15.16$, $p = 0.0005$). The sites were therefore separated for analysis of the effect of sex on discontinuation. The survival functions comparing males and females at each site are shown in Figures 9a-c.



9a. Number of days on risperidone



9b. Number of days on risperidone



9c. Number of days on risperidone

Figures 9 a-c. Survival functions displaying the discontinuation patterns in males and females on risperidone over one year.

9a = Site 1, 9b = Site 2, 9c = Site 3.

Results of hypothesis testing using the logrank statistic for each site are shown in Table 16.

Table 16. Logrank statistic results comparing male and female discontinuation rates of risperidone.

Site	*Sex*	*N Total*	*N Events*	*Logrank*	*P value*
1	M	62	37	9.90	0.0016
	F	20	18		
2	M	26	12	0.66	0.4158
	F	22	8		
3	M	61	20	6.13	0.0133
	F	39	23		

Site 1 (Figure 9a) demonstrates a difference between male and female patients, as can be seen in the survival curves and the accompanying logrank statistic. Females had a 10% probability of remaining on risperidone for a full year, compared to a 40% probability of a male remaining on risperidone for one year. This is a significant difference, as indicated by the logrank statistic and accompanying p-value comparing these functions (Table 16).

Male patients at Site 2 (Figure 9b) demonstrated a 54% probability of remaining on risperidone compared with a 64% probability of a female patient remaining on risperidone for the full year. The log rank statistic was non-significant for this site (Table 16), indicating no evidence to reject the null hypothesis that the sexes are the same with regards to discontinuation rates, contrary to the other two sites.

Female patients at Site 3 (Figure 9c) demonstrated a 41% probability of remaining on risperidone for one year, compared with a 67% probability of the same in the male patients. Similar to Site 1, this difference was also statistically significant (Table 16).

3.4 SECONDARY ANALYSIS - SEXUAL SIDE EFFECTS OF RISPERIDONE

Odds ratios were constructed comparing frequencies of patients experiencing sexual side effects in each sex. As indicated previously, site was found to significantly affect rates of sexual side effects. Therefore, patients were stratified by site to obtain stratum-specific odds ratios as well as the crude odds ratio for the whole sample. (Figures 10-13). (For all calculations see Appendix 2). All side effects were those determined from chart review.

	Sexual Side Effects	*No Sexual Side Effects*	
Females	30	51	81
Males	27	122	149
	57	173	230

$OR_c = (30)(122)/(51)(27) = 2.66$

Figure 10 - Contingency table examining sex and sexual side effects and corresponding crude odds ratio for all sites combined.

	Sexual Side Effects	*No Sexual Side Effects*	
Females	12	8	20
Males	17	45	62
	29	53	82

$OR_1 = (12)(45)/(8)(17) = 3.97$

Figure 11 - Contingency table examining sex and sexual side effects and corresponding odds ratio for Site 1.

	Sexual Side Effects	*No Sexual Side Effects*	
Females	7	15	22
Males	4	22	26
	11	37	48

$OR_2 = (7)(22)/(15)(4) = 2.57$

Figure 12 - Contingency table examining sex and sexual side effects and corresponding odds ratio for Site 2.

	Sexual Side Effects	*No Sexual Side Effects*	
Females	11	28	39
Males	6	55	61
	17	83	100

$OR_3 = (11)(55)/(28)(6) = 3.60$

Figure 13 - Contingency table examining sex and sexual side effects and corresponding odds ratio for Site 3.

Logistic regression was used to test for interaction between the variables of site and gender. As can be seen from the regression output (Table 17), there was no evidence to suggest interaction between these two variables. All contrasts used were simple whereby the reference category used for comparison was Site 3.

Table 17. Logistic regression output incorporating gender, site and the interaction term into the model.

Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
GENDER(1)	-1.2009	.3505	11.7378	1	.0006	-.1944	.3009
SITE			11.7504	2	.0028	.1735	
SITE(1)	1.2909	.3876	11.0945	1	.0009	.1879	3.6362
SITE(2)	.3415	.4518	.5713	1	.4497	.0000	1.4070
GENDER * SITE			.2472	2	**.8837**	.0000	
INT_1	-.0977	.7751	.0159	1	**.8997**	.0000	.9070
INT_2	.3386	.9036	.1405	1	**.7078**	.0000	1.4030
Constant	-1.0308	.1753	34.5904	1	.0000		

Odds ratios were tested for homogeneity and no evidence was found against the null hypothesis, therefore the ratios were considered to be homogeneous at the 5% level of significance ($T = 0.2473$, $p > 0.2$). A summary odds ratio of 3.45 was calculated using the Mantel-Haenszel statistic. This odds ratio indicates that the odds of experiencing sexual side effects on risperidone was 3.45 times higher for female patients than for male patients. The corresponding 95% confidence interval for this summary odds ratio is 1.78 - 6.75.

The Mantel-Haenszel odds ratio can be seen to be different from the crude odds ratio (2.66,

Figure 10), indicating that site is confounding the relationship between sex and the occurrence of sexual side effects.

Logistic regression was used to confirm the findings obtained with the contingency tables and odds ratios. As can be seen in Table 18, when the variable of gender alone was incorporated into the model, the "Exp(B)" term, or e^b, which corresponds to the odds ratio between the two levels of gender, equals 0.3763. Due to the way the variable for gender was coded, this number represents the relative odds of male patients experiencing a sexual side effect compared to female patients. To correctly interpret the increased odds of female patients, this number is inversed (Table 18) to produce a value of 2.66 (1/0.3763). This number is the crude odds ratio, i.e. without controlling for the variable of site. And as expected, this number matches the crude odds ratio obtained with the contingency tables and odds ratio calculations.

Table 18. Logistic regression output incorporating gender into the model.

Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
GENDER(1)	-.9775	.3133	9.7325	1	.0018	-.1733	**.3763***
Constant	-1.0194	.1567	42.3382	1	.0000		

*** 1/.3763 = 2.66**

When both gender and site were incorporated into the model (Table 19), the resultant value

of Exp(B) for gender was 0.2879. When inversed, this results in an odds ratio of 3.47. This value represents the odds of female patients experiencing a sexual side effect relative to males when the variable of site is controlled. In other words, this is an unconfounded odds ratio estimate, which is the same as seen with the contingency tables and Mantel-Haenszel odds ratio calculation ($OR_{MH} = 3.45$).

Table 19. Logistic regression output incorporating gender and site into the model.

Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
GENDER(1)	-1.2453	.3408	13.3478	1	.0003	-.2099	**.2879***
SITE			11.7564	2	.0028	.1735	
SITE(1)	1.2583	.3785	11.0503	1	.0009	.1874	3.5195
SITE(2)	.3063	.4484	.4666	1	.4946	.0000	1.3584
Constant	-1.0501	.1694	38.4290	1	.0000		

*** 1/.2879 = 3.47**

CHAPTER FOUR: DISCUSSION

4.1 DESCRIPTIVE ANALYSES

4.1.1 Demographics

In terms of demographic variables, the sample in this study appears to be relatively homogeneous. While the lifetime prevalence statistics report a 1:1 ratio of males to females with schizophrenia, the 65%:35% split may be a more realistic picture of patients receiving treatment at these clinics. As discussed earlier, there may be relatively more males seeking structured treatment such as is offered in the centres used for this study. This may be due to a lower level of social and family support for males, perhaps due to the earlier age of onset. Alternatively, more females may be able to function with less intensive treatment, such as through their family physicians or private psychiatrists.

The differential in distribution of males and females between the sites was a somewhat unexpected result. It appears that Site 1 had the lowest proportion of females in the sample (25%) while Site 2 had the highest (46%). Two possible reasons may exist for these findings. There may be more female patients at Site 2 than at the other sites. This may be due to the fact that this site, unlike the other two sites is a non-hospital based clinic, and as such is less intensive in terms of treatment. Patients are seen less often at this site and have less health care staff involved in their care. In this regard, it may be true that proportionately more

females may utilize this clinic as the illness of schizophrenia in women has been reported to be less severe on average and therefore they may require less intensive treatment.

A second explanation for this finding may be that the psychiatrist directly involved in the initiation of this research was located at Site 1, and therefore may have been more sensitive to potential problems with risperidone in female patients. This may have resulted in fewer female patients being prescribed risperidone relative to males, and therefore a lower potential sample size available for this study. It would not have been a reflection of the actual numbers of females at this site.

The large majority of patients were Caucasian, although this is likely representative of the population in the Calgary area rather than being indicative of any differential incidence of the illness between different races. Slightly more males were Caucasian, while a few more females were East Asian in background. The numbers of patients from each site included in the study are also fairly representative of the numbers treated at these clinics at any one time: Site 2 is the smallest site treating approximately 200 patients, Site 1 treats approximately 240 patients, while Site 3 is largest treating up to 350 patients.

Premenopausal women outnumbered perimenopausal and postmenopausal women in the study by a factor of three to one. This observation may be representative of the numbers of these groups in the populations served by these clinics. According to prior reports, there may be proportionately more postmenopausal women requiring treatment as some do not

experience illness onset until this life stage.[93] However, it is also possible that less postmenopausal women were being prescribed risperidone at the time of its release as they may have been sufficiently stabilized on other medications.

The difficulties with collecting data on menopausal status are numerous, and often a best estimation had to be made taking into consideration the chart notes and the age of the patient. While there were notes on the charts to confirm menopausal status for most patients, it was not noted for others. Fortunately for these patients, the attending clinic staff was knowledgeable as to this information, although errors are possible. Another confounding variable in determining menopausal status is the previous antipsychotic treatment the patient may have received. Most antipsychotics elevate prolactin levels, and these effects on the central nervous system may extend beyond their actual administration. If a patient is maintained on antipsychotics continuously, she may not have menstruated for years, often leading the clinician to believe she is postmenopausal, when in fact she is premenopausal and experiencing amenorrhea due to chronic hyperprolactinemia. Elevated prolactin due to depot neuroleptics may be particularly persistent and should be considered when assessing menopausal status. Unfortunately, some patients may have been classified as perimenopausal for lack of a better category in which to place them. As there were only 3 patients coded as perimenopausal, all classified based on either chart notes or information provided by clinic staff, this should not have affected the data to a significant extent.

The median age at onset of illness did not differ greatly between the sexes, contrary to

previous reports of higher ages in females. However, this may be a sample size issue, as the range of ages in the female group is larger and shows a definite skew towards higher ages, while the spread is less in the males around the central age. These results would suggest that males do have somewhat younger ages of onset. Comparing ages at the time of starting risperidone, there is more similarity between the groups. Most patients were between 30 and 50 years of age, with women making up most of the 40 - 50 age group. The median ages for starting risperidone are obviously higher than age at onset, as illness onset occurs once, commonly in the early to mid 20s, while risperidone may be started at any time during the patient's life. Many patients would have been older at the time of the drugs release on the market; it would not have been available to them at younger ages. The median ages for starting risperidone may represent a median age for patients in the clinic, as the wide range indicates that no age group was excluded from being prescribed the medication.

There were site differences in the age of starting risperidone; specifically, Sites 1 and 3 were found to differ significantly from each other (averages: Site 1 = 33.9 yrs, Site 2 = 38.3 yrs, Site 3 = 39.8 yrs). These differences may reflect a difference in the mean age of patients treated at these sites, although age data from the entire clinic population was not collected, therefore this theory cannot be tested. Sites 1 and 3 are both hospital programs, although they do differ in terms of support services offered. Therefore, there may be differences in the patient populations, including different referral sources to the clinics leading to younger patients receiving treatment at Site 1. There may also be different attitudes among clinicians at each site as to the appropriateness of risperidone for patients of different ages.

4.1.2 Risperidone Dosages

Risperidone is considered to be a high potency/low dose antipsychotic. It is generally prescribed in doses with intervals of 2 mg (ie. 2, 4, 6, 8 mg/day) as a result of the formulation of the tablets, although some psychiatrists have found success with manipulating dosages between these increments. For these reasons, dosing intervals were used for analysis which represent low, medium and high dose ranges of the medication.

Males and females had the same median highest dose (6 mg/day) of risperidone. It can be seen that proportionately more males are distributed in the 'high' dose interval, however this did not reach statistical significance (although it could be interpreted as borderline at $p = 0.071$).

Lowest doses of risperidone in males and females does appear to differ to the extent that it was statistically significant. The median doses were different, and proportionately more females were distributed in the 'low' dose interval than in the 'medium/high' dose interval.

In the subgroup discontinuing medication within one year, (49 female, 69 male), female patients were taking lower doses at the time. The median dose in the females was 4 mg/day relative to 6 mg/day in the males, and more females were distributed in the 'low' dose range than were males.

Overall the risperidone dosage data would suggest that doses in males and females may be similar across the patient population, although the average dose range appears to be lower in females. This appears to be particularly true in the lower range of each patient's individual treatment. While median doses of females are consistently lower than males, there is a large range of doses in all categories, which emphasizes the variation in dose requirements between patients.

Although for many patients, the reasons for discontinuation may not be related to risperidone dosage, there may also be some who were not taking an appropriate dose for their illness. It is possible that patients of either sex may have been on too high or too low doses, causing various problems with treatment response. Doses that are too low would be expected to result in a lack of efficacy, while higher doses can result in many side effects. Both of these situations can be expected to result in non-compliance or discontinuation for many patients. As previous literature has determined that females as a group should be on lower doses [101], the increased discontinuation in this sex is not explained by risperidone dosage data, as females were on lower doses, including at the time of stopping risperidone.

Both males and females continued to show similar levels of symptoms; approximately 65% demonstrated positive symptoms and 45% presented with negative symptoms on risperidone in each sex. Unfortunately it is not possible to ascertain all the factors involved in treatment failure, however dosages do give further insight into such issues including appropriate doses for therapeutic response and possible non-compliance, as the dosages recorded were the

amounts the patient was noted as taking, though this may not have been the dose prescribed.

Females showed significantly higher rates of compliance (81%) than did male patients (70%). These rates may represent an underestimation as all patients coded as "possibly noncompliant" were included in the non-compliant group for these calculations. The literature reports compliance rates of around 50% with various antipsychotic medications.[145] Therefore, compliance with risperidone in this sample represents values in the higher range compared to other neuroleptics. In most reports, women have been found to have higher rates of compliance than do men, but these differences are rarely quantified.[146]

Interestingly, site differences in compliance were found to exist in this sample. In particular, Site 2 appeared to have a very high compliance rate (90%) compared to Site 1 (62%) and Site 3 (77%). This may either be due to patient differences or differences in staff and charting procedures (or both). Since these patients came in less frequently than at the other sites, this may represent a slightly different population of patients. Presumably patients which do not need to come in as often are more stable and may be more reliable to take their own medications without much supervision or intervention. The fact that discontinuation occurred at a lower rate at Site 2 may support this hypothesis. Staff may also be less likely to document compliance at Site 2, as in general, this site did involve less comprehensive charting.

4.1.3 Adverse Events/Side Effects and Concomitant Medication

Another important factor in discontinuation is the occurrence of adverse events or side effects. Various effects categorized as psychiatric (according to the product monograph)[144] including insomnia, somnolence, depression, anxiety and agitation occurred at similar frequencies in both sexes. The use of concomitant medications are often correlated with the existence of side effects, therefore these issues are discussed simultaneously. As many patients require supportive medication during titration on to a new antipsychotic, drugs prescribed during this period were not included as concomitant medications. In addition, if a titration scheme was used with the antipsychotic the patient was switched to when risperidone was discontinued, ie. taken simultaneously with risperidone, it was not included as a concomitant medication, although other drug classes were recorded. It must be noted that for many of the events listed, it can not be determined whether it is a direct result of risperidone treatment, a result of concomitant medication or a factor of the underlying psychosis.

Insomnia occurred in approximately 40% of both male and female patients. It is thought to occur due to the fact that risperidone has been proven to be less sedating than other neuroleptics,[119] therefore the switch results in withdrawal symptoms. Insomnia is thought to dissipate after the initial period on risperidone, although the temporal relationship of side effects were not measured in this study, so it is impossible to determine tolerance in this sample. Approximately 20% of all patients were prescribed sedatives which represents only

half of those in the sample apparently suffering from insomnia, however some patients may not have had the side effect for a long enough duration to warrant treatment. As sedative medication is generally addictive, there is likely a common attitude among clinicians to avoid, if possible, the use of such drugs in the long term. Other classes of medications are known to be prescribed for insomnia, including some antipsychotics and anxiolytics, therefore it is possible that a proportion of the increase in these categories can be attributed to the treatment of insomnia.

Anxiety and agitation occurred in approximately 16% and 14% of patients respectively. Anxiolytics are often used in these patients to treat this problem and were prescribed in 50% more females than males, despite the fact that females only experienced a slightly higher frequency of these side effects. This may have been due to the fact that the women who were prescribed medication for their anxiety had their symptoms controlled before it could appear and be recorded as a side effect on the chart, in other words anxiety started before risperidone treatment. However, a second explanation exists in that clinicians may have differential tendencies to prescribe anxiolytic medications to males and females; although the frequency of anxiety is the same in the two sexes, medication may be prescribed either more quickly or more often or both to the female patients.

Extrapyramidal symptoms (EPS) were a common side effect of risperidone, which is somewhat surprising considering the fact that it is classified as an 'atypical' neuroleptic, the most common definition of which is the low propensity to cause such effects. Prior trials of

risperidone report frequencies of EPS in the range of 12 - 31% across dose groups of 2 - 16 mg/day, with amount of EPS directly related to dose group.[113] As doses of risperidone above 6 mg/day have been shown to produce higher rates of EPS [34], it is possible that patients demonstrating EPS in this sample may have been on higher doses of risperidone, although this was not measured.

EPS occurred in approximately 60% of both male and female patients, causing many patients to require adjunctive therapy. Antiparkinsonian medications, also known as anticholinergics, treat EPS by acting on acetylcholine receptors and reversing some of the motor dysfunction associated with this syndrome. Antiparkinsonians were prescribed in different amounts in men and women. Approximately 70% of female patients took these medications compared with 55% of male patients. It would appear that this difference in prescription rates is unexplained by the occurrence of EPS, which was approximately 60% in both sexes. As with anxiety, this difference may be due to a variety of treatment issues, including perhaps that women did not respond as well as did men to antiparkinsonian medications and continued to experience symptoms of EPS, while at least a portion of the men were successfully treated.

Tardive dyskinesia (TD) occurred in twice as many women as men which is not surprising given previous reports of a higher incidence in the older female population with schizophrenia.[109] As TD is hypothesized to be due to neurophysiological changes arising from long term neuroleptic therapy [54], risperidone is likely not to blame for this effect in the majority of patients. However, this data may point to the fact that unlike many typical

neuroleptics, risperidone may not have the same masking effect on the symptoms of TD. As antiparkinsonian medications are contraindicated in these patients as they may exacerbate symptoms of TD, it would seem unlikely that the higher proportion of women with TD was a factor in the higher prescription rates of these medications in females. However some patients with TD may also show signs of other EPS and may be prescribed antiparkinsonians for these side effects.

Weight gain was a common side effect of risperidone, occurring in 21% of female patients and 12% of male patients. The differential effect between the sexes is not entirely understood, although weight gain has been hypothesized to be due to antagonism at central $5HT_2$ receptors.[47] It is a possibility that there is a different level of antagonism in men and women, and the natural tendency for women to have higher levels of body fat may also be a factor. Although there has not been empirical evidence to confirm the involvement of prolactin, a theory involving elevation of the hormone in the process of weight gain has been postulated.[113,147]

Nausea and vomiting were a major side effect in the female group, affecting 17% of patients; 6% of men were similarly affected. The reasons for this effect are not clear as the monograph for risperidone states that in clinical trials this side effect occurred in 1.5 - 3% of patients.[144]

Approximately 30% of females and 20% of males were taking additional antipsychotic medication with risperidone. These results indicate that the antipsychotic effects of

risperidone may not have been sufficient for amelioration of their symptoms, which were shown to persist in a high number of patients in this sample. Alternatively, some antipsychotics are prescribed for other indications, such as anxiety or nausea, so the conclusion of inefficacy cannot be made without further information.

Sexual side effects showed significant differences between the sexes, occurring at twice the rate in females compared to males. As these effects were analyzed separately, they will be discussed in Section 4.3.

4.1.4 Continuers vs. Discontinuers

As the investigation of discontinuation rates was central to this study, it is integral to examine these two groups for differences in possible variables attributing to discontinuation. While most demographic variables of the subgroups within each sex appear to be similar, the same is not true for other variables more directly related to treatment.

Although premenopausal women and postmenopausal women were not found to differ statistically in terms of discontinuation rates (logrank = 1.34, p = 0.246), it is worth noting the results. The discontinuation rate in postmenopausal women in this study was 47%, which is much more comparable to the rate in males (46%), than the rate in premenopausal women (61%). Had more postmenopausal women been included in this study (N = 19), more power may have allowed detection of a difference. Regardless, this data may underscore the

importance of separating these groups of women when comparing response and outcome variables.

Postmenopausal women were also found to experience much lower rates of sexual side effects (11%, 2 patients) than seen in premenopausal women (42%), although again this sample size is obviously not sufficient for powerful statistical analysis. Part of this decrease in sexual side effects is due to the fact that these women do not experience amenorrhea (by definition), the most common sexual side effect in premenopausal women. However postmenopausal women demonstrated lower rates of other sexual side effects including galactorrhea (0 patients) and those effects involving sexual function (2 patients). If such side effects are in fact contributing to discontinuation of risperidone, it is plausible that postmenopausal women may find such medications more tolerable than do premenopausal women. Accordingly, if proportionately more postmenopausal women were included in clinical trials of the medication before its release (as was likely the case given the legislations of the FDA at the time), this may have resulted in falsely high levels of response rates in women.

Concomitant medication use was found to differ between discontinuers and continuers, with continuers taking more concomitant medications in both sexes. This data may indicate that continuing patients were achieving better management of side effects with the use of other medications, allowing them to tolerate risperidone. Of course these percentages include all concurrent therapies, including those unrelated to the treatment of side effects. This is

indicated by the fact that in both males and females, considerably more continuers were prescribed medications classified as 'other'. However, three times as many male continuers as discontinuers were also prescribed antidepressants, indicating that these patients may have discontinued due to a lack of appropriate management. Although depression has not been attributed to the use of risperidone, it may represent a symptom of the illness, the control of which is important in other aspects of clinical management. Similarly, female continuers were prescribed anxiolytics at twice the rate of discontinuers. As anxiety has been attributed to risperidone [144], the differential in prescription rates in this group may directly indicate better management of side effects, although it may also reflect management of a symptom of the illness itself. Anxiety was found to be noted on the charts of more discontinuing females (18.4%) than continuers (12.5%).

Side effect profiles of patients stratified by discontinuation status provide some insight into issues surrounding the termination of risperidone therapy. Interestingly, several side effects were shown to occur at higher rates in continuing patients than in discontinuing patients. These included anxiety and EPS in males and weight gain in both males and females. The reasons for these observations are not entirely understood, unless the amelioration of other side effects with concomitant medications resulted in these remaining side effects appearing comparably less bothersome. Alternatively, these effects (particularly weight gain) may not have appeared until longer periods on the medication, therefore not occurring in patients discontinuing risperidone before they would have had time to arise.

Other side effects occurred in higher proportions of discontinuers than continuers, as would normally be expected. These included agitation, labile mood and fatigue in females, reduced concentration in males and nausea/vomiting in both sexes. These observations may directly explain discontinuation in some patients. Nausea and vomiting showed large differences: 26.5% of females and 10.1% of males discontinuing from risperidone suffered from this effect compared to 3.1% and 2.5% of female and male continuers, respectively. Certainly it is likely that this side effect would result in much distress for the patient and could understandably result in discontinuation of risperidone. Nausea may also not be as treatable with concurrent therapy as some side effects, leaving fewer options for clinical management.

4.1.5 Interviews of Discontinuers

As only 20 patients were interviewed of a possible 118 discontinuers, obviously no generalizations can be made from the interview data. However, it is worth noting that of the 20 patients questioned on the side effects experienced while on risperidone, 6 (30%) stated they did experience sexual side effects when there was no indication on the chart of such events. While this data may suffer from inaccuracies due to the length of time between the interview and risperidone discontinuation (average = 29.5 months), it may also indicate a failure on the part of some clinicians to inquire about sexual side effects. While more solid research is required in this area, this may be an indication of support for these hypotheses.

However, it must be cautioned that these patients may not be representative of the population

prescribed risperidone, and they may be different from those who were not interviewed in terms of the outcome variable of interest i.e. patients who were interviewed may have been more or less likely either to have side effects from risperidone or be compliant with medications.

4.2 PRIMARY ANALYSIS - DISCONTINUATION OF RISPERIDONE

In this sample, there were significant differences between discontinuation rates in males and females, although these rates were also significantly influenced by the site of treatment. Overall, Site 1 demonstrated the highest dropout rates of the sample (67%), while Sites 2 and 3 had a 42-43% dropout rate. These observations may be due to patient and/or physician differences at Site 1. This site was the location of one of the investigators directly involved with the research; this fact could result in patients at this site being observed more critically for side effects and other problems while taking risperidone. As a result patients may have been discontinued for side effects which would have been overlooked by other physicians. This site may also be treating more chronic or severely ill patients than do the other two sites, which would likely increase the probability of patients not responding to a given antipsychotic.

Site 1 demonstrated both the highest dropout rates in both sexes of any site, as well as the greatest difference between males and females within a site. These findings are likely due to both patient and physician differences at this site as outlined above. Patients at Site 1 usually come into clinic at least once a week; many are full time patients attending the program 5 days a week. Aside from frequent psychiatric assessments, these patients are assigned a clinical team worker who monitors their progress continually. The fact that these patients are involved in a highly structured day program may indicate that they require more support and are more chronic, more severely ill, or both. This also may indicate that these patients are

already non-responsive or poorly responsive to many antipsychotics. If these patients are more chronically ill than those at other clinics, then female patients at this clinic may represent a more severe subset of the female schizophrenic population as well. If risperidone is less tolerable by women as these results suggest, then it is possible that women at this site may be more likely than average to fail to respond to a new medication.

Alternatively, differences in physician practices may also affect discontinuation in this group, as doctors may be more likely to switch a patient to another medication earlier than at other sites. This may be due to more careful scrutiny and therefore earlier detection of a problem with the medication. As previously indicated, physicians at this site may also be more sensitive to the response of female patients to risperidone, and may therefore be alert to sex specific problems, including sexual side effects and perhaps an increased sensitization to medication dosages.

A third possibility explaining the higher discontinuation rate at this site may be related to the differences demonstrated in age between the sites. Subjects at Site 1 were found to have a significantly lower average age at risperidone initiation. Younger patients may be more difficult to treat or more prone to non-compliance with medications due to problems accepting a diagnosis of schizophrenia. These patients may therefore be more likely to discontinue risperidone, resulting in the higher rate seen at Site 1.

Site 2 demonstrated a different result from Sites 1 and 3: males and females at this site

discontinued risperidone at essentially the same rate; in fact, males discontinued at a slightly higher rate. These results obviously do not fit with the hypothesis, contrary to the other two sites. This site was different from the others in that it was a non-hospital based community clinic. Treatment at this clinic was less involved in terms of patient-worker contact; patients also came into the clinic less frequently than at the other clinics, on average once a month. In addition, these patients only had physician visits anywhere from one to three months apart, at which time they had their medication reviewed. This type of clinic is suited to patients who are more stable and who do not need the intensive intervention of hospital based clinics. On the other hand, this clinic may also be utilized by patients who will not comply with treatment at clinics offering more rehabilitation services.

These differences may account for the lower proportion of patients discontinuing at Site 2. If physicians did not meet with the patients for medication review more often than 3 months between visits, problems with medications may not have been detected as early as at the other sites which saw patients more frequently. In addition, less contact between patients and staff members may have resulted in less time for teaching about potential side effects about certain medications and also less observation of compliance issues.

As females and males discontinued at essentially the same rate, this site may also represent a subset of patients with schizophrenia. If Site 2 is typical of a clinic serving more stable patients, then perhaps in a less severe form of the disease, the two sexes are more similar to each other in terms of treatment response than is seen with more chronically ill

schizophrenics.

Differences between males and females were significant at Site 3, although the actual dropout rates are more similar to those at Site 2 than Site 1, and the actual difference between the sexes is smaller than at Site 1. Females discontinued risperidone at a rate of 59%, while 33% of males discontinued. It may be fitting that discontinuation rates at this site are quantitatively between the other two sites, as this clinic can be described as a hybrid of the other two clinics in terms of treatment and services offered. Patients generally come into the clinic once every two weeks for medication review. Therefore their visits are more frequent than Site 2, although they do not involve the extent of treatment and rehabilitation of the program in place at Site 1. These parallels would offer explanation of the different results seen at these three clinics if one considers the effects of treatment and charting differences. The patient population is also likely representative of a group of patients in between the other two clinics in terms of severity, due to the type of clinic and treatment it offers.

In summary, the differences in discontinuation of risperidone between sites raises a variety of issues. If such variation has arisen due to differences in data inquiry and recording practices between sites, then it is important to note such differences and utilize them to work towards improving recording practices in clinical medicine. Alternatively, if these site differences are indications of real differences between patients, then it is indicating that perhaps there exists a subset of patients with schizophrenia which do not demonstrate the same (poor) rate of response to medications, and which do not demonstrate differences in

male and female patients. Perhaps in those patients less severely ill or requiring less support, male and female patients are more comparable to each other with regards to their illness and treatment response.

Overall, in the discontinuers, 69% of patients were compliant with their medication while 80% of continuers were considered to be compliant. This was found to be a significant difference and may indicate a plausible reason for discontinuation in these patients. Non-compliance can obviously be expected to negatively affect a patient's ability to respond to a given treatment; it may be weeks of careful and consistent dosing by the physician to maintain a stable response in a psychotic patient, and any tampering with these dosing strategies can hamper the treatment regime.

In the complete sample, the discontinuation rate was 51%, which may be comparable to rates with other medications. However most trials are less than one year in length so a direct comparison is impossible. One large clinical trial of risperidone reported rates ranging from 23 - 70% (23 - 36% if the group taking 2 mg/day is excluded), although dropout rates in clinical trials may not be representative of the situation in clinical practice as patients are expected to undergo more rigerous procedures and discontinuation of the trial may not be due to the medication per se. Two longer term studies of risperidone have been completed spanning one year; Addington et al [148] studied 74 patients which demonstrated a discontinuation rate of 64%, while Mertens et al [149] found a 30% discontinuation rate in 264 patients. Evident from this literature is the fact that discontinuation rates appear to vary

widely and are likely vulnerable to a variety of external factors. As the current study is the only long term trial of risperidone with a gender breakdown, this variable adds another dimension to the issue of treatment response beyond those described in these previous studies.

Sex differences in dropout rates are likely due to a variety of factors, most of which will undoubtedly require much more research to determine. As this research is novel in its focus on both discontinuation and sex differences, it is not known whether such results are common to all medications or specific to risperidone. Discontinuation may occur most often due to adverse effects, although the monograph for risperidone states that only 9% of patients discontinued treatment due to an adverse event.[144] Presumably the rest of patients discontinued due to other factors, including lack of efficacy and non-compliance. Once again, data on sex differences are not provided.

In this study, males and females experienced almost equal levels of both symptoms of schizophrenia and most side effects. In the small sample interviewed, lack of efficacy for psychosis was the most frequently stated reason for discontinuation. However, the same percentage of males and females experienced persistent positive (65%) and negative (44%) symptoms. Although lack of efficacy may have contributed to discontinuation, one would expect similar sex-specific dropout rates correlating with the rates of symptoms seen in these patients.

Contrary to previous reports with risperidone, a very high proportion of patients experienced EPS (60%) although this was also the same rate in each sex. EPS has been shown to be a frequent reason for discontinuation [53], although the equality of this side effect between the sexes does not lend insight into the difference in discontinuation rates. The same problem is encountered with the similar rates for many other side effects: although the data is there to suggest sufficient levels of side effects were present to cause discontinuation, there is still no data to suggest differential rates between the sexes.

One facet of treatment examined in this study which may lend useful information to the interpretation of differential discontinuation rates is the frequency of multiple concomitant medication use in males compared to females. Overall, females were found to use higher numbers of different classes of concomitant medication than did their male counterparts. Furthermore, in most of the drug classes where there were differences in user rates between the sexes, it was females demonstrating higher rates than males. These observations would lead to the possible explanation that the female physiological system may be unable to tolerate such polypharmacy and this may be related to discontinuation of risperidone.

However, when the patients were stratified by discontinuation status, continuers were found to take more concomitant medications, both in terms of frequency of patients taking any concurrent therapy (in the male patients), and in the number of classes taken (in the female patients). Therefore there is evidence to suggest that at least for some patients, concomitant medication use may allow better tolerance of risperidone. This was seen in particular with

the use of anxiolytics in female patients and antidepressants in male patients.

Another variable which is important yet more difficult to measure, is that of the patient-doctor relationship involved in the treatment of patients with schizophrenia. Ultimately, this balance may be important in determining the course of treatment which is prescribed and followed. It is possible that males and females differ with respect to this relationship which may result in differing rates of drug discontinuation. Females may be less trusting or dependent on their psychiatrist's direction and advice, preferring to retain more control over their own treatment. Alternatively, females may be subject to more interpersonal influences on their treatment decisions, such as those from spouses and other family members, while males may have less social support to consult for advice. The sex of the clinician treating the patient may also be a factor in the patient's level of engagement in the relationship. Of course all of these issues are subject to a large amount of personal variation between patients, between clinicians and between the partnerships of both. As such variables were not measured in this investigation, the effects of these cannot be incorporated in these results.

In summary, although differences were found in discontinuation rates, obviously a more pertinent question attempts to address the cause of such differences. While it is certain that a single cause, or even a set of defined causes, will not be found for each patient, factors such as correct pharmacological management including dose of risperidone and amount of concomitant medications prescribed will be important to a patient's success.

4.3 SECONDARY ANALYSIS - SEXUAL SIDE EFFECTS OF RISPERIDONE

Perhaps the most notable difference between the sexes pertaining to side effects were those categorized as sexual side effects. Overall, more than twice the number of females (37%) experienced at least one sexual side effect compared to males (18%). Odds ratio analysis resulted in female patients having 3.45 times the odds of male patients of experiencing a sexual side effect while taking risperidone. Although the 95% confidence interval is fairly wide for this odds ratio (1.78 - 6.75), the low end of the range still indicates a significantly higher risk of sexual side effects in female patients, almost twice the risk for male patients.

Site of treatment was found to be a confounder in the relationship between sex and the occurrence of sexual side effects. All sites demonstrated female patients having increased odds over male patients, however the strength of the association varied with site. This most likely reflects a varied distribution of the two genders between the sites, and a resultant distorted odds ratio which is not reflective of the true association between sex and sexual side effects. This is further demonstrated by the fact that the crude odds ratio (2.66) is lower than the unconfounded estimate (3.45); the confounding factor of site is diluting the effect towards the null value.

Most notable of the sexual side effects were the frequencies of amenorrhea (24%) and galactorrhea (14%). These estimates are similar to the few examples in the literature, which cite rates of 22% for amenorrhea and 19% for galactorrhea in patients on a variety of

standard antipsychotics [46,107]. Combining all menstrual disturbances, 34% of all premenopausal women experienced amenorrhea, dysmenorrhea or irregular menses. Females also suffered from a variety of side effects involving sexual function, including hyposexuality, anorgasmia and painful intercourse, albeit in much smaller numbers. The most common sexual side effects in males were erectile dysfunction (9.4%), retrograde ejaculation (6.0%) and hyposexuality (5.4%).

Similar to non-sexual side effects, many sexual side effects were seen in higher proportions of continuing patients compared to discontinuers. Overall approximately 10% more continuers in each sex exhibited sexual side effects than did those discontinuing risperidone. Specific examples demonstrating this observation included hyposexuality and dysmenorrhea in women and retrograde ejaculation in men.

Two explanations are possible for these findings. With regards to side effects involving sexual function, these individuals may not have been as bothered by these effects if they were not involved in sexual relationships, although one would not normally expect the proportion of those involved in such relationships to differ between discontinuers and continuers, unless this was somehow interrelated with compliance, i.e. if more compliant patients were more likely to be able to maintain a stable relationship due to personality characteristics involved in both situations.

Possibly a more likely explanation involves the fact that in many patients, these side effects

may require longer periods of exposure to risperidone to arise. Therefore, discontinuers may have stopped risperidone before these side effects occurred, resulting in a higher rate in continuers who remained on the drug for a year. It would be interesting to examine temporal relationships between appearance of these side effects and discontinuation, as many of the patients remaining on risperidone for one year (continuers) may have in fact discontinued shortly thereafter due to the appearance of latent side effects.

These results indicate that sexual side effects may have been a factor in discontinuation for some patients, and may in part explain the higher discontinuation rate in female patients. However, the observation of both the frequencies of these effects in all patients and their differential amounts between males and females may highlight a more important point. These side effects are not rare occurrences in either sex treated with risperidone and should be considered in the management of these patients rather than tolerated for the sake of antipsychotic improvement. Female patients may be particularly at risk for adverse health outcomes due to the high rate of possibly chronic amenorrhea and galactorrhea in these patients.

The product monograph for risperidone does not state precise values for these side effects; all that is stated is that these side effects *'caused deterioration during treatment compared to baseline in at least 10% of patients'*.[144] Therefore we do not have any previous estimates of many of these side effects with which to compare our own. It is interesting to note that while the monograph explicitly lists *'all adverse events occurring at frequencies* $\geq$ *1%'*,

sexual side effects are not included among this group, despite the earlier statement that they occurred at a *'frequency greater than 10%'*. These observations serve to underscore the lack of importance placed on sexual side effect in the overall safety profiles of these medications.

It is important to note the fact that side effects collected in this sample do not necessarily represent incidence rates, or new cases. Some side effects may have been present prior to risperidone treatment. However, it is perhaps as important to note that the side effect persisted while on risperidone as it is to note that it started while on risperidone.

4.4 LIMITATIONS OF THE STUDY:

Although this study contained patient numbers sufficient to analyze data for the objectives identified, sample size was a limitation when the groups were stratified beyond gender, as in the analysis of discontinuers vs. continuers, or examining separate side effects. If these variables were to be investigated, one would need to include larger patient numbers to increase power to detect existing differences.

Retrospective studies in general are often much more difficult from which to generalize reliable data. Researchers do not have the same amount of control over many factors which can interfere with relationships between dependent and independent variables being investigated. While prospective trials are often seen as the preferable analytical design, or 'gold standard', retrospective studies are often regarded as useful for pilot data as evidence for further larger scale studies. In this study, the retrospective design was used for various reasons, including financial reasons and in order to comply with time limitations of the academic program involved. However, there are scientific advantages of this design which will be discussed in the next section.

Perhaps a larger problem with the study design in terms of reliable data is the fact that the data was for the most part collected by chart review. Furthermore, as the chart data even for one patient, not to mention across all charts, was recorded by several individuals, a great degree of variability in data is a concern. While we all assume data to be recorded correctly

by health care professionals trained to do so, this may not always be the case. Omissions of data are also common, as many variables which are of research interest many not be considered to be clinically relevant, however results of this study may indicate otherwise. Measures were taken to ensure data was correct, including consulting other charts and staff for validation, however in most cases, the information is only as reliable as the staff charting it.

Certain variables may be particularly susceptible to error with this method of data collection. Information on menopausal status may be difficult to determine clinically in some patients, and is obviously even more difficult to ascertain using retrospective chart data. Often such variables are not charted unless they become relevant to the patient's clinical case. For this reason rather arbitrary criteria had to be used. While this may produce accurate results for the majority of cases, undoubtedly a few women will be misclassified in each category.

Similarly, information pertaining to concomitant medications was difficult to obtain with a high degree of accuracy. As only drugs prescribed at the clinic used were included, this may have missed many medications taken, including those prescribed by the family physician or other specialist. Particularly important to the objectives of this study would be the omission of data on oral contraceptive use in the female patients, as this would very likely affect the occurrence of sexual side effects. Obviously illegal drug use was not recorded in this study, which also may have played a role in a patient's response to antipsychotic treatment. Indications for use of concomitant medications were also difficult to determine in some

cases, where drugs may be prescribed for a variety of reasons. An example is medications such as carbamazepine which may be used for either its antimanic properties, treating manic episodes, or for its antiepileptic properties in the treatment of seizures.

A major problem of research in schizophrenia is the uncertainty of the cause of various effects seen. For many of the 'side effects' classified as psychiatric such as anxiety, agitation and insomnia may be due to either drugs or the disease; to determine cause is difficult and in most cases impossible. For this reason these effects were not given a significant amount of discussion in this investigation.

As with any study relying on patient subjective response to past events, recall bias is a concern. Since the interview numbers were very small, it is not as integral to this study as no conclusions were made based on the interviews. However, it is still an important point to make as the data on the patients interviewed was included. Recall bias may arise when individuals in a particular outcome group remember experiences differently from the other outcome group.[150] In this study, the concern applies to the fact that interviewed patients were all discontinuers and may have remembered more adverse effects of risperidone than would continuers. However, this is not a concern in this investigation as these patients were not being compared to continuers with regards to their interview data and were only providing supplemental data to the variables already collected from the chart. Although it must be cautioned that these patients may not be representative of the population prescribed risperidone, and they may be different from those who were not interviewed in terms of the

outcome variable of interest, i.e. patients who were interviewed may have been more or less likely to have side effects from risperidone or be compliant with medications.

This study was an examination of one medication used in the treatment of schizophrenia. Therefore there was no comparison group either on another neuroleptic or from the population without the illness. Inclusion of such a comparison group would allow for more direct comparisons with respect to the objectives investigated.

4.5 STRENGTHS AND FUTURE DIRECTIONS:

This study is novel in both its observation period examined and its focus on gender differences in treatment. As most investigations cover shorter time periods, they may not be adequate to determine the long-term outcome for treatment of patients with schizophrenia. It is not surprising that many studies conducted in 8 weeks or 12 weeks do not report as high discontinuation rates as are reported here; the survival functions in this sample indicate that problems with treatment resulting in discontinuation occur long after these rather arbitrary endpoints.

The focus on differences between male and female patients is one which has been overlooked in many similar investigations. The information sex-specific analyses provides is crucial to the optimal treatment of both men and women. The separation of women into different groups based on menopausal status appears to be investigated even less in current research, which also suggested important differences in how these women may respond to medications.

Contrary to clinical trials and many prospective investigations on treatment response, this study utilized a retrospective design, allowing for observation of treatment in a typical clinical environment. Therefore these findings represent clinical practice more closely than is described with results of clinical trials, which introduce other variables into the treatment milieu.

Important future directives in research would involve closer examination of reasons for discontinuation in population subgroups, which was beyond the scope of this investigation. Included in these could be more precise definition of indications for medications, similarly with side effects: more thorough examination of these is necessary to determine cause and relationship to other variables. Temporal relationships of side effects would be very useful information, as these would assist in the attribution of such effects to the medication of interest. It would also be interesting to determine the time points at which various side effects arise.

In summary, this research is novel in terms of several facets of treatment investigated, in particular length of follow up and sex differences involved. Increasing the research activity in either of these aspects would be an important addition to the body of knowledge on response of all patients, both male and female, to medications required for their illnesses. Investigation of other antipsychotics and sex differences in response involved over the long term is crucial to understanding a complete clinical profile of medications in this patient population.

4.6 CONCLUSIONS:

This investigation of a novel antipsychotic used in the treatment of schizophrenia provides insight into several treatment issues. Although several variables are involved in response to a medication, the discontinuation or lack thereof may be the most inclusive indicator of treatment outcome.

In this study, slightly more than half of all patients discontinued risperidone within one year. This contradicts former claims that risperidone, as an atypical antipsychotic, is more effective and tolerable for more patients, and should therefore result in lower discontinuation rates. This indicates that in this sample, risperidone is no better than standard neuroleptics in terms of overall response.

Females were found to have significantly higher discontinuation rates than did male patients at two of the three sites in this sample, while the third site demonstrated no difference between the sexes. These results indicate that at least in some patients, which may represent the more severely ill population, females have more problems with risperidone treatment causing them to cease treatment more frequently than do males.

Although these differences have been found, the exact reasons are still unclear in some patients. Discontinuers and continuers appeared to experience the same rate of most side effects, however continuers did appear to take more concomitant medications in both sexes,

which may be a clue to tolerating risperidone.

Site differences found may be suggesting that in less severe cases of schizophrenia, males and females may be more comparable in terms of treatment response. In a more chronically ill population, females may have more problems tolerating risperidone than do male patients.

Female patients were found to have three times the odds of developing sexual side effects as a result of risperidone treatment compared to male patients. These side effects may arise due to elevation of prolactin levels known to occur with risperidone treatment. Furthermore, these effects may be more marked in premenopausal women than in postmenopausal women.

While novel antipsychotics appear to be an improvement over standard therapies with respect to some side effects, they may also cause higher rates of other side effects which may be just as distressing to patients. These side effects are likely underestimated in the literature due to the failure of clinicians to recognize them. Clearly more research is required into these newer treatments to weigh risks and benefits for patients.

Discontinuation of medication is a very complex issue involving many factors, indicated by the fact that the discontinuers and continuers in this sample were similar on many parameters including side effect profiles and concomitant medication usage. Further research is crucial to determine the factors involved in discontinuation, and how these may vary between male and female patients.

As drugs are not sufficiently investigated prior to their release on the market for their effects in subpopulations, these questions must be addressed in postmarket investigations. New medications need to be studied to determine sex differences in order that risks of side effects can be minimized in both males and females.

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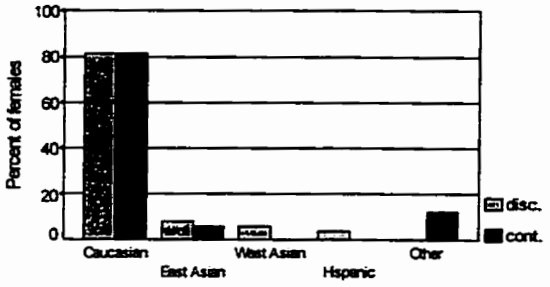
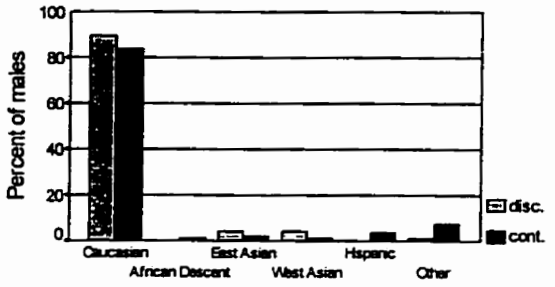
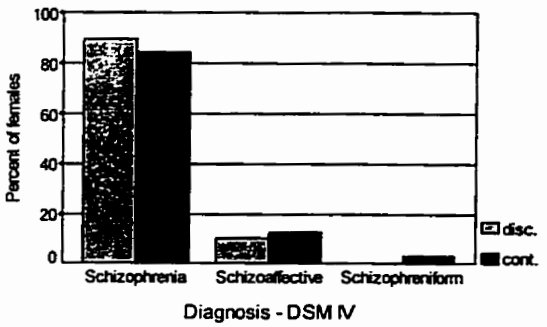
APPENDIX ONE:

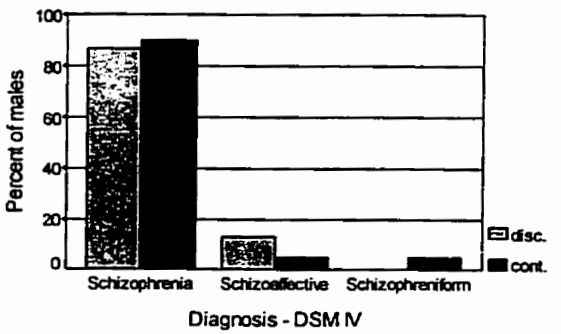
Additional results:

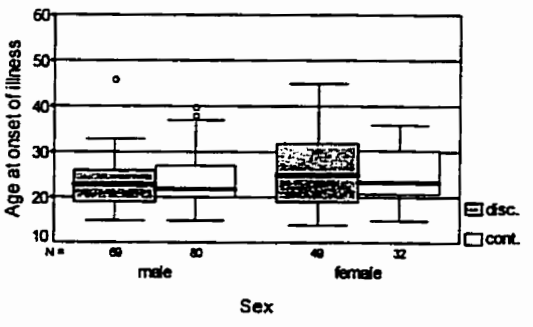
Subgroup analyses: variables stratified on both discontinuation status and gender:

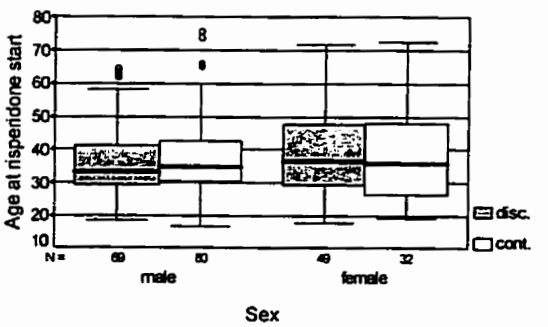












Side effects occurring in female patients at frequencies of <5% (less than 5 patients):

dreams/nightmares
day/night reverse
lethargy
increased appetite
decreased appetite
weight loss
heartburn
increased thirst
reduced energy
obsessiveness
poor balance
heart palpitations
urine incontinence
fecal incontinence
constipation
diarrhea
dry mouth
slurred speech
facial rash
double vision
blurry vision
irritated eyes
muscle pain
reduced memory
shortness of breath
seizures

Side effects occurring in male patients at frequencies of <5% (less than 8 patients):

dreams/nightmares
day/night reverse
lethargy
increased appetite
decreased appetite
heartburn
polydipsia
reduced energy
obsessiveness
poor balance
heart palpitations
urine incontinence
dysuria
urine retention
constipation
increased saliva
dry mouth
slurred speech
stuffy nose
itchy scalp

Interview data for each patient:

Pt #	Sex	Age	Compliant? (chart)	DAI score (interview)	Side effects (chart)	Side effects (interview)	Reason(s) for discontinuing*
1	F	21	yes	6	NS	NS	lack of efficacy
2	F	51	yes	8	S, NS	S, NS	lack of efficacy, EPS
3	F	30	yes	0	S, NS	S, NS	galactorrhea, wt gain, lack of efficacy
4	F	31	yes	8	S, NS	S, NS	EPS, lack of efficacy
5	F	41	yes	4	**NS**	**S, NS**	agitation
6	F	17	yes	6	S, NS	S, NS	agitation, EPS
7	F	35	yes	8	S, NS	S, NS	wt gain
8	F	48	yes	10	**S, NS**	**NS**	lack of efficacy
9	M	33	yes	8	S, NS	S, NS	orgasmic dysfunction, hyposexuality
10	M	30	yes	4	**S, NS**	**NS**	anxiety, insomnia, EPS
11	M	28	yes	8	**NS**	**S, NS**	heart palpitations
12	M	38	yes	8	NS	NS	insomnia, EPS
13	M	33	yes	6	**NS**	**S, NS**	lack of efficacy
14	M	52	yes	2	**NS**	**S, NS**	lack of efficacy
15	M	41	yes	8	**NS**	**S, NS**	palpitations, lack of efficacy
16	M	30	yes	4	NS	NS	lack of efficacy
17	M	42	yes	10	**NS**	**no side effects**	lack of efficacy
18	M	38	poss. non-compl.	6	**no side effects**	**S**	lack of efficacy
19	M	27	yes	6	NS	NS	lack of efficacy
20	M	36	yes	4	NS	NS	nausea, lack of efficacy

S = sexual side effects NS = non-sexual side effects

* lack of efficacy = persistant symptoms of schizophrenia despite risperidone treatment

APPENDIX TWO:

Calculations and Statistics for Secondary Analysis
(comparison of sexual side effects between males and females)

Calculation of Test of Homogeneity of Odds Ratios

$y_1 = \ln(OR_{CGH}) = 1.3789$ $\quad w_1 = w_{CGH} = 1/a^{-1}+b^{-1}+c^{-1}+d^{-1} = 3.456$
$y_2 = \ln(OR_{AMH}) = 0.9426$ $\quad w_2 = w_{AMH} = 1/a^{-1}+b^{-1}+c^{-1}+d^{-1} = 1.980$
$y_3 = \ln(OR_{FHH}) = 1.2813$ $\quad w_3 = w_{FHH} = 1/a^{-1}+b^{-1}+c^{-1}+d^{-1} = 3.211$

$$Y = w_1y_1 + w_2y_2 + w_3y_3 / w_1 + w_2 + w_3 = 1.243$$

$$T = w_1(y_1 - Y)^2 + w_2(y_2 - Y)^2 + w_3(y_3 - Y)^2 = 0.243$$

Using X^2 distribution, $p > 0.2$

Calculation for Mantel-Hanszael Summary Odds Ratio and Confidence Interval:

$$OR_{MH} = (a_1d_1/T_1 + a_2d_2/T_2 + a_3d_3/T_3)/(b_1c_1/T_1 + b_2c_2/T_2 + b_3c_3/T_3)$$

$OR_{MH} = 3.45$

$$SE(Y) = 1/(w_1 + w_2 + w_3)^{1/2} = 0.340$$

95% CI for $\ln(OR_{MH}) = Y \pm 1.96(SE[Y]) = [0.5766 - 1.9094]$

95% CI for OR_{MH} = [1.78 - 6.75]

Calculation for Hypothesis test for Summary OR_{MH}:

$H_o = OR_{MH} = 1$ $\quad m_n = Exp(a_n) = (a+b)(a+c)/(a+b+c+d)$

$H_a = OR_{MH} \neq 1$

$a_1 = 12$ $\quad m_1 = 7.07$

$a_2 = 7$ $\quad m_2 = 5.04$

$a_3 = 11$ $\quad m_3 = 6.63$

$$\sigma_n^2 = (a_n+b_n)(a_n+c_n)(b_n+d_n) / (a_n+b_n+c_n+d_n)^2(a_n+b_n+c_n+d_n-1)$$

$\sigma_1^2 = 3.499$ $\quad \sigma_2^2 = 2.150$ $\quad \sigma_3^2 = 3.391$

$$T = (\Sigma a - \Sigma m)^2/\Sigma \sigma^2$$

$T = 14.03$ $\quad$ Using X^2 distribution, $p < 0.001$

APPENDIX THREE:

Copies of Research Instruments:

Drug Attitude Inventory (10 item version):

1	For me, the good things about medication outweigh the bad.	T	F
2	I feel weird, like a 'zombie', on medication.	T	F
3	I take medications of my own free choice.	T	F
4	Medications make me feel more relaxed.	T	F
5	Medication makes me feel tired and sluggish.	T	F
6	I take medication only when I am sick.	T	F
7	I feel more normal on medication.	T	F
8	It is unnatural for my mind and body to be controlled by medications.	T	F
9	My thoughts are clearer on medication.	T	F
10	By staying on medications I can prevent getting sick.	T	F

Side Effect Checklist:

(To be asked by the interviewer and recorded)
(underlined sections are specific to one sex)

1)	**While taking risperidone did you experience:**	
a)	any anxiety, agitation, depression?	(Psychiatric)
b)	problems sleeping too little or too much? headaches? dizziness?	(Autonomic)
c)	problems with stiffness, walking, shakiness? restlessness? problems with your vision or speaking?	(Neurological)
d)	heart problems you saw another doctor for? increased heart rate?	(Cardiovascular)
e)	skin problems such as rashes? increased amount of sweating?	(Dermatological)
f)	nausea, vomiting? diarrhea, constipation?	(Gastrointestinal)
g)	problems with hormone levels your doctor took a special blood test for?	(Endocrinological)
h)	problems with sexual function? changes in your libido? problems with orgasm, <u>erection/lubrication</u>?	(Sexual Function)
i)	<u>changes in your periods?</u> <u>milk production in your breasts?</u>	(Reproductive Function)

2) **Have you gone through menopause? (When?)**

3) **Were you experiencing any symptoms of schizophrenia while taking risperidone, such as hallucinations, delusions, lack of motivation, lack of emotional response?** (Efficacy)

4) **Did you take all of your risperidone at the correct times as directed by your doctor?** (Compliance)

5) **What do you feel were the main reasons for stopping treatment with risperidone?**

6) **Is there anything else you remember about your experience with risperidone?**

NOTES: _____

Glossary of psychiatric symptoms as classified in the Diagnostic and Statistical Manual of Mental Disorders - Version IV.*

Positive Symptoms:

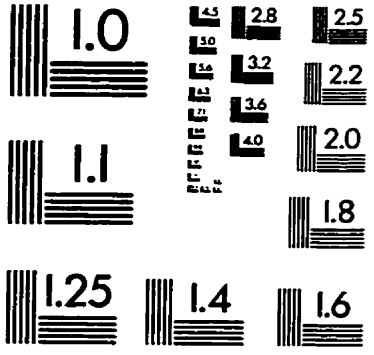
hallucination	a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ.
delusion	a false belief based on incorrect inference about external reality that is firmly sustained despite what almost everyone else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary.
disorganized thinking	(assessed by the presence of :) disorganized speech: severely impaired communication by tangentality, loose associations, perhaps to the point of incoherence
disorganized behaviour	ranges from childlike silliness to unpredictable agitation, difficulty in performing activities of daily living

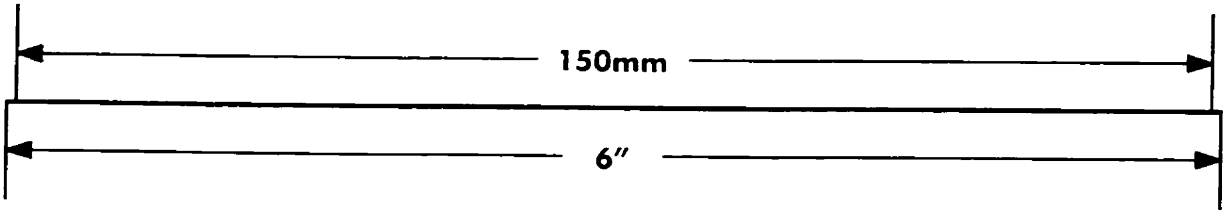
Negative symptoms:

blunted affect	significant reduction in the intensity of emotional expression
avolition	an inability to initiate and persist in goal-directed activities
alogia	an impoverishment in thinking that is inferred from observing speech and language behaviour

* Although other symptoms are noted to be involved in the course of schizophrenia, the symptoms listed above are considered to be most important to the diagnosis by the DSM-IV.

TEST TARGET (QA-3)





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