EXHIBIT 43

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	**MDL DOCKET NO.**
This document relates to:	**6:06-MDL-1769-ACC-DAB**
ALL CASES	

DECLARATION OF WILLIAM C. WIRSHING, M.D.

1. My name is William C. Wirshing, M.D. I am competent to make this declaration and the facts stated herein are within my personal knowledge and are true and correct.

2. I graduated in 1978 from the College of Engineering at the University of California at Berkeley with highest honors (cumulative G.P.A. 3.93) and a Bachelors of Science degree in Electrical Engineering and Computer Science (minor in bioelectric systems). I received my M.D. from the University of California at Los Angeles in 1982, graduating with a 3.97 G.P.A. and receiving the Sandoz Awared for "Excellence in the Behavioral Sciences." I remained at UCLA for both my rotating internship, during which I focused on internal medicine, neurology, and pediatrics and for my three-year residency training in psychiatry. My final year of residency was at the West Los Angeles Veterans Affairs Medical Center. Over the next two years, I was a Post Doctoral Research Scholar at UCLA, a fellowship position through the National Institute of Mental Health during which I learned and applied clinical research techniques for the study of persons with severe schizophrenia.

3. I am the Vice-President in charge of research and continuing medical education for Exodus Inc. in Culver City, California and also Clinical Director of Exodus Real Recovery in Agoura Hills, California. In my clinical psychiatric practice, I see approximately 325 new patients in a typical month; supervise nearly a dozen psychology doctoral candidates; and teach over a dozen nursing, social work, and nurse practitioner students.

4. Over the decades between 1986 and 2006, both my clinical work and research focus remained on the treatment of persons with schizophrenia. I was the Chief of the Schizophrenia Treatment Unit at the VA Medical Center during the vast bulk of this epoch, and was also the Co-Chief of the Schizophrenia Outpatient Research Clinic during the last ten years. I have attached my curriculum vitae and the report I submitted to counsel for Plaintiffs in this litigation as Exhibits A and B respectively, and I incorporate those documents by reference herein.

5. In my 25-plus years of clinical and research experience, I have had countless, significant, and frequent opportunities to read, review, and apply to my clinical practice with patients the information contained on FDA-approved prescription medicine labels/package inserts. I am particularly familiar with the warnings and other labeling information accompanying a class of antipsychotic medications commonly referred to as second generation antipsychotics such as risperidone ("Risperdal"), olanzapine ("Zyprexa"), ziprasidone ("Geodon"), aripiprazole ("Abilify"), and quetiapine (Seroquel).

6. With particular respect to Seroquel's 1997-to-present label concerning weight gain, it is my opinion that, rather than adequately "warn" about the 23%-33% or higher risk

of statistically significant weight gain that AstraZeneca observed in clinical trials of Seroquel, the company obscured and buried the weight gain data and, more importantly, the effect of the data by putting it in the "adverse reaction" section of the label. AstraZeneca has never "warned" about weight gain because the necessary information concerning weight gain is not clearly stated in the "warnings" section of the label. As a practicing clinician, it is unclear, ambiguous, and misleading to prescribing doctors for the single most prominent serious toxic characteristic of this drug (statistically significant weight gain) not to be included in the "warnings" section of the label where a prescribing physician would expect to find such information. The "adverse reactions" section on the package insert is near the end of the labeling, very often several dozen paragraphs following the "warnings" section, and is akin to a laundry list. In practice, it is quite simply not given the same attention or priority by prescribers as the "warnings" and "precautions" sections near the beginning of the label. Therefore, the warning given regarding weight gain is inadequate. As shown by the true and correct copy of the Physicians' Desk Reference section on Seroquel from 2004, attached as Exhibit C, the highlighted weight gain information is dwarfed by the overwhelming balance of other information about the drug.

7. The 1997-to-present Seroquel label is also unclear, inaccurate, and misleading because weight gains of the magnitude that Seroquel causes, according to its own label and the company's data, are impressively large and impact an amazingly large and consistent percentage of patients. The serious and frequently deadly health consequences associated with weight gain (namely hyperglycemia and diabetes mellitus, and complications therefrom) necessitated adequate warning. Such warning should have appeared in the "warnings" not

"adverse reactions" section of the label. Placement of the weight gain clinical trials data in the "adverse reactions" section inadequately conveys to prescribing physicians the severity of the health consequences associated with a 23%-33% or more weight increase associated with Seroquel treatment, further rendering the inclusion of such data in the adverse reactions section inadequate. Additionally, the label fails to describe any of the health consequences for which weight gain creates an increased risk—i.e., hyperglycemia and diabetes mellitus, among other serious and potentially lethal health concerns including increases in total cholesterol and triglycerides in the blood, secondary risks for cardiovascular disease, increased rates of degenerative osteoarthritis, and even increased risks for certain malignancies (e.g., colon cancer). To put it another way, the labeling fails to state a "cause and effect" relationship between the statistically significant weight gain accompanying Seroquel use and the increase in glucose dysregulation that was also revealed by AstraZeneca's clinical trials and company data that I have reviewed.

8. Regarding AstraZeneca's marketing materials during this same period with respect to weight gain, as well as sales representatives' direct messages (discussions) to physicians, the materials that I have reviewed, including Doctor Brecher's 2000 article and Doctor Nasrallah's 2002 article, informed doctors that Seroquel did not cause weight gain or had favorable weight profiles. Sales materials profiling patient experiences with Seroquel by a Doctor Reinstein, which I have reviewed, implied that weight loss along with improvement of diabetes was a beneficial side effect of Seroquel. Further, despite information identifying weight gain as a dose-dependent side effect, AstraZeneca has repeatedly stated in its sponsored literature and marketing material that I reviewed (e.g., the Brecher and Nasrallah

articles) that there is no dose-dependent relationship between Seroquel and weight gain Other marketing messages included claims that Seroquel is "weight neutral" or causes "minimal weight gain," further obscuring and diluting the severity of any mention of clinically significant weight gain in the label's adverse reaction section. At best, such promotional messages further render the so-called "adverse reaction" regarding seriously hazardous weight gain unclear and ambiguous because on the one hand, the label and company data revealed that 23%-33% or more of Seroquel users will experience clinically significant weight gain, but the sales message was that the drug is "weight neutral" causes "minimal weight gain" or has a "favorable weight profile." These sales messages not only contradicted what AstraZeneca knew about weight gain and Seroquel, from my review of Seroquel clinical trial data and company documents, they actually contradicted Seroquel's own approved label, undermining the clarity, accuracy, and unambiguousness of the label.

9. With respect to the pre-2004 label concerning hyperglycemia and diabetes mellitus, it is my opinion that AstraZeneca obscured and buried any mention of hyperglycemia and diabetes in the pre-2004 label by simply mentioning those words and characterizing the conditions as "infrequent" in the adverse reactions section of the label. AstraZeneca further obscures and confuses the issue by also listing "hypoglycemia" and "weight loss" as "infrequent" adverse reactions. This is simply no warning at all as to the true frequency and severity of those side effects suffered by Seroquel users. Documents I have reviewed showed that the company knew, prior to Seroquel's launch, that statistically significant weight gain increases by Seroquel users, would seriously impact patient health in terms of glucose dysregulation. Moreover, at least by 2000, documents I reviewed showed

that the company's medical safety director had concluded that Seroquel can cause impaired glucose dysregulation including diabetes.

10. The pre-2004 label is inadequate to warn prescribing physicians of the nature, severity, and frequency of the risk of hyperglycemia and diabetes mellitus associated with Seroquel, and for the above reasons is unclear, inaccurate, and ambiguous. It does not convey in a meaningful way the toxic potential of the drug and is confusing.

11. In addition, AstraZeneca's marketing materials and sales representatives' direct message "discussions" to physicians during this time further undermined any attempt by AstraZeneca to warn of hyperglycemia and diabetes mellitus in the pre-2004 label. For example, Dr. Nasrallah's 2002 paper cites a now discredited study by Dr. Reinstein suggesting that Seroquel patients lost weight and had their diabetes cured after taking Seroquel for ten weeks.

12. With respect to the 2004-2007 label for Seroquel regarding hyperglycemia and diabetes mellitus, the so-called "class label" warning section on hyperglycemia and diabetes is inadequate, unclear, and ambiguous because it is laced with generalities, disclaimers, and distracting verbiage. Specifically, it fails to accurately and clearly state the measured increases in new onset diabetes that are specific to Seroquel, which were significantly greater based on clinical trials and company documents that I have reviewed as compared to certain other second generation antipsychotics that also bear the class label warning.

13. Moreover, the class label neglects to accurately describe the level of Seroquel's risk of those side effects, which was extraordinary according to the clinical trials

and company documents that I have reviewed and as compared to second generation antipsychotics such as aripiprazole and ziprasidone, which studies show do not cause clinically significant weight gain and hyperglycemia/diabetes. Instead, the 2004-2007 label describes merely that hyperglycemia and related serious complications "has been reported" without any data whatsoever quantifying the rate of incidents and severity of such risks and complications, or identifying which second generation antipsychotics were the subject of such "reports." The label language then further waters down the "warning" by indicating that measurement of glucose abnormalities is complicated by factors such as an increased rate in diabetes among the schizophrenic or general populations. This warning is far from a model of clarity and unambiguousness given the conclusions that the company and other foreign regulatory bodies reached that a reasonable association between Seroquel and hyperglycemia/diabetes (if not a causal association as well) had already been established before and during the time period this label was in effect.

14. In addition, AstraZeneca's marketing materials and sales representatives' direct message "discussions" to physicians during this time further undermined and diluted the warning. For example, company documents reveal that physicians were still receiving correspondence from the company referencing the Reinstein study concluding that Seroquel may cause weight loss and reverse diabetes in sizeable numbers of patients. Other internal company communication revealed that the Brecher article was still being disseminated. The FDA also reprimanded AstraZeneca in 2006 for failing to disclose in promotional material the increased risk of hyperglycemia and diabetes mellitus in patients treated with Seroquel, resulting in the promotional material being "misleading" and "undermin[ing] the warning."

15. Based on clinical experience, the so-called class label warning is inadequate to communicate the true nature and severity of the hyperglycemia/diabetes mellitus risk associated with Seroquel alone to physicians prescribing Seroquel to their patients.

16. Additionally, based on documents I have reviewed, language associated with the class label warning was a product of negotiations between AstraZeneca and the FDA. For example, with respect to the January 2004 "Dear Doctor" letter relative to the "class label" warning sent by AstraZeneca, earlier correspondence between the FDA and AstraZeneca revealed that AstraZeneca desired to characterize the new "warning" as simply being "about hyperglycemia and diabetes in patients taking these medications," but the FDA stated that it "preferred" the statement "describing increased risk of hyperglycemia and diabetes in patients taking these medications." From the correspondence I reviewed, it appears as though AstraZeneca determined not to further press the issue with the FDA.

17. With respect to the label change that occurred in 2007 regarding the hyperglycemia and diabetes mellitus warning contained on Seroquel, while it directs one to new language in the "adverse events" section, it is my opinion that the 2007 label change is still inadequate because it fails to clearly, accurately, and unambiguously describe the alarming rate at which Seroquel users in long-term clinical trials contracted diabetes, and the necessary warning language that a prescribing physician would expect to see relative to that very significant risk is not contained in the "warnings" section. Instead mere cross-reference is made to clinical trials data the "adverse reactions" section. The "adverse reactions" section does not mention the word "diabetes," but examination of the data reveals that Seroquel patients in long-term clinical trials were over twice as likely to suffer diabetes than

patients taking placebo. Company documents that I have reviewed show that AstraZeneca has characterized the risk of diabetes-level blood glucose abnormalities associated with Seroquel as "common." The label is facially unclear, inaccurate, and misleading because the frequency and severity of the diabetes risk is not mentioned in the "warnings" section but instead is buried in the "adverse reactions" section, and because what is truly diabetes-level blood sugar is characterized merely as "hyperglycemia" and "increased blood sugar"—i.e., fasting blood glucose measurements (those taken 8 hours after a meal) that are $\geq$ 126 mg/dL or non-fasting blood glucose measurements $\geq$ 200 mg/dL is frank diabetes, not merely hyperglycemia. The label is also inadequate because it fails to clearly and unambiguously warn of a "cause and effect" relationship between Seroquel use and diabetes-level blood glucose abnormalities.

18. The FDA is not satisfied with AstraZeneca's most recent Seroquel label change, as indicated in the June 2008 correspondence I have reviewed from the FDA to AstraZeneca. The FDA requested that the updated label be changed to add the additional information that "[t]he mean change in glucose from baseline was +5.0 mg/dl for SEROQUEL and –0.05 mg/dl for placebo," indicating that the FDA desires for AstraZeneca to reveal that there was more than a 5-fold increase in blood glucose levels between those subjects taking Seroquel and those taking placebo. The FDA also asked that AstraZeneca add the statement: "Because of limitations in the study design of these long-term trials as well as lack of confirmed fasting glucose data, the effects of Seroquel on blood glucose may be underestimated." In its letter, the FDA supported the additional statement above as follows:

> Since the 2-week long-term placebo-controlled bipolar maintenance trial studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of Seroquel on blood glucose could be underestimated.

Thus, the FDA wanted to provide clarity that the already negative blood glucose results stated in the new label—based on studies that effectively prescreened participants who did not well-tolerate Seroquel—actually may be even worse than the label reveals. AstraZeneca has not made the labeling changes that the FDA has requested as of the date of execution of this Declaration. AstraZeneca's evasive treatment and abstruseness with respect to this label change further confirms my opinion that AstraZeneca has not been forthright with physicians who prescribe Seroquel in the sense of "full disclosure" of pertinent, potentially life threatening (or certainly life-altering) healthcare information such that physicians may fully consider the risks and benefits and adequately advise and consult with their patients.

19. Overall, the inadequacy of Seroquel's labeling and accompanying misstatements of the risks associated with its use make it prohibitively difficult for a physician relying on such information to appreciate the true nature of Seroquel's risks and discuss those risks with his or her patients.

20. Furthermore, in my opinion, AstraZeneca's warnings for Seroquel appear to have been designed to obscure known risks associated with the drug, rather than to clearly, accurately, and unambiguously communicate risks to prescribing physicians in a frank,

explanatory manner such that they would have ready access to such critical information in treating their patients.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on this the 19th day of November, 2008.

William C. Wirshing, M.D.

CURRICULUM VITAE

WILLIAM C. WIRSHING, M.D.

Address

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Culver City, CA 90232

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Home: 6433 Topanga Canyon Blvd. #429
Woodland Hills, CA 91303

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Birthdate 11 June, 1956

Birthplace Palo Alto, CA

Education

1982 M.D. - UCLA

1978 B.S. Electrical Engineering & Computer Science, University of CA, Berkeley

Internship, Residency, & Fellowship

1986-88 Postdoctoral Research Fellowship in Schizophrenia Research, UCLA, Department of Psychology, Los Angeles, CA

1983-86 Resident in Psychiatry, UCLA Neuropsychiatric Institute, Los Angeles, CA

1982-83 Intern in Medicine, UCLA Center for the Health Sciences & Wadsworth VA Medical Center, Los Angeles, CA

Licensure

1983 California License No. G 50986, DEA No. FW0654447

Certification

1991 Added Qualification in Geriatric Psychiatry, American Board of Psychiatry and Neurology (#000479)

1988 Diplomat, American Board of Psychiatry and Neurology (#30125)

Academic Appointments/Positions

2008- Medical Director Real Recovery. Agoura Hills, CA

2007- Vice President in charge of continuing medical education and research Exodus Corp. Los Angeles, CA

1996-06 Professor of Clinical Psychiatry, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine

1993-06 Chief, Schizophrenia Treatment Unit, West Los Angeles VA Medical Center, Brentwood Division

1993-96 Associate Professor of Clinical Psychiatry, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine

1987-06 Director, Brentwood Movement Disorders Laboratory, West Los Angeles VA Medical Center

1988-93 Co-Chief, Schizophrenia Treatment Unit, West Los Angeles VA Medical Center, Brentwood Division

1986-93 Adjunct Assistant Professor of Psychiatry, Department of Psychiatry & Biobehavioral Sciences, UCLA School of Medicine

1986-88 Postgraduate Research Scholar, Department of Psychology, UCLA

1986-88 Co-Chief, Geropsychiatry Treatment Unit, West Los Angeles Veterans Administration Medical Center

1985-86 Chief Resident, Geropsychiatry Treatment Unit, West Los Angeles Veterans Administration Medical Center, Brentwood Division

Awards & Honors

2006 Nominated for Golden Apple Award for Clinical years by graduating class of 2006

2003 Award in Recognition of Dedication in Teaching Excellence from the Graduating Class of 2003, David Geffen School of Medicine at UCLA

1999 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1999 Lucien B. Guze Golden Apple Award for Outstanding Teaching Class of 2001, UCLA School of Medicine

1998 Certificate of Excellence, West Los Angeles Success 98 Award Program, West Los Angeles Veterans Administration Medical Center

1996 Distinguished Educator Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1994 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1993 UCLA Medical School. Class of 1995 - Outstanding Teacher Award

1991 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1988 Travel scholarship to attend the 4th Biannual Workshop on Schizophrenia in Badgastein, Austria.

1982 Sandoz Award for Excellence in the Behavioral Sciences

1982 Alpha Omega Alpha

1978 Tau Beta Pi (Engineering National Honor Society)

1978 Phi Beta Kappa

1978 B.S. Summa Cum Laude

Major Teaching Experience

2007- Weekly Continuing Medical Education Lecture Exodus Urgent Care Center, Culver City, CA.

2000-06 Case Conference: Diagnostic Dilemmas - Psychiatry (#425 Sec. 5) This weekly case conference focuses on differential diagnosis, with an emphasis on the various etiologies of psychotic symptoms including schizophrenia, substance-induced psychosis, malingering,and other disorders.

1995-06 Movement Disorders Seminar - Psychiatry (#446) a weekly, clinical based, interactive seminar focusing on the examination and treatment of patients with a broad range of movement disorders for psychiatry residents,

	neurobehavior fellows, medical students, and research staff (with DA Wirshing, M.D., CS Saunders, M.D., and JM Pierre, M.D.). (1.5 hrs/week)
1992-2004	Course director - Psychopathology (#201) for 2nd-year medical students. (6 hrs/week)
1991-2002	Faculty sponsor - Student Research Program. (1-8 hrs/week)
1990-1992	Faculty advisor for biweekly seminar for psychiatry residents on critical reading of the literature (with Joel Yager, MD, and Alison Doupe, MD, PhD). (1 1/2 hrs/2 weeks)
1989-92	Movement Disorders Seminar (Psychiatry Course #453), a weekly forum for psychiatry residents, neurobehavior fellows, and medical students (with JL Cummings, MD). (1 hr/week)
1988-1991	Class Organizer/Lecturer of "Topics in Geropsychiatry", a weekly seminar for psychiatry residents, medical students, and psychology interns. (1 1/2 hrs/week)
1988-06	Ward teaching supervisor (Psychiatry Course #403) for 1st- and 3rd-year psychiatric residents and for 3rd- and 4th-year medical students on the Schizophrenia Treatment Unit, BVAMC. (9 hrs/week)
1986-06	Off-ward teaching supervisor (Psychiatry Course #403) for 1st-, 2nd-, and 3rd-year psychiatric residents in the UCLA Residency Training Program. (2-4 hrs/week)
1986	Lecturer: "The Psychiatric Hospital in Historical Perspective" (with Dora B Weiner, PhD), a class for undergraduates, College of Letters and Sciences, UCLA.
1985-88	Ward teaching supervisor for first- and second-year psychiatric residents and for first-year geriatric medicine fellows on the Geropsychiatry Ward, WLA/VAMC.
1985	Lecturer: "The Historical Roots of Modern Medicine" (with Dora Weiner, PhD), a class for undergraduates, College of Letters and Sciences, UCLA.

Hospital/University Committees

2005-06	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
2000-02	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
1999-03	Medical Student Education Strategic Planning Committee
1999-02	Human Subjects Protection Committee, Veterans Affairs
1998	Neuroscience Sub Committee, UCLA School of Medicine
1997- 00	Faculty Executive Committee
1997- 01	Voluntary Clinical Faculty Academic Appointments and Adjustments Committee

1996-99	Second Year Curricular Block Planning Committee, UCLA School of Medicine
1995-98	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
1992-94	Ad Hoc Committee for Dementia, UCLA School of Medicine
1992-96	Student Affairs Committee, UCLA School of Medicine
1992-94	Human Subjects Protection Committee, Veterans Affairs
1991-93	Residency Fellowship Nominating Committee, UCLA
1991	Chief of Psychiatry Search Committee, Veterans Affairs
1990-93	Residency Education Curriculum Committee, UCLA
1988-90	Human Subjects Protection Committee, Veterans Affairs
1988-03	Pharmacy and Therapeutics Committee, Veterans Affairs

Grants Awarded

2005-06 "Management of Antipsychotic Medication Associated Obesity"
Co-Principal Investigator Donna A. Wirshing, M.D. PI
VA Merit Review

2005-06 "Relapse Prevention: Long Acting Atypical Antipsychotics"
Co-Investigator , Donna A. Wirshing, M.D. PI
NIMH RO1 (Multicenter Collaborative)

2002-05 Veterans Affairs Merit Review
"Cigarette Smoking by Schizophrenic Patients (Phase II)"
Collaborator. Jarvik Murray, M.D., Ph.D. - P.I.

2000-02 National Institute of Mental Health, MH41573-11A1
"Management for Risk of Relapse in Schizophrenia"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

2000-03 National Institute of Mental Health, MH59750-01A1
"Treatment of Negative Symptoms and Cognitive Impairments"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1998-00 Veterans Affairs Merit Review
"Brief Hospitalization for Schizophrenia: Strategies to Improve Treatment Outcome"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1997-02 Veterans Affairs Merit Review
"Quetiapine vs. Haloperidol Decanoate for the Long-Term Treatment of Schizophrenia and Schizo-Affective Disorder"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1995-98 National Institute of Health, 1R01-DA09570-01A1
"Dopaminergic Modulation of Nicotine Reinforcement"
Co-Investigator. Murray E. Jarvik, MD, PhD - P.I.

1995-99 National Institute of Health, 1R01-MH46484-01
"New Antipsychotics: Clinical Trials and Naturalistic Follow-up."
Co-Investigator. Stephen R Marder, MD - P.I.

1993-95 Veterans Affairs Merit Review to examine cigarette smoking by schizophrenic patients.
Co-Investigator. Murray E. Jarvik, MD, PhD - P.I.

1993-96 Veterans Affairs Merit Review to examine the risks and benefits of typical and atypical antipsychotic drugs in the treatment of acute psychotic episodes.
P.I.

1992-95 National Institute of Health: MH46484-03
"Clozapine - Treatment Response and Disability."
Co-Investigator.

1990-92 NARSAD (National Alliance for Research on Schizophrenia and Depression) Young Investigators Grant to develop a method of quantifying drug-induced akathisia and to apply this method of determining the relative akathisic liability of the atypical neuroleptic clozapine.

1986-05 National Institute of Health: MH41573
"Management of Risk of Relapse in Schizophrenia."
Co-Investigator. Stephen R Marder, MD and Robert P. Liberman, MD Co-P.I.s

1988-90 Veterans Affairs Merit Review to examine the feasibility of using a battery of electromechanical instruments to prospectively follow patients with tardive dyskinesia.
Co-Investigator. JL Cummings, MD, P.I.

1988-89 NARSAD Young Investigators Grant to continue research on the instrumentation of drug-induced movement disorders.

1987-88 Biomedical Research Support Grant from the Department of Psychiatry, UCLA School of Medicine, to develop a system to measure and analyze the movements of the human larynx.

Industry Sponsored

Investigator Designed and Initiated

1999-03 Janssen Pharmaceutica: Investigator designed protocol.
"Brief Hospitalization for Schizophrenia: Strategies to Improve Treatment Outcome"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

2000-05 Eli Lilly, Inc.: Investigator designed protocol.
"Olanzapine vs. Risperidone in Treatment Refractory Schizophrenia"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

Industry Designed and Initiated

1998-99 Merck & Company, Inc.
"A Double-Blind, Active and Placebo-Controlled, Safety Tolerability, and Preliminary Antipsychotic Activity Study of MK-0869 in Hospitalized Schizophrenia Patients"
P.I. William C. Wirshing, M.D.

1998-99 Hoechst Marion Roussel, Inc.
"A Multicenter, Placebo and Active Control, Double-Blind Randomized Study of the Efficacy, Safety and Pharmacokinetics of M100907 (10 and 20 mg/d in Schizophrenic and Schizoaffective Patients."
Co-Investigator. Donna A Wirshing, M.D. - P.I

1997-00 Organon 041002
"A Double Blind, Five-Armed, Fixed Dose, Active and Placebo Controlled Dose-Finding Study With Sublingual ORG 5222 in Subjects With Acute Phase Schizophrenia"
P.I. William C. Wirshing, M.D.

1997-99 Otsuka America: 42,776
"An Open Label Follow-on Study on the Long-Term Safety of Aripiprazole in Patients with Psychosis"
P.I. William C. Wirshing, M.D.

1997-99 Otsuka America: 31-97-202
"A Phase III Double-Blind Study of Aripiprazole and Risperidone in the Treatment of Psychosis"
P.I. William C. Wirshing, M.D.

1997-98 Janssen Pharmaceutica: RIS-USA-112
"A Multicenter, Randomized, Double Blind, Parallel Group Trial Comparing the Safety and Efficacy of Risperidone and Olanzapine in the Treatment of Psychosis in Patients with Schizophrenia and Schizoaffective Disorder."
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1997-99 Janssen Pharmaceutica: RIS-USA-113
"A Multicenter, Randomized, Double Blind, Parallel Group Trial Comparing the Safety and Efficacy of Risperidone and Olanzapine in the Treatment of Psychosis in Patients with Schizophrenia and Schizoaffective Disorder."
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1995-98 Hoechst Marion Roussel
"An Open-Label, Follow-Up, Multicenter, Long-Term Maintenance Study of MDL 100, 907 in Patients with Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1995-98 Otsuka: 31-95-201
"OPC-14597: An Open-Label Tolerability Study in Schizophrenic Patients."
P.I. William C. Wirshing, M.D.

1995-96 Hoechst Marion Roussel: IND# 47,372
"A Randomized, Double-Blind, Placebo-Controlled, Parallel, Multiple Dose, Multicenter Study to Determine the Safety, Tolerability, Pharmacokinetics, and Biochemical Activity of MDL 100,907 in Patients with Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1995-96 Merck & Company, Inc.
"A Double-Blind, Placebo-Controlled, Safety, Tolerability and Preliminary Antipsychotic Activity Study of L-745,870 in Hospitalized Schizophrenic Patients"
P.I. William C. Wirshing, M.D.

1995-96 Otsuka: 31-94-202
"A Dose Ranging Study of the Efficacy and Tolerability of OPC-14597 in Acutely Relapsing Hospitalized Schizophrenic Patients."
P.I. William C. Wirshing, M.D.

1993-97 Eli Lilly Incorporated: F1D-MC-HGAP
"Fixed Dose Olanzapine versus Placebo in the Treatment of Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1994-99 Pfizer, Inc.: 128-116B
"A 52-Week, Open Extension Study Evaluating the Safety and Outcome of 40-80 mg BID of Oral Ziprasidone (CP-88,059-1) Daily in the Treatment of Subjects Who Have Participated in Previous Ziprasidone Clinical Trials."
Co-Investigator. Donna Ames, M.D. - P.I.

1993-94 R.W. Johnson: M92-083
"Multi-Center, Randomized, Double-Blind, and Controlled, 4 Week, Multiple Oral Rising Dose Study to Determine Safety Tolerability, Pharmokinetics and Behavioral Activity of RWJ-37796 in Male Schizophrenic Subjects Phase II."
P.I. William C. Wirshing, M.D.

1992-98 Abbott Laboratories - Neuroscience Venture: M92-795
"An Open Label Assessment of the Long Term Safety of Sertindole in the Treatment of Schizophrenic Patients."
Co-Investigator. Donna Ames, M.D. - P.I.

1994-96 Pfizer, Inc.: 128-115
"Phase III, Six Week, Double Blind, Multi-Center, Placebo Controlled Study Evaluating the Efficacy and Safety of Three Fixed Doses of Oral Ziprasidone (CP-88,051-1) and Haloperidol in the Acute Exacerbation of Schizophrenia and Schizo-Affective Disorder."
Co-Investigator. Donna Ames, M.D. - P.I.

1992-94 Glaxo, Inc.: S3B-201
"A Randomized, Double-Blind, Placebo-Controlled, Crossover Evaluation of the Effects of GR68755C on Serum Levels of Haloperidol in Patients with a Diagnosis of Schizophrenia."
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1992-93 Abbott Laboratories - Neuroscience Venture: M92-762
"A Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Sertindole in Schizophrenic Patients."
Co-Investigator. Stephen R Marder, M.D. - P.I.

1992-93 Schering Plough Research Corporation: SCH39166
"Safety, Tolerance and Pilot Efficacy of Rising Multiple Doses of SCH39166: An Open Label Trial."
Co-Investigator. Stephen R Marder, M.D. - P.I.

1988-89 Astra Pharmaceuticals
"Raclopride in Schizophrenia: a Haloperidol-Controlled, Double-Blind, Dose-Finding Clinical Trial."
Co-Investigator. Theodore Van Putten, M.D. - P.I.

1990-91 Sandoz Pharmaceuticals
"A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Multi-Stage, Dose-Finding Study of SDZ HDC 912 in DSM-III-R Defined Hospitalized Schizophrenic Patients."
Co-Investigator. Theodore Van Putten, M.D. - P.I.

Reviewer / Editor

Reviewer:

American Journal of Psychiatry
Archives of General Psychiatry
Biological Psychiatry
Brain Dysfunction
CNS Spectrums
Comprehensive Psychiatry

International Journal of Psychiatry in Medicine
Journal of Clinical Psychiatry
Journal of Psychiatric Research
Journal of Clinical Psychopharmacology
Neuropsychiatry, Neuropsychology, and Behavioral Neurology
Psychiatry Research
Psychopharmacology
Psychopharmacology Bulletin
Psychosomatics
Schizophrenia Bulletin

Invited Presentations

04/07 "Schizophrenia and Related Psychoses" Grand Rounds Northridge Hospital, Northridge CA 15 Apr 2007

08/06 "Tailored Management of Schizophrenia in the Real World: A Naturalistic Approach" Presented at Evansville State Hospital, Evansville, IN, 17 Aug 06

08/06 "The Metabolic Mayhem of Atypicals: The TD of the New Millennium" Grond Rounds Antelope Valley Hospital 11 Aug 06.

08/06 "Use of Atypical Antipsychotics in Bipolar Illness"1 Aug 06 Honolulu, HI.

03/06 "Treatment of Agitation with Behavioral Interventions and Atypical Antipsychotics in Schizophrenia" Presented at American Association for Geriatric Psychiatry, San Juan, Puerto Rico, 11 Mar 06.

02/06 "Addressing Metabolic Disturbances with Antipsychotic Treatments" Presented at San Francisco General Hospital, Dept of Psychiatry, San Francisco, CA, 24 Feb 06

12/05 "Metabolic Impact of Atypical Antipsychotics: The View from Two Decades of Experience" Presented at Eden Medical Center, Castro Valley, CA 7 Dec 2005

11/05 "Clinical Management of Behavioral and Psychological Symptoms in Dementia" Presented at Salem Hospital, Salem, OR, 16 Nov 05

10/05 "Marketing Atypical Antipsychotics and the Opacity of Adiposity" Presented at Grand Rounds, Sepulveda VA, Los Angeles, CA, 26 Oct 05

07/05 "Treatment of Agitation in Elderly Demented Patients" Presented at Grand Rounds, Hawaii State Hospital, Kaneohe, HI, 12 Jul 05

07/05 "Metabolic Disturbances During Antipsychotic Treatment" Presented at Grand Rounds, Castle Medical Center, Kailua, HI, 12 Jul 05

04/05 "Metabolic Disturbances During Antipsychotic Treatment" Presented at Grand Rounds, Battle Creek VA Med Center, Battle Creek, MI, 7 Apr 05

12/04 "Considerations in Long-Term Management of Schizophrenia" Presented at Grand Rounds, Corcoran State Prison, Corcoran, CA 1 Dec 04

12/04 "Management of Associated Comorbidities of Schizophrenia" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA 1 Dec 04

09/04 "Pharamacological Treatment of Psychosis and Agitation in Dementia of the Elderly" Presented at Grand Rounds, Scripps Mercy Hospital, San Diego, CA, 7 Sep 04

08/04 "Metabolic Disorder" Presented at Grand Rounds, Kedren Hospital, Los Angeles, CA 16 Aug 04

06/04 "Atypical Antipsychotics in Special Populations" Presented at Grand Rounds Terrell State Hospital, Terrell, TX, 21 Jun 04

06/04 "The Many Faces of 'Wartime' PTSD" Presented at Grand Rounds, Mountain Crest Hospital, Fort Collins, CO, 15 Jun 04

05/04 "Pharmacology Treatment of Psychosis and Agitation in Dementia of the Elderly" Presented at Grand Rounds, Utah State Hospital, Provost, UT, 20 Mau 04

05/04 "Psychiatric Research Ethics" Presented at NIH Neuroscience Center, Bethesda, MD, 17 May 04

05/04 "Lab Science to Clinical Practice: Neurochemical Model of Antipsychotic Effects" Presented at Grand Rounds, Metropolitan State Hospital, Norwalk, CA, 12 May 04

04/04 "New Indications for Antipsychotics for Bi-Polar Disorders" Presented at Grand Rounds, Cedars Sinai, Los Angeles, CA, 29 Apr 04

03/04 "A Century after Bleuler, What Do We Really Know About Schizophrenia, Its Origin, Cause, and Treatment?" Presented at WASP (World Association of Social Psychiatry), 1st Regional Congress of Social Psychiatry in Africa; Johannesburg, Gauteng, 24 Mar 04

03/04 "The Antipsychotics: Their Developmental History, Clinical Limitations, Major Toxicities, and Anticipated Future." Presented at WASP (World Association of Social Psychiatry), 1st Regional Congress of Social Psychiatry in Africa; Johannesburg, Gauteng, 24 Mar 04

02/04 "Consideration in the Long-term Management of Schizophrenia" Presented at Grand Rounds, Stanford University Hospital, Stanford, CA, 19 Feb 04

02/04 "The Marketing of Atypical Antipsychotic Drugs: A War for Our "Loyalties" Moves Into its Guerilla Phase" Presented at Grand Rounds, Sepulveda VA Mental Health Center, Los Angeles, CA, 11 Feb 04

02/04 "Drug Induced Metabolic Symptoms with Antipsychotic Paradigm Shift in an Approach to Patient Care" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA, 4 Feb 04

01/04 "Risperdal Consta" Presented at Grand Rounds, Indianapolis VA, Indianapolis, IN, 15 Jan 04

12/03 "Strategies for Controlling Psychotic Symptoms" Presented at Grand Rounds, Riverside County Department of Mental Health, Hemet CA, 9 Dec 03

12/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, Castle Medical Center, Kailua, HI, 2 Dec 03

11/03 "Monitoring Patients on Antipsychotic Drugs for Glucose Intolerance and Other Features of the Metabolic Syndrome" Presented at Alexandria, VA, 19-20 Nov 03

11/03 "Antipsychotics: Overcoming Side Effect Treatment Barriers" Presented at Grand Rounds, Long Beach VA Medical Center, Long Beach, CA, 12 Nov 03

11/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, Fresno, CA, 11 Nov 03

11/03 "A Broad Spectrum in Psychotropics" Presented at Grand Rounds, Golden Valley Health Center-Corner of Hope, Modesto, CA, 6 Nov 03

10/03 "The Mechanistic Similarities and Distinctions Among Antipsychotics: A Treatment Refractory Model" Presented at Grand Rounds, Hawaii State Hospital Auditorium, Oahu, HI, 24 Oct 03

10/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, San Francisco Clinic, San Francisco, CA, 4 Oct 03

10/03 "Kaiser/Group Health Cooperative AP Advisory Board" Presented at San Francisco, CA, 4 Oct 03

10/03 "Improvement in Cognitive Function, Dosing and Titration" Presented at Grand Rounds, Olive View Hospital, Sylmar, CA, 2 Oct 03

09/03 "Strategies for Controlling Psychotic Symptoms" Presented at Grand Rounds, Seattle Hospital, Seattle, WA, 11 Sep 03

08/03 "Neurocognition and Schizophrenia Including Issues on Nicotine Receptors" Presented at Grand Rounds, Ventura County Behavioral Health Inpatient Unit, Ventura, CA, 13 Aug 03

05/03 "Switchover from Clozapine to Quetiapine: Mixed Results" Presented at Biological Psychiatry, San Francisco, CA, 15 May 03

05/03 "Effects of Novel Antipsychotics on Glucose and Lipid Levels" Presented at Grand Rounds, Eugene VA Clinic, Eugene, OR, 13 May 03

05/03 "Effects of Novel Antipsychotics on Glucose and Lipid Levels" Presented at Grand Rounds, VA Medical Center, Portland, OR, 12 May 03

05/03 "Atypical Antipsychotics: Marketing Mischief or Metabolic Mayhem" Presented at Grand Rounds, Harbor-UCLA Medical Center, Torrance, CA, 6 May 03

04/03 "Metabolic Consequences of Antipsychotic Therapy" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA, 30 Apr 03

03/03 "Metabolic Toxicities of Atypical Antipsychotic Agents: Speculations, Etiology, and Treatment" Presented at Grand Rounds, RJ Donovan Correctional Facility, San Diego, CA, 12 Mar 03

03/03 "Aripiprazole" Presented at Grand Rounds, Patton State Hospital, Patton, CA, 5 Mar 03

02/03 "Applied Neuropsychopharmacology: The Spectrum of Clinical Outcomes with Atypical Antipsychotics" Presented at the CNS Advisory Summit, Scottsdale AZ, 22 Feb 03

02/03 "The Use of Atypical Antipsychotics in Mood Disorders" Presented at Grand Rounds, Region IV Parole Headquarters, Diamond Bar, CA, 21 Feb 03

01/03 "Metabolic Side Effects of Atypical Antipsychotics" Presented at Grand Rounds, King Drew Medical Center, Los Angeles, CA, 28 Jan 03

01/03 "TD - What if Anything is New?" Presented at Grand Rounds, VA Hospital, Neurology Department, Los Angeles, CA, 24 Jan 03

01/03 "Metabolic Toxicities of Atypical Antipsychotic Agents: Speculations, Etiology, and Treatment" Presented at Grand Rounds, Sepulveda VA, Los Angeles, CA, 22 Jan 03

12-02 "Aripiprazole" Presented at Grand Rounds, Loma Linda University, Redlands, CA 20 Dec 02

12-02 "Aripiprazole" Presented at Grand Rounds, Arrowhead Regional Medical Center, Colton, CA, 17 Dec 02

12-02 "Treatment Emergent Movement Disorders in Current Clinical Practice" Presented at Grand Rounds, Queens Hospital, Honolulu, HI, 13 Dec 02

12-02 "Advancement in Treatment of Schizophrenia" Presented at Grand Rounds, Tripler VA Army Hospital, Honolulu, HI, 11 Dec 02

11-02 "Evolution of Antipsychotic Therapies: A Pathophysiologic Approach" Presented at National Network if Psychiatric Educators, Laguna Niguel, CA, 15 Nov 02.

10-02 "Side Effects Involving Newer Antipsychotic Medications Including Risk of Cardiovascular Disease and Diabetes" Presented at Grand Rounds, Bakersfield Memorial Hospital, Bakersfield CA, 24 Oct 02.

03-02 "The Atypical Antipsychotic Compounds: What is the Crucial Difference Among Them?" Presented at Psychopharmacology Course, Stanford University, Stanford CA, 9 Mar 02.

03-02 "The Relative Metabolic Toxicities Among the Newer Antipsychotic Compounds." Presented at Grand Rounds, Waco, TX, 7 Mar 02

03-02 "The Relative Metabolic Toxicities Among the Newer Antipsychotic Compounds." Presented at Grand Rounds, Dallas VA Medical Center, Dallas, TX, 7 Mar 02

11-01 "Aripiprazole: Is anything Really New in the Wold of Antipsychotic Medications?" Presented at Abilitat Investigators Meeting, Scottsdale, AZ, 29 Nov 01.

09-01 "The Past, Present, and (Near) Future of Antipsychotic Medications: The Under-appreciated Role of Luck!" Presented at The Annual Meeting of the Northern California Psychiatric Society, Saratoga, CA, 19 Sep 01.

07-01 "The Metabolic Side Effects of the Newer Antipsychotic Compounds: The TD of the New Millennium." Presented at Grand Rounds, UC Irvine, Irvine, CA, 17 Jul 01.

05-01 "The Toxicities of the So-Called 'Atypical Antipsychotics'--Focus on Dyslipidemia." Presented at Grand Rounds, Utah Neuropsychiatric Institute, Salt Lake City, Utah, 22 May 01.

04-01 "Prodromal Phase of Schizophrenia: Diagnosis and Treatment." Presented at W. Covina Mental Health Office, W. Covina, CA, 19 April 01.

03-01 "Risperidone: A Clinical Research Update." Presented at Le Royal Meridien, Toronto, Ontario, Canada, 31 Mar 01.

03-01 "Ziprasidone: A New Treatment Option for Schizophrenia." Presented at University Of Tennessee, Memphis, TN, 9 Feb 01

03-01 "Ziprasidone: A New Treatment Option for Schizophrenia." Presented at University Of Arkansas for Medical Science, Little Rock, AR, 8 Feb 01

02-01 "Use of Antipsychotic Drugs on Treatment Approach for Drug Induced Psychosis." Presented at San Quentin State Prison, San Quentin, CA, 21 Feb 01.

01-01 "EPA and TD with Novel Antipsychotics." Presented at Lanterman State Hospital, Pomona, CA, 25 Jan 01.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at VA Hospital, Seattle, WA, 15 Dec 00.

12-00 "Efficacy and Safety Data of the Atypical Antipsychotics." Presented at Atascadero State Hospital, Atascadero, CA, 14 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Grand Rounds, VA Hospital Outpatient Clinic, Roseburg, OR, 12 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly" Presented at Grand Rounds, USC Ingleside Hospital, Rosemead, CA, 8 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Grand Rounds, University of Southern California, Los Angeles, CA, 6 Dec 00.

11-00 "Safety and Efficacy Among Atypicals; Treatment Refractory Schizophrenia." Presented at Los Angeles County Jail, Los Angeles, CA, 30 Nov 00.

11-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Olive View Hospital, Sylmar, CA, 16 Nov 00.

11-00 "Long-Term Outcomes with Antipsychotic Medications: The limitations of Our Current Technology." Presented at Ziprasidone National Consultants Forum, Scottsdale, AZ, 14 Nov 00.

11-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at USC Ingleside Hospital, Rosemead, CA, 9 Nov 00.

10-00 "Newer Antipsychotics: Approaches to Treatment Refractory Patients." Presented at 2000 MIRECC Retreat, Los Angeles, CA, 25 Oct 00.

10-00 "Weight Gain and Atypical Antipsychotic Medications: The TD of the New Millennium?" Presented at MHC of Greater Manchester, Manchester, NH, 12 Oct 00.

09-00 "Side Effects of Typical and Atypical Antipsychotic Agents." Presented at the UCLA Medical Plaza, Los Angeles, CA, 11 Sep 00.

09-00 "Safety and Efficacy Among Atypicals." Presented at Sacred Heart Hospital, Spokane, WA, 12 Sep 00

09-00 "Safety and Efficacy Among Atypicals." Presented at Skagit Valley Mental Health, Mt. Vernon, WA, 13 Sep 00.

09-00 "Update on Atypical Antipsychotics." Presented at Porterville Developmental Center, Porterville, CA, 14 Sep 00.

07-00 "Schizophrenia: Treatment with Risperdal." Presented at the Office of Mental Health, New Orleans, LA, 25 Jul 00.

07-00 "Atypicals and Treatment Resistant Schizophrenia." Presented at Loma Linda Behavior Medicine Center, Redlands, CA, 21 Jul 00.

06-00 "Movement Disorders." Presented at Palacio de Exposiciones y Congresos, Seville, Spain, 16 Jun 00.

06-00 "Tools for Assessing Symptoms: Side Effect Scales." Presented at Palacio de Exposiciones y Congresos, Seville, Spain, 17 Jun 00.

05-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at UC Irvine Medical Neuropsychology Center, Orange, CA, 30 May 00.

05-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Dave & Buster's, Orange, CA, 24 May 00.

05-00 "The Side Effects of Antipsychotic Compounds." Presented at Kaiser Permanente, Fontana, CA, 17 May 00.

04-00 "Atypical Antipsychotics" Presented at Riverside County Inpatient, Riverside, CA, 27 Apr 00.

03-00 "The Novel Antipsychotics." Presented at Loma Linda University, Loma Linda, CA, 29 Mar 00.

03-00 "The Cardiovascular Liabilities of the Atypical Antipsychotics: The Next 'Big' Thing." Presented at Grand Rounds, University of Hawaii, 24 Mar 00.

03-00 "The New Antipsychotic Compounds Really 'New'?" Presented at Grand Rounds, Contra Costa County Regional Medical Center, Martinez, CA, 14 Mar 00.

03-00 "Treatment Refractory Schizophrenia: Is there a rational approach?" Presented at American Psychiatric Association & Nevada Association of Psychiatric Physicians, Las Vegas, NV, Sat, 4 Mar 00.

02-00 "The Use of Risperidone in Acutely Psychotic Patients." Presented at Italian Society of Psychopathology (V SOPSI Congress), Rome, Italy, 23 Feb 00.

02-00 "The Differential Toxicities Among the Atypical Antipsychotics." Presented at Grand Rounds, Cedars Sinai Medical Center, Los Angeles, CA, 17 Feb 00.

12-99 Visiting Scholar-numerous presentations, Presented at University of Arkansas, Little Rock, AR, 5-8 Dec 99

11-99 "The Novel Antipsychotic Medications." Presented at Anaheim, CA, 12 Nov 99.

11-99 "The Side Effects of Antipsychotic Compounds." Presented at University of Kansas Medical Center, Kansas City, MO, 5 Nov 99.

11-99 "Atypicals Antipsychotics: Efficacy and Side Effects." Presented at The American Restaurant, Kansas City, MO, 4 Nov 99.

11-99 "Side Effects of Antipsychiatric Compounds." Presented at Colmery O'Neil V A M C, Topeka, KS, 4 Nov 99.

11-99 "The Side Effects of Antipsychotic Compounds." Presented at Western Missouri Mental Health South Auditorium, Kansas City, MO, 4 Nov 99.

10-99 "Is Clozaril still relevant?" Presented at Atascadero State Hospital, San Luis Obispo, CA, 14 Oct 99.

10-99 "Interested in Geriatric population & Economics of the drugs." Presented at Grand Rounds, Loma Linda University, Loma Linda, CA, 8 Oct 99.

09-99 "Side Effects of Atypical Antipsychotics: What can we expect in the short and long term?" Presented at Riverside, CA, 30 Sep 99.

09-99 "New Treatment Options in the Acute Management of Psychosis." Presented at New York, NY, 26 Sep 99.

08-99 "How to Choose the Correct Medication Regimen for the Treatment of Psychotic Manifestations." Presented at Lanterman Developmental Center, Pomona, CA, 26 Aug 99.

07-99 "Schizophrenia and Overview Movement Disorders." Presented at UCLA School of Nursing, Westwood, CA, 26 Jul 99.

07-99 "New and Novel Antipsychotics." Presented at Fairview Developmental Center, Costa Mesa, CA, 15 July 99.

06-99 "Schizophrenia-Current and New Treatment Trends." Presented at San Joaquin County Mental Health Services, Sacramento, CA, 24 Jun 99.

05-99 "Research Experience with the Newer Neuroleptics-Grand Rounds." Presented at Kaiser, San Francisco, CA, 25 May 99.

05-99 "New Treatment Options in the Acute Management of Psychosis." Presented at Boston Marriott Long Wharf, Boston, MA, 22 May 99.

05-99 "The Neurophysiology of Schizophrenia: Focus on the action of the Novel Antipsychotics." Presented at Kaiser, Woodland Hills, CA, 12 May 99.

04-99 "The New Generation of Antipsychotic Medications." Presented at Kaiser Sunset Family Practice, Los Angeles, CA, 26 Apr 99.

04-99 "Relative Efficacies and Toxicities of Risperidone and Olanzapine." Presented at Leeds, England, United Kingdom, 9 Apr 99.

04-99 "Relative Efficacies and Toxicities of Risperidone and Olanzapine." Presented at Southampton, England, United Kingdom, 8 Apr 99.

04-99 "The Neurophysiology of Schizophrenia: Focus on the Action of the Novel Antipsychotics." Presented at The Schizophrenic Patient: Profiles, Diagnosis and Treatment Conference, Loma Linda University, Loma Linda, CA, 7 Apr 99.

03-99 "Pharmacological Bases for the Putative Neurocognitive Enhancing Impact of Atypical Antipsychotic Agents." Presented at Neurocognitive Impairment in Schizophrenic and Alzheimer's Disorders: Therapeutic Approaches Workshop, International Academy for Biomedical and Drug Research, Paris, FR, 12-13 Mar 99.

02-99 "Antipsychotic Toxicity in the Elderly." Presented at 9th Annual Geriatric Psychiatry Conference, Dallas, TX, 13 Feb 99.

02-99 "Typical and Atypical Neuroleptics: A Geropsychiatric Perspective." Presented at 9th Annual Geriatric Psychiatry Conference, Dallas, TX, 13 Feb 99.

02-99 "Somatic Treatments of Psychotic Disorders" Given with course entitled "Recovery from Madness", Alex Kopelowicz, MD and Robert Liberman, MD--Course Chairs.

02-99 "The Comparative Toxicities of the New Antipsychotic Medications." Presented at Harbor UCLA, Torrance, CA, 2 Feb 99.

01-99 "The Treatment of Schizophrenia at the Turn of the Millennium: What Have We Learned?" Presented to local lay chapter of the California Alliance for the Mentally Ill, UCLA Medical Plaza, Los Angeles, CA, 14 Jan 99.

01-99 "Treatment Refractory Schizophrenia: The Role of the "New" Antipsychotic Compounds" Presented at Grand Rounds, UCI Medical Center, Irvine, CA, 5 Jan 99.

11-98 "Treatment of Schizophrenia." Presented at Grand Rounds, UC Davis Medical Center, Sacramento, CA, 11 Nov 98.

11-98 "Atypicals and Side Effects." Presented at Sutter Family Practice Residency Program, Sacramento, CA, 11 Nov 98.

11-98 "Treatment of Refractory Patients and Partial Response." Presented at Janssen-Cilag SpA Laboratories, Beerse, Belgium, 6 Nov 98.

10-98 "The Role of Novel Antipsychotics in the Control of the Acute Psychotic Symptoms." Presented at the WPA Symposium, Guadalajara, MX, 30 Oct 98.

10-98 "Efficacy of Risperdal and the Atypical Antipsychotics." Presented at Grand Rounds, Porterville State Hospital, Porterville, CA, 21 Oct 98.

10-98 "Treatment of the Refractory Patient." Presented at the Grand Geneva Resort Symposium, Lake Geneva, IL, 3 Oct 98.

10-98 "Treatment Resistant Schizophrenia" Presented at the APA-IPS Symposium, Los Angeles, CA, 2 Oct 98.

09-98 "Treatment Refractory Schizophrenia." Presented at Grand Rounds, Oregon Health Sciences University Department of Psychiatry, 29 Sep 98.

09-98 "The Second Generation of 'Anti-schizophrenic' Drugs." Presented at the 1998 William Rondeau Memorial Lecture, Oregon Health Sciences University Department of Psychiatry, 28 Sep 98.

09-98 "Movement Disorders in Psychiatry." Presented at VA Hines, IL, 23 Sep 98.

09-98 "The Role of Atypical Antipsychotics." Presented at Napa State Hospital, CA, 19 Sep 98.

09-98 "Atypical Antipsychotics and Schizophrenia." Presented at Grand Rounds, Menlo Park VAMC, Menlo Park, CA, 11 Sep 98.

08-98 "New Treatment Options in Schizophrenia." Presented at ComCare, Phoenix, AZ, 18 Aug 98.

07-98 "Schizophrenia Overview and Movement Disorders." Presented at the Neuropsychiatric Nurse Practitioner Program, UCLA School of Nursing, Los Angeles, CA, 27 Jul 98.

07-98 "New Treatment Interventions for Psychotic Disorders." Presented at San Joaquin County Mental Health Services, Stockton, CA, 16 Jul 98.

07-98 "Strategies for Rapidly Controlling Acute Psychotic Symptoms." Presented at Napa State Hospital, Napa, CA, 3 Jul 98.

06-98 "New Directions in Psychosis." Presented at Grand Rounds, San Francisco General Hospital, San Francisco, CA, 26 Jun 98.

06-98 "The Clinical Choice: Is an Algorithm Possible?" Presented at Riverview Hospital, Vancouver, BC, 12 Jun 98.

06-98 "Treatment of Refractory Psychosis: Is There a Rational Approach?" Presented at Riverview Hospital, Vancouver, BC, 12 Jun 98.

06-98 "Drug Treatment of Schizophrenia" Presented as course number 63 with faculty S Marder, J Davis, P Janicak, at the 151st APA Annual Meeting in Toronto, Canada, 2 Jun 98.

05-98 "New Atypical Antipsychotics: Similarities and Differences" Presented via satellite program for Indio and Riverside County Mental Health Inpatient Treatment Facility, Riverside, CA, 28 May 98.

05-98 "New Advances in the Treatment of Schizophrenia" Presented by CME, Inc. at Sheraton Gateway, Los Angeles, CA, 17 May 98.

05-98 "Psychopharmacology Update: A Comparison of Current Antipsychotic Drugs" Presented at Merritheu Memorial Hospital, Martinez, CA, 12 May 98.

05-98 "Management of Cognitive Disruption in Schizophrenia" Presented at University of Illinois at Chicago Symposium in Bloomingdale, IL, 5 May 98.

05-98 "Neurocognition, Schizophrenia, and the Role of the Novel Antipsychotic Medications" Presented at the Panhellenic Psychiatric Congress, Limnos, Greece, 2 May 98.

04-98 "Neurocognitive and Functional Assessment - Rationale for M100907 Superiority" Presented at second Neuropsychiatry Forum of Hoechst Marion Roussel in Bridgewater, NJ, 24 Apr 98.

04-98 "Treatment Resistant Schizophrenia: Is there a Rational Approach?" Presented at Bergen Pines County Hospital, Paramus, NJ, 23 Apr 98.

04-98 "Treatment Resistant Schizophrenia: Is there a Rational Approach?" Presented at Rockland Psychiatric Center, Orangeburg, NY, 22 Apr 98.

04-98 "Update on Anti-psychotic Medications." Presented at Alaska Psychiatric Association's 5th Annual Spring Education Meeting, Anchorage, AK, 18 Apr 98.

03-98 "Psychopharmacology Update: A Comparison of Current Antipsychotic Drugs." Presented at Washington State Psychiatric Association Spring Meeting in Vancouver, BC, 28 Mar 98.

03-98 "Schizophrenia and Cognitive Function - Approaching the New Millennium" Presented at National Schizophrenia Symposium, Scottsdale, AZ, 27 Mar 98.

03-98 "Challenge: Making the most of Therapy with Atypical Antipsychotics" Presented at Eastern State Mental Hospital, Williamsburg, VA, 20 Mar 98.

03-98 "Past, Present and Future of Antipsychotic Drugs" Presented for the Virginia State Psychiatric Society, Richmond, VA, 21 Mar 98.

03-98 "Pharmacologic Impact on Neurocognitive Deficits in Schizophrenia:" Presented at Grand Round, Long Beach VA Medical Center, 4 Mar 98.

02-98 "Neurocognition in Schizophrenia: Magnitude, Functional Correlates and Pharmacologic Responsivity" Presented at USC School of Medicine Grand Rounds, 10 Feb 98.

02-98 "Biological bases for Schizophrenia" Presented at the seminar course for undergraduates Psychiatry 98P Professional Schools Seminar Program, UCLA, CA, 4 Feb 98.

11-97 "The New Generation of Antipsychotic Medications: Similarities and Differences" - Presented at V.A.Psychiatry Service Grand Rounds, Minneapolis, MI, 21 Nov 97.

11-97 "The New Generation of Antipsychotic Medications: Similarities and Differences" - Presented at HCMC Psychiatry Grand Rounds, MI. 21 Nov 97.

11-97 "Neurocognition in Schizophrenia: Magnitude, Functional Correlates, and Pharmacologic Responsivity" Presented at the Atascadero State Hospital, Atascadero, CA, 19 Nov 97.

11-97 "Pharmacologic Approach to Chronic and Treatment Refractory Schizophrenia" Presented at the Vancouver BCPA Conference, in Vancouver, Canada, 15 Nov 97.

11-97 "New Serotonin/Dopamine Antagonist" - Presented for the Loma Linda Psychiatric Residency Program, Loma Linda, CA, 14 Nov 97

11-97 "The Role of New Generation Antipsychotics in Treatment-Resistant Schizophrenia" - Presented in Grand Rounds at The Chicago Medical School Department of Psychiatry and Behavioral Sciences, Chicago, IL, 6 Nov 97.

10-97 "Beyond Conventional Symptoms" - Presented in Riyadh, Saudi Arabia, 20 Oct 97.

10-97 "Neurocognitive Changes in Schizophrenia" Clinical Pertinence and Impact of Pharmacotherapy" - Presented in Grand Rounds at the University of Nebraska Medical Center, Omaha, NE, 15 Oct 97.

09-97 "Treatment Resistance in Psychosis"- Presented at the Annual Meeting of the Huron Valley Medical Center in in Ypsilanti, MI, 24 Sep 97.

09-97 "Toxic Side Effects of Antipsychotic Medications - Focus on Neuromotor Syndromes" Presented at The Fall 1997 Symposium of Charter Behavioral Health Systems of New England, Nashua, New Hampshire, 20 Sep 97.

09-97 "Risperidone: Efficacy Beyond Conventional Symptoms" Presented at the 10th Annual Meeting of European College of Neuropsychopharmacology, Vienna, Austria, 15 Sep 97.

09-97 "Schizophrenia, Neurocognition, and Antipsychotic Meds" Presented in Grand Rounds at Oregon Health Science University, 9 Sep 97.

09-97 "Past, Present and Future of Antipsychotics" Presented at the Mendota Mental Health Institute Conference Center, Madison, WI, 29 Aug 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in East Midlands, England, 19 Jun 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in East Kilbride, England, 18 Jun 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in Aberdeen, Scotland, 17 Jun 97.

06-97 "Antipsychotics: The Evidence from Experience" Presented at the Janssen Research Foundation in Beerse, Belgium, 16 Jun 97.

06-97 "Atypical Neuroleptics: Newer Antipsychotics" Presented at the Northampton VA Medical Center, Northampton, MA, 4 Jun 97.

05-97 "Beyond Conventional Symptoms: Focus on Risperidone" Presented in Grand Rounds at Vanderbilt University Medical Center, Nashville, TN, 27 May 97.

05-97 "Psychopharmacology in the Geriatric Patient: Utility and Limitations" Presented at the California Society of Internal Medicine annual meeting, San Diego, CA, 24 May 97.

05-97 "The Recognition and Management of Side Effects of Typical and Atypical Neuroleptics" Presented as course number 54 with faculty SR Marder, J Davis, G Simpson, P Janicak at the 150th APA Annual Meeting, San Diego, CA, 17-22 May 97.

05-97 "Overview of Treatment of Psychosis with New Atypical Antipsychotic Medications" Presented at the Psychiatric Institute, Washington, DC, 16 May 97.

05-97 "Overview of Treatment of Psychosis with New Atypical Antipsychotic Medications" Presented at the Commission on Mental Health, Washington, DC, 15 May 97.

05-97 "Practical Applications in Atypical Antipsychotics: Clients with Movement Disorders" Presented at Cambridge Hospital, Boston, MA, 14 May 97.

05-97 "The Newer Antipsychotics: Differences and Applications" Presented at Butler Hospital, Providence, RI, 13 May 97.

04-97 "Risperidone and Neurocognition". Presented at the Annual Meeting of the Dutch Psychiatric Society, Amsterdam, Netherlands, 18 Apr 97.

04-97 "Clozapine vs. Haloperidol: Drug Intolerance in a Controlled Six Month Trial" Presented at the International Congress on Schizophrenia Research, Colorado Springs, CO, 14 Apr 97.

04-97 "Antipsychotic Drug Side-Effects: Objective and Subjective". Presented at the International Congress on Schizophrenia Research, Colorado Springs, CO, 14 Apr 97.

03-97 "An Update on Atypcial Antipsychotics". Presented in Hyannis, MA, 28 Mar 97.

03-97 "An Update on Atypical Antipsychotics". Presented in New Bedford, MA, 27 Mar 97.

03-97 "The Management of Acute Exacerbations in Chronic Schizophrenia". Presented at Evidence From Experience, Lisbon, Portugal, 21 Mar 97.

03-97 "Beyond the Conventional Symptoms". Presented at Evidence From Experience, Lisbon, Portugal, 21 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Beijing, China, 17 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Nanjing, China, 15 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Shanghai, China, 14 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Wuhan, China, 12 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Guangzhou, China, 11 Mar 97.

01-97 "Rational Approach to Antipsychotic Medications and Patient Selection". Presented at the Midwinter Program for Psychiatrists, Lake Tahoe, NV, 28 Jan 97.

01-97 "Current Therapy Options: Efficacy and Side Effects". Presented at the Reintegration: Therapeutic Horizons for Psychotic Disorders Symposium in Salt Lake City, UT, 25 Jan 97.

01-97 "Issues in Diagnosis of Schizophrenia". Presented at the Reintegration: Therapeutic Horizons for Psychotic Disorders Symposium in Salt Lake City, UT, 25 Jan 97.

12-96 "The New Generation of Antipsychotic Medications: Similarities & Differences". Presented to the Hawaii Psychiatric Medical Association, Waikiki, HI, 3 Dec 96.

12-96 "The New Generation of Antipsychotic Medications: Similarities & Differences". Presented at Hawaii State Hospital, Kaneohe, HI, 2 Dec 96.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Newcastle, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Glasgow, Scotland.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Birmingham, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Manchester, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented at Kyoto Prefectural University, Kyoto, Japan.

11-96 "Risperidone: The Controlled Clinical Experience". Presented at Hiroshima University, Hiroshima, Japan.

11-96 "Treatment Resistant Schizophrenia: Is There a Rational Approach?" Presented in Kurashiki (Okayama City), Japan.

08-96 "New Solutions to Treatment Resistant Schizophrenia". Presented at the 10th World Congress of Psychiatry, Madrid, Spain, 23 Aug 96.

07-96 "Critical Issues in Psychoses: Dementia, First-Break Patients, Refractory Cases, and Pharmacoeconomics of Schizophrenia". A CME presentation, Costa Mesa, CA.

06-96 "Critical Issues in Psychoses: Dementia, First-Break Patients, Refractory Cases, and Pharmacoeconomics of Schizophrenia". A CME presentation, San Francisco, CA.

06-96 "The New Generation of Antipsychotic Medications: How Are They Different?". A CME presentation, Staunton, VA.

05-96 "Treatment Resistant Schizophrenia" an industry-sponsored symposium presented at the 149th APA Annual Meeting, New York, NY, May 4-9, 1996.

05-96 "The Recognition and Management of Side Effects of Typical and Atypical Neuroleptics" Presented as course number 61 with faculty SR Marder, J Davis, G Simpson, P Janicak at the 149th APA Annual Meeting, New York, NY, May 4-9, 1996.

03-96 "Treatment Resistant Schizophrenia: Is There a Rational Approach?" Presented at Evolving Attitudes Across the Spectrum of Schizophrenia, Amsterdam, Netherlands.

03-96 "The Natural History of the 'Schizophrenias'". Presented at Evolving Attitudes Across the Spectrum of Schizophrenia, Amsterdam, Netherlands.

03-96 "Update on New Antipsychotic Medications". Presented at University of California, Davis, Davis, CA.

03-96 "Special Populations with Psychoses: First Break Patients, Adolescents and Geriatric Patients". A CME presentation, Long Beach, CA.

02-96 "Psychopharmacology in the Elderly: Cognition and Psychosis". Presented at the Area 7 Symposium, Las Vegas, NV.

02-96 "Side Effects of Antipsychotics: Recognition and Treatment". Presented at Grand Rounds, Stanford University Medical Center, Palo Alto, CA.

01-96 "The History and Current Status of Antipsychotic Drug Development". Presented at Grand Rounds, The Palos Verdes Regional Psychiatric Hospital, Tucson, AZ.

01-96 "The Risk Benefit Profiles of the Serotonin-Dopamine Antagonists". Presented at the University of Arizona, Tucson, AZ.

12-95 "Rational Approaches to Antipsychotic Pharmacotherapy". Presented at the Quarterly Meeting of the County of San Diego Mental Health Services, San Diego, CA.

11-95 "Special Populations with Psychosis: Adolescents, Geriatrics, and First Break Patients". A CME presentation, Seattle, WA.

11-95 "Special Populations with Psychosis: Adolescents, Geriatrics, and First Break Patients". A CME presentation, San Francisco, CA.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Hirosaki University Department of Neuropsychiatry, Hirosaki University, Hirosaki, Japan.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Akita University School of Medicine Department of Psychiatry, Akita University, Akita, Japan.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Hokkaido University Department of Psychiatry, Hokkaido University, Hokkaido, Japan.

10-95 "Polypharmacy in the Treatment of Psychosis: Is There a Rational Approach?" presented at the SinYang Park Hotel, KwangJu, Korea.

10-95 "Polypharmacy in the Treatment of Psychosis: Is There a Rational Approach?" presented at the KwangJu Severance Mental Hospital, KwangJu, Korea.

10-95 "Updáte on Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Meeting of the Korean Neuropsychiatric Association at the Seoul Education Culture Center, Seoul, Korea.

09-95 "Pharmacologic Treatment of Depression" presented to the Quarterly Meeting of the Hawaii Psychiatric Association, Honolulu, Hawaii.

09-95 "Anti-psychotic Medications & Patient Selection: Is There a Rational Approach?" presented to the Hawaii Medical Association at the University of Hawaii, Honolulu, Hawaii.

08-95 "Side Effects of Antipsychotic Medications" presented at the Quarterly Meeting of the Memphis Psychiatric Association, Memphis, TN.

07-95 "Polypharmacy: When is it Reasonable?" Grand Rounds, Alameda County Psychiatric Hospital, Alameda, CA.

07-95 "Behavioral Skill Training in Schizophrenia: Utility and Limitation" Grand Rounds, Atascadero State Hospital, Atascadero, CA.

06-95 "Side Effects of Antipsychotic Medications" Grand Rounds, Loma Linda VA Hospital, Loma Linda, CA.

06-95 "The Treatment of Psychosis in the Elderly" Los Encinas Hospital Annual Symposium, Pasadena, CA.

06-95 "Update on the New Antipsychotic Medications" presented to the Annual Meeting of the California Department of Corrections Psychiatrists, Diamond Bar, CA.

05-95 "How to do research without an NIMH grant" presented at the 148th Annual Meeting of the American Psychiatric Association, Miami, FL, 20-25 May 95.

05-95 "The recognition and management of the side effects of typical and atypical neuroleptics" presented as Course 69 with Director SR Marder, and Faculty J Davis, G Simpson, Philip Janicek, and myself, at the 148th APA Annual Meeting, Miami, FL, 20-25 May 95.

05-95 "Behavioral Skills Training in Chronic Schizophrenia" presented at the Annual Conference of Western Reserve Psychiatric Hospital, Northfield, OH, 5 May 95.

03-95 "Dopaminergic Modulation of Cigarette Smoking" presented at the Society for Research on Nicotine and Tobacco with Murray E Jarvik, MD, PhD and Nicholas H Caskey, PhD, San Diego, CA.

03-95 "The Safety and Efficacy of Serotonin-Dopamine Antagonists" a Continuing Medical Education presentation, St. Louis, MO.

03-95 "The Safety and Efficacy of Serotonin-Dopamine Antagonists" a Continuing Medical Education presentation, Philadelphia, PA.

02-95 "The Next Generation of Antipsychotic Medications" presented at Grand Rounds, Veterans Affairs Hospital, Tuskegee, AL.

11-94 "Dosing Strategies with Antipsychotic Compounds: Conventional, SDAs, and Atypicals" presented at the Fall Symposium of New Approaches to Treating Schizophrenia, Chicago, IL, 12 Nov 94.

10-94 "Risperidone: Is It Really Different?" presented at the Fall Conference of the California Alliance For the Mentally Ill, San Francisco, CA, 29 Oct 94.

05-94 "The recognition and management of the side effects of typical and atypical neuroleptics" presented as Course 71 with Director SR Marder, and Faculty J Davis, G Simpson, Philip Janicek, and myself, at the 147th APA Annual Meeting, Philadelphia, PA, 24 May 94.

05-94 "Dementia and Movement Disorders in the Elderly," presented as Course 6 with Director JL Cummings, and Faculty WE Reichman, D Sultzer, and myself, at the 147th APA Annual Meeting, Philadelphia, PA, 20 May 94.

04-94 "Risperidone, is it really different?" presented at a Stanford University sponsored symposium on the treatment of schizophrenia Palo Alto, CA.

03-94 "The New Atypical Antipsychotics--Focus on Risperidone" presented to the Utah State Alliance for the Mentally Ill, Salt Lake City, Utah.

02-94 "The New Atypical Antipsychotics--Focus on Risperidone" presented to the Washington State mental health workers (psychiatrists and pharmacists), Seattle, WA.

01-94 "The Real Cost of Neuroleptic Treatments" presented to the California State Legislature, Sacramento, CA.

01-94 "The Rational Use of Neuroleptics" presented at the annual educational meeting of the Los Angeles Chapter of Family Practioners, Santa Monica, CA.

10-93 "The Therapeutic Window--The Role of Subjective Experiences" presented at the Quarterly Meeting of the Royal College of Psychiatrists in London, England.

05-93 "Optimum Dosing in Maintenance Treatment." Marder SR, Van Putten T, Wirshing WC, Lebell MB, McKenzie J, Johnston-Cronk K, presented at the 146th APA Annual

Meeting, San Francisco, CA, 26 May 93. In: 1993 CME Syllabus & Proceedings Summary, p. 238. (No. 87B)

05-93 "Combined Skills Training and Early Intervention." Marder SR, Wirshing WC, Van Putten T, Eckman TA, Liberman RP, presented at the 146th APA Annual Meeting, San Francisco, CA, 24 May 93. In: 1993 CME Syllabus & Proceedings Summary, p. 156. (No. 28D)

05-93 "Clinical Use of Neuroleptic Plasma Levels." presented at the 146th APA Annual Meeting, San Francisco, CA, 25 May 93.

05-93 "Dementia and Movement Disorders in the Elderly," presented as Course 2 with Director JL Cummings, and Faculty WE Reichman and myself, at the 146th APA Annual Meeting, San Francisco, CA, 22 May 93.

01-93 "Hyperkinetic Syndromes in the Elderly" presented at the Geriatric Supercourse in Marina del Rey, CA, 20 Jan 93.

11-92 "Clinical Consequences of Akinesia and Akathisia", presented as first author with T Van Putten and SR Marder at the Association of European Psychiatrists Congress, Barcelona, Spain, 5 Nov 92.

10-92 "The New Atypical Antipsychotics", presented to the South Coast Chapter of the Alliance for the Mentally Ill, Torrance, CA.

06-92 "Impact of Public Opinion and News Media on Psychopharmacology in the 1990's", with Louis Jolyon West, MD, at the College of International Neuropsycho-pharmacology Annual Meeting (CINP), 30 Jun 92, Nice, France.

05-92 "Drug-Induced Movement Disorders in the Elderly," presented at the 145th Annual American Psychiatric Association Meeting, Washington, DC.

03-92 "Fluoxetine-Induced Suicidality: Science, Spurious, or Scientology?" presented at the Daniel X. Freedman Journal Club, UCLA.

01-92 "The Placebo-Controlled Treatment of the Schizophrenic Prodrome," Biannual Winter Workshop on Schizophrenia, Badgastein, Austria.

01-92 "Management of the Neuroleptic-Intolerant Patient," presented with D Ames and T Van Putten at UCLA Grand Rounds, Los Angeles, CA.

01-92 "Akathisia with the New Atypical Neuroleptics," presented at Psychiatry Grand Rounds, UCLA-Harbor Medical Center, Torrance, CA.

12-91 "Management of Risk of Rèlapse in Schizophrenia," presented at the Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico.

10-91 "Extrapyramidal Symptoms and the Atypical Antipsychotics," presented to the Southern . California Chapter of the California Alliance for the Mentally Ill, Los Angeles.

06-91 "Neuroleptic-Induced Extrapyramidal Symptoms," presented at the Southern California Psychiatric Society, West Hollywood, CA.

05-91 "Pharmacokinetics of Long-Acting Neuroleptics," presented with SR Marder, T Van Putten, J Hubbard, M Aravagiri, and KK Midha, at the American Psychiatric Association 144th Annual Meeting, New Orleans, LA.

05-91 "Fluphenazine Dose in Chronic Schizophrenia," presented with SR Marder, T Van Putten, M Lebell, J McKenzie, and K Johnston-Cronk, at the American Psychiatric Association Annual Meeting, New Orleans, LA.

05-91 "Early Prediction of Schizophrenic Relapse," presented with SR Marder, T Van Putten, M Lebell, K Johnston-Cronk, and J Mintz, at the American Psychiatric Association Annual Meeting, New Orleans, LA.

04-91 "Instrumental Quantification of Akathisia," presented with T Van Putten, SR Marder, JL Cummings, G Bartzokis, and MA Lee at the International Congress on Schizophrenia Research, Tucson, AZ.

04-91 "Antipsychotic Drugs of the Future: The Legacy of Clozapine," presented at the Annual Meeting of the Southcoast Alliance for the Mentally Ill, Fountain Valley, CA.

02-91 "Free Radicals, Movements Disorders, and their Possible Interrelationship," presented to the College of Pharmacy, University of Saskatchewan, Saskatoon, Canada.

11-90 "Primary and Secondary Effects of the Neuroleptics: An Historical Perspective." California Alliance for the Mentally Ill, Fall Conference, Ventura, CA.

11-90 "Antipsychotic Drugs of the Future: The Legacy of Clozapine." California Alliance for the Mentally Ill, Fall Conference, Ventura, CA.

10-90 "Instrumental Quantification of the Akathisic Liability of Clozapine." 2nd Annual NARSAD Scientific Symposium, Washington, DC.

06-90 "Instrumental Quantification of the Akathisic Liability of Clozapine." Regional Meeting of NARSAD Supporters, Pasadena, CA.

02-90 "Instrumentation of Drug-Induced Movement Disorders." Neurology Grand Rounds, West LA VAMC, Los Angeles, CA.

02-90 "Functional Versus Organic Psychoses." Psychiatry Grand Rounds, UCLA Harbor Medical Center, Torrance.

10-89 "Use of Quantitative Instruments in the Assessment of Neuroleptic-Induced Movement Disorders." Presented to regional representatives of NARSAD.

04-89 "Management of Risk of Relapse in Schizophrenia. "The Annual Spring Scientific Meeting of the Southern California Psychiatric Society, Hollywood, CA.

03-89 "Quantitative Approaches to Drug-Induced Movement Syndromes." Medical Staff of Camarillo State Medical Facility, Camarillo, CA.

01-89 "Social Skills Training in the Chronic Schizophrenic: A Workshop." 2nd Annual Winter Conference of the American Assn. of Community Psychiatrists, Charleston, SC.

11-88 "Instrumentation of Drug-Induced Movement Disorders." Presented to California state legislators, their aides, and advocates of national mental health groups (NAMI and NARSAD).

08-88 "Classical Cases in Schizophrenia", with JA Talbot, MD, Professor and Chair, Department of Psychiatry, University of Maryland. Program produced with an educational grant from Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.

08-88 "Drug-Induced Extrapyramidal Syndromes in Psychiatric Patients." Texas State Hospital medical staff, Big Springs, TX.

06-88 "Role of Psychopharmacology in the Treatment of the Chronic Mental Patient." Department of Corrections at the California Medical Facility in Vacaville, CA.

04-88 "Psychosocial Rehabilitative Treatment of the Chronic Schizophrenic Patient." Presented to the staff of the Roseburg VA Medical Center, Roseburg, OR.

03-88 "Behavioral Rehabilitation of the Chronic Mental Patient." Workshop presented at the First Annual Winter Conference of the American Society of Community Psychiatrists, Colorado Springs, CO.

01-88 "Electromechanical Characteristics of Tardive Dyskinesia." The Biannual Winter Workshop on Schizophrenia, Badgastein, Austria.

10-87 "Medication/Consent." Symposium with Drs. R Liberman, J Vaccaro, and J Kane, presented at the 1987 Institute on Hospital and Community Psychiatry, Boston, MA.

09-87 "Medication Management and Patient Education." Annual Department of Mental Health Conference at Michigan State University, East Lansing, MI.

05-87 "Quantitative Assessment of Extrapyramidal Symptoms and Involuntary Movement," presented at a symposium on Acute and Chronic Extrapyramidal Symptoms and Tardive Dyskinesia, at the Annual Meeting of the APA, Chicago, IL.

10-86 "The Affective Disorders Spectrum," presented to the Graduate School of Psychology of the California Lutheran College in Thousand Oaks, CA.

04-86 "Unique Issues of Older Adults with Chronic Mental Health Problems, Focus on Schizophrenia." Mental Health and Aging Conference in Los Angeles, CA.

02-86 "The Geriatric Patient with Cardiac and Psychiatric Problems: Pharmacologic Concerns." VA Nursing Service for their Continuing Education Series in Los Angeles, CA.

10-85 "Psychopharmacologic Treatment of the Geriatric Population," presented to the Psychology interns at the VA as part of their Continuing Education Series in Los Angeles, CA.

Publications

Articles

98. Murphy D, Bailey K, Stone M, Wirshing WC. Addictive potential of quetiapine. *Am J Psychiatry.* 2008 Jul;165(7):918.
97. Tabibian JH, Wirshing DA, Pierre JM, Guzik LH, Kisicki MD, Danovich I, Mena SJ, Wirshing WC. Hepatitis B and C among veterans on a psychiatric ward. *Dig Dis Sci.* 2008 Jun;53(6):1693-8.
96. Pierre JM, Peloian JH, Wirshing DA, Wirshing WC, Marder SR. A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. *J Clin Psychiatry.* 2007 May;68(5):705-10.
95. Buckley PF, Wirshing DA, Buchan P, Pierre JM, Resinck SA, Wirshing WC. Lack of insight in schizophrenia: impact on treatment adherence. CNS Drugs. 2007;21(2):129-41.
94. Wirshing DA, Pierre JM, Wirshing WC, Guzik LH, Resinck SA, Goldstein D, Zorick TS: Community re-entry program training module for schizophrenic inpatients improves treatment outcomes. *Schizophr Res.* 2006 Oct;87(1-3):338-9.
93. Meyer J, Loh C, Leckband SG, Boyd JA, Wirshing WC, Pierre JM, Wirshing DA: Prevalence of the metabolic syndrome in patients with schizophrenia. *Journal of Psychiatric Practice* 2006; 12(1): 6-10
92. Wirshing DA, Smith RA, Erickson ZD, Mena SJ, Wirshing WC: A wellness class for inpatients with psychotic disorders. *Journal of Psychiatric Practice* 2006; 12(1): 24-29
91. Pierre JM, Peloian J, Wirshing DA, Wirshing WC, Marder SM. A placebo controlled trial of modafinil for negative symptoms in schizophrenia. *Schizophrenia Bulletin* 2005; 31:501
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89. Pierre JM, Wirshing DA, Wirshing WC: High-dose antipsychotics: desperation or data-driven? *Current Psych* 2004, 3(8): 31-37.
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85. Wirshing DA, Danovitch I, Erhart SM, Pierre JM, Wirshing WC. Practical tips to manage common side effects. *Current Psychiatry*, 2003 2(3): 49-57

84. Pierre JM, Wirshing DA, Wirshing WC: "Iatrogenic malingering" in VA substance abuse treatment. *Psychiatric Services*, 2003, 54(2): 253-4

83. Wirshing DA, Wirshing WC: Aripiprazole: a viewpoint. *CNS Drugs*, 2002,16(11): 779-786

82. Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC: The effects of novel antipsychotics on glucose, and lipid levels. *J Clin Psychiatry 2002*; 63: 856-865

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- Pierre JM, Wirshing DA, Wirshing WC: Reply to: In response to Furst et al, "possible association of QTc interval prolongation with co-administration of quetiapine and lovastatin." *Biological Psychiatry* 2002; 52: 911-915.

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Updated—20 Mar 08

William C. Wirshing, M.D. Date

William C. Wirshing, M.D.

Educational and Professional Background

Education
I graduated in 1978 from the College of Engineering at the University of California at Berkeley with highest honors (cumulative G.P.A. 3.93) and a Bachelors of Science degree in Electrical Engineering and Computer Science (minor in bioelectronic systems). During my tenure there, I was elected to membership in the Phi Beta Kappa and Tau Beta Pi honor societies. The former is traditionally reserved only for those pursuing a "liberal" educational experience (e.g., College of Letters and Science) and the latter is the equivalent entity for students in the science-intensive curriculum of the School of Engineering. Although I then began medical school at UCLA almost immediately following my undergraduate studies, my education was interrupted when my youngest brother developed and then succumbed to brain cancer during my first and second years. During several lengthy arranged absences from school in southern California, I assisted my mother in caring for my brother and worked as an engineer in Mountain View (i.e., "Silicon Valley") California through the beginning of my third year at UCLA.

I completed my undergraduate medical schooling ("on time", despite my protracted absences from campus) with a 3.97 GPA and was given the Sandoz award for "Excellence in the Behavioral Sciences" at graduation in 1982. In addition, I was elected to the Alpha Omega Alpha Medical Honor Society at the end of my third year. I remained at UCLA for both my rotating internship during which I focused on internal medicine, neurology, and pediatrics and for my three-year residency training in psychiatry. My final year of residency training I was the Chief Resident in Geropsychiatry at the West Los Angeles Veterans Affairs Medical Center. Over the next two years, I was a Post Doctoral Research Scholar at UCLA, a fellowship position through the National Institute of Mental Health during which I learned and applied clinical research techniques for the study of persons with severe schizophrenia. My mentors were Professors Van Putten, Goldstein, and Marder.

Clinical, Research, and Teaching Background
I remained at both UCLA and the affiliated West Los Angeles Veterans Affairs Medical Center until late in 2006. Over the two decades between 1986 and 2006 though, both my clinical work and research focus remained on the treatment of persons with schizophrenia. I was the Chief of the Schizophrenia Treatment Unit at the VA Medical Center during the vast bulk of this epoch, and was also the Co-Chief of the Schizophrenia Outpatient Research Clinic during the last ten years. Though I rose through the traditional academic ranks at UCLA and even reached the level of full Professor over five years ahead of "schedule", I never lost my fascination with clinical care and never traded it for more administrative tasks as my career wandered through the decades. Since leaving the traditional ranks of academia, I have been able to continue and even expand my dual interests in clinical work and teaching. Over the last year I have been Vice President in charge of research and continuing medical education for Exodus Inc. in Culver City, CA and also Clinical Director of Exodus Real Recovery in Agoura Hills,

CA. In a typical month, I now see approximately 325 new patients; supervise nearly a dozen psychology doctoral candidates; and teach over a dozen nursing, social work, and nurse practitioner students. Over the course of my career, I have taken care of over twenty five thousand patients, the vast majority of which have suffered from one or another psychotic illness.

As is usual among clinical academicians, my patient care tasks and research interests dovetailed consistently and have always taken place in a setting with medical trainees at every level of experience. Teaching these persons over the years has been the third major leg of my vocational life. Unlike most of my academic colleagues, I never thought of these teaching duties as on obligation to be tolerated and where possible shunted to my younger colleagues. In fact, it generally occupied the top spot in my personal emotional ranking of our traditional tasks (i.e., teaching, research, and patient care). My teaching has been honored over the years with several awards from both my students and colleagues, including 2006 when I was again nominated for the Golden Apple Award by the graduating medical school class (the highest teaching accolade in the School of Medicine). I currently give over 125 routine lectures per year at my various work sites.

Within the context of these various positions and responsibilities, I have been able to experience, study, and then teach others about the care of seriously mentally ill patients. While I have been most consistently compelled by and fascinated with the prototypic psychotic illness schizophrenia, persons with bipolar illness (i.e., "manic depressive disorder") have taken up a close second place over the years. Like any academician in my area, I have sought and received grants to continue my studies and have published in the peer reviewed literature (with the substantial aide of my colleagues and assistants—see my attached CV for the details). I believe that I have been fortunate in the extreme to have had these professional opportunities. They have permitted me to live an enviable work life that I was never able to master and was therefore neither predictable nor routine.

Experience With Industry

These sundry positions also brought me into contact with the pharmaceutical industry that coincidentally became increasingly interested in the treatment of psychotic persons at the very onset of my career in the mid 1980's. This time marked the beginning of the second significant epoch of pharmacologic treatment of psychosis (The first one having begun in the early 1950's but which had plateaued by the late 1960's). This period saw the development, testing, and subsequent marketing of what came to be known as the "Second Generation" or "Atypical" antipsychotic compounds. Though not truly revolutionary or even novel per se (see below), they did constitute a significant advance in many, though not all, aspects over the older medications. This mutual interest in the treatment of psychosis allowed me to "test" potential medications in my patients under controlled protocol conditions from the beginning of their development by industry. Although not every medication that we tested over the years survived the gauntlet of clinical testing, we were able to test every medication that did receive the approval to market by the Food and Drug Administration.

The approval process for medications is a lengthy one that has become increasingly burdened by regulation and requirements over the years. As a consequence, it can take years for a given compound to move from first testing in patients to full marketing approval. Among the medications that we tested and studied that went on to receive approval have been risperidone (approval 1994), olanzapine (1996), ziprazadone (2000), aripiprazole (2002), and quetiapine (1997). The early and prolonged nature of this experience allowed us to develop a clinical knowledge of the real world effects of these drugs that was often at the very forefront of the entire field. As is usual with pharmacologic compounds, our novel discoveries and observations generally involved the toxic effects rather than the therapeutic impacts of the drugs.

In the early to mid 1990's we were among the very first to report on the curious metabolic effects. In particular, we noticed that many of our patients gained weight when first begun on these drugs and at a rate that was, on occasion, singular in our experience. We also noted that these patients soon began to suffer the usual downstream consequences of gaining weight (e.g., glucose intolerance, frank diabetes, and even severe hyperglycemia with resultant hyperosmolar coma). As is customary in the academic world, we described our experience in the peer reviewed literature and reported it at any number of scientific meetings. In addition, though, we worked with industry to extend, understand, and hopefully find ways to remediate these various toxicities. The increasingly high economic stakes of the field sometimes lead those in industry to confuse the message and the messenger (at least from my perspective). As a consequence, our relationships would, or at least could, sour and blossom suddenly, depending on the details of our latest report. As one might expect, our observations and conclusions were not infrequently challenged by one company only to be embraced and promoted by its competitor.

I did not have any direct dealings with Imperial Chemical Industries, as Zeneca was called prior to their name change, while they were developing their antipsychotic compound ICI 204636 (quetiapine's "name" prior to its receiving a formal designation by the nomenclature committee). I was, however, very familiar with the published preclinical and clinical literature on the drug in the 1980's and early 1990's. Immediately after launch in the United States in 1997, I began to lecture for the company and started negotiations with them to perform a high dose clinical trial in a subpopulation of persons with schizophrenia whose symptoms were unresponsive to other available antipsychotic compounds. While a variety of regulatory, legal, and logistical impediments conspired to ultimately thwart my hopes for such a trial, our interest in and experience with high dose treatment did result in a single publication (Pierre, et al, 2005). I continued to lecture and provide ad hoc consultation at the company's request (the last time was August of 2008), though the frequency of these interactions has diminished considerably over time. I have, however, kept them apprised of my concerns about and observation of their drug, including this last spring when I sent them a prepublication copy of a letter that was recently published in the American Journal of Psychiatry (Murphy, et al, 2008). Through out this lengthy association, I would characterize our relationship as mutually respectful and professionally cordial. In notable contrast to some of their corporate peers in the pharmaceutical industry, Astra Zeneca never treated

me dismissively or disrespectfully simply because I would describe an observed toxicity or express an unflattering opinion about quetiapine's clinical characteristics.

History of Antipsychotic Drugs

It can, I think, be persuasively argued that the origins of the "modern" biological theories of psychiatry can be traced directly to the serendipitous discovery of antipsychotic medications in the early 1950's. During that epoch, a trio of French physicians (psychiatrists Delay and Deniker and neurosurgeon Henri Laborit) determined that the experimental Rhône-Poulenc compound RP 4609 (i.e., chlorpromazine or "Thorazine") had a singular power to reduce psychotic symptoms in chronically and severely ill patients with schizophrenia. Schizophrenia is the prototypic psychotic illness that consistently afflicts 0.9 percent of the population, is life long and incurable, runs in families, and generally has its origins in late adolescence or early adulthood. It is further the exclusive province of the human animal—even our closest primate relatives do not develop schizophrenia. It would be difficult to overstate the magnitude of this pharmacologic discovery, coming as it did at a time when wet wraps, hydrotherapy, and frontal lobotomies were the only "effective" palliative treatments. The pharmacologic efficacy of chlorpromazine, though, came with an apparently obligatory neurotoxicity that developed after about two weeks of treatment. This neurotoxicity, which came to be called extrapyramidal symptoms or EPS, included parkinsonism (i.e., slowed movements and mentation, a specific tremor, and muscular rigidity), akathisia (i.e., an intensely dsyphoric sense of restlessness), and dystonia (i.e., sustained, uncontrollable, and functionally disruptive muscular contractions). While these acute EPS could be dramatic and overwhelming, they were transitory and would eventually disappear once the offending agent was discontinued. Unfortunately, there also developed a later, sometimes grotesque disorder of excessive motor movement that was termed tardive dyskinesia (literally "late bad movement"). It was eventually observed that this tardive dyskinesia (TD) would accrue with each passing year of cumulative exposure to the medication at a rate of three to five percent of the treated population per annum. More ominous still was the observation that unlike acute EPS, TD proved to be lifelong and irreversible in a large number of those afflicted (circa 50%), even if the causal agent were permanently discontinued. These neurotoxicities were so consistent, predictable, and uniform that they eventually came to be seen as the hallmark of this class of medications which were termed "neuroleptics" (i.e., "to seize the neuron"). In other words, these antipsychotic medications were defined quite literally by the toxicities they produced.

Though these EPS were the clinical bane of antipsychotic compounds, they were a crucially exploitable characteristic for drug developers. Because there is no animal model for schizophrenia per se, it is not possible to screen potential molecular candidates for this property. There are, however, many excellent animal models for EPS and related behavioral toxicities. It was thus possible to search for potential antipsychotic compounds by simply screening for extrapyramidal liability in one or another of these models. It should come as no surprise then that all antipsychotic medications shared the neurotoxic characteristic—it was this toxicity that allowed them to be discovered in the first place. Arvid Carlsson and colleagues detailed the mechanisms that are believed to underlie this duality (i.e., antipsychotic potential and neurotoxic liability) in the early

1960's. In a series of clever animal experiments and brilliant deductions he proposed that antipsychotics exerted both effects by binding to and blocking dopamine receptors (more specifically the D2 receptor subtype) in the brain. It is of historical note that he shared psychiatry's first Nobel Prize for Medicine in 2000 for these discoveries.

As an ultimate consequence of this process, there came to clinical market an array of often times chemically dissimilar compounds that had equipotent antipsychotic efficacy and were uniformly neurotoxic. They did, of course, vary in a number of secondary characteristics (e.g., anticholinergic potency, sedative potential, tendency to induce orthostatic hypotension, etc.), but their primary efficacies and core toxicities were effectively equivalent. It is important to note that these dopamine receptors are important not only in motor control and psychotic symptoms, but they are also crucial in mediating reward learning. Thus, any antipsychotic molecule that blocks these dopamine receptors will attenuate and possibly destroy an animal's (or a person's) ability to normally experience pleasure. In clinical practice these drugs are notoriously dysphorogenic and exceedingly difficult to subjectively tolerate.

The singular exception to these generalizations about antipsychotics is the compound clozapine. This molecule is a modified structural analog of the tricyclic antidepressant imipramine (a revolutionarily useful and powerful antidepressant medication that has no antipsychotic power whatsoever) and was synthesized by Sandoz Pharmaceuticals in 1959. Though its road to market was torturously long and marred by a number of tragically toxic detours, it ultimately proved itself to be a truly different antipsychotic. It was eventually shown that clozapine had greater antipsychotic power than conventional neuroleptics (as the rest of the antipsychotic market came to be named) and at ordinary antipsychotic doses it failed to cause the EPS that characterized its conventional counterparts. Clozapine then became the prototypic "atypical" antipsychotic in that it alone was a non-neuroleptic antipsychotic: a drug capable of separating antipsychotic efficacy from neurotoxic liability. While a number of often clever and sometimes even compelling explanations of how clozapine is able to exert these clinical behaviors have been elaborated, none have to date been proven. In addition, though the group of more recently developed and marketed antipsychotics (i.e., risperidone, olanzapine, quetiapine, aripiprazole, and ziprazidone) have claimed kinship to clozapine by usurping its "atypical" label, none has matched clozapine's antipsychotic power and all are variably more neurotoxic. This is not to say that as a "class" they have failed to improve upon the conventional compounds, but only that they have not succeeded in truly inheriting clozapine's legacy.

Quetiapine's Development

Imperial Chemical Industries first elaborated what they designated ICI 204636 in the early 1980's. It is a structural analog of clozapine and technically considered a dibenzothiazepine. Its receptor (i.e., the proteinaceous components on the lipid neural membranes of the central nervous system [CNS]) binding profile indicates that it has weak and easily reversible affinity for the classic D2 receptor that Carlsson identified in 1963. It also binds with weak to moderate intensity to a wide spectrum of other receptors in the CNS, but in a pattern that is really unlike any other antipsychotic compound,

including clozapine, upon which its structure is based. These other binding characteristics are conceptualized to account for quetiapine's observed clinical effects. In brief, they confer on quetiapine: sedation, low EPS liability, minimal impact on prolactin, orthostatic hypotension (i.e., a fall in blood pressure when standing), anticholinergic toxicity (i.e., constipation, dry mouth, blurred vision, memory disturbances, and tachycardia), and weight gain liability. All of these ultimately observed characteristics would be expected based only on the neuromolecular characteristics of quetiapine.

Though the knowledge of quetiapine's unique receptor binding profile allowed for the easy prediction of its pattern of toxicity in humans, its low and weak affinity at the critical D2 receptor posed a challenge for protocol designers during its early years of clinical testing. For all conventional compounds the appropriate dose to achieve optimal antipsychotic activity is exactly the dose that also begins to produce EPS. With an "atypical" drug though, the appropriate dose would be an unknown amount lower. Thus, an early hurdle for quetiapine was determining just where the optimal antipsychotic dose range was located. Ultimately quetiapine's FDA registration trials involved multiple doses (five) of quetiapine over a ten fold dosing range compared to single dose of the reference conventional neuroleptic haloperidol. Despite the methodologic asymmetry of this design that markedly favored quetiapine, it failed to beat its conventional comparator at any dose. In fact, the haloperidol arm was generally slightly better (though not statistically so) than any of the five doses of quetiapine. This pattern of being marginally equal to or slightly inferior to comparator drugs has been repeated numerous times over the years of testing. When AZ attempted to perform a meta-analysis (i.e., combining multiple trials to achieve greater statistical power in an effort to show a small effect that is not apparent in any single study) on its accrued dataset, they discovered this very pattern. This disappointing result prompted the marketing personnel within AZ to "spin" these conclusions by touting that quetiapine had "unsurpassed efficacy". While technically correct from a statistical point of view because no single study had shown that any conventional comparator was statistically superior to quetiapine, such hype is clearly disingenuous sophistry.

When considered across many trials involving schizophrenic subjects, quetiapine has been demonstrated to be about 10-20 percent less effective than standard doses of conventional medications. This was shown most clearly in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that was reported in late 2005. This NIMH funded trial compared four atypical medications (quetiapine, ziprazidone, risperidone, and olanzapine) to a single typical medication (perphenazine) and involved 1460 subjects treated over an 18-month epoch. The primary outcome variable was "time to discontinuation" of the assigned drug. The results revealed that quetiapine was about 20 percent less effective than the conventional agent perphenazine (4.6 vs. 5.6 months) and about 50 percent less effective than olanzapine (9.2 months).

While these efficacy facts were disappointing and clearly contributed to quetiapine's dismal market share when it was first approved for use in 1997, it also suggested to me a tantalizing possibility. Because conventional antipsychotic medications were all

essentially equi-efficacious and seemed to share a single underlying mechanism of action, any drug that had demonstrably less efficacy might possibly work through a dissimilar mechanism. This possibility was a major motivating factor in my wanting to pursue a higher than standard dose experimental trial with the company after the drug was launched. I continue to believe that quetiapine does, in fact work through largely distinct mechanisms. Unfortunately this distinction translates into slightly less pharmacologic power on average than conventional medications. AZ has "oversold" quetiapine's efficacy in their marketing endeavors for years.

Quetiapine's Toxic Metabolic Profile

The dataset that Zeneca had compiled on quetiapine prior to its launch in 1997 clearly indicated that clinically significant weight gain was a common side effect of quetiapine. The data from Zeneca's Phase II/III trials demonstrated a clear dose related impact on weight that compellingly worsened over time. Using the FDA's definition of clinically pertinent weight gain (i.e., a 7% increase), quetiapine routinely impacted over 25 percent of the treated population (somewhat lower for lower doses of quetiapine and somewhat higher with higher quetiapine doses). The average shift in weight was 6.2 lbs over the first six months of treatment and 11 lbs after six months of treatment. This is approximately halfway between the weight gain induced by risperidone and olanzapine—quetiapine's major competitors at launch. Weight gains of this magnitude are impressively large and impact an amazingly large and consistent percentage of patients. Despite these data, which have been available to the company since before launch, the label for quetiapine has never, even to the present day, "warned" of this predictable and serious toxicity. Instead, the label has merely listed in the adverse experiences section that quetiapine is "sometimes associated with increases in body weight". Further, their marketing materials over the years have consistently touted that quetiapine is "weight neutral". This is palpably inappropriate and inadequate at best and deceptively misleading at worst. It is my opinion that this labeling deficiency rises to the legal definition of gross negligence (i.e., "willful disregard for the safety of others"). It is unconscionable that after more than a decade's time that the warnings section is still silent about the single most prominent serious toxic characteristic of the compound.

There are a number of well-known health consequences to increases in adiposity. Among these are increased risks for glucose intolerance and even frank diabetes, increases in total cholesterol and triglycerides in the blood, secondary risks for cardiovascular disease, increased rates of degenerative osteoarthritis, and even increased risks for certain malignancies (e.g., colon cancer). The fact that quetiapine use results in weight gain and therefore causes diabetes in susceptible patients cannot be rationally disputed. This was confirmed by the APA/ADA consensus conference on the metabolic toxicities of the atypical antipsychotics held in 2004. That conference of independent (i.e., non-industry) experts (at which I provided the presentation on the monitoring protocol) concluded that quetiapine use could result in significant weight gain, increased rates of diabetes, and pathologic changes in lipid profiles. Although the current label change implemented in 2007 does direct one to a new section in the adverse events section that documents, to a degree, some of the measured increases in new onset diabetes, it remains inadequate and misleading. Firstly, the "class labeling" warning section on endocrinologic toxicities is

laced with generalities, disclaimers, and distracting verbiage. It fails completely to state the measured increases in new onset diabetes that are specific to quetiapine and that are detailed in the adverse experiences section. Secondly, it fails to make the known connection between increases in adiposity and subsequent changes in glucose regulation. It gives the mistaken impression that the risks of diabetes only apply to a decidedly minor (circa 2-4%) portion of treated patients when, in fact, nearly one third of patients treated with standard doses for as little as a year are at decidedly increased risk of glucose disregulation. The company personnel have opined in depositions that the details of quetiapine's measured risk of diabetes and related endocrinologic disturbances were unknown until the results of these later done studies were completed. Such rhetoric is intellectually and clinically dishonest as it requires one to deny the clinical fact that increases in adiposity that are caused by quetiapine (and were known to the company before launch in 1997) will result in predictable increase in endocrinologic dysfunction. It is axiomatic that increases in obesity will result in subsequent increases in hyperglycemia, frank diabetes, hyperosmolar coma, and even death due to endocrinologic complications. To deny otherwise, as AZ officials continue to do to the present day, is negligently irresponsible.

Additionally, the label is virtually silent (or at least it is decidedly unclear) about quetiapine's ability to induce massive changes in circulating triglycerides and thereby lead to secondary and potentially lethal pancreatitis (i.e., marked inflammation of the pancreatitis). When a person gains significant adiposity, there is a predictable increase in the levels of circulating lipid pools (i.e., triglycerides, VLDL, LDL, etc.) because to body must manage a larger flow of fats from the gut and to and from the tissues. These changes, while potentially of long-term clinical pertinence, are usually of ordinary magnitude. Quetiapine, though, also results in massive acute elevations in triglycerides that can, on occasion, overwhelm the body's fat management system and cause secondary pancreatitis. The precise mechanisms whereby this toxicity is mediated have yet to be elucidated, however, it is likely that interference with one of the early lipid management enzymes in the liver (e.g., lipoprotein lipase A) causes a "backup" of the triglyceride transport vehicle (i.e., chylomicrons) from the gut that leads to the hypertriglyceridemia. This additional metabolic-like toxicity is unrelated to changes in weight, tends to occur during the first several months of treatment, and is markedly more acutely serious than the more pedestrian increases in the sundry lipid pools that predictably follow increases in adiposity. This toxicity has clearly emerged during the post marketing surveillance period, has been reported frequently in the case report literature, and was discussed at length at the consensus conference in 2004.

Addictive Potential

The single most consistent toxic effect of quetiapine is sedation. This property when coupled with quetiapine's low EPS profile has prompted clinicians to use the drug excessively off-label for such conditions as anxiety and insomnia. These characteristics also raise a reasonable concern that quetiapine may have some addictive potential. In fact clinical experience and a number of case reports have suggested that certain patients will abuse, divert for sale, and become physically dependent on quetiapine (Pierre, et al,

2004; Murphy et al, 2008). Despite these facts the label has been virtually silent about this reality.

Off Label Use

Quetiapine has come to dominate the atypical antipsychotic market primarily because it is used excessively off label (current estimates are about two thirds of the prescriptions are off-label). I am of the opinion that primary among the reasons for this disproportionate off label use are the facts that quetiapine is sedating and highly subjectively tolerable and the inaccurate clinical impression that it is also comparatively free of concerning toxicities and devoid of abuse potential. A secondary reason is that quetiapine's share of the on label market is reduced because it is simply not as potent an antipsychotic as other available products. While prescribing a drug for off label use is a common and often clinically reasonable practice, promoting a drug for off label use is illegal. AZ was clearly aware of the excessive off label use of quetiapine over the years. Their officials have stated repeatedly in depositions that AZ endeavored to provide label support of these "passively observed" prescriptive habits by investing heavily in confirmatory studies. Though many such studies were performed, I consider the claim largely dishonest. If true, then it would have been imperative for AZ to study the largest and most excessive off label use, to wit, insomnia. Such a study would have been logistically and economically trivial to perform, at least in comparison to the studies done in mood and psychosis based disorders. There is to date no evidence of any quality that demonstrates that quetiapine decreases sleep latency, increases total sleep time, normalizes sleep architecture, or improves daytime wakefulness. There is, in fact, ample evidence that quetiapine impairs significantly daytime wakefulness. I believe that AZ knew that any real detailed sleep study would ultimately be an indictment of clinical practice and would potentially cut the total use of their product by more than half. It is further my opinion that AZ mischaracterized the true toxic potential of their product and that this behavior has in part prompted clinicians to use their product inappropriately and excessively off label. If clinicians had been aware of the true metabolic toxicities and addictive liabilities of quetiapine then I do not believe that we would have the amount of off label usage we see today. It is my opinion therefore that AZ has been engaged in "indirect" off label marketing. While their behavior may have in fact been technically within the "letter of the law", it was and continues to be irresponsible, improper, and ethically indefensible.

Conclusions/Summary

AZ's marketing of quetiapine has consistently exaggerated the true efficacy of the compound.

AZ has been aware of the true metabolic toxicities of quetiapine since before launch in 1997. Despite this they have engaged in a marketing campaign that has minimized, obfuscated, or frankly denied these metabolic realities. Their product label has been consistently and continuously inadequate in its warnings about the impact on lipid and glucose metabolism, hyperglycemia, and diabetes. Their label continues to be wholly inadequate to the point of being decidedly misleading in its warnings about weight gain.

Additionally, the current label is inadequate regarding quetiapine's ability to markedly disrupt normal lipid metabolism and cause massive hypertriglyceridemia and secondary pancreatitis.

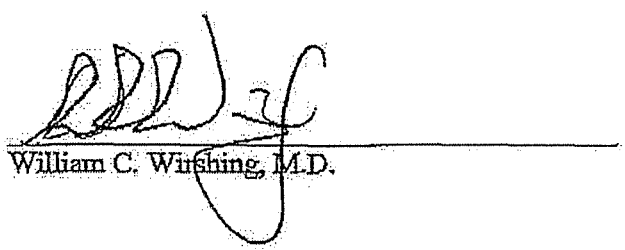
The current label is inadequate in its description about the abuse potential of quetiapine. AZ should have identified and warned of this abuse liability based on the clinical characteristics of quetiapine and the curious and excessive off label use patterns. Further, their tacit acceptance of the excessive use of their product for routine insomnia for the past decade without ever having investigated the effects of their product on sleep, is tantamount to passive marketing for an off label indication. This failure to investigate has been compounded by their insistence that they have behaved responsibly by investing heavily in research to establish on label support for the prescriptive patterns they knew to exist.

AZ's behavior has given prescribing clinicians an inaccurate impression of quetiapine's toxic profile and addictive potential which has robbed physicians of the ability to make informed risk/benefit analysis prior to prescribing quetiapine to a patient. This has led in part to the excessive and inappropriate off label use of the product and to injury and damage to patients who would not have otherwise ever received the medication.

My opinions as stated in this report are based on my education, training, and experience and my review of the relevant literature, internal Astra Zeneca documents, corporate depositions, and public documents and are stated to a reasonable degree of medical probability. It is my understanding that discovery is ongoing and I thus reserve my right to supplement or expound upon my opinions pending review of additional information.

My fees for work in this litigation are $500 per hour.

A list of my testimony for the past 4 years is attached.



William C. Wirshing, M.D.

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prescription or non-prescription (over-the-counter) medications, particularly if you are taking warfarin to thin your blood.

- You should not become pregnant when taking NOLVADEX or during the two months after you stop taking it as NOLVADEX may harm your unborn child. Please contact your doctor for birth control recommendations. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX.

What should I avoid or do while taking NOLVADEX?

- You should contact your doctor immediately if you notice any of the following symptoms. Some of these symptoms may suggest that you are experiencing a rare but serious side effect associated with NOLVADEX (see **"What are the possible side effects of NOLVADEX?"**).
  - — new breast lumps
  - — vaginal bleeding
  - — changes in your menstrual cycle
  - — changes in vaginal discharge
  - — pelvic pain or pressure
  - — swelling or tenderness in your calf
  - — unexplained breathlessness (shortness of breath)
  - — sudden chest pain
  - — coughing up blood
  - — changes in your vision

  If you see a health care professional who is new to you (an emergency room doctor, another doctor in the practice), tell him or her that you take NOLVADEX or have previously taken NOLVADEX.
- Because NOLVADEX may affect how other medicines work, always tell your doctor if you are taking any other prescription or non-prescription (over-the-counter) medicines. Be sure to tell your doctor if you are taking warfarin (Coumadin) to thin your blood.
- You should not become pregnant when taking NOLVADEX or during the 2 months after you stop taking it because NOLVADEX may harm your unborn child. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX. Please talk with your doctor about birth control recommendations. If you are taking NOLVADEX to reduce your risk of getting breast cancer, and you are sexually active, NOLVADEX should be started during your menstrual period. If you have irregular periods, you should have a negative pregnancy test before you start NOLVADEX. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity.
- If you are taking NOLVADEX to reduce your risk of getting breast cancer, you should know that NOLVADEX does not prevent all breast cancers. While you are taking NOLVADEX and after you stop taking NOLVADEX and in keeping with your doctor's recommendation, you should have annual gynecological check-ups which should include breast exams and mammograms. If breast cancer occurs, there is no guarantee that it will be detected at an early stage. That is why it is important to continue with regular check-ups.

What are the possible side effects of NOLVADEX?

Like many medicines, NOLVADEX causes side effects in most patients. The majority of the side effects seen with NOLVADEX have been mild and do not usually cause breast cancer patients to stop taking the medication. In women with breast cancer, withdrawal from NOLVADEX therapy is about 5%. Approximately 15% of women who took NOLVADEX to reduce the chance of getting breast cancer stopped treatment because of side effects.

The most common side effects reported with NOLVADEX are: hot flashes; vaginal discharge or bleeding; and menstrual irregularities (these side effects may be mild or may be a sign of a more serious side effect). Women may experience hair loss, skin rashes (itching or peeling skin) or headaches; or inflammation of the lungs, which may have the same symptoms as pneumonia, such as breathlessness and cough; however, hair loss is uncommon and is usually mild. A rare but serious side effect of NOLVADEX is a blood clot in the veins. Blood clots stop the flow of blood and can cause serious medical problems, disability, or death. Women who take NOLVADEX are at increased risk for developing blood clots in the lungs and legs. Some women may develop more than one blood clot, even if NOLVADEX is stopped. Women may also have complications from treating the clot, such as bleeding from thinning the blood too much. Symptoms of a blood clot in the lungs may include sudden chest pain, shortness of breath or coughing up blood. Symptoms of a blood clot in the legs are pain or swelling in the calves. A blood clot in the legs may move to the lungs. If you experience any of these symptoms of a blood clot, contact your doctor immediately.

NOLVADEX increases the chance of having a stroke, which can cause serious medical problems, disability, or death. If you experience any symptoms of stroke, such as weakness, difficulty walking or talking, or numbness, contact your doctor immediately.

NOLVADEX increases the chance of changes occurring in the lining (endometrium) or body of your uterus which can be serious and could include cancer. If you have not had a hysterectomy (removal of the uterus), it is important for you to contact your doctor immediately if you experience any unusual vaginal discharge, vaginal bleeding, or menstrual irregularities; or pain or pressure in the pelvis (lower stomach). These may be caused by changes to the lining (endometrium) or body of your uterus. It is important to bring them to your doctor's attention without delay as they can occasionally indicate the start of something more serious and even life-threatening.

NOLVADEX may cause cataracts or changes to parts of the eye known as the cornea or retina. NOLVADEX can increase the chance of needing cataract surgery, and can cause blood clots in the veins of the eye. NOLVADEX can result in difficulty in distinguishing different colors. If you experience any changes in your vision, tell your doctor immediately.

Rare side effects, which may be serious, include certain liver problems such as jaundice (which may be seen as yellowing of the whites of the eyes) or hypertriglyceridemia (increased levels of fats in the blood) sometimes with pancreatitis (pain or tenderness in the upper abdomen). Stop taking NOLVADEX and contact your doctor immediately if you develop angioedema (swelling of the face, lips, tongue and/or throat) even if you have been taking NOLVADEX for a long time.

If you are a woman receiving NOLVADEX for treatment of advanced breast cancer, and you experience excessive nausea, vomiting or thirst, tell your doctor immediately. This may mean that there are changes in the amount of calcium in your blood (hypercalcemia). Your doctor will evaluate this.

In patients with breast cancer, a temporary increase in the size of the tumor may occur and sometimes results in muscle aches/bone pain and skin redness. This condition may occur shortly after starting NOLVADEX and may be associated with a good response to treatment.

Many of these side effects happen only rarely. However, you should contact your doctor if you think you have any of these or any other problems with your NOLVADEX. Some side effects of NOLVADEX may become apparent soon after starting the drug, but others may first appear at any time during therapy.

This summary does not include all possible side effects with NOLVADEX. It is important to talk to your health care professional about possible side effects. If you want to read more, ask your doctor or pharmacist to give you the professional labeling.

How should I store NOLVADEX?

NOLVADEX Tablets should be stored at room temperature (68–77°F). Keep in a well-closed, light-resistant container. Keep out of the reach of children.

Do not take your tablets after the expiration date on the container. Be sure that any discarded tablets are out of the reach of children.

This leaflet provides you with a summary of information about NOLVADEX. Medicines are sometimes prescribed for uses other than those listed. NOLVADEX has been prescribed specifically for you by your doctor. Do not give your medicine to anyone else, even if they have a similar condition because it may harm them.

If you have any questions or concerns, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about NOLVADEX written for health care professionals that you can ask to read. For more information about NOLVADEX or breast cancer, call 1-800-34 LIFE 4.

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Shown in Product Identification Guide, page 306

SEROQUEL®

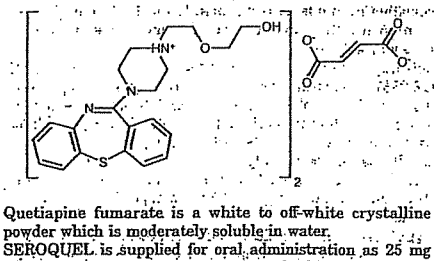
[serō-quēl]

(quetiapine fumarate)

TABLETS

DESCRIPTION

SEROQUEL (quetiapine fumarate) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo[*b*,*f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (peach), 100 mg (yellow), 200 mg (round, white), and 300 mg (capsule-shaped, white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL.

SEROQUEL's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly *via* hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole.

Continued on next page

Seroquel—Cont.

Dose adjustment of quetiapine will be necessary if it is co-administered with phenytoin or ketoconazole (See **Drug Interactions** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION.**)

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (See **Drug Interactions** under **PRECAUTIONS**).

Clinical Efficacy Data

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

(2) In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

(3) In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION.**)

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Two possible cases of NMS [2/2387 (0.1%)] have been reported in clinical trials with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

PRECAUTIONS

General

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (22/2162) of the patients treated with SEROQUEL, compared with 0% (0/206) on placebo and about 0.5% (2/420) on active control drugs. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications).

Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see **Animal Toxicology**). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.

Seizures: During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared to 0.5% (1/206) on placebo and 1% (4/420) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment.

Cholesterol and Triglyceride Elevations: In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis.) Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia and close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5

day period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on SEROQUEL

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION.**)

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established.

Geriatric Use: Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for SEROQUEL included over 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL. Of these 2600 subjects, approximately 2300 were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 865 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 750 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%).

Table 1. Treatment-Emergent Adverse Experience Incidence in 3- to 6-Week Placebo-Controlled Clinical Trials[1]

Body System/ Preferred Term	SEROQUEL (n=510)	Placebo (n=206)
Body as a Whole		
Headache	19%	18%
Asthenia	4%	3%
Abdominal pain	3%	1%
Back pain	2%	1%
Fever	2%	1%
Nervous System		
Somnolence	18%	11%
Dizziness	10%	4%
Digestive System		
Constipation	9%	5%
Dry Mouth	7%	3%
Dyspepsia	6%	2%
Cardiovascular System		
Postural hypotension	7%	2%
Tachycardia	7%	5%
Metabolic and Nutritional Disorders		
Weight gain	2%	0%
Skin and Appendages		
Rash	4%	3%
Respiratory System		
Rhinitis	3%	1%

Continued on next page

Seroquel—Cont.

Special Senses		
Ear pain	1%	0%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, myalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, dry skin, amblyopia and urinary tract infection.

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

Dose Groups	Placebo	SEROQUEL 75mg	150mg	300mg	600mg	750mg
Parkinsonism EPS	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
incidence	16%	6%	6%	4%	8%	6%
Anticholinergic Medications	14%	11%	10%	8%	12%	11%

In three additional placebo-controlled clinical trials using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Nervous System: *Frequent:* hypertonia, dysarthria; *Infrequent:* abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; *Rare:* aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: *Frequent:* flu syndrome; *Infrequent:* neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; *Rare:* abdomen enlarged.

Digestive System: *Frequent:* anorexia; *Infrequent:* increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; *Rare:* glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: *Frequent:* palpitation; *Infrequent:* vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; *Rare:* angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: *Frequent:* pharyngitis, rhinitis, cough increased, dyspnea; *Infrequent:* pneumonia, epistaxis, asthma; *Rare:* hiccup, hyperventilation.

Metabolic and Nutritional System: *Frequent:* peripheral edema; *Infrequent:* weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; *Rare:* glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: *Frequent:* sweating; *Infrequent:* pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; *Rare:* exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: *Infrequent:* dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; *Rare:* gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: *Infrequent:* conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; *Rare:* abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: *Infrequent:* pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: *Frequent:* leukopenia; *Infrequent:* leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; *Rare:* hemolysis, thrombocytopenia.

Endocrine System: *Infrequent:* hypothyroidism, diabetes mellitus; *Rare:* hyperthyroidism.

*adjusted for gender

Post Marketing Experience: Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include the following: rarely leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly, and in patients who are debilitated or who have a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (See Drug Interactions under **PRECAUTIONS**).

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to SEROQUEL, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on

one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

ANIMAL TOXICOLOGY

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2 year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

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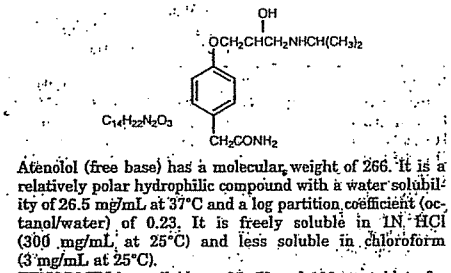
Shown in Product Identification Guide, page 306

TENORMIN® ℞
[ten-or-min]
(atenolol)
ONE TABLET A DAY

DESCRIPTION

TENORMIN® (atenolol), a synthetic, beta$_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. The molecular and structural formulas are:



Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 25, 50 and 100 mg tablets for oral administration.

Inactive Ingredients: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

CLINICAL PHARMACOLOGY

TENORMIN is a beta$_1$-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, TENORMIN inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Pharmacokinetics and Metabolism: In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between two (2) and four (4) hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, TENORMIN undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. TENORMIN also differs from propranolol in that only a small amount (6%-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a fourfold interpatient variation.

The elimination half-life of oral TENORMIN is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of TENORMIN is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73m^2. (See DOSAGE AND ADMINISTRATION.)

Pharmacodynamics: In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of TENORMIN has been demonstrated by: (1) reduction in resting and exercise heart rate and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia, and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of TENORMIN, as measured by reduction of exercise tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an intravenous dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma TENORMIN concentration. The effect on exercise tachycardia of a single 10 mg intravenous dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration. However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the beta$_1$ selectivity of TENORMIN has been shown by its reduced ability to reverse the beta$_2$-mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of TENORMIN producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equipotent oral doses of several beta blockers, TENORMIN produced a significantly smaller decrease of FEV$_1$ than nonselective beta blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, TENORMIN increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. TENORMIN is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

In controlled clinical trials, TENORMIN, given as a single daily oral dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. TENORMIN has been studied in combination with thiazide-type diuretics, and the blood pressure effects of the combination are approximately additive. TENORMIN is also compatible with methyldopa, hydralazine, and prazosin, each combination resulting in a larger fall in blood pressure than with the single agents. The dose range of TENORMIN is narrow and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several possible mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of TENORMIN with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, atenolol increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure, particularly in patients with heart failure.

In a multicenter clinical trial (ISIS-1) conducted in 16,027 patients with suspected myocardial infarction, patients presenting within 12 hours (mean = 5 hours) after the onset of pain were randomized to either conventional therapy plus TENORMIN (n = 8,037), or conventional therapy alone (n = 7,990). Patients with a heart rate of < 50 bpm or systolic blood pressure < 100 mm Hg, or with other contraindications to beta blockade were excluded. Thirty-eight percent of each group were treated within 4 hours of onset of pain. The mean time from onset of pain to entry was 5.0 ± 2.7 hours in both groups. Patients in the TENORMIN group were to receive TENORMIN I.V. Injection 5-10 mg given over 5 minutes plus TENORMIN Tablets 50 mg every 12 hours orally on the first study day (the first oral dose administered about 15 minutes after the IV dose) followed by either TENORMIN Tablets 100 mg once daily or TENORMIN Tablets 50 mg twice daily on days 2-7. The groups were similar in demographic and medical history characteristics and in electrocardiographic evidence of myocardial infarction, bundle branch block, and first-degree atrioventricular block at entry.

During the treatment period (days 0-7), the vascular mortality rates were 3.89% in the TENORMIN group (313 deaths) and 4.57% in the control group (365 deaths). This absolute difference in rates, 0.68%, is statistically significant at the P < 0.05 level. The absolute difference translates into a proportional reduction of 15% (3.89-4.57/4.57 = -0.15). The 95% confidence limits are 1%-27%. Most of the difference was attributed to mortality in days 0-1 (TENORMIN - 121 deaths; control - 171 deaths).

Despite the large size of the ISIS-1 trial, it is not possible to identify clearly subgroups of patients most likely or least likely to benefit from early treatment with atenolol. Good clinical judgment suggests, however, that patients who are dependent on sympathetic stimulation for maintenance of adequate cardiac output and blood pressure are not good candidates for beta blockade. Indeed, the trial protocol reflected that judgment by excluding patients with blood pressure consistently below 100 mm Hg systolic. The overall results of the study are compatible with the possibility that patients with borderline blood pressure (less than 120 mm Hg systolic), especially if over 60 years of age, are less likely to benefit.

The mechanism through which atenolol improves survival in patients with definite or suspected acute myocardial infarction is unknown, as is the case for other beta blockers in the postinfarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

Atenolol Geriatric Pharmacology: In general, elderly patients present higher atenolol plasma levels with total clearance values about 50% lower than younger subjects. The half-life is markedly longer in the elderly compared to younger subjects. The reduction in atenolol clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

INDICATIONS AND USAGE

Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS

TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

TENORMIN is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components.

WARNINGS

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending car-

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